Methadone versus buprenorphine in pregnant addicts: a double-blind, double-dummy comparison study

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ABSTRACT

Aims To evaluate the efficacy and safety of methadone versus buprenorphine treatment in pregnant opioid-dependent women. Design Randomized, double-dummy, double-blind, flexible-dosing comparison study. Setting Addiction Clinic at the Medical University of Vienna, Austria. Participants Eighteen women were assigned randomly to receive either methadone (n = 9) or buprenorphine (n = 9) during weeks 24–29 of pregnancy. After dropouts, data were available from 14 cases (six in the methadone and eight in the buprenorphine group). Intervention Sublingual buprenorphine tablets (8–24 mg/day) or oral methadone solution (40–100 mg/day), with matched placebos. Measurements Mothers: retention in treatment, urine toxicology and nicotine use. Neonates: Routine birth data, neonatal abstinence syndrome (NAS) in severity and duration. Findings There was somewhat greater retention in the buprenorphine group but significantly lowered use of additional opioids in the methadone group (P = 0.047). Neonates: There was earlier onset of NAS in neonates born to the methadone (mean 60 hours) than to the buprenorphine groups (mean 72 hours after last medication); 43% did not require NAS-treatment with short treatment duration in both groups (mean 5 days). Conclusion This preliminary study had limited power to detect differences but the trends observed suggest this kind of research is practicable and that further studies are warranted.

Keywords Buprenorphine, methadone, neonatal abstinence syndrome, opioid dependence, pregnancy.

INTRODUCTION

There is an increase in prevalence in illicit opiate use among women of childbearing age in many countries [1,2]. This group warrants special attention, not least because of maternal and neonatal health and wellbeing. Some of the factors that play a significant role in both maternal and neonatal outcomes in pregnant substance-dependent women include relatively late discovery of pregnancy (ensuring in utero exposure to illicit drugs), general self-neglect, poor nutritional habits, substandard living conditions, exposure to high-risk behaviours (infectious diseases, prostitution, suicide), polysubstance abuse, significant levels of nicotine use, lack of interest in treatment, discontinuation of treatment and/or poor treatment compliance and obstetric complications (stillbirths, spontaneous abortion, placenta praevia, abruptio placenta) [3–6]. The cumulative effects of these factors on the children born to substance-dependent women include low birth weight, premature delivery, poor nutritional status, developmental delays, increased risk of sudden infant death syndrome (SIDS) and neonatal abstinence syndrome (NAS) [3–8]. These issues emphasize the need for the development of a treatment strategy that would engage pregnant substance-dependent women in treatment as early as possible during pregnancy, focus on retention in treatment and abstinence from continued illicit substance use, provide adequate psychosocial support, provide medically monitored choice of adjunct pharmacotherapy, perinatal and postnatal care and include an educational component emphasizing the consequences of maternal behaviours on neonatal outcomes.

While for most cases of maternal opioid dependence, detoxification until delivery would be the ideal management goal, this is difficult to achieve.
Since the 1970s, methadone maintenance has been the standard of care for opioid-dependent pregnant women. The use of methadone maintenance has helped to stabilize pregnant opioid-dependent women, thus allowing for better medical management and prenatal care and the use of methadone has been shown to decrease the prevalence of premature births in the population [9,10]. While methadone treatment has proved beneficial, it is known to cause NAS in newborns [8,10]. Newborns whose mothers receive this treatment are usually small for gestational age, although this might also be related to factors other than to the use of methadone, such as concomitant use of other opioids, smoking or low weight gain by the mother [11].

With the introduction, world-wide, of additional pharmacotherapies for the treatment of opioid dependence, recent studies have begun to explore the safety and efficacy of these newer treatments in pregnant women to determine their relative efficacy in comparison to methadone treatment, for opioid-dependent mothers and their offspring. Slow-release morphine has been studied in comparative, controlled trials investigating the differential treatment benefits for both women and children. Results to date suggest that there are no major differences between oral slow-release morphine and methadone in terms of incidence, occurrence, duration or intensity of NAS [12,13]. However, these studies did find a significant decrease in concomitant consumption of benzodiazepines and opiates by the mothers treated with morphine rather than with methadone. Slow-release morphine, however, is not a common treatment for opiate dependence throughout most of the world.

