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Article *in* Drug and Alcohol Dependence · August 2005

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Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome

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Received 19 April 2004; received in revised form 22 November 2004; accepted 22 November 2004

Abstract

This study was designed to compare the neonatal abstinence syndrome (NAS) in neonates of methadone and buprenorphine maintained pregnant opioid-dependent women and to provide preliminary safety and efficacy data for a larger multi-center trial. This randomized, double-blind, double-dummy, flexible dosing, parallel-group controlled trial was conducted in a comprehensive drug-treatment facility that included residential and ambulatory care. Participants were opioid-dependent pregnant women and their neonates. Treatment involved daily administration of either sublingual buprenorphine or oral methadone using flexible dosing of 4–24 mg or 20–100 mg, respectively. Primary a priori outcome measures were: (1) number of neonates treated for NAS; (2) amount of opioid agonist medication used to treat NAS; (3) length of neonatal hospitalization; and (4) peak NAS score. Two of 10 (20%) buprenorphine-exposed and 5 of 11 (45.5%) methadone-exposed neonates were treated for NAS ($p = .23$). Total amount of opioid-agonist medication administered to treat NAS in methadone-exposed neonates was three times greater than for buprenorphine-exposed neonates (93.1 versus 23.6; $p = .13$). Length of hospitalization was shorter for buprenorphine-exposed than for methadone-exposed neonates ($p = .021$). Peak NAS total scores did not significantly differ between groups ($p = .25$). Results suggest that buprenorphine is not inferior to methadone on outcome measures assessing NAS and maternal and neonatal safety when administered starting in the second trimester of pregnancy.
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Keywords: Opioids; Women; Buprenorphine; Methadone; NAS; Infants; Prenatal

1. Introduction

Methadone is the only recommended pharmacotherapy in the United States for the treatment of opioid-dependent pregnant women (CSAT, 1993). Methadone given as part of comprehensive care during pregnancy is associated with positive maternal and infant outcomes (Kandall et al., 1976; Connaughton et al., 1977; Finnegan, 1991; Fischer, 2000; Lejeune et al., 2002). However, there is a neonatal abstinence syndrome (NAS) associated with methadone that often requires medical intervention. The NAS is a constellation of signs and symptoms indicating dysfunction of the autonomic nervous system, gastrointestinal tract, and respiratory system (Kaltenbach and Finnegan, 1990; Connaughton et al., 1975; Blinick et al., 1969).

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doi:10.1016/j.drugalcdep.2004.11.013

Buprenorphine, a partial mu-opioid agonist recently approved for the treatment of non-pregnant opioid-dependent adults, may reduce the incidence and/or severity of NAS. In non-pregnant adults, little or no autonomic signs or symptoms of opioid withdrawal are observed following abrupt withdrawal from buprenorphine (Jasinski et al., 1978; Mello and Mendelson, 1980; Mello et al., 1982; Reisinger, 1995; Seow et al., 1986; Fudala et al., 1990). Likewise, prospective open-label controlled studies of neonates born to buprenorphine-treated mothers have found no to mild NAS, with only 17% of neonates requiring short-term treatment (Fischer et al., 2000; Johnson et al., 2001, 2003). Because buprenorphine may be associated with a qualitatively and quantitatively different NAS from that observed with full mu-opioid agonists (Auriacombe et al., 1999), it may be more advantageous for the neonate than methadone. The primary hypothesis of this study is that antepartum treatment with buprenorphine will result in reduced NAS and length of hospitalization in the neonate relative to antepartum treatment with methadone.

This study was designed to compare the NAS in neonates of methadone and buprenorphine maintained pregnant opioid-dependent women and to provide preliminary safety and efficacy data for a larger multi-center trial. It was well-controlled, utilizing a randomized, double-blind, double-dummy design, and the primary focus was on several outcome variables hypothesized to be important in neonatal responsiveness to buprenorphine. However, the small sample size limited our ability to detect differences on these outcome measures at conventional levels of statistical significance. Nonetheless, this study provides valuable initial information about both the safety and efficacy of buprenorphine and methadone and their relative impacts on the neonatal abstinence syndrome and other important neonatal and maternal outcomes.

2. Methods

2.1. Participants

Participants were recruited from heroin-dependent patients admitted between May 2000 and March 2003, inclusive, to the residential unit of the Center for Addiction and Pregnancy (CAP), a multi-disciplinary treatment program (Jansson et al., 1996). The study was approved by the Johns Hopkins Bayview Medical Center Institutional Review Board. Participants provided written informed consent before participating.

