Addiction

REVIEW

doi:10.1111/j.1360-0443.2012.04035.x

Buprenorphine treatment of opioid-dependent pregnant women: a comprehensive review

Hendrée E. Jones[1,2], Sarah H. Heil[3], Andjela Baewert[4], Amelia M. Arria[5], Karol Kaltenbach[6], Peter R. Martin[7], Mara G. Coyle[8], Peter Selby[9], Susan M. Stine[10] & Gabriele Fischer[11]

Departments of Psychiatry and Behavioral Sciences and Obstetrics and Gynecology, Johns Hopkins University School of Medicine, Baltimore, MD, USA,[1] RTI International, Research Triangle Park, NC, USA,[2] Departments of Psychiatry and Psychology, University of Vermont, Burlington, VT, USA,[3] Department of Psychiatry and Psychotherapy, Medical University Vienna, Vienna, Austria,[4] Center on Young Adult Health and Development, School of Public Health, University of Maryland, College Park, MD, USA,[5] Departments of Pediatrics, and Psychiatry and Human Behavior, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA, USA,[6] Department of Psychiatry, Vanderbilt University, Nashville, TN, USA,[7] Department of Pediatrics, The Warren Alpert Medical School of Brown University, Providence, RI, USA,[8] Department of Family and Community Medicine, Department of Psychiatry, and Dalla Lana School of Public Health, Sciences, University of Toronto, Toronto, Ontario, Canada,[9] Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI, USA[10] and Center of Public Health, Medical University Vienna, Vienna Austria[11]

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 three randomized clinical 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 physiological 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** While buprenorphine produces a less severe neonatal abstinence syndrome than methadone, both methadone and buprenorphine are important parts of a complete comprehensive treatment approach for opioid-dependent pregnant women.

Keywords Buprenorphine, opioid dependence, pharmacological treatment, pregnancy.

Correspondence to: Hendrée E. Jones, Cornerstone/JHBMC, Mason F. Lord Building, E353, 4940 Eastern Avenue, Baltimore, MD 21224, USA. E-mail: hjones18@jhmi.edu

Submitted 29 November 2010; initial review completed 10 November 2011; final version accepted 6 June 2012

INTRODUCTION

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 the empirical evidence of longer durations of maternal drug abstinence and obstetric 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, in part because it may reduce the incidence and/or severity of the neonatal abstinence syndrome. This paper reviews the published literature regarding maternal, fetal, neonatal and infant developmental outcomes for buprenorphine-maintained pregnant women. Space limitations preclude a detailed review of methadone treatment outcomes; however, some attention is paid to methadone and buprenorphine comparisons.

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 or film available through maintenance clinics and office-based practices by certified physicians in the United States, with prescription privileges and practices varying elsewhere (e.g. Austria, Belgium, France, and parts of Canada 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 [8]. 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. [9,10]). Theoretically, buprenorphine may not be as effective in patients requiring higher doses of methadone for the full therapeutic effect [11], although some research fails to support this contention [12,13]. Conversely, this feature of buprenorphine may make overdose deaths less likely with buprenorphine than with methadone [14,15]. Buprenorphine also has higher receptor affinity [8,16] 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 papers 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'. The resulting papers were reviewed for their appropriateness for inclusion in the present paper. 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 clinical trials and then for the non-randomized studies, which include prospective studies, case reports and series, and retrospective chart reviews.

The three randomized clinical 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 Pregnancy and Reduction of Opiates: Medication Intervention Safety and Efficacy (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 that differed from the PROMISE study in the details of concomitant medications used during double-blind medication induction, 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 1–4, only 28 contain independent samples. Therefore, summaries of the non-randomized studies are limited to the results of the primary study, unless noted otherwise.

Table 1 Summary of maternal outcomes in studies of opioid-addicted pregnant women administered buprenorphine.

