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Buprenorphine Treatment of Opioid-Dependent Pregnant Women: A Comprehensive Review

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Declaration of Interest

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Abstract

Aims—This paper reviews the published literature regarding outcomes following maternal treatment with buprenorphine in five areas: maternal efficacy, fetal effects, neonatal effects, effects on breast milk, and longer-term developmental effects.

Methods—Within each outcome area, findings are summarized first for the 3 randomized controlled trials and then for the 44 non-randomized studies (i.e., prospective studies, case reports and series, and retrospective chart reviews), only 28 of which involve independent samples.

Results—Results indicate that maternal treatment with buprenorphine has comparable efficacy to methadone, although difficulties may exist with current buprenorphine induction methods. The available fetal data suggest buprenorphine results in less physiologic suppression of fetal heart rate and movements than methadone. Regarding neonatal effects, perhaps the single definitive conclusion is that prenatal buprenorphine treatment results in a clinically significant less severe neonatal abstinence syndrome (NAS) than treatment with methadone. The limited research suggests that, like methadone, buprenorphine is compatible with breastfeeding. Data available thus far suggest that there are no deleterious effects of in utero buprenorphine exposure on infant development.

Conclusions—Buprenorphine produces a less severe neonatal abstinence syndrome than methadone, but there is still a role for methadone in the treatment of opioid dependence during pregnancy.

Keywords

pregnancy; opioid dependence; pharmacologic treatment; buprenorphine

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Given the increasing prevalence of use of opioids by pregnant women, and the potentially serious maternal, fetal, and neonatal risks attendant to such use, the provision of effective treatment for this population should be a public health priority. Historically, treatment options for opioid-dependent pregnant women have included medication-assisted withdrawal (i.e., detoxification) and methadone maintenance [1-5]. Methadone maintenance is the recommended standard of care over no treatment or medication-assisted withdrawal given empirical evidence of longer durations of maternal drug abstinence and obstetrical care compliance, avoidance of associated risk behaviors, reductions in fetal illicit drug exposure, avoidance of repeated intoxication and withdrawal associated with continued opioid abuse, and enhanced neonatal outcomes (i.e., heavier birth weight [1, 4-5]). More recently, buprenorphine has been utilized to treat opioid dependence as it may reduce the incidence and/or severity of the neonatal abstinence syndrome. This paper reviews the literature regarding maternal, fetal, neonatal and infant developmental outcomes for buprenorphine-maintained pregnant women. Space limitations preclude detailed comparisons to methadone treatment outcomes; however, some attention is paid to such comparisons when warranted.

Buprenorphine: General Information

Buprenorphine, Subutex® (buprenorphine alone), and Suboxone® (buprenorphine/naloxone 4:1 – naloxone is added to reduce the risk of individuals crushing and injecting the tablets [6]) are administered as sublingual tablets available through maintenance clinics and office-based practices by certified physicians in the U.S.A., with prescription privileges and practices varying elsewhere (e.g., physician training is required in Singapore similar to that required in the U.S.A.; Austria, Belgium, and France do not require buprenorphine-prescribers to receive special training). Although buprenorphine and methadone both act on the μ-opioid receptor, each has a unique pharmacology. Methadone, a full μ-agonist, has approximately 90% oral bioavailability. During pregnancy, the plasma half-life of methadone decreases and clearance increases, resulting in lower methadone trough levels and concomitant withdrawal symptoms [7]. In contrast, buprenorphine is a partial μ-agonist and κ-antagonist with approximately 50% oral bioavailability due to extensive first-pass metabolism [15]. Buprenorphine has lower intrinsic activity (i.e., does not activate the receptor like a full μ-opioid agonist) and, consistent with this effect, has maximal subjective and physiological effects that are less than a full μ-agonist's maximal effect (i.e., a plateau effect) (e.g., [8-9]). Theoretically, buprenorphine may not be as effective in patients requiring higher doses of methadone for full therapeutic effect [10], although some research fails to support this contention [11-12]. On the other hand, this feature of buprenorphine may make overdose deaths less likely with buprenorphine than with methadone [13-14]. Buprenorphine also has higher receptor affinity [15-16] and thus a longer duration of action than methadone. Finally, as with methadone, pregnancy-induced metabolic changes may require increases in buprenorphine dose as gestation advances [17-21].

It is important to note that buprenorphine's primary metabolite, norbuprenorphine, has opioid receptor activity similar to its parent compound [22]. While norbuprenorphine's effects have been less studied than buprenorphine's, norbuprenorphine has been found in biological matrices associated with reproduction (e.g., umbilical cord [23], placenta [24], maternal and neonatal urine [17],and breast milk [25]) and one study reported a positive correlation between norbuprenorphine concentrations on postnatal day 1 and length of neonatal hospital stay [26].

Buprenorphine Treatment during Pregnancy: Overview

A systematic literature review regarding buprenorphine treatment for opioid-dependent pregnant women was conducted using the National Library of Medicine's MEDLINE Pubmed, the Cochrane Library, EMBASE databases and PsychINFO. Reference lists of relevant studies and review articles were reviewed by one author (H.E.J.) to locate further eligible studies. Papers published in languages other than English were reviewed for relevance by their English titles and translations were sought where necessary. Search terms were “buprenorphine” or “subutex” or “suboxone” with “pregnancy” or “pregnant” or “fetus” or “neonate”. Resulting papers were reviewed for their appropriateness for inclusion in the present article. Only archival publications were maintained for review; all abstracts, posters, presented papers, theses, and dissertations were excluded.

This presentation of the results reported in this literature is organized by five main outcome areas summarizing available study findings on buprenorphine-maintained pregnant women and their offspring exposed in utero to buprenorphine. These areas include: maternal efficacy, fetal effects, neonatal effects, effects on breast milk, and developmental effects. Within each outcome area, findings are summarized first for the three randomized controlled trials and then for the non-randomized studies, which include prospective studies, case reports and series, and retrospective chart reviews.

The three randomized controlled trials include the Maternal Opioid Treatment: Human Experimental Research (MOTHER) study [18, 27], an eight-site, international, double-blind, double-dummy, flexible-dosing trial that compared buprenorphine and methadone in the context of comprehensive care in 175 opioid-dependent pregnant women, of whom 131 delivered while in the study. The PROMISE study [19], a small-scale, single-site randomized clinical trial comparing buprenorphine to methadone, provided pilot data for the design of the MOTHER study. The Fischer et al. study [20] was a second small-scale, single-site randomized clinical trial comparing buprenorphine to methadone, which differed from the PROMISE study in the details of dose scheduling and contingency management.

The non-randomized studies category is complex as multiple studies report on the same sample or a subsample of participants. Although 44 non-randomized studies are abstracted in **Tables 1**, **2**, **3**, and **4**, only 28 contain independent samples. Therefore, summaries of the non-randomized studies are limited to the results of the primary study, unless otherwise noted.

Buprenorphine: Maternal Efficacy

Table 1 summarizes the studies reporting maternal outcomes results in buprenorphine-maintained pregnant women.

Treatment Retention

Of pregnant women assigned to buprenorphine treatment, MOTHER retained 67% (58/86), PROMISE retained 60% (9/15) and Fischer et al. retained 89% (8/9). In comparison, MOTHER retained 78% (57/73), PROMISE 73% (11/15), and Fisher et al. 67% (6/9) of methadone condition participants. Jones et al. [18] reported the two medications did not significantly differ in treatment completion. Neither Jones et al. [19] nor Fischer et al. [20] conducted a test for differential drop-out; re-analyses of their respective data found no significant differences in terms of treatment completion.

Although there was no statistically significant differential attrition between the MOTHER medication conditions, there was a 33% (28/58) and 18% (16/73) drop-out rate in the buprenorphine and methadone conditions, respectively. Moreover, 29% (8/28) of buprenorphine condition drop-outs left on the day of study entry. These findings underscore the need to systematically examine various buprenorphine induction procedures for opioid-dependent pregnant women entering agonist-treatment [28]. Until more definitive research on buprenorphine induction procedures in opioid-dependent pregnant women has been conducted, studies of male and non-pregnant female patients suggest that administering the initial induction dose in smaller increments throughout the day may facilitate induction [29].

For the non-randomized studies, meaningful treatment retention data are unavailable. Because retention data were not directly reported in these studies, we used data that were available in the articles to calculate the number and percentage of mothers who delivered while taking buprenorphine in **Table 1**. An initial review of the table would suggest that buprenorphine treatment retention was 100% in 13/15 of the independent prospective studies, 10/10 of the independent case reports and series, and 3/3 of the retrospective chart reviews, with the remaining two prospective studies showing treatment retention of 93% (84/90) and 61% (23/38), respectively. However, inclusion and/or exclusion criteria for the non-randomized studies were often not reported; in the remaining cases, the criteria would guarantee 100% 'treatment retention' (see **Table 1** *Notes*). Thus, these data should be interpreted with caution.