2.2. Sampling

Inclusion criteria were: 21–40 years of age; estimated gestational age (EGA) by sonogram of 16–30 weeks; DSM-IV diagnosis of current opioid dependence; requesting maintenance pharmacotherapy; recent self-reported opioid use (more than 4 days of use in the past 7 days); and an opiate-positive urine specimen at intake. Exclusion criteria were: a urine positive for undocumented methadone during intake; a current DSM-IV diagnosis of alcohol abuse or dependence; self-reported use of benzodiazepines (more than seven times per month and/or more than once a week); currently taking medication for another Axis I disorder; presence of a serious concurrent medical illness contraindicating study participation; diagnosis of pre-term labor; evidence of fetal malformation; positive HIV test; or positive sickle cell trait. Fig. 1 shows the flow of participants into the study. The number of mothers screened represents the total number of women who contacted CAP during the time the study was conducted. Most women did not qualify for continued screening because they were entering treatment outside the gestational age allowed in the study or because they did not arrive for CAP admission. The strict inclusion and exclusion criteria were necessary to ensure the safety of the participants especially given the limited knowledge about buprenorphine during pregnancy.

Eligible applicants were stratified at study entry on cocaine use (yes/no), estimated gestational age (16–23 weeks and 6 days; 24–30 weeks) and opioid use (less than three or greater than three times per day). They were assigned to one of the two treatment groups using a computerized dynamic balanced randomization (Signorini et al., 1993) procedure. Research staff, with no other study involvement, generated the randomized allocation sequence.

A total of 30 women were randomized to methadone ($n = 15$) and buprenorphine ($n = 15$). The final sample size enrolled in treatment at delivery was 11 women stabilized on methadone and 9 women stabilized on buprenorphine.

2.3. Procedures

2.3.1. Medication induction and administration

Upon treatment admission, participants received methadone (standard of care for opioid-dependent patients at CAP) for 3–5 days until signing written informed consent. Following consent and during medical screening, participants were switched from daily methadone to an equivalent dose of immediate-release morphine divided into four daily doses. Once medically cleared and randomized, participants were switched from their individualized dose of immediate-release morphine onto an equivalent dose of double-blind study medication. This first day total dose for methadone ranged from 20–60 mg to 8–12 mg for buprenorphine.

Medications were administered double-blind and double-dummy (i.e., each dosing day 12 sublingual tablets followed by 40 ml of oral liquid were administered). A participant assigned to active methadone received 12 sublingual placebo tablets followed by her dose of methadone HCl (20–100 mg) in 40 ml liquid, while a study participant assigned to active buprenorphine received her dose (4–24 mg) in 12 sublingual buprenorphine HCl (Subutex^{TM} 2 mg) tablets followed by 40 ml of placebo liquid. Methadone HCl (Methadose^{TM}) oral concentrate, USP 10 mg/ml (Mallinckrodt Inc., St. Louis,