Study description				*Maternal outcomes*			
		Baseline		*Delivery*			
		Number of mothers administered buprenorphine prenatally		*Number of mothers who delivered while taking buprenorphine*			
Author(s)	*Country*	*Total sample*	*Subsample*	*Total sample*	*Subsample*	*Opioid use measure*	*Number of mothers with positive result for illicit opioids at delivery*
• Large-scale randomized clinical trials							
Jones *et al.* [18]	USA, Austria	86		58 (67%)		Biological: urine	5 (9%)
• Small-scale randomized clinical 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%[a,b]
• Other prospective studies							
Winklbaur *et al.* [60]	Austria	22		22 (100%)		Biological: urine	24%[a]
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%[d]
Lejeune *et al.* [65][e]			153				
Lejeune *et al.* [66]			153		153 (100%)	Not specified	19%[a]
Simmat-Durand *et al.* [67]			159		159 (100%)	Self-report	24 (15%)[f]
Colombini *et al.* [40]	France	13		13 (100%)			
Vert *et al.* [68]	France	19		19 (100%)		Biological: urine	6 (32%)[g]
Lacroix *et al.* [69]	France	90		84 (93%)		Biological: urine	15 (17%)[c]
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%)[g]
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%)[h]		Biological: urine	15 (40%)
Bakstad *et al.* [75]	Norway	12		12 (100%)		Biological: urine[i]	0 (0%)
Sarfi *et al.* [55]			11		11 (100%)	Biological: urine[i]	1 (9%)[d]
Bläser *et al.* [76]	Germany	3		3 (100%)			
Brulet *et al.* [77]	France	62		70 (100%)[j]		Self-report	
Sandtorv *et al.* [78]	Norway	4		4 (100%)		Biological: urine; self-report	

Table 1 *Cont.*

Study description		*Maternal outcomes*					
		Baseline		*Delivery*			
		Number of mothers administered buprenorphine prenatally		*Number of mothers who delivered while taking buprenorphine*			
Author(s)	*Country*	*Total sample*	*Subsample*	*Total sample*	*Subsample*	*Opioid use measure*	*Number of mothers with positive result for illicit opioids at delivery*
• 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%)
Marquet *et al.* [79]			6		6 (100%)	Urine, hair	1 (17%)[f]
Regini *et al.* [80]	Italy	1		1 (100%)			
Herve & Quenum [81]	France	1		1 (100%)			
Jernite *et al.* [39] retrospective group	France	13		13 (100%)[k]		Self-report	
Jernite *et al.* [39] prospective group		11		11 (100%)			
Auriacombe *et al.* [82]		4		3 (75%)		Not specified	
Eder *et al.* [83][e]	Austria	1		1 (100%)		Biological: urine	0 (0%)
Kayemba-Kay's & Laclyde [53]	France	13		13 (100%)			
Siedentopf *et al.* [84][e]	Germany	33		33 (100%)			
Ross [85]	Australia	1		1 (100%)			
Unger *et al.* [86][l]	Austria		3		3 (100%)	Biological: urine	
• Retrospective chart reviews							
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%)

Table 1 summarizes the results of one large-scale and two small-scale randomized clinical trials, 15 other prospective studies (of 28 such studies abstracted), 10 case reports (of 12 such studies abstracted, not counting Unger *et al.* [86], a MOTHER substudy [18]) and three 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 clinical 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 clinical 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 two non-randomized studies with less than 100% treatment retention, Lacroix *et al.* [69] lost six of 90 patients due to two spontaneous abortions, two voluntary abortions, one therapeutic abortion and one stillbirth. Binder & 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 two studies, failure to achieve 100% treatment retention was not due to a maternal participant prematurely terminating treatment. [a]Urine specimens were taken over entire pregnancy or does not specify whether or not collected at delivery. [b]Reported median value only. [c]This count and percentage is for heroin. five women (6%) tested positive for 'opioid analgesic'. [d]Data from whole sample instead of buprenorphine mothers only. [e]Paper not in English. [f]Reported in 4 weeks prior to pregnancy or last trimester. [g]Mothers positive for any drug without differentiation between opioid and other drug use. [h]Fifteen mothers were excluded from the study for using illicit drugs. [i]Compared to European Addiction Survey Index. [j]During the study, eight women switched to buprenorphine maintenance. [k]The paper indicates one miscarriage among 24 total cases, but reports on neonatal data for 13 and 11 infants in the two groups. [l]Subsample from Jones *et al.* [18] and so not included in the total sample count.

Table 2 Summary of studies examining fetal outcomes in fetuses exposed to buprenorphine *in utero*.