The more commonly used new treatment in opioid dependence is buprenorphine, which is administered as a sublingual tablet and has an opioid receptor profile different from that of morphine and methadone [14]. Buprenorphine has been shown to be a safe and efficacious treatment for opiate dependence and is being used almost world-wide. Published literature on the use of buprenorphine during pregnancy from a large cohort in France (70 000 patients treated with buprenorphine and more than 200 children who were born to buprenorphine-maintained women) also suggests a good safety profile for both women and children. However, the results are based on a naturalistic, observational design, with no routinely collected information regarding use of additional opioids or other substances of abuse during the course of pregnancies [15,16].

The aims of this study were to provide a preliminary indication of the relative safety and efficacy of buprenorphine and methadone in opioid-dependent pregnant women in terms of:

- the frequency and amount of additional opioids used by the mother as measured by urine toxicology;
- the frequency and amount of use of other substances of abuse (such as cocaine and benzodiazepines) by the mother as measured by urine toxicology;
- retention in treatment as measured by completion of the study;
- the severity and duration of the NAS as measured by the Finnegan Scale in the context of morphine treatment for this [17].

METHODS

Subjects

Opioid-dependent pregnant women (Diagnostic and Statistical Manual version IV (DSM-IV), 304.0), older than 18 years, who presented at the addiction clinic of the Medical University Vienna, were included in the study if they provided informed consent and were willing to follow the protocol and to avoid use of illegal drugs whenever possible. Study entry was between weeks 24 and 29 of pregnancy. All subjects considered for entry had opioid-positive urine toxicology, but a cocaine-, benzodiazepine- and methadone-negative urinalysis result in addition to a negative result on an alcohol breath analyser at the screening visit. Women with tetrahydrocannabinol (THC)-positive urine toxicology results were allowed to enter the study. Women were excluded if they had severe somatic or other severe psychiatric diseases or a high-risk pregnancy.

Treatment

Subjects were randomized externally by the hospital pharmacy using a double-blind, double-dummy design and received supervised medication daily from the study pharmacist at the addiction clinic. Patients received food vouchers as compensation (the maximum amount possible was the equivalent of €1000 for 20 weeks’ participation), which was dependent on completion of the study assessments but was not related to the consumption of the study medication.

During screening, all subjects were maintained on oral slow-release morphine hydrochloride (Compensan retard®), a registered medication for the treatment of opioid dependence in Austria. Prior to enrolment, subjects had received a mean daily dose of 330.56 mg (range: 90–600 mg) of slow-release morphine in 24 hours. The final dose of slow-release morphine (mean 164.44, range 30–460; SD 95.50) was taken a mean of 17 hours prior to the first dose of study medication.

Subjects were admitted to the clinic for a minimum of 3 days during the induction of methadone or buprenorphine treatment in order to achieve 24-hour care. Subjects received either 8 mg buprenorphine or 40 mg methadone at the onset of moderate withdrawal symptoms on day 1 (Wang score between 5 and 10) [18]. The
doses were titrated according to a predefined titration algorithm: day 1 dosing was followed by either 55 mg methadone or 12 mg buprenorphine if withdrawal was present. Dose titration increments to 70, 85 and 100 mg per day were available during induction onto methadone (depending on clinical status) and increments to 16, 20 and 24 mg per day were available during buprenorphine induction (matched with placebo tablets/solution). The dosing schedule applied during the titration period of 5 days. However, flexible dosing was allowed during the entire study period, depending upon clinical wellbeing and Wang score. Doses of buprenorphine were between 8 and 24 mg/day and doses of methadone ranged between 40 and 100 mg/day throughout the study.

Subjects who received more than 400 mg/day of oral slow-release morphine prior to the onset of the study started treatment with 55 mg methadone or 12 mg buprenorphine. Adjuvant medication with oxazepam and dextromethorphan oral solution was given to treat agitation and insomnia. The European Addiction Severity Index (ASI) was also used to assess the severity of addiction. The self-assessed daily smoking was also monitored.

Assessments
Supervised urine toxicology tests, full blood count, clinical biochemistry, HIV and hepatitis serology, electrocardiogram (ECG), gynaecological examination and fetal sonography were undertaken prior to starting study medication. The Hamilton Depression Scale (HDS) was completed on day 1 of treatment. Hamilton Depression scores (HDS) were used to assess the severity of depression. The Wang Withdrawal scores (WWS) were used to assess the severity of withdrawal. The visual analogue scales for craving were assessed daily during the titration period and weekly during the entire investigational period [21,22]; the self-reported number of cigarettes smoked daily was also obtained. Urine samples were taken twice-weekly throughout the study. Gyneacological investigations were undertaken on day 1, weeks 28, 32, 36 and 38 of pregnancy, and at the expected time of delivery. Following delivery, the women were investigated for congenital infections and anomalies.