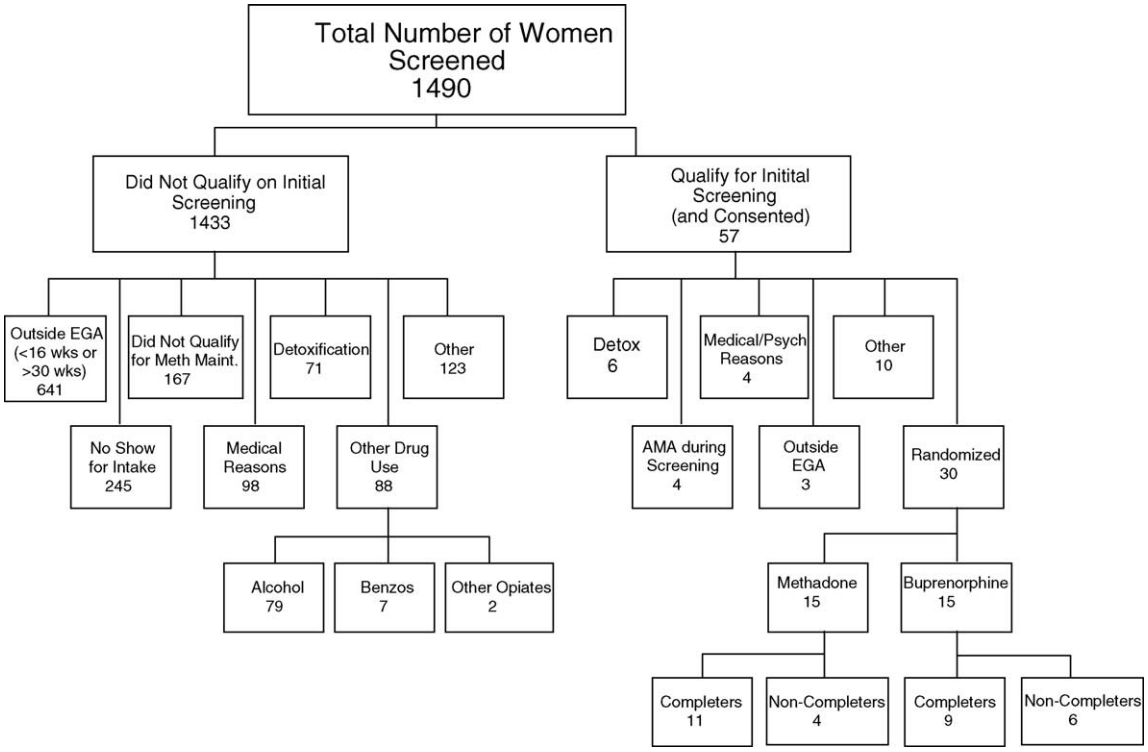

Fig. 1. The flow of patients into the study is shown. The most common reason for failure to qualify for continued screening was that women entered treatment outside the gestational age allowed in the study. The second most common reason for failing to qualify for continued screening was that women did not arrive on their scheduled day of admission to the treatment program.

MO, 63134) was diluted to 4 mg/ml with distilled water. Each dose was delivered as 40 ml using diluted (4:1) concentrated cherry syrup (Mallinckrodt Inc.) masked with 0.3 mcg/ml of diantonium benzoate. Placebo methadone contained the same masked 4:1 concentrated cherry syrup. Active buprenorphine HCl and placebo sublingual tablets were provided by Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA through the National Institute on Drug Abuse, Rockville, MD. The study blind was assessed twice during the study (prior to and after delivery). Most patients thought they were receiving the test medication, with 96.4% of the buprenorphine and 65.5% of the methadone group identifying their blind medication as buprenorphine.

2.3.2. *Dosing*

Doses of 60 mg methadone and 12 mg buprenorphine were selected as target doses based on results from controlled clinical trials in non-pregnant participants (Ling et al., 1996; Strain et al., 1994; Johnson et al., 2000). Induction onto double-blind medication doses occurred within 3 days (Jones et al., in press) and produced little to no opioid withdrawal signs or symptoms. Subsequently, a flexible (i.e., individualized) dosing schedule was used to minimize possible bias resulting from over- or under-medication and to potentially avoid confounding comparisons between medications due to possible differences in dose adequacy that sometimes occur in clinical trials where all participants receive the same dose (Strain et al., 1994; Johnson et al., 2000). Double-blind medication dose increases or decreases were made through clinical decisions based on compliance in taking medication, participant request, urine toxicology and participant self-reports of opioid withdrawal symptoms or craving. Dose changes were made no more often than every 2 weeks unless clinically indicated. A unit dose increase or decrease was 5–10 mg of methadone and 2 mg of buprenorphine. To maintain the double-blind, the actual dose changes were known only to pharmacy staff. Dose decreases were approved if the participant ingested the double-blind medication as scheduled, requested a decrease, and had negative urine toxicologies for illicit drug use and no reports of withdrawal symptoms or craving.

Across medication groups, an average of 3.5 dose increases were made (range 0–6), 3.7 for methadone and 3.3 for buprenorphine until delivery. One participant on methadone requested and received a dose decrease during her pregnancy.

2.3.3. *Urine testing*

Urine samples were collected Monday, Wednesday, and Friday and assayed for opiates, cocaine, benzodiazepines, and marijuana (cutoff levels of 300 ng/ml, 300 ng/ml, 200 ng/ml, and 100 ng/ml, respectively) using the enzyme-multiplied immunoassay technique (EMIT; Dade Behring Diagnostics Inc., Deerfield, IL). One sample was selected at random weekly and sent to an independent laboratory

and tested for amphetamine (cutoff level 1000 ng/ml) and cannabinoids (cutoff level 100 ng/ml) using EMIT. Barbiturates and other drugs[1] were tested using thin layer chromatography. Breath samples (Alco-Sensor III, Alcopro, Knoxville, TN) were assessed randomly once weekly for alcohol use.

2.3.4. Behavioral incentives

In order to minimize the confound of concomitant drug use, patients could earn voucher payments for providing an ethanol-negative breath sample and an urine sample free of opioid, cocaine, benzodiazepines, THC, barbiturates, amitryptilines, amphetamines, clonazepams, doxepins, PCP, phenothiazines, and propoxyphene. Patients earned a $ 7.50 voucher for their first drug-negative breath and urine sample, and vouchers for subsequent consecutive drug-negative samples increased by $ 1. Maximum possible earnings were $ 1200. This schedule of increasing monetary amounts with continued drug abstinence was based upon previous studies in cocaine-dependent (Higgins et al., 1991, 1993, 1994) and methadone-maintained patients showing increased rates of abstinence with this schedule (Silverman et al., 1996). The buprenorphine and methadone groups earned similar amounts of voucher money, $ 855.67 (S.E.M. ± 174) and $ 681 (S.E.M. ± 160), respectively.