Buprenorphine treatment retention remains an important scientific question, given that a review [30] of 23 randomized controlled trials in non-pregnant participants concluded that flexible-dose buprenorphine maintenance was less effective than methadone for treatment retention. However, the extent to which this attrition can be attributed to buprenorphine's pharmacology and/or induction protocols remains unknown.

Illicit Drug Testing during Pregnancy

Among buprenorphine participants in the MOTHER study, 33% of the urine test results were positive for illicit opioids during the entire study period [18], while in the PROMISE study, 17% of the urine samples collected during participation in the study tested positive for opioids [19]. Fischer et al. reported that the median percentage of urine samples positive for illicit opioid(s) during the entire course of pregnancy among the buprenorphine participants was 35%[20]. In comparison, 23% of the urine samples from the methadone participants in the MOTHER study tested positive for illicit opioids during the entire study period, while in the PROMISE study, 16% of the urine samples tested during the course of participation in the study were positive for opioids. Fischer et al. reported the median percentage of urine samples positive for illicit opioid(s) during the entire course of pregnancy for their methadone participants was 4%. The MOTHER study's buprenorphine and methadone conditions did not differ in the rates positive for cocaine, benzodiazepines, and marijuana, either throughout the course of the study, or in the last four weeks prior to delivery. The PROMISE study found similar rates of cocaine-, benzodiazepine-, and marijuana rates of urine-positive test results for the buprenorphine and methadone conditions during the course of the study, with 78% (7/9) of the buprenorphine- and 73% (8/11) of the methadone-maintained participants urine-negative for all illicit substances during the final 4 weeks of pregnancy. Fischer et al. reported that the methadone condition had significantly fewer urine samples positive for illicit opioids during the entire course of the study relative to the buprenorphine condition.

Illicit Opioids at Delivery

For buprenorphine, 9% (5/58) of the MOTHER participants and 0% (0/9) of the PROMISE participants tested positive for illicit opioid(s) at delivery. In contrast, for methadone, 15% (11/73) of the MOTHER participants and 0% of the PROMISE (0/11) participants tested positive for illicit opioids at delivery. The difference between the buprenorphine and methadone conditions on the drug use measures was not significant in either the MOTHER or PROMISE studies [18-19]. Fischer et al.[20] Did not report urine results at delivery.

For the 9 of 36 independent samples of non-randomized studies with frequency data on urine drug screening for illicit opioid use at delivery, the percentage of urine samples positive for opioids at delivery was highly variable, ranging from 0% to 65%, with an unweighted mean of 19%.

Average Dose Increases in Randomized Controlled Trials

The mean number of 2 mg dose increases in the MOTHER study was 0.1, 1.3, and 1.2 during the first, second, and third trimesters, respectively, while there was a mean of 3.3 dose increases over the course of the PROMISE trial, Fischer et al.[20] noted an increase of 0.5 mg buprenorphine during the last trimester. The number of 5 or 10 mg dose increases in the MOTHER methadone condition was 0.1, 1.2, and 1.5 during the first, second, and third trimesters, respectively. PROMISE reported a mean of 3.7 dose increases of 5 or 10 mg of methadone.[19] Fischer et al.[20] reported a 5 mg increase in methadone dose during the last trimester.

Findings from these three randomized clinical trials suggest the need for dose increases throughout pregnancy in order to effectively manage withdrawal symptoms in expectant mothers. These findings are consistent with pharmacokinetic research that has shown the need to increase buprenorphine dose during the course of pregnancy in order to maintain therapeutic blood levels [17]. Moreover, findings from all three randomized trials suggest that comparable methadone dose increases during the course of pregnancy are necessary. These findings are consistent with past research that has found lowered trough plasma concentrations and greater total and unbound methadone clearances during pregnancy than following delivery in a sample of methadone-maintained pregnant women [31]. This line of research suggests that periodic evaluation of methadone dose should be conducted throughout pregnancy, because it may be necessary to increase dosage in order to maintain therapeutic blood levels necessary to maintain abstinence in methadone-maintained pregnant women [18-19, 31].

Pain Management: Labor and Delivery and Postpartum

No randomized controlled trials have been published examining pain management for opioid-dependent pregnant women during labor and delivery and postpartum. However, three retrospective analyses, two from PROMISE [32-33], and one from the European MOTHER site [34], reported pain management findings during buprenorphine or methadone maintenance. In the PROMISE study, similar Day 1-5 postpartum pain ratings and pain medication usage were found between methadone- and buprenorphine-maintained women delivering vaginally [32]. Following cesarean delivery, women treated daily with either buprenorphine (18 mg) or methadone (80 mg) showed adequate pain control postpartum with the use of a patient-controlled analgesia (PCA) pump for 24 hours, followed by opioids in combination with acetaminophen [33]. Finally, no significant differences were found between the European MOTHER buprenorphine and methadone conditions in terms of pain management, either during delivery or in the immediate postpartum period [34]. A comparison of the combined opioid-agonist-maintained groups with a matched non-opioid-dependent control group of pregnant women showed that the opioid-agonist-maintained group was significantly more often prescribed epidural anesthesia for vaginal deliveries, non-steroidal anti-inflammatory drugs for cesarean deliveries, and opioids during the first three days postpartum.

Meyer et al. [35][1] conducted a retrospective case-control study, matching 68 opioid-dependent pregnant women treated with buprenorphine with a non-opioid-dependent control sample. Relative to controls, buprenorphine-maintained women had increased pain during vaginal delivery and increased postpartum pain and opioid utilization following cesarean delivery, requiring 47% more opioid analgesic.

These findings suggest that opioid-dependent pregnant patients are hyperalgesic and that neither buprenorphine nor methadone alone provides adequate ante- or postpartum pain control. Therefore, many opioid-dependent pregnant women need tailored pain medication regimens that include pain medications in addition to their prescribed opioid agonist during both labor and delivery and the immediate postpartum period.

Buprenorphine: Fetal Effects

Table 2 summarizes available results of fetal outcome in studies of buprenorphine-maintained pregnant women reporting fetal outcomes. Two prospective analyses examining fetal behavior in MOTHER subsamples are reported [36-37].

Among fetuses (*n*=10) of 32-35 weeks gestation, the methadone-exposed condition showed greater motor activity suppression and shorter duration of movements than the buprenorphine-exposed condition [36]. Further, for fetuses (*n*=81) assessed between 31-33 weeks gestation, there was a significantly higher incidence of a non-reactive non-stress test for methadone-exposed compared to buprenorphine-exposed fetuses [37]. Finally, among non-randomized studies, there are reports of intrauterine growth restriction (IUGR) in 54% (7/13) of buprenorphine-maintained pregnant women in one sample, 50% (3/6) in a second sample, and 31% (49/159) in a third sample.

Findings from these two fetal behavior studies suggest that buprenorphine produces less suppression of fetal heart rate, fetal heart rate reactivity, and results in a superior biophysical profile after medication dosing. Thus, fetal risk may be no greater, and possibly less, for buprenorphine than for methadone. There are recurring reports of IUGR in pregnant women maintained on buprenorphine. However, the extent to which the occurrence of IUGR is due to factors other than buprenorphine use (for example, tobacco smoking), and/or whether

[1]Meyer et al. [35] does not appear in the tables because none of the outcomes summarized in the tables were reported in this article.

IUGR occurs more or less frequently as a result of buprenorphine than methadone maintenance treatment remains unaddressed.

Buprenorphine: Neonatal Effects

Safety

Table 3 summarizes physical birth outcomes for studies of buprenorphine-maintained pregnant women.

The MOTHER study reported no physical birth anomalies, with the mean values for birth weight, length, and head circumference close to the 50^{th} percentile of World Health Organization (WHO) standards, and only 4 preterm (<37 weeks) infants [18]. The PROMISE study reported no physical birth anomalies, with mean values for birth weight, length, and head circumference all exceeding the 50^{th} percentile of WHO standards, and no preterm (<37 weeks) births [19]. Fischer et al. provided no data regarding the presence or absence of physical birth anomalies, or prenatal buprenorphine-exposed mean values for the outcomes of birth weight, length, or head circumference [20].

A number of the non-randomized studies report at least some safety data, all of which are generally unremarkable. Unweighted means for estimated gestational age (14 studies: 39.0 weeks), weight (20 studies: 3087.2 gm), length (10 studies: 49.4 cm), and head circumference (9 studies: 34.0 cm), extracted from all such studies that reported summary data (see **Table 3**), suggest most neonates were full-term and within normal limits.

NAS Treatment

Table 4 summarizes studies of NAS treatment outcomes of infants born to buprenorphine-maintained pregnant women. Assessment methods to measure NAS have typically been some type of modified Finnegan scale, although other methods have occasionally been utilized.