Neonates were observed for a minimum of 10 days on an in-patient basis under blinded conditions for the mothers’ treatment condition and scored every 4 hours using the Finnegan scale (range 0–45) [17]. Infants with scores higher than 10 points were treated with oral morphine hydrochloride drops, according to body weight and total NAS score. Routine birth data (gestational age, weight, length, head circumference and Apgar score standardized 1, 5 and 10 minutes after delivery; range 0–10) were documented. The double-blind, double-dummy code remained blinded until 30 days after delivery.

Standardized perinatal and postnatal care was provided through close cooperation between a multi-disciplinary team of psychiatrists, nurses, social workers, a psychologist, pharmacists, gynaecologists and neonatologists at the Addiction Clinic, Department of Psychiatry, Department of Gynaecology, and Department of Neonatology, Medical University Vienna, Austria.

Statistics
Given the small sample sizes, inferential statistics have been included to a limited extent, mostly for baseline comparisons; $\chi^2$ or Fisher’s exact tests were used for baseline comparisons of categorical variables. Data on interval level scales were analysed using $t$-tests for independent samples, or the Mann–Whitney test was used for highly skewed non-parametric data.

Ethics
The Human Subjects Ethical Committee at the Medical University of Vienna, approved the protocol. All subjects gave written informed consent prior to randomization.

RESULTS
During the 3-year period between 2000 and 2002, 146 opioid-dependent pregnant women were screened for entry into the study. However, a very high proportion of women screened did not meet the inclusion criteria. The most common reasons were the presence of severe polysubstance dependence (20%), lack of consent to participate in daily visits to the clinic (30%), already being maintained on methadone (15%) or buprenorphine (15%) or seeking treatment after week 29 of pregnancy (15%) and deciding to undergo abortion prior to week 12 (10%) or had pregnancy complications (10%).

In total 18 HIV-negative subjects were enrolled. Nine women were randomized to receive methadone and nine received buprenorphine. There were no differences between the two treatment groups on demographic variables (see Table 1).

Twelve participants were single, three were married and three divorced. Eleven of the 18 subjects had completed at least 9 years of education, four had attended vocational school and three had completed high school/A level. For 10 of the participants this was their first reported pregnancy, and for the remaining eight participants their second. Participants’ hepatitis serology
proved negative for eight women, and 10 screened positive for hepatitis C by polymerase chain reaction (PCR). Two of the latter were also positive for hepatitis B antibody, and one had a combination of hepatitis A and B antibodies.

Four dropouts occurred during the study period. One subject maintained on methadone (70 mg/day) experienced a stillbirth caused by a sudden intrauterine death during week 38 of pregnancy. After a postmortem pathological examination, no morphological abnormalities were observed in the fetus (a normal ultrasound result was obtained 2 days prior to the fetal death). However, in analysing the urine toxicology of the mother we found 66% opioid-positive results over the study period and 48% cocaine-positive results, as well as 16% benzodiazepine-positive results (14 weeks’ total study duration). During weeks 36 and 38 all results were opioid-positive, but cocaine- and benzodiazepine-negative. Cigarette consumption was a mean of 35 per day. A second woman had a late abortion during week 28 (85 mg/day methadone; all urine toxicology results were negative for illicit drugs and benzodiazepine consumption).

Two other subjects were withdrawn from the study due to lack of compliance with the scheduled visits. One patient was taking buprenorphine (20 mg, week 26) and the other methadone (70 mg, week 32). This attrition left 14 participants who completed the study, six in the methadone group and eight in the buprenorphine group.

The four women who failed to complete the study were older (\(P = 0.01\); mean age 31.5 versus 24.3 years) and had a longer duration of opioid dependency (\(P = 0.004\); 9.8 versus 3.6 years) than those who completed the study, whereas no significant differences in socio-demographic characteristics were seen at enrolment (see Table 1).

At the end of the titration period, all subjects reached stable levels of study medication, with mean doses of 47.5 mg methadone and 13.5 mg buprenorphine. The transfer from oral slow-release morphine (Compensan retard\textsuperscript{®}) was unproblematic and the first dose of study medication was given following mild scores on the Wang Withdrawal Scale—mean Wang Scale scores decreased significantly from 9.57 on day 1 of treatment to 4.71 on day 2, 2.79 on day 3, 3.86 on day 4 and 1.07 on day 5 and remained low thereafter throughout the study period for both groups. No differences were found between the two groups on the Wang Withdrawal Scale.