2.3.5. Biological samples

Blood and urine samples were collected every 4 weeks after admission and at delivery in order to document safety of the medication by laboratory tests.

2.3.6. Adverse events

Open-ended adverse event forms were completed weekly by trained research staff.

2.3.7. Delivery

Participants were admitted to the Johns Hopkins Bayview Medical Center's General Clinical Research Center (GCRC) 7 days before their estimated delivery date. Participants remained in the GCRC until labor onset at which time they were taken to labor and delivery. Data pertaining to the delivery were abstracted from the mothers' medical records.

2.3.8. Neonatal

Our hospital's standard medical practice is to hospitalize all opioid-exposed neonates for 4 days for observation of NAS signs. The neonate was housed in the same room as the mother after birth, except when admission to the neonatal intensive care unit (NICU) was necessary. Because mothers routinely stay two nights post-partum (three nights for cesarean section), the neonate was moved to the newborn nursery (NBN) or pediatrics floor for the remaining days of hospitalization. Neonates not treated for NAS were discharged after 4 days. Neonates treated for NAS were discharged following 24 h of no medication and NAS scores less than or equal to eight. Following hospital discharge, NAS observations were continued by trained staff through day 10, while the mother and neonate resided in the GCRC.

2.3.9. NAS

NAS was systematically assessed for 10 days (240 h) using a 19-item modified Finnegan Scale. The Finnegan Scale (Finnegan and Kaltenbach, 1992) was modified by the hospital administration from the 1986 Version in the following ways: (1) items of myoclonic jerks, mottling, and excessive sucking were removed from the scale; and (2) respiration rate >60 min^{-1} with and without retractions was changed to one item measuring tachypnea. Number of NAS observations varied from six to eight per day while in the hospital to two per day while in the GCRC. The number of observations was decreased in the GCRC due to availability of trained staff to evaluate NAS. In accord with standard hospital practice, treatment for NAS was initiated when a neonate received two consecutive scores of nine or greater. Morphine solution (equivalent to morphine 0.02 mg/drop) was the pharmacotherapy treatment for NAS (Fischer et al., 2000; Langenfeld et al., 2005). Once the infant was discharged to the GCRC, one score of nine resulted in the infant being admitted to the hospital for NAS observation and possible treatment. Doses of morphine sulfate were given every 3–5 h with feeding. Neonates scoring 9–12 received 2 drops, those scoring 13–16 received 4 drops and those scoring 17–20 received 6 drops. Weaning was initiated after a neonate was maintained on a stable dose for 48 h. Neonates were reduced in medication by one drop per day if every score for 24 h was 8 or below. If scores were nine or greater at any time that day, weaning was deferred. Only total NAS scores, not individual item scores, are reported.

2.4. Primary outcome measures included

Primary outcome measures included:

(1) number of neonates requiring morphine drops for NAS;
(2) peak NAS score;
(3) total amount of morphine drops administered to treat NAS; and
(4) total days of neonatal hospital stay from delivery until discharge from the hospital.

These outcome measures were specifically chosen based on existing literature on prenatal exposure to buprenorphine. Only neonatal measures were selected as primary outcome measures because methadone and buprenorphine appear similarly effective for the mother yet NAS, physical birth parameters, and length of hospital stay may be improved in buprenorphine-exposed neonates.

[1] Amitriptyline, Ativan/Dalmane, Barbiturates, Benzodiazepines, Clonazepam, Codeine, Demerol, Dilaudid, Doxepins, Glutethimide, Hydrocodone, Hydroxyzine, Imipramine, LAAM, Meprobamate, Morphine, PCP, Phenmetrazine, Phenobarbital, Phenothiazines, Propoxyphene, Quinine, Valium and benzoylecgonine.

2.5. Secondary outcome measures

Secondary outcome measures obtained from the medical record included birth-weight, head circumference, length, prematurity, gestational age at delivery, sex, Apgar scores at 1 min and 5 min, neonatal and maternal urine toxicology (tested for opioids, cocaine, barbiturates, and benzodiazepines), type of birth, birth presentation, use of anesthesia, and maternal days of hospital stay in the postpartum unit. Maternal secondary outcome measures included: the average number of days in treatment from day of randomization until delivery to document equivalent drug exposure; the overall percentage of urine samples positive during treatment for each illicit drug and Complete Blood Counts and Blood Chemistry Panels performed at study entry and every 4 weeks until study discharge.