In the MOTHER study, 47% (27/58) of the buprenorphine-exposed neonates were treated for NAS, while 22% (2/9) of the PROMISE study's buprenorphine-exposed neonates were treated for NAS. Fischer et al. reported that 63% (5/8) of the buprenorphine-exposed neonates were treated for NAS. In contrast, 57% (41/73) of the methadone-exposed neonates in the MOTHER study, and 46% (5/11) in the PROMISE study were treated for NAS, while Fischer et al. reported that 50% (3/6) of the methadone-exposed neonates were treated for NAS.

The percentage of neonates treated for NAS in the non-randomized studies varied between 0% and 100%, with an unweighted mean of 48%, compared to an unweighted mean of 44% for the 3 randomized controlled trials. This wide variability in the percentage of neonates treated for NAS is likely due to multiple factors. Notably, there were differences in study eligibility criteria and NAS medication protocols among the studies, which in some cases assessed neonates who had already been diagnosed with NAS or failed to exclude pregnant women who were using benzodiazepines or other substances during pregnancy that might either result in NAS or impact the clinical features of NAS. Moreover, the NAS medication initiation criteria varied among the studies. Finally, in contrast to the MOTHER, PROMISE, and Fischer et al. studies, raters in the non-randomized studies were not blind to the neonate's medication status. Moreover, the nature and extent of rater training in the latter studies is largely unknown.

Despite the wide variability in the non-randomized studies, there is a remarkable similarity between both the randomized and non-randomized studies in the percentage of prenatally buprenorphine-exposed neonates treated for NAS – approximately 50%. Estimates for the rates of NAS of sufficient severity to require treatment of neonates exposed in utero to maternal methadone treatment likewise vary widely, and many of the studies on which these estimates are based are also uncontrolled. Results of the MOTHER study, in which there were no differences in the rates at which the neonates in the buprenorphine [47% (27/58)] and methadone [57% (41/73)] conditions were treated for NAS would also suggest that the rates at which neonates exposed to either medication are comparable, and around 1 in 2 neonates [25].

Medication for NAS

Morphine was the primary medication used to treat NAS (**Table 4**). Not displayed in **Table 4** is information regarding the total amount of medication used to treat NAS, only available for the three randomized controlled trials.

The mean total amount of morphine given to the 27 MOTHER neonates of buprenorphine-maintained mothers during the course of their NAS treatment was 2.8 mg[2], while PROMISE administered the equivalent mean total of 0.47 mg of morphine to the 2 neonates of buprenorphine-maintained mothers treated for NAS. Fischer et al. reported that the mean cumulative dose of morphine needed to treat the 5 infants treated for NAS was 2.0 mg. In contrast, the total amount of morphine given to 41 MOTHER neonates of methadone-maintained mothers during the course of their NAS treatment was 18.6 mg[2], while the equivalent mean total of 1.9 mg of morphine was administered to the 5 PROMISE neonates of methadone-maintained mothers treated for NAS. Fischer et al. reported that the mean cumulative dose of morphine needed by 5 methadone-exposed infants treated for NAS was 2.7 mg. The only significant difference between methadone and buprenorphine in the total amount of morphine administered to neonates treated for NAS occurred in the MOTHER study, likely due in part to the small sample sizes and attendant low power to test for such differences in PROMISE [19] and Fischer et al. [20].

Although considerable variability by participant and by study exists, the mean time to NAS onset among buprenorphine-exposed infants was 52.7 hours, peaking within approximately 72-96 hours (**Table 4**). Exceptions to this onset history have been the few neonates with NAS onset of 8-10 days postnatal age.[38-40] When this delayed onset occurs, such a

[2]Jones et al. [18] reported the mean values for the total amount of morphine for the entire sample of neonates in the buprenorphine and methadone conditions, respectively, regardless of whether or not they were in treatment, because such estimates were based on information from the entire sample, and the test conducted was considered more conservative. The values reported here are for the neonates who were treated for NAS. These values were estimated with a zero-inflated Poisson regression model, and the test of the medication condition difference, adjusted for site, yielded $p < 0.0001$.

protracted withdrawal syndrome may to be due to withdrawal from concomitant drug exposure (e.g., benzodiazepines) rather than a direct effect of buprenorphine withdrawal.

The correlation between buprenorphine dose and NAS severity [19-20, 41-42] has been inconsistent in the extant literature. This relationship has been explored in two different biological matrices. Neonatal urine data suggest that norbuprenorphine is predictive of the duration of NAS medication treatment, perhaps because the neonate is delivered with a high concentration of buprenorphine [26]. Consistent with this reasoning, meconium assays showed that total buprenorphine concentrations and buprenorphine/norbuprenorphine ratios were significantly related to the presence of a diagnosable NAS (not necessarily requiring pharmacotherapy) [43].

Length of Hospital Stay for NAS Treatment

The mean duration of hospital stay for NAS treatment for the 27 buprenorphine-exposed neonates in the MOTHER study was 9.7 days[3]. Fischer et al. reported a mean of 4.8 days for NAS treatment of 5 buprenorphine-exposed neonates in their study. In contrast, mean length of hospital stay for NAS treatment for the 41 prenatally methadone-exposed neonates in the MOTHER study was 17.8 days[3], while Fischer et al. reported a mean of 5.3 days for NAS treatment of 5 prenatally methadone-exposed infants in their study. Neither difference was statistically significant. PROMISE did not report length of neonatal hospital stay for NAS treatment for either medication.

Reports of the mean length of hospital stay for NAS treatment in the non-randomized studies are highly variable, ranging from a minimum of 4.7 days to a maximum of 37 days with an unweighted mean of 21.3 days for the 6 primary non-randomized studies for which such data could be extracted. (**Table 4**).

Total Length of Hospital Stay

Table 4 shows that MOTHER reported that the mean number of days in the hospital for the 58 neonates of buprenorphine-maintained mothers was 10.0 days, while PROMISE reported that the mean number of days in the hospital for the 9 neonates of buprenorphine-maintained mothers was 6.8 days. (It should be noted that the MOTHER protocol for length of hospitalization of neonates varied by site.) Fischer et al. did not separately report mean number of days in the hospital. Reports of length of hospital stay for neonates in the 18 non-randomized studies are highly variable, ranging from a minimum of 4-5 days to a maximum of 27.3 days (reported as a median value). The unweighted mean was 14.7 days for the 18 primary non-randomized studies for which such data could be extracted.

In summary, length of hospital stay for NAS treatment and overall length of hospital stay for neonates exposed to buprenorphine was generally twice as long in non-randomized studies as in the randomized trials. It is somewhat difficult to interpret these findings given wide

[3]Jones et al. [18] reported the mean values for number of days of hospital stay for NAS treatment for the entire sample of neonates in the buprenorphine and methadone conditions, respectively, regardless of whether or not they were in treatment, because such estimates were based on information from the entire sample, and the test conducted was considered more conservative. The values reported here are for the neonates who were treated for NAS. These values were estimated with a zero-inflated Poisson regression model, and the test of the medication condition difference, adjusted for site, yielded $p< 0.0001$.

differences in recruitment and eligibility criteria, especially among the non-randomized studies. However, each of the randomized trials provided comprehensive care to their participants, which might have been responsible, in part, for the lower mean length of hospitalization for these trials compared to the non-randomized studies. Finally, it is important to note that the MOTHER study showed that prenatally buprenorphine-exposed neonates had a significantly shorter mean hospital stay and a significantly shorter duration of NAS treatment than did prenatally methadone-exposed neonates [18]. In contrast, the PROMISE study [19] did not find a significant difference between buprenorphine and methadone conditions in neonatal length of hospital stay, and Fischer et al.[20] did not reveal a significant difference between medication conditions in duration of NAS treatment.

Buprenorphine and Breast Milk

No randomized controlled trials have been conducted to examine opioid agonist medication levels in breast milk in opioid-dependent women during the postpartum period. **Table 5** summarizes the results of the case report research as it relates to breast milk and buprenorphine concentrations.

Buprenorphine is excreted into breast milk approximately 2 hours following maternal ingestion [44]. Concentrations of buprenorphine and norbuprenorphine in breast milk were highly variable, due to variations in both milk protein and fat content [25]. However, neither buprenorphine nor norbuprenorphine concentrations were found to exceed plasma concentrations. Marquet et al.[45] reported low concentrations of both buprenorphine and particularly norbuprenorphine (3.28 μg and 0.33 μg, respectively) in the breast milk of a single buprenorphine-maintained patient. Moreover, the infant showed no signs of withdrawal signs when weaned at 8 weeks of age. Johnson et al.[46] reported that concentrations of buprenorphine in breast milk were similar to plasma concentrations on day 3 (0.5 ng/mL for both matrices) and day 6 (0.7 and 0.6 ng/mL, respectively) postpartum. Finally, Lindemalm et al.[44] reported in a study of 7 infants breastfed by buprenorphine-maintained mothers that the relative dose per kg of infant body weight was less than 1% of the dose per body weight of the mother. However, Hirose et al. [47] reported that the neonates of non-opioid-addicted pregnant women who underwent cesarean section and were subsequently treated for pain management with a combination of bupivacaine and buprenorphine ingested less breast milk than neonates whose mothers were treated with bupivacaine alone. The implications of these findings for buprenorphine-treated opioid-dependent pregnant women and their neonates are unclear.