There was a slight increase in the mean dose of study medication taken during the last trimester of pregnancy (+5 mg for methadone, +0.5 mg for buprenorphine). Dosing was based on medical judgement and applied rating scores. The mean study duration in both groups was 14 weeks until delivery [13.5 weeks (range 10–16 weeks) for methadone and 14.5 weeks (range 11–16 weeks) for buprenorphine].

Urine toxicology data (completer analysis from 323 samples) indicated that methadone was more effective than buprenorphine in preventing additional opioid consumption (\(U = 7,500, P = 0.029\)), while benzodiazepine and cocaine abuse was low in both groups without significant differences (Table 2). Caution must be used in interpreting or making inferences from these data due to the sample size, as well as the 20% larger number of samples provided by the buprenorphine group.

The mean weight gain in the sample was low from a mean of 63 kg (SD 8.3) at treatment induction (mean

### Table 1 Characteristics of the study population.

<table>
<thead>
<tr>
<th></th>
<th>Methadone ((n = 9))</th>
<th>Buprenorphine ((n = 9))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>25.6 ± 6.1</td>
<td>26.2 ± 4.6</td>
<td>0.797</td>
</tr>
<tr>
<td>Age at first heroin injection</td>
<td>20.9 ± 6.3</td>
<td>20.3 ± 4.6</td>
<td>0.834</td>
</tr>
<tr>
<td>Duration of heroin consumption</td>
<td>5.1 ± 3.7</td>
<td>4.9 ± 4.7</td>
<td>0.912</td>
</tr>
<tr>
<td>Polysubstance use</td>
<td>7 (77.8%)</td>
<td>7 (77.8%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Number of polysubstances abused</td>
<td>1.86 ± 0.90</td>
<td>2.14 ± 0.90</td>
<td>0.563</td>
</tr>
<tr>
<td>Money spent on drugs (last 30 days, €)</td>
<td>776 ± 495</td>
<td>663 ± 378</td>
<td>0.593</td>
</tr>
<tr>
<td>Week of pregnancy at first contact</td>
<td>15.2 ± 10.4</td>
<td>13.0 ± 5.9</td>
<td>0.698</td>
</tr>
<tr>
<td>Week of pregnancy at enrolment</td>
<td>24.6 ± 1.6</td>
<td>24.0 ± 0.0</td>
<td>0.377</td>
</tr>
<tr>
<td>Study duration in weeks</td>
<td>17.5 ± 2.5</td>
<td>18.5 ± 2.1</td>
<td>0.437</td>
</tr>
</tbody>
</table>

### Table 2 Positive urine samples for illicit substances among study completers.

<table>
<thead>
<tr>
<th></th>
<th>Methadone ((n = 6))</th>
<th>Buprenorphine ((n = 8))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>4.35</td>
<td>35.26</td>
<td>0.029</td>
</tr>
<tr>
<td>Cocaine</td>
<td>0.00</td>
<td>0.00</td>
<td>0.950</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>7.82</td>
<td>5.36</td>
<td>0.950</td>
</tr>
</tbody>
</table>
week 24 of pregnancy) to a mean of 68 kg (SD 9.6) at delivery, with no differences found between the two treatment groups.

Eleven women had a vaginal delivery. One subject maintained on methadone required vacuum extraction due to a prolonged delivery, while two women maintained on buprenorphine were delivered by planned Caesarean section at week 40.

All children were healthy, but five (n = 3 methadone, n = 2 buprenorphine) were delivered prematurely before week 37 of pregnancy; one was delivered at week 34, one at week 35 and three at week 36. There was no difference in birth weights (mean 2820 g) between the two treatment groups, either for premature or mature deliveries (P = 0.489). Apgar scores ranged from 8.5 at 1 minute to 10 at both 5 minutes and 10 minutes in both groups and for both premature and full term neonates, with no difference found between treatment groups.

Of the 14 neonates, six (three from mothers in each treatment group) experienced no more than mild NAS and did not require treatment (Finnegan score never exceeded 8). For the eight neonates who required treatment for their NAS symptoms, neonates of methadone-maintained mothers required treatment on average 12 hours earlier (mean 60 hours after last dose of study medication, range 52–68: SD 11.3) than those born to the buprenorphine maintained group (mean after 72 hours; range 35–109: SD 35.2) (P = 0.537). The mean duration of treatment for NAS was 5.3 (range 4–7; SD 1.5) and 4.8 days (range 1–8; SD 2.9) in the methadone and buprenorphine groups, respectively (P = 0.766). There was no difference in the mean cumulative dose of morphine required to manage NAS in the two groups (methadone: 2.71 ± 1.68 mg; buprenorphine: 2.00 ± 2.00 mg; P = 0.640). In addition, no positive correlation between mean doses of medication at delivery and intensity of NAS was observed (methadone: r = -0.201, P = 0.703; buprenorphine: r = 0.298, P = 0.517).