2.6. Statistical analysis

Given the small sample size associated with this initial study of the effects of buprenorphine on neonates, alpha was set at .05 for each of the four primary analyses. Although this choice of an error rate increases the cumulative error rate, a more conservative rate would run the risk of failing to detect a small but potentially important difference between the neonates in the two treatment groups. Moreover, the simplest possible suitable linear model was employed to conduct the analyses. In the case of the binary outcome variable treated for NAS, a chi-square goodness of fit test was conducted. The discrete outcome variables of total amount of opioid-agonist medication administered to treat NAS and length of neonatal stay in the hospital were assumed to follow a Poisson distribution and thus Poisson regressions were conducted. The primary explanatory variable in the statistical model was the binary variable representing Treatment Group (buprenorphine versus methadone); two additional binary explanatory variables were included: gender and treated for NAS (yes versus no). Gender was included in order to control for possible differences between male and female neonates. Treated for NAS was included to better estimate the error term in the statistical model. In this instance, the test of the treatment group effect was adjusted for gender, ignoring the treated for NAS effect (because NAS treatment could be, in part, a result of treatment group membership). No interaction terms were included. Finally, in the case of daily peak NAS scores, an additional repeated-measures factor representing observation day was included in the statistical model, as well as the first-order interactions of this factor with the factors of treatment group, gender, and treated for NAS. Estimation and tests of significance were conducted using a mixed model approach, in which all available data were included in the model, irrespective of the number of days for which each neonate was observed. This model assumed a normal distribution for NAS scores, a compound symmetric error structure (due to the relatively small number of observations, this assumption was the only such assumption that would allow estimation), and error degrees of freedom determined by the Satterthwaite's method.

3. Results

3.1. Participant characteristics

Of the 30 randomized patients, 20 delivered while enrolled in the study; the remaining 10 dropped out during the study. Of those randomized to buprenorphine reasons for drop-out included discharged for medical condition ($n = 1$), missed consecutive dosing days ($n = 4$), and elected to withdraw ($n = 1$). Of those randomized to methadone reasons for discharge included, missed consecutive dosing days ($n = 3$) and elected to withdraw ($n = 1$). No significant demographic differences were observed between completers and non-completers (data not shown) or between buprenorphine and methadone groups (Table 1). All subsequent analyses utilize only the completer sample. One buprenorphine-maintained mother delivered twins. Data for variables known to be altered by twin status (i.e., gestational age at delivery, birth weight, head circumference, and length) were therefore not included in the statistical analyses (Gardner et al., 1995; Blonde and Kaminski, 2003; Blondel et al., 2002).

3.2. Primary outcomes

Twenty percent of buprenorphine-exposed and 45.5% of methadone-exposed neonates were treated for NAS ($p = .23$). The total amount of medication administered to treat NAS in methadone-exposed neonates was three times greater than for buprenorphine-exposed neonates ($p = .13$). Buprenorphine-exposed neonates remained in the hospital for a significantly ($p = .021$) shorter period of time (1.3 days difference) than methadone-exposed neonates. One buprenorphine-exposed neonate and two methadone-exposed neonates were admitted to the NICU and spent 2, 4 and 7 days, respectively. None of the NICU admissions were due to opioid withdrawal. The one buprenorphine-exposed neonate NICU admission was due to streptococcal septicemia. The methadone-exposed neonate NICU admissions were due to a high bilirubin level ($n = 1$) and respiratory distress ($n = 1$). Finally, daily peak NAS total scores over all observation days did not significantly differ between groups ($p = .25$). Fig. 2 shows time-course data of average daily peak NAS score for methadone- and buprenorphine-exposed neonates. This pattern of NAS scores with gradually increasing, peaking and then decreasing scores is typical of what is observed with both buprenorphine and methadone.

3.3. Secondary outcomes: birth and maternal treatment outcomes

Table 2 presents summary data regarding the secondary outcome measures. Buprenorphine-exposed neonates were not statistically significantly heavier at birth than the metha-

Table 1
Baseline characteristics of buprenorphine and methadone completers

Measure	Methadone ($n = 11$)	Buprenorphine ($n = 9$)	F or χ^2 (d.f.)	p
Demographics				
Mean age	30.3 (1.1)	30.0 (1.2)	0.03 (1, 18)	0.871
Race (%)			1.89 (2)	0.390
African–American	63.6	88.9		
White	27.3	11.1		
Other	9.1	0.0		
Mean estimated gestational at entry	23.6 (1.17)	22.8 (1.27)	0.20 (1, 18)	0.663
Mean years of education	10.0 (1.1)	10.33 (1.3)	.04 (1, 18)	0.844
Employment (%)			3.61 (2)	0.165
Unemployed seeking	72.7	33.3		
Unemployed not seeking	27.3	55.6		
Homemaker	0	11.1		
Drug use				
Cocaine use (past 30 days) (%)	63.6	88.9	1.68 (1)	0.195
Opioid use >4× day (%)	54.5	55.6	0.002 (1)	0.964
**Days of alcohol use in past 30 days	1.0 (0.53)	0.78 (0.49)	0.10 (1, 17)	0.761
Nicotine use in past 30 days (%)	81.8	77.8	–	–
Income				
Public assistance in past month ($)	94.9 (75.7)	114.0 (52.9)	0.809 (1, 17)	0.381
Pregnancy history				
Mean previous number of pregnancies	3.9 (0.68)	5.2 (0.87)	1.45 (1, 18)	0.245
Mean previous number of full term deliveries	2.45 (0.52)	3.22 (0.65)	0.87 (1, 18)	0.363
Mean previous number of pre-term deliveries	0.18 (0.12)	0.44 (0.21)	1.28 (1, 18)	0.273
Mean previous number of miscarriages/induced abortions	0.91 (0.34)	1.11 (0.42)	0.14 (1, 18)	0.712
Mean number of living children	2.64 (0.48)	3.44 (0.60)	1.14 (1, 18)	0.301
Medical complications				
% Positive for hepatitis C	18.2	11.1	–	–