In summary, the limited published research suggests that concentrations of buprenorphine and norbuprenorphine in breast milk vary due to variations in both milk protein and fat content [25], but are generally low and approximate maternal plasma concentration levels. Thus, a buprenorphine-maintained mother's breastmilk does not appear to place her infant at risk of experiencing adverse effects. Moreover, no known neonatal or child adverse consequences related to exposure to buprenorphine in breast milk have been reported in the literature. Finally, the most recent guidelines recommend breastfeeding for mothers stabilized on either methadone or buprenorphine [48] unless there are clear contraindications (e.g., HIV).

Developmental Effects of Buprenorphine in Infants and Children

Information regarding longer-term effects of prenatal buprenorphine exposure is summarized in **Table 6**. No randomized controlled trials have been conducted to examine the longer-term effects of prenatal buprenorphine exposure on child development. However, two ancillary studies from the PROMISE and MOTHER trials, respectively [49-50], conducted secondary analyses of neonatal neurodevelopment.

Neonatal Neurobehavioral Development

Two secondary studies examined the neurobehavioral development of prenatal buprenorphine-exposed neonates using the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS), a measure of behavioral, neurological, and stress/abstinence functioning. In the PROMISE sample [49], compared to methadone-exposed neonates (*n*=11), buprenorphine-exposed neonates (*n*=10) were more excitable and aroused during the first postnatal week. In a MOTHER subsample[50], neonates prenatally buprenorphine-exposed (*n*=18) displayed fewer stress-abstinence signs, were less excitable, less over-aroused, less hypertonic, had better self-regulation, and required less handling to maintain a quiet alert state than prenatally methadone-exposed neonates (*n*=21) during the first postnatal month. Finally, two infants who had been buprenorphine-exposed from conception to delivery showed no abnormal neurodevelopment signs on clinical examination at either 6 or 12 months of age [51].

Infant Development: Anatomic and physiologic studies of the brain and special senses

Magnetic resonance imaging (MRI) brain scans of 7 in-utero buprenorphine-exposed infants before 2 months of age observed neither structural anomalies nor evidence of irregular MRI signal intensity [52].

A retrospective review of 13 prenatally buprenorphine-exposed infants at 6 and 9 months of age reported no anomalies on electroencephalogram recordings or cranial ultrasounds. However, transient hypertonic was reported in 7 infants, with 2 infants needing subsequent specialized care. Results for the Denver Developmental Screening Test were found to be within normal limits for 11 of the 13 infants at both follow-ups [53].

Visual evoked potentials of 30 four-month-old prenatally buprenorphine-exposed infants showed no significant differences compared to a sample of 33 control infants in terms of visual maturation [54].

Sari et al. [55] examined differences in 10 measures of diurnal and nocturnal rhythm city in sleep patterns between 35 infants prenatally methadone- or buprenorphine-exposed and 36 comparison, low-risk infants at 3 months of age. Despite the observation that 47% of the agonist-exposed sample had exhibited NAS and that the agonist-exposed group as a whole had lower birth weight and length than the low-risk group, there were no significant differences between the two groups on any sleep measure. Unfortunately, possible differences between buprenorphine- and methadone-exposed infants were not reported.

Social Interaction: Materna-Infant interaction

Sari et al. [56] examined differences on the quality of maternal-infant interaction between 38 6-month-old children prenatally methadone- or buprenorphine-exposed and 36 comparison, low-risk infants. Maternal behavior served as the single significant predictor of the maternal-infant relationship. Prenatal agonist medication exposure was not a significant predictor of maternal-infant quality interaction. Again, any differences between buprenorphine- and methadone-exposed infants were not reported.

Early Childhood Cognitive Development

Silo et al. [57] assessed the cognitive development of prenatally buprenorphine-exposed children whose mothers were out-of-treatment buprenorphine users. Compared to 13 non-exposed children, the 21 in-utero buprenorphine-exposed children scored significantly lower on the Cognitive and Language Scales of the Bailey Scale of Infant Development (BSID-III) at age 3. The Language Scale results remained significant following adjustment for birth weight and height, gestational age, maternal age, socioeconomic status, and number of foster placements. However, failure to account for drug use other than buprenorphine – which was not provided as a pharmacotherapeutic agent in this study – makes interpretations of these findings quite difficult, because the differences between the two groups may have been due to concomitant drug use or any of a number of other factors such as differences in parenting practices between the groups. The need to account for the potential effects of confounding variables in interpreting results of gestational exposure to agonist medication is not unique to buprenorphine, as these factors also cloud the interpretation of the outcomes of prenatal exposure to methadone [58-59].

Setting aside for the moment Salo et al., as this study focused on non-therapeutic buprenorphine exposures, current findings do not suggest any deleterious outcomes associated with pharmacotherapy with buprenorphine for opioid-dependent pregnant women when buprenorphine is provided in the context of comprehensive care. However, more research and longer-term follow-up periods are needed before definitive conclusions are drawn in this regard. To that end, a large subsample of the MOTHER infants have been followed for up to 36 months and examined on a variety of physical, behavioral and cognitive developmental outcomes. Findings from this follow-up study are expected in the near future.

Conclusions

Definitive conclusions based upon the collective research summarized above are limited due to study design issues associated with non-randomized studies. However, comparing the above review with what is known about methadone treatment of opioid-dependent pregnant women, buprenorphine appears generally similar to, and in some cases superior to, methadone in terms of maternal, fetal, and neonatal outcomes.

Second, like methadone, prenatal buprenorphine exposure appears to be associated with a clinically significant NAS requiring pharmacological intervention in approximately half of the cases. However, results from the MOTHER study suggest that buprenorphine is associated with a less severe NAS than methadone. Nonetheless, other correlates of prenatal buprenorphine exposure (e.g., its potential impact on neonatal birth weight and length and longer term outcomes) are not fully understood and need further research.

Third, buprenorphine treatment during pregnancy brings a renewed interest in clinical challenges that also exist with methadone treatment during pregnancy. However, with the exception of buprenorphine induction, guidance regarding dose changes, acute pain management, and breastfeeding are similar to the guidance given for methadone.

The generally positive outcomes for both mother and child following buprenorphine exposure in the randomized controlled trials were achieved in the context of receipt of flexible and adequate buprenorphine dosing during pregnancy and postpartum, and comprehensive treatment from a multi-disciplinary team. Concluding that buprenorphine is an effective treatment for opioid dependence during pregnancy does not mean that methadone should no longer be considered a useful and effective medication for opioid dependence, nor does it mean that all opioid-dependent pregnant women should be treated with buprenorphine without regard to their preferences and life circumstances. While the nature of science is to compare and contrast treatments in order to discover which treatment is better, the reality is that no one treatment will be maximally effective for all patients. Our collective commitment should be towards researching which treatment works best for which patients. Patients will be optimally served when a variety of medications are available, and when matching patients to pharmacotherapy is a treatment consideration.

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Table 1

Summary of Maternal Outcomes in Studies of Opioid-addicted Pregnant Women Administered Buprenorphine

Study description		Maternal outcomes					
		Baseline		Delivery			
Author(s)	Country	Number of mothers administered buprenorphine prenatally		Number of mothers who delivered while taking buprenorphine		Opioid use measure	Number of mothers with positive result for illicit opioids at delivery
		Total sample	Subsample	Total sample	Subsample		
Large-scale Randomized Controlled Trials							
Jones et al. [18]	USA, Austria	86		58 (67%)		biological: urine	5 (9%)
Small-scale Randomized Controlled Trials							
Jones et al. [19]	USA	15		9 (60%)		biological: urine	0 (0%)
Fischer et al. [20]	Austria	9		8 (89%)		biological: urine	35.3% #,**
Other Prospective Studies							
Winklbaur et al. [60]	Austria	22		22 (100%)		biological: urine	24% #
Fischer et al. [61]			9		9 (100%)	biological: urine	0 (0%)
Ebner et al. [62]			14		14 (100%)	biological: urine	0 (0%)
Fischer et al. [63]			15		15 (100%)	biological: urine	
Schindler et al. [51]			2		2 (100%)	biological: urine	0 (0%)
Johnson et al. [46]	USA	3		3 (100%)		biological: urine, blood	0 (0%)
Rohrmeister et al. [64]	Austria	16		16 (100%)		biological: urine	
Lejeune et al. [41]	France	159		159 (100%)		self-report	16%¦
Lejeune et al. [65]*			153				
Lejeune et al. [66]			153		153 (100%)	not specified	19%#
Simmat-Durand et al. [67]			159		159 (100%)	self-report	24 (15%) ##
Colombini et al. [40]	France	13		13 (100%)			