Finnegan scores of neonates from mothers with high rates of cigarette use (greater than 10 per day) appeared to be higher than those from mothers who reported smoking less than 10 cigarettes per day.

Fifty per cent of mothers in both groups nursed their neonates: five of the six neonates who did not need treatment for NAS were nursed, whereas in the group of seven neonates with NAS only three were nursed.

**DISCUSSION**

The strict selection criteria and visit schedules adopted in our study appeared to be somewhat incompatible with the life-style of the targeted participants and many did not meet the inclusion criteria, as only 12% of screened subjects were eligible for entry. It was also noted that, despite the flexibility for the study physicians to adjust the medication dosage on a daily basis, the mean doses of methadone (53 mg) and buprenorphine (14 mg) at delivery were relatively low.

Over the study period until delivery, a considerable rate of additional consumption of opiates was seen in the buprenorphine-treated group when compared with the methadone-treated group. However, in comparing these data, it should be considered that 20% more urine samples were analysed in the buprenorphine group based on the higher retention. Cocaine and benzodiazepine consumption was low in both groups. However, if these urine toxicology results are compared to similarly designed studies in a non-pregnant population, even the opioid concomitant consumption appears comparatively low in our sample, also considering the small sample size [23,24].

One possible reason for the higher illegitimate use of opioids in the buprenorphine group might relate to published observations that some subjects attain a ‘clear mind status’ while receiving buprenorphine and these subjects therefore might have taken illicit opioids to reverse this status [25,26].

The provision of daily contact with physicians throughout the study should have provided opportunity for women to address their needs, but clearly this did not happen in practice. A potentially better approach to this problem would have been to provide feedback on the outcome of their urine tests and to reward subjects with vouchers each time they achieved negative urine results for opioids, cocaine and/or benzodiazepines, as contingency management techniques have proved very successful in other studies in reducing or eliminating illicit substance use. This technique could have been employed while still maintaining the blinding for the study medication [27]. Compensation was provided in the study but it was unrelated to urine toxicology.

Nicotine consumption also needs to be addressed in a more controlled fashion in future studies with this population. We found that nicotine appeared to influence neonatal outcome, which is consistent with other studies that have found low birth weight, decrease in length of neonate and head circumference in women who smoked during pregnancy [28]. However, statistical analysis of our data was not possible due to the small sample size.

Despite the design limitations, small sample size and additional illicit drug use, the limited results of the present study show that the mean duration of neonatal treatment in both the methadone and buprenorphine groups (5 days) was shorter than that described in any other published trial using methadone treatment (i.e. 11–28 days) [29,30]. This finding may also be due, in
part, to the standardized treatment of NAS with morphine, rather than a difference in the severity or duration of NAS found in other studies [31, 32].

Also the standardized, multi-disciplinary approach adopted in our study (having daily visits with a multi-disciplinary team at the addition clinic with predefined contacts at gynaecology, including a structured duration of hospitalization for the neonates with standardized ratings of NAS) appears to offer benefits over the more traditionally available heterogeneous approaches. The mean onset of NAS at 2.5–3 days after the last administration of medication is an important finding because it implies that premature discharge might not allow recognition of the symptoms of NAS, as many neonates are released within 24–48 hours following birth. It is unlikely that the onset of NAS would not be noticed, or it would be mislabelled, in a home setting and its treatment would be delayed or mis-treated due to mislabelling.

Also, from larger study trials special attention needs to be drawn from a general public health point of view on opioid-dependent women, as they still do not tend to seek medical help soon after conception or in their early pregnancy and most pregnancies are detected only in a progressed state. There is a need to provide adequate support for the patient by assembling a trained multi-disciplinary treatment team including the assistance of health authorities in addition to diversification in opioid maintenance [33].

There is a continuous need, however, for standardized evidence-based studies, as this investigation could not clarify definitively which treatment was most beneficial to either the women or the neonates. In addition, many of the variables affecting neonates and mothers requires a larger sample size in order to draw firm conclusions and inferences. Studies with an increased number of patients, a broader randomization frame and less stringent inclusion/exclusion criterion, would allow for a determination of individual variables associated with efficacy of treatment of the mother and neonatal outcome of the children. It appears, from our limited sample, that to answer the relevant outstanding questions a large-scale multi-centre trial is needed.

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