Notes: The initial five participants were stratified using five strata of age (18–29 or 30–40); cocaine use past month (0–3 or 4–8); alcohol use past month (0 or >1 day); opioid use (≤3 or >3 times per day); or liver disease (yes/no). The remaining 25 participants were stratified using strata described before. The strata were reduced and changed following the advice of the Data Safety Monitoring Board.
Values in parenthesis are S.E. values.

done-exposed neonates. On average, buprenorphine-exposed neonates weighed 528 g more than the methadone-exposed group. Group means were not statistically significantly for head circumference or length (Table 2). Gestational age at delivery and Apgar scores at 1 min and 5 min were similar between the two treatment groups. Importantly, none of the neonates were observed to have illicit drugs in their urine at delivery.

All but one birth in each group were vaginal, all births were normal presentation, use of anesthesia and maternal length of hospital stay were similar among groups. Only one mother (methadone treated) was positive for any illicit drugs (opiates) at delivery. No complications were observed and mothers from both treatment groups were discharged from the hospital after a similar time period. No major or minor congenital abnormalities were observed in either group.

The average doses at delivery for methadone and buprenorphine were 79.1 mg and 18.7 mg, respectively. Low rates of illicit drug use prior to delivery were observed during the study in both groups due in part to the voucher program. Methadone and buprenorphine groups had percentages of urine samples positive for opioid (15.6, 16.7), cocaine (11.2, 15.2), benzodiazepines (0.4, 2.5), amphetamine (0, 0), and marijuana (7.5, 0), respectively. Eight of 11 methadone and 7 of 9 buprenorphine maintained women were negative from all illicit drugs for 4 weeks or more prior to delivery. Methadone and buprenorphine groups attended a similar number of prenatal care appointments with the Obstetrician while enrolled in the study, 3.4 and 3.6, respectively. In addition to these intensive exams, women were seen weekly by midwife staff for monitoring of blood pressure, weight gain, fundal growth, fetal heart rate, and any other arising medical issues. Complete Blood Counts and Blood Chemistry Panels showed similar pregnancy related changes and were comparable between groups (data not shown). The profile of adverse events were similar for both medications and included typical opioid- or pregnancy-like effects with the most common being vomiting, fever, pain, constipation, headache, and insomnia.

4. Discussion

This is the first study to compare the effects of buprenorphine and methadone on the NAS under rigorous scientific conditions using randomized, double-blind, double-dummy methodology. Results of this study show no statistically significant differences between medication groups on the percentage of neonates treated for NAS, NAS peak score