Study description		**Maternal outcomes**					
		Baseline		**Delivery**			
Author(s)	**Country**	**Number of mothers administered buprenorphine prenatally**		**Number of mothers who delivered while taking buprenorphine**		**Opioid use measure**	**Number of mothers with positive result for illicit opioids at delivery**
		Total sample	**Subsample**	**Total sample**	**Subsample**		
Vert et al. [68]	France	19		19 (100%)		biological: urine	6 (32%) §
Lacroix et al. [69]	France	90		84 (93%)		biological: urine	15 (17%)◆
Lacroix et al. [38]			34		31 (91%)	biological: urine	2 (6%)
Lacroix et al. [70]			34		31 (91%)		
Whitham et al. [54]		30		30 (100%)		self-report; biological: urine	
Kahila et al. [71]	Finland	66		66 (100%)		biological: urine	9 (14%)
Kahila et al. [52]			7		7 (100%)		
Kahila et al. [72]			27		27 (100%)	biological: urine	10 (37%) §
Hytinantti et al. [26]			54		54 (100%)	biological: urine	1 (2%)
Kakko et al. [73]	Sweden	39		39 (100%)			
Binder & Vavrinkova [74]	Czech Republic	38		23 (61%) ||		biological: urine	15 (40%)
Bakstad et al. [75]	Norway	12		12 (100%)		biological: urine ¥	0 (0%)
Sarfi et al. [55]			11		11 (100%)	biological: urine ¥	1 (9 %) |
Bläser et al. [76]	Germany	3		3 (100%)			
Brulet et al. [77]	France	62		70 (100%)§§		self-report	
Sandtorv et al. [78]	Norway	4		4 (100%)		biological: urine; self-report	
Case Reports and Series							
Marquet et al. [42]	France	23		23 (100%)		self-report; biological: urine	2 (6%)
Marquet et al. [45]			1		1 (100%)	biological: blood, urine	0 (0%)

Study description		Maternal outcomes					
		Baseline		Delivery			
Author(s)	Country	Number of mothers administered buprenorphine prenatally		Number of mothers who delivered while taking buprenorphine		Opioid use measure	Number of mothers with positive result for illicit opioids at delivery
		Total sample	Subsample	Total sample	Subsample		
Marquet et al. [79]			6		6 (100%)	Urine, hair	1 (17%) ##
Regini et al. [80]	Italy	1		1 (100%)			
Herve & Quernum [81]	France	1		1 (100%)			
Jernite et al. [39] retrospective group	France	13		13 (100%) ⌐		self-report	
Jernite et al. [39] prospective group		11		11 (100%)			
Auriacombe et al. [82]		4		3 (75%)		not specified	
Eder et al. [83] *	Austria	1		1 (100%)		biological: urine	0 (0%)
Kayemba-Kay's & Laclyde [53]	France	13		13 (100%)			
Siedentopf et al. [84] *	Germany	33		33 (100%)			
Ross [85]	Australia	1		1 (100%)			
Unger et al. [86]†	Austria		3		3 (100%)	biological: urine	
Retrospective Chart Review							
Czerkes et al. [87]	USA	68		68 (100%)			
Blandthorn et al. [88]	Australia	20		20 (100%)			
O'Connor et al. [89]	USA	22		22 (100%)		biological: urine	9 (41%)

Notes. **Table 1** summarizes the results of 1 large-scale and 2 small-scale randomized controlled trials, 15 other prospective studies (out of 28 such studies abstracted), 10 case reports (out of 12 such studies abstracted, not counting Unger et al. [86], a MOTHER substudy [18]), and 3 retrospective chart reviews. Multiple reports of the same mothers or a shared subsample appear in the same row, with the primary study on the far left margin and studies from the same sample indented and listed below the primary citation. Blank cells indicate data not reported for mothers. Medication procedures in all three randomized controlled trials were quite similar. The first day's induction dose was divided in half, with administrations separated by 30-120 minutes. Medications were given double-blind and double-dummy. Clinical care in all three randomized controlled trials was comprehensive in nature, and quite similar in extent and focus. All three studies provided access to case management, obstetric, medical, and psychiatric care as well as a variety of other ancillary services (for example, transportation). The PROMISE [19] and MOTHER [18] studies provided individual and group counseling. The non-randomized studies do not provide sufficient information to determine dosing procedures or clinical care standards with any degree of certainty. Caution must be exercised in interpreting reports of 100% treatment retention. For example, Lejeune et al. [41] state that an inclusion criterion was that "the women had to be monitored up to their delivery", by definition yielding 100% treatment retention. For the 2 non-randomized studies with less than 100% treatment retention, Lacroix et al. [69] lost 6 of 90 patients due to 2 spontaneous abortions, 2 voluntary abortions, 1 therapeutic abortion, and 1 stillbirth. Binder and Vavrinkova [74] excluded 15 of 38 patients from follow-up due to use of illicit drugs at any point during the study. Thus, even in these 2 studies, failure to achieve 100% treatment retention was not due to a maternal participant prematurely terminating treatment.

[#] Urine specimens were taken over entire pregnancy or does not specify whether or not collected at delivery.

[**] Reported median value only.

[◆] This count and percentage is for heroin. 5 women (6%) tested positive for "opioid analgesic".

[ˈ] Data from whole sample instead of buprenorphine mothers only.

[*] Article not in English.

[##] Reported in 4 weeks prior to pregnancy or last trimester.

[§] Mothers positive for any drug without differentiation between opioid and other drug use).

[ˈˈ] Fifteen mothers were excluded from the study for using illicit drugs.

[¥] Compared to European Addiction Survey Index.

[§§] During the study, 8 women switched to buprenorphine maintenance.

[⌐] The article indicates 1 miscarriage among 24 total cases, but reports on neonatal data for 13 and 11 infants in the two groups.

Table 2

Summary of Studies Examining Fetal Outcomes in Fetuses Exposed to Buprenorphine in utero

Study description			Fetal deaths								
Author(s)	Number of buprenorphine-exposed fetuses		Total		Number of miscarriages		Number of elected abortions		Number of Stillbirths		Number of IUGR cases
	Total sample	Sub-sample	Total sample	Sub-sample	Total sample	Sub-sample	Total sample	Sub-sample	Total Sample	Sub-sample	
Large-scale Randomized Controlled Trials											
Jones et al. [18]	58										
Small-scale Randomized Controlled Trials											
Jones et al. [19]	9										
Fischer et al. [20]	8										
Other Prospective Studies											
Winklbaur et al. [60]	22										
Fischer et al. [61]		9	0		0		0				
Ebner et al. [62]		14		0		0		0			
Fischer et al. [63]		15		0		0		0			
Schindler et al. [51]		4		0		0		0			
Johnson et al. [46]	3		0		0		0				
Rohrmeister et al. [64]	16		0		0		0				
Lejeune et al. [41]	159			0							49 (31%)
Lejeune et al. [65][*]		153		0		0		0			
Lejeune et al. [66][*,‡]		153		0		0		0			
Simmat-Durand et al. [67]		160									

Study description			Fetal deaths								
Author(s)	Number of buprenorphine-exposed fetuses		Total		Number of miscarriages		Number of elected abortions		Number of Stillbirths		Number of IUGR cases
	Total sample	Sub-sample	Total sample	Sub-sample	Total sample	Sub-sample	Total sample	Sub-sample	Total Sample	Sub-sample	
Colombini et al. [40]	13		0		0		0				
Vert et al. [68]	20		0		0		0				
Lacroix et al. [69]	91		6		3		2			1	3 (50%)
Lacroix et al. [38]		34		3		1		1			
Lacroix et al. [70]		34		3		1		1			
Whitham et al. [54]		30									
Kahila et al. [90]	67		11		1		10				
Kahila et al. [52]		7		0		0		0			
Kahila et al. [72]		27									
Hytinantti et al. [26]		58									
Kakko et al. [73]	47		2		2		0		1		
Binder & Vavrinkova [74]	28										
Bakstad et al. [75]	12										
Sarfi et al. [55]		11									
Bläser et al. [76]	3										
Brulet et al. [77]	70										
Sandtorv et al. [78]	4		0		0		0				
Case Reports and Series											
Marquet et al. [42]‡	23		0		0		0				