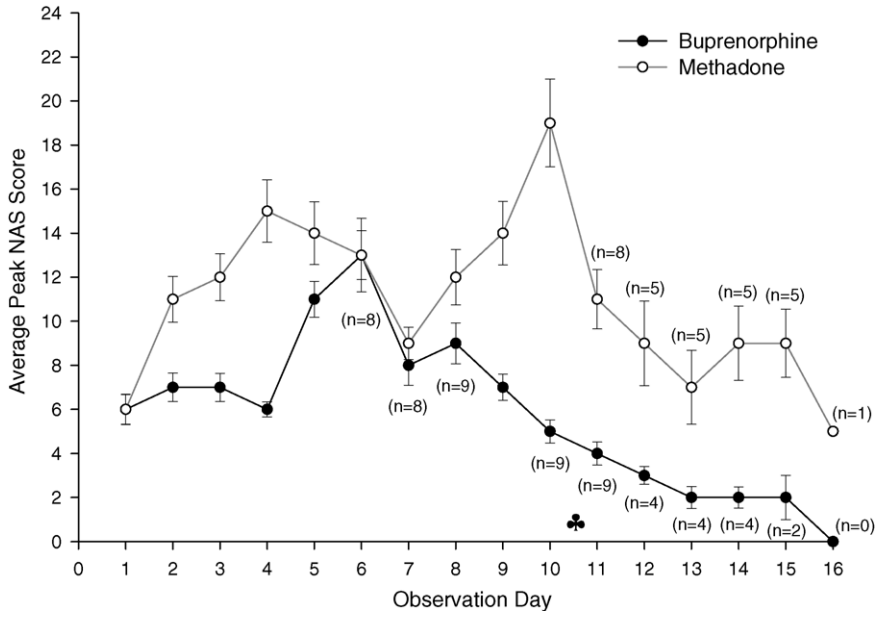

Fig. 2. The time courses of average peak NAS scores for buprenorphine- and methadone-exposed neonates are shown. Due to nursing error, two methadone-exposed neonates received tincture of opium (containing 0.8% alcohol) rather than morphine drops (containing no alcohol) for NAS treatment. Both solutions contain equivalent amounts of morphine. On days where data are missing, the numbers of neonates providing data for the group are indicated in parentheses. For the first 10 days, data from all 11 methadone-exposed neonates are available. The original protocol was designed to collect NAS data for the first 14 days after birth; however, after the first 9 neonates showed very low NAS scores after day 10, the number of days of data collection was reduced (in agreement with the Data Safety Monitoring Board) to the first 10 days after delivery. The club (♣) between days 10 and 11 indicate that neonates not treated for NAS were discharged and NAS scores were not collected after day 10.

over all days or total number of morphine drops administered. There was a statistically significant difference between the two groups in the length of neonatal hospitalization. Buprenorphine-exposed neonates were discharged from the hospital 1.3 days earlier than methadone-exposed neonates.

The daily hospitalization cost for an infant born to a heroin or methadone dependent mother is $ 750–1200 (Kandall, 1993). Using these cost data and the conservative 8 day duration of hospitalization with methadone observed in this study, the annual cost of hospitalization for the 7000 opioid-exposed neonates (NIDA, 1996) would be $ 42–67 million per year. A reduction in hospitalization days of 17% as observed in this study with buprenorphine would amount to a conservative $ 7–11 million annual savings.

Overall, NAS treatment rates following prenatal exposure to buprenorphine and methadone in general treatment populations are higher (e.g., 49% for buprenorphine versus 60–87% for methadone) (Auriacombe et al., 1999; Stimmel et al., 1982–1983; Doberczak et al., 1991, 1993; Blatman, 1973; Kaltenbach and Finnegan, 1987; Berghella et al., 2003) than rates found in the present study. This discrepancy may be due to the low rates of concomitant illicit drug use in this study, or a reflection of potential staff bias towards medication and dose that is possible in non-blinded studies.

The rates of treatment for NAS observed in this study are consistent with a previous non-randomized open-label study (Rohrmeister et al., 2001) comparing methadone and buprenorphine (76% versus 19%, respectively). In contrast, another non-randomized open-label study (Lejeune et al., 2002) reported that 52% and 48% of buprenorphine- and methadone-exposed neonates, respectively, required treatment. Discrepant results between the present and previous (Lejeune et al., 2002) studies are unexplained, but could be due to less rigorous scientific methodology, multiple versus single clinic settings, the use of different NAS scales and NAS treatment criteria and/or the rates of concomitant illicit drug use by the mothers.

There were several strengths of the present study. First, the lack of negative birth outcomes (i.e., lack of prematurity, fetal or neonatal morbidity or mortality) in both groups demonstrates the utility of providing medication within the context of a comprehensive care model. Second, although the low rate of positive urine drug screens at delivery is not reflective of the general population, it does provide greater certainty that the observed NAS is due to the medications administered during treatment. The extent to which drug abstinence based contingent vouchers reduced the use of multiple illicit drugs and alcohol in this study is impressive and extends previous results showing reduced relapse to multiple drugs in non-pregnant patients using a fixed schedule of reinforcement (Chutuape et al., 1999). Third, all dependence treatment, obstetrical care, deliveries, and neonatal observations were performed within one hospital and by one group of experienced medical practitioners. Fourth, a flexible dosing schedule ensured dose adequacy within patients.