Study description			Fetal deaths								
Author(s)	Number of buprenorphine-exposed fetuses		Total		Number of miscarriages		Number of elected abortions		Number of Stillbirths		Number of IUGR cases
	Total sample	Sub-sample	Total sample	Sub-sample	Total sample	Sub-sample	Total sample	Sub-sample	Total Sample	Sub-sample	
Marquet et al. [45]		1		0		0		0			
Marquet et al. [79]		6		0		0		0			
Regini et al. [80]	1		0		0		0				
Herve & Quernum [81]	1		0		0		0				
Jernite et al. [39] retrospective group ⌐	13										7 (54%)
Jernite et al. [39] prospective group ⌐	11						0				
Auriacombe et al. [82]		3						0			
Eder et al. [83] *	2		0		0		0				
Kayemba-Kay's & Laclyde [53]	13		0		0		0				
Siedentopf et al. [84] *	33		0		0		0				
Ross [85]	1		0		0		0				
Unger et al. [86]†		3		0		0		0			
Jansson et al. [36] Group 1†		4		0		0		0			

Study description			Fetal deaths								
Author(s)	**Number of buprenorphine-exposed fetuses**		**Total**		**Number of miscarriages**		**Number of elected abortions**		**Number of Stillbirths**		**Number of IUGR cases**
	Total sample	**Sub-sample**	**Total sample**	**Sub-sample**	**Total sample**	**Sub-sample**	**Total sample**	**Sub-sample**	**Total Sample**	**Sub-sample**	
Jansson et al. [36] Group 2 †		5		0		0		0			
Salisbury et al. [37]†		33		0		0		0			
Retrospective Chart Review											
Czerkes et al. [87]	68										
Blandthorn et al. [88]	20										
O'Connor et al. [89]	23		0		0		2				

Study description	Prenatal testing				
Author(s)	**Week(s) at which fetal testing was conducted**	**Fetal heart rate (FHR) [M ± *SE*]**	**Number of FHR accelerations**	**FHR reactivity in the fetal non-stress test (NST)**	**Biophysical Profile (BPP) score [M ± *SE*]**
Large-scale Randomized Controlled Trials					
Jones et al. [18]					
Small-scale Randomized Controlled Trials					
Jones et al. [19]					
Fischer et al. [20]					
Other Prospective Studies					
Winklbaur et al. [60]					
Fischer et al. [61]					
Ebner et al. [62]					
Fischer et al. [63]					
Schindler et al. [51]					
Johnson et al. [46]	Periodic NST and BPP monitoring from study entry was unremarkable				

Study description	Prenatal testing				
Author(s)	**Week(s) at which fetal testing was conducted**	**Fetal heart rate (FHR) [M ± *SE*]**	**Number of FHR accelerations**	**FHR reactivity in the fetal non-stress test (NST)**	**Biophysical Profile (BPP) score [M ± *SE*]**
Rohrmeister et al. [64]					
Lejeune et al. [41]					
Lejeune et al. [65]*					
Lejeune et al. [66]*,‡					
Simmat-Durand et al. [67]					
Colombini et al. [40]					
Vert et al. [68]					
Lacroix et al. [69]					
Lacroix et al. [38]					
Lacroix et al. [70]					
Whitham et al. [54]					
Kahila et al. [90]					
Kahila et al. [52]					
Kahila et al. [72]					
Hytinantti et al. [26]	28/32/36/40				
Kakko et al. [73]					
Binder &Vavrinkova [74]					
Bakstad et al. [75]					
Sarfi et al. [55]					
Bläser et al. [76]					
Brulet et al. [77]					
Sandtorv et al. [78]					
Case Reports and Series					
Marquet et al. [42]‡					

Study description	Prenatal testing				
Author(s)	**Week(s) at which fetal testing was conducted**	**Fetal heart rate (FHR) [M ± *SE*]**	**Number of FHR accelerations**	**FHR reactivity in the fetal non-stress test (NST)**	**Biophysical Profile (BPP) score [M ± *SE*]**
Marquet et al. [45]					
Marquet et al. [79]					
Regini et al. [80]					
Herve & Quernum [81]					
Jernite et al. [39] retrospective group ⌐					
Jernite et al. [39] prospective group ⌐					
Auriacombe et al. [82]					
Eder et al. [83] *					
Kayemba-Kay's & Laclyde [53]					
Siedentopf et al. [84] *					
Ross [85]					
Unger et al. [86] †					
Jansson et al. [36] Group 1 †	24/28	136 ± 7.8	1.3 (1.9)		
Jansson et al. [36] Group 2 †	32/36	135 ± 7.1	2.8 ± 3.8		
Salisbury et al. [37] †	32	132 ± 1.2	2.9 ± 0.2		8.7 ± 0.2
Retrospective Chart Review					
Czerkes et al. [87]					
Blandthorn et al. [88]					
O'Connor et al. [89]					

Notes. In addition to the studies listed in **Table 1**, **Table 2** includes 2 studies that focus only on fetal outcomes (Jansson et al. [36] and Salisbury et al. [37]). Multiple reports of the same mothers or a shared subsample of mothers appear in the same row. Blank cells indicate data not reported for fetus. The total number of buprenorphine-exposed fetuses included in **Table 2** does not equal its corresponding value for the number of mothers administered buprenorphine prenatally in **Table 1** due to multiple births, miscarriages, abortions, and stillbirths. The studies that report IUGR do not provide sufficient information to assess how it was defined or determined with any certainty.

[*] Article not in English.

[⌐] The article states there were “6 terminations (25%) and a single miscarriage” among the 24 total cases, but reports on neonatal data for 13 and 11 infants in the two groups.

[†] Subsample from Jones et al. [18] and so not included in the total sample count.

Table 3

Summary of Studies Examining Physical Birth Outcomes in Neonates Prenatally Exposed to Buprenorphine

Author(s)	Number of buprenorphine-exposed neonates: Total sample	Number of buprenorphine-exposed neonates: Sub-sample	Cesarean section (%)	Age at delivery (weeks) [If reported: *M* ± *SE* or *M* (*SD*)]	Physical anomalies	Mean Apgar scores: 1 min	Mean Apgar scores: 5 min	Mean Apgar scores: 10 min	Mean birth weight (gm) [If reported: *M* ± *SE* or *M* (*SD*)]	Mean length (cm) [If reported: *M* ± *SE* or *M* (*SD*)]	Mean head circumference (cm) [If reported: *M* ± *SE* r *M* (*SD*)]
Large-scale Randomized Controlled Trials											
Jones et al. [18]	58		17 (29%)	39.1 ± 0.3	None	8.1 ± 0.2	9.0 ± 0.1		3094 ± 73	49.8 ± 0.5	33.8 ± 0.3
Small-scale Randomized Controlled Trials											
Jones et al. [19]	9		1 (11%)	38.8 ± 0.8	None	8.1 ± 0.2	8.7 ± 0.2		3530 ± 163	52.8 ± 1.1	34.9 ± 6.4
Fischer et al. [20]	8		2 (25%)								
Other Prospective Studies											
Winklbaur et al. [60]	22										
Fischer et al. [61]		9									
Ebner et al. [62]		14									
Fischer et al. [63]		15	5 (33%)	39.6 (1.5)	None	9	9.9	10	3049 (346)	50 (1.9)	34 (1.8)
Schindler et al. [51]		4	2 (50%)	39.3 (1.5)¶	None	9	10	10	3182 (294)¶	50.3 (1.0)¶	33.8 (1.0)¶
Johnson et al. [46]	3		1 (33%)	39 - 40 (39.3) 39 - 42 40.3)◇	None	8	9		3183 (range: 2830-3500)	50.7 (range: 50-52)	34.3 (range: 33-36)
Rohrmeister et al. [64]	16		7 (44%)	40 ± 2.4		9	10	10	3060 ± 408	50 ± 2.5	
Lejeune et al. [41]	159		31 (19%)△	38.8			9.8		2843		
Lejeune et al. [65]*		153	30 (20%)△	38.4			9.8		2860		
Lejeune et al. [66]*,‡		153	30%	38.8			9.8		2860		
Simmat-Durand et al. [67]		160		38.8 ± 2		9.4 ± 1.4	9.8 ± 0.9		2842.9 ± 482	47.38 ± 2.75	33.3 ± 1.6
Colombini et al. [40]	13			39.9 ± 0.8					3093 ± 342		
Vert et al. [68]	20								3029 ± 273¤		

Author(s)	Number of buprenorphine-exposed neonates: Total sample	Number of buprenorphine-exposed neonates: Sub-sample	Cesarean section (%)	Age at delivery (weeks) [If reported: *M* ± *SE* or *M* (*SD*)]	Physical anomalies	Mean Apgar scores: 1 min	Mean Apgar scores: 5 min	Mean Apgar scores: 10 min	Mean birth weight (gm) [If reported: *M* ± *SE* or *M* (*SD*)]	Mean length (cm) [If reported: *M* ± *SE* or *M* (*SD*)]	Mean head circumference (cm) [If reported: *M* ± *SE* r *M* (*SD*)]
Lacroix et al. [69]	85				4				2892 ± 506	47.6 ± 2.5	
Lacroix et al. [38]		31		38.4 ± 2.5	2				2796 ± 558	47.4 ± 2.1	
Lacroix et al. [70]		31			2						
Whitham et al. [54]		30		38.7±1.9					3055.5±511.6	47.9 ± 2.5	33.7 ± 1.8
Kahila et al. [52]	67								3180	49.0 ± 2.3	34.2 ± 1.3
Kahila et al. [71]		7	2 (29%)	41	None				3396#		
Kahila et al. [72]		27	3 (2%)	40 (1.6)					3640 (303)	50#	35#
Hytinantti et al. [26]		58	13 (22%)	39.7 (1.6)		9 (1)			3267 (459)	49 (2.2)	34 (1.3)
Kakko et al. [73]	47		10 (21%)	40 (2.0)					3250 (528)	48.4 (2.5)	34 (1.4)
Binder & Vavrinkova [74]	38		3 (8%)	39 (3.7)		8.4	9.3	9.7	3050 (485)		
Bakstad et al. [75]	12		4 (33%)	39 (2.1)		8.4 (1.4)	9.1 (0.9)	9.4 (0.5)	3130 (416)	48.5 (1.4)	34.3 (1.7)
Sarfi et al. [55]		11									
Bläser et al. [76]											
Brulet et al. [77]											
Sandtorv et al. [78]	4				None						
Case Reports and Series											
Marquet et al. [42]‡	23										
Marquet et al. [45]		1									
Marquet et al. [79]		6									
Regini et al. [80]	1		1 (100%)	35		3	7		2600		32.8
Herve & Quernum [81]	1			41					3680		35

Author(s)	Number of buprenorphine-exposed neonates: Total sample	Number of buprenorphine-exposed neonates: Sub-sample	Cesarean section (%)	Age at delivery (weeks) [If reported: *M* ± *SE* or *M* (*SD*)]	Physical anomalies	Mean Apgar scores: 1 min	Mean Apgar scores: 5 min	Mean Apgar scores: 10 min	Mean birth weight (gm) [If reported: *M* ± *SE* or *M* (*SD*)]	Mean length (cm) [If reported: *M* ± *SE* or *M* (*SD*)]	Mean head circumference (cm) [If reported: *M* ± *SE* r *M* (*SD*)]
Jernite et al. [39] retrospective group	13		3 (23%)								
Jernite et al. [39] prospective group	11										
Auriacombe et al. [82]		3									
Eder et al. [83] *	1		0 (0%)	40	None	9	10	10	3415 (21.2) ¶	50.5 (.7) ¶	
Kayemba-Kay's & Laclyde [53]	13			39		"within normal limits"			3000		
Siedentopf et al. [84]	33					9	10	10	2827		
Ross [85]	1		0 (0%)	At term		6	9				
Unger et al. [86]†	3		1 (17%)¶	271.3 (13.6) days¶					2846.9	50.3 (1.5)	34.3 (1.0)
Retrospective Chart Review											
Czerkes et al. [87]	68			38.5		7.8	8.8		3130		
Blandthorn et al. [88]	20										
O'Connor et al. [89]	23		7 (30%)	20 delivered at term; 1 at 36; 1 at 36 3/7; 1 at 36 6/7		8.3	9.0		3148 (471)		

Notes. Multiple reports of the same neonates or a shared subsample of neonates appear in the same row. Blank cells indicate data not reported for neonates. The total number of buprenorphine-exposed neonates included in **Table 3** does not equal its corresponding value for the number of mothers administered buprenorphine prenatally in **Table 1** due to multiple births, miscarriages, abortions and stillbirths.

⌐ The article simply states "9/10/10".

∞ At 3 minutes.

¦ Reported in only 86% of the sample.

¶ Calculated based on data reported in the article.

◇ Age at delivery was assessed by both obstetrical and pediatric assessments, respectively; both are include in the table.

△ Noted as emergency cesarean section or instrumental vaginal delivery.

* Article not in English.

[¤] Only for the 15 term neonates; 5 born between 32-36 weeks not included.

[#] Reported median only.

[†] Subsample from Jones et al. [18] and so not included in the total sample count.

Table 4

Summary of Studies Examining Neonatal Abstinence Syndrome (NAS) in Neonates Prenatally Exposed to Buprenorphine

Author(s)	Number of buprenorphine-exposed neonates		Number of neonates treated for NAS		Time to onset of NAS [If reported: *M* ± *SE* or *M* (*SD*)]	NAS Assessment Method	NAS Treatment Medication(s)	Neonatal treatment: symptom-based, weight-based, or not specified	Mean days in treatment for NAS [If reported: *M* ± *SE* or *M* (*SD*)]	Mean number of days neonates in hospital [If reported: *M* ± *SE* or *M* (*SD*)]
	Total sample	Sub-sample	Total sample	Sub-sample						
Large-scale Randomized Controlled Trials										
Jones et al. [18]	58		27 (47%)			Modified-Finnegan	morphine	symptom	4.1 ± 1.0[Δ]	10.0 ± 1.2
Small-scale Randomized Controlled Trials										
Jones et al. [19]	9		2 (22%)			Modified-Finnegan	morphine	symptom		6.8
Fischer et al. [20]	8		5 (63%)		72.0 (35.2) hours	Finnegan	morphine		4.8 (2.9)	
Other Prospective Studies										
Winklbaur et al. [60]	22		1 (5%)			Finnegan	phenobarbital; morphine	weight		
Fischer et al. [61]		9		0		not specified	N/A	N/A	N/A	N/A
Ebner et al. [62]		14		3		Finnegan	morphine, phenobarbital	weight+symptom		
Fischer et al. [63]		15		3		Finnegan	morphine	symptom	1.1 (2.5)	
Schindler et al. [51]		4		0		Finnegan	N/A	N/A	N/A	N/A
Johnson et al. [46]	3		0 (0%)		“within first 12 h hours”	Modified-Finnegan; NICU Network Neurobehavioral Scale (NNNS); Infant Acoustic Cry	N/A	N/A		4-5
Rohrmeister et al. [64]	16		3 (19%)		34.5[#] ± 16 hours	Finnegan	phenobarbital; morphine	symptom	8.3 ± 2.6[#] days	8.0 ± 5.9[#] days
Lejeune et al. [41]	159		83		37.5 hours				16.9	23[§]
Lejeune et al. [65][*]		153			38.5hours	Lipsitz	Morphine hydrochloride, paregoric, morphine derivate, chlorpromazine, phenobarbital, diazepam paregoric elixir; phenobarbital; chloropromazine	not specified	16	23
Lejeune et al. [66][*,‡]		153	52%		38.5 hours	Lipsitz				23[§]
Simmat-Durand et al. [67]		160		80 (50%)	37.5 ± 30.8 hours		Morphine hydrochloride		16.3 ± 10.5	22.6 ± 14.2

Author(s)	Number of buprenorphine-exposed neonates: Total sample	Number of buprenorphine-exposed neonates: Sub-sample	Number of neonates treated for NAS: Total sample	Number of neonates treated for NAS: Sub-sample	Time to onset of NAS [If reported: *M* ± *SE* or *M* (*SD*)]	NAS Assessment Method	NAS Treatment Medication(s)	Neonatal treatment: symptom-based, weight-based, or not specified	Mean days in treatment for NAS [If reported: *M* ± *SE* or *M* (*SD*)]	Mean number of days neonates in hospital [If reported: *M* ± *SE* or *M* (*SD*)]
Colombini et al. [40]	13		13 (100%)		24 - 68 hours	Lipsitz	morphine	symptom	28.2 ± 10.1	
Vert et al. [68]	20		12 (60%)		1 - 5 days	Finnegan	morphine	symptom		16.1 - 20.0
Lacroix et al. [69]	85		20 (24%)		2.8 ± 1.9 days	Finnegan		not specified		
Lacroix et al. [38]		31		8	1 – 8 days	Finnegan	opiates	not specified		
Lacroix et al. [70]		31		8	3 days	not specified	opiates			
Whitham et al. [54]		30	14 (47%)			Modified-Finnegan	morphine; phenobarbitone	weight		
Kahila et al. [52]	67		39 (58%)		2.5 days	Finnegan	morphine; phenobarbital	not specified		18.8 (15)
Kahila et al. [71]		7		6		not specified	morphine	not specified		25 (19)
Kahila et al. [72]		27				not specified	not specified	not specified		
Hytinantti et al. [26]		58		38		Finnegan	morphine; phenobarbital	weight	20 ± 10	
Kakko et al. [73]	47		7 (15%)			Finnegan	morphine	not specified		9.4 (8.4)
Binder & Vavrinkova [74]	38		33 (81%)		24 - 48 hours[|]	Finnegan	opium tincture; phenobarbital	not specified		
Bakstad et al. [75]	12		8 (67%)		4 (1.2) days	Finnegan; Lipsitz			37 (23.7)	
Sarfi et al. [55]		11		8		Finnegan; Lipsitz				
Bläser et al. [76]	3					Finnegan	phenobarbital; morphine	symptom		
Brulet et al. [77]	70							N/A		
Sandtorv et al. [78]	4		2 (50%)				morphine	not specified		
Case Reports										
Marquet et al. [42][‡]	23		10 (47%)		33.1 hours	Finnegan	morphine; chloropromazine; diazepam	not specified		16.5
Marquet et al. [45]		1	0 (0%)			Finnegan				6
Marquet et al. [79]		6	3 (50%)		2 days[**]	Finnegan	morphine; paregoric elixir	symptom		