Table 2
Buprenorphine versus methadone exposed neonatal and maternal outcomes

Measure	Methadone ($n = 11$)	Buprenorphine ($n = 9$)	F or χ^2 (d.f.)	p
Neonatal				
NAS				
Treated for NAS, *n* (%)	5 (45.5)	2 (20.0)	1.46 (1)	0.227
NAS peak score over all observation days	4.9	3.9	1.43 (1, 20.3)	0.246
Total number of morphine drops administered	93.1 (23.5)	23.6 (19.3)	3.57 (1, 4)	0.132
Total LOS baby	8.1 (0.78)	6.8 (0.86)	6.45 (1, 17)	0.021
LOS nursery	2.1 (0.46)	1.1 (0.37)	1.96 (1, 17)	0.179
LOS pediatrics	5.0 (0.97)	4.8 (1.2)	1.16 (1, 17)	0.296
LOS NICU	0.23 (0.22)	0.65 (0.44)	0.59 (1, 17)	0.453
NICU admission, *n* (%)	2 (18)	1 (10)	0.59 (1, 17)	0.453
Birth weight grams	3001.8 (120.7)	3530.4 (162.7)	3.26 (1, 15)	0.091
Head circumference (cm)	33.2 (.48)	34.9 (6.40)	2.95 (1, 15)	0.106
Length (cm)	49.6 (.76)	52.8 (1.05)	3.19 (1, 14)	0.096
Preterm birth, *n* (%)	1 (9.1)	0 (0.0)	–	–
Gestational age at delivery	38.8 (0.56)	38.8 (0.76)	0.01 (1, 15)	0.911
Female, *n* (%)	5 (45.5)	6 (55.6)	–	–
APGAR 1 min	8.3 (.24)	8.1 (.18)	0.15 (1, 17)	0.707
APGAR 5 min	8.9 (.09)	8.7 (.15)	1.33 (1, 17)	0.265
Urine toxicology positive at delivery (%)	0	0	–	–
Delivery				
Cesarean section, *n* (%)	1 (9.1)	1 (11.1)	–	–
Normal presentation, *n* (%)	11 (100)	9 (100)	–	–
Use of anesthesia during delivery, *n* (%)	7 (63.6)	7 (77.8)	0.47 (1)	.492
Maternal urine toxicology positive at delivery, *n* (%)	1 (9.1)	0 (0.0)	–	–
Maternal length of hospital stay	2.2	2.2	–	–
Maternal medical complications	0.0	0.0	–	–
Maternal treatment				
Days in treatment	99.9 (8.15)	115.6 (9.7)	1.54 (1, 18)	.230

Notes: Twin data from the set of buprenorphine-exposed neonates were removed from the analyses of gestational age at delivery, birth weight, head circumference, and length. The variable of length has one data point missing, although measured it was not recorded. LOS: length of hospital stay.
Values in parenthesis are S.E. values.

The limitations of this study need mention. The primary limitation of this study is the small sample size that limits the power associated with the tests of significance. It was estimated that based on these data and depending on the primary outcome measure of interest and the power (i.e., .8 or .95) and alpha level (i.e., .05 or .01), 35–360 participants would be needed to detect an effect. These preliminary data demonstrate that buprenorphine was clearly not inferior to methadone and supports the need for a large controlled study to provide definitive data on this critical clinical issue. Second, because this was an efficacy and not and effectiveness study, the extent to which these results can be generalized is not known. Third, women were not enrolled in the study until gestational week 16 to minimize any possible physical teratogenic effects. Thus, the extent to which these findings generalize to neonates conceived during methadone or buprenorphine maintenance is unknown. Historically, this has not been a problem with methadone (Kaltenbach et al., 1998) and does not appear to be a problem with buprenorphine (Schindler et al., 2003). Additionally, the role of amount, duration, and gestational age at time of exposure to licit and illicit drugs on neonatal outcomes is unknown. Finally, the level of nicotine exposure during pregnancy could have affected the observed NAS (Choo et al., 2004). However, no dose relationship between number of cigarettes and peak NAS score were observed in this study.

Overall, this controlled study provides additional data supporting the literature demonstrating the utility, safety, and efficacy of both of these medications during pregnancy. These results further support the need for a larger multicenter controlled trial powered sufficiently to detect potential differences between the medications.

Acknowledgements

We are indebted to the patients who participated in this study. We also thank Judy Jakubowski and Jenna Schulcz for the countless hours of hard work and dedication in seeing this study to completion. We also thank the following individuals and groups (listed alphabetically) for their assistance with this study: Gad Alpan; Behavioral Pharmacology Research Unit clinic, dispensary and pharmacy staff; Center for Addiction and Pregnancy staff; Robin Clay; Ed Cone; Data Safety Monitoring Board members (J.T. Christmas, Joseph Collins, Paul Fudala, Charles Gorodetzky, Karol Kaltenbach, and Sidney Schnoll); Meade Eggelston; Joan Hamilton, Chuka Jenkins; Johns Hopkins Bayview Medical Center General Clinical

Research Center staff, Johns Hopkins Bayview Medical Center Labor and Delivery, pediatric, NICU and A2West staff; Sherri Kacinko; Tim Mudric; Tina Robilotto; Patricia Suess, Martha Velez, and Vickie Walters. Dr. Johnson is now employed by Reckitt Benckiser (the manufacturer of buprenorphine). This research was supported by grants DA R01 12220 from the National Institute on Drug Abuse and M01RR-02719 from the General Clinical Research Centers Program of the National Center of Research Resources, National Institutes of Health.

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