Author(s)	Number of buprenorphine-exposed neonates		Number of neonates treated for NAS		Time to onset of NAS [If reported: *M* ± *SE* or *M* (*SD*)]	NAS Assessment Method	NAS Treatment Medication(s)	Neonatal treatment: symptom-based, weight-based, or not specified	Mean days in treatment for NAS [If reported: *M* ± *SE* or *M* (*SD*)]	Mean number of days neonates in hospital [If reported: *M* ± *SE* or *M* (*SD*)]
	Total sample	Sub-sample	Total sample	Sub-sample						
Regini et al. [80]	1		1 (100%)		2 days		methadone	symptom		
Herve & Quernum [81]	1		1 (100%)		3 days	Finnegan	paregoric	weight	36¶	
Jernite et al. [39] retrospective group	13		8 (64%)		1-10 days		and/or: phenobarbital; morphine; benzodiazepine; paregoric		16	19.5
Jernite et al. [39] prospective group	11		7 (64%)						9	10.2
Auriacombe et al. [82]		3			before day 5					
Eder et al. [83]*	2		0 (0%)		N/A	Finnegan	N/A	N/A		
Kayemba-Kay's & Laclyde [53]	13		10 (77%)		1-5 days	Finnegan	paregoric; morphine	weight	21 (11.1)¤	27.3
Siedentopf et al. [84]	33					Finnegan				12.2
Ross [85]	1		0(0%)		3 days**	Finnegan	N/A	N/A		7
Unger et al. [86]†		3		2 (67%)		modified-Finnegan	morphine	symptom	4.7 (4.2)	
Retrospective Chart Review										
Czerkes et al. [87]	68		33 (49%)							8.4
Blandthorn et al. [88]	20					Modified-Finnegan	morphine; phenobarbitone	not specified		
O'Connor et al. [89]	23		8 (35%)		66.2 hours	Finnegan	phenobarbital	not specified		7.7 (2.7)

Notes. Multiple reports of the same neonates or a shared subsample of neonates appear in the same row. Blank cells indicate data not reported for neonates. N/A indicates no neonates were treated for NAS. The total number of buprenorphine-exposed neonates included in **Table 4** does not equal its corresponding value for the number of mothers administered buprenorphine prenatally in **Table 1** due to multiple births, miscarriages, abortions, and stillbirths.

$^{\Delta}$Mean for all 58 infants (with 31 infants having 0 days, and so their data was not included in the average of the means of the number of days treated for NAS reported in the text).

#Reported median only ◇Lejuene et al. indicated that 100 women were maintained on methadone, and 159 on buprenorphine, and that there are 260 neonates born to 259 mothers, with one methadone-maintained mother delivered twins (260 neonates). Lejeune et al. [41] report on 159 while Simmat-Durand et al. [40] report on 160 neonates exposed in utero to buprenorphine.

|Reported in only 86% of the sample.

¤Calculated based on data reported in the article.

[*] Article not in English.

[§] Mean length of stay after newborn was transferred to Department of Neonatology.

[¶] Determined from article narrative – neonate was treated from 6 days old to 6 weeks old.

[**] Infants had NAS, but were not treated.

[†] Subsample from Jones et al.[18] and so not included in the total sample count.

Table 5

Summary of Studies Examining Breast Milk in Neonates Perinatally Exposed to Buprenorphine

Author(s)	Number of buprenorphine-exposed neonates	Number of buprenorphine-exposed neonates who were breastfed	Buprenorphine dose administered to mother	Postpartum day(s) when samples taken	Buprenorphine concentration in breast milk	Norbuprenorphine concentration in breast milk	Relative dose per kg of infant body weight per body weight of the mother	Plasma-to-milk ratio
Hirose et al. [47]†	0	10						
Grimm et al. [25]‡			8 mg/day for 7 months	Days 8-11	1.0 to 14.7 ng/mL	0.6 to 6.3 ng/mL	Estimated: <10 µg for 4-kg infant over 24-hour period	
Johnson et al. [46]	3	1	2 received 8 mg daily 1 received 12 mg daily§	Day 3	520 g/nl			1.0
				Day 6	720 g/nl			
				Day 9¥	230 g/nl			
Lindemalm et al. [44]	7	6	0.06 mg/kg – 0.41 mg/kg	Days 5-8	0.06 - 0.2 mg.h / L	0.03 -0.15 mg.h / L	0.18% - 0.77%	Median: 1.7 Range: 0.9 - 4.3
Marquet et al. [45]	1	1	4 mg/day for 5 months	Day 28	3280 ng over 24-hour period	330 ng over 24-hour period		

Notes. Blank cells indicate data not reported for neonates.

† "Patients received 5 ml 0.25% bupivacaine with buprenorphine 200 µg extradurally after clamping of the umbilical cord, followed by a continuous infusion of 0.25% bupivacaine 0.7 ml h^{-1} containing buprenorphine 12 µg ml^{-1}" for the next 3 days. The weight of breast milk and infant weight gain was significantly less after 11 days compared to a group not treated with buprenorphine.

‡ No infant data collected. The ingested 24-hour dose is calculated from the mother's data.

§ The article does not state which of the three women chose to breastfeed. The values in the next two columns are from the infant of the one mother who breastfed.

¥ Mother stopped breastfeeding after day 4 and this reason is given as explanation for low values on day 9.

Table 6

Summary of Longer-term Effects for Neonates Prenatally Exposed to Buprenorphine

Author(s)	Number of buprenorphine-exposed neonates included in each study		Age of infants		Outcome measure(s)	Findings
	Total sample	Sub-sample	Total sample	Sub-sample		
Neurobehavioral Development						
Jones et al. [49][†]		10		during first 30 days	Neonatal Intensive Care Unit Network Neurobehavioral Scale	• Buprenorphine-exposed neonates initially showed increased and then decreased arousal scores over time. Buprenorphine-exposed neonates first exhibited more irritiability, state lability, and less consolability but by day 14 displayed less excitability.
Coyle et al. [50][‡]		18		during first 30 days	Neonatal Intensive Care Unit Network Neurobehavioral Scale	• Buprenorphine-exposed neonates showed fewer stress-abstinence signs, were less excitable and over-aroused, exhibited less hypertonia, had better self-regulation, and required less handling to maintain a quiet alert state than methadone-exposed neonates
Infant Development						
Schindler et al. [51]	4		6 and 12 months		"neurodevelopmental examinations"	• "Normal and not different from children of mothers without a substance related disorder"
Kahila et al. 52]	7		>2 mos		Magnetic resonance imaging (MRI)	• All MRI scans were normal
Kayemba-Kay's & Laclyde [53]	13		6 and 9 months		Denver Development Screening Tests II	• 11 children (85%) scored within normal limits • Abnormal test results in 2 children who required specialized care for peripheral hypertonia
Sarfi et al. [55]	35[*]		3 months		Sleep patterns	• No significant differences between the group of infants exposed in utero to agonist medication and low-risk group
Whitham et al. [54]	30		4 months		Visual evoked potential	• No significant difference from the control group in P1 latency, suggesting no problem with visual maturation
Social: Maternal-Infant Interaction						
Sarfi et al. [56]	38[*]		6 months		Maternal-infant interaction	• Prenatal exposure to agonist medication was not a significant predictor of quality of maternal-infant interaction
Early Childhood Cognitive Development						
Salo et al.[57][¥]	21		3 years		Emotional Availability (EA) Scales Bayley Scales of Infant Development (BSID-III)	• Buprenorphine-exposed infants scored lower than the group of non-exposed infants on the

Author(s)	Number of buprenorphine-exposed neonates included in each study		Age of infants		Outcome measure(s)	Findings
	Total sample	Sub-sample	Total sample	Sub-sample		
						EA scales of Child Responsiveness and Involvement and the BSID-III EA scales of Child Responsiveness and Involvement and the BSID-III

Notes:

†Subsample from Jones et al. [19].

‡Subsample from Jones et al. [18].

*Total sample size of agonist-exposed infants. Differences between infants exposed in utero to methadone and buprenorphine were not examined.

¥Mothers were out-of-treatment buprenorphine users.