Study description			*Fetal deaths*									*Prenatal testing*				
	Number of buprenorphine-exposed fetuses		*Total*		*Number of miscarriages*		*Number of elected abortions*		*Number of stillbirths*		*Number of intrauterine growth restriction (IUGR) cases*	*Week(s) at which fetal testing was conducted*	*Fetal heart rate (FHR) (mean ± SE)*	*Number of FHR accelerations*	*FHR reactivity in the fetal non-stress test (NST)*	*Biophysical profile (BPP) score (mean ± SE)*
Author(s)	*Total sample*	*Subsample*	*Total sample*	*Subsample*	*Total sample*	*Subsample*	*Total sample*	*Subsample*	*Total sample*	*Subsample*						
• Large-scale randomized clinical trials																
Jones *et al.* [18]	58															
• Small-scale randomized clinical 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					Periodic NST and BPP monitoring from study entry was unremarkable				
Rohrmeister *et al.* [64]	16		0		0		0									
Lejeune *et al.* [41]	159			0							49 (31%)					
Lejeune *et al.* [65][a]		153		0		0		0								
Lejeune *et al.* [66][a]		153		0		0		0								
Simmat-Durand *et al.* [67]		160														
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.* [71]	67		11		1		10									
Kahila *et al.* [52]		7		0		0		0								
Kahila *et al.* [72]		27														
Hytinantti *et al.* [26]		58										28/32/36/40				
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									

Table 2 *Cont.*

Study description			*Fetal deaths*									*Prenatal testing*				
	Number of buprenorphine-exposed fetuses		*Total*		*Number of miscarriages*		*Number of elected abortions*		*Number of stillbirths*		*Number of intrauterine growth restriction (IUGR) cases*	*Week(s) at which fetal testing was conducted*	*Fetal heart rate (FHR) (mean ± SE)*	*Number of FHR accelerations*	*FHR reactivity in the fetal non-stress test (NST)*	*Biophysical profile (BPP) score (mean ± SE)*
Author(s)	*Total sample*	*Subsample*	*Total sample*	*Subsample*	*Total sample*	*Subsample*	*Total sample*	*Subsample*	*Total sample*	*Subsample*						
• Case reports and series																
Marquet *et al.* [42]	23		0		0		0									
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 & Quenum [81]	1		0		0		0									
Jernite *et al.* [39] retrospective group[b]	13										7 (54%)					
Jernite *et al.* [39] prospective group[b]	11						0									
Auriacombe *et al.* [82]		3						0								
Eder *et al.* [83][a]	2		0		0		0									
Kayemba-Kay's & Laclyde [53]	13		0		0		0									
Siedentopf *et al.* [84][a]	33		0		0		0									
Ross [85]	1		0		0		0									
Unger *et al.* [86][c]		3		0		0		0								
Jansson *et al.* [36] Group 1[c]		4		0		0		0				24/28	136 ± 7.8	1.3 (1.9)		
Jansson *et al.* [36] Group 2[c]		5		0		0		0				32/36	135 ± 7.1	2.8 ± 3.8		
Salisbury *et al.* [37][c]		33		0		0		0				32	132 ± 1.2	2.9 ± 0.2		8.7 ± 0.2
• Retrospective chart reviews																
Czerkes *et al.* [87]	68															
Blandthorn *et al.* [88]	20															
O'Connor *et al.* [89]	23		0		0		2									

In addition to the studies listed in Table 1, Table 2 includes two 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 intrauterine growth restriction (IUGR) do not provide sufficient information to assess how it was defined or determined with any certainty. [a]Paper not in English. [b]The paper 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. [c]Subsample from Jones *et al.* [18] and so not included in the total sample count. SE: standard error.

Table 3 Summary of studies examining physical birth outcomes in neonates prenatally exposed to buprenorphine.

Author(s)	*Number of buprenorphine-exposed neonates*		*Cesarean section (%)*	*Age at delivery (weeks) [if reported: mean ± SE or mean (SD)]*	*Physical anomalies*	*Mean Apgar scores*			*Mean birth weight (gm) [If reported: mean ± SE or mean (SD)]*	*Mean length (cm) [if reported: mean ± SE or mean (SD)]*	*Mean head circumference (cm) [if reported: mean ± SE or mean (SD)]*
	Total sample	*Subsample*				*1 minute*	*5 minutes*	*10 minutes*			
• Large-scale randomized clinical 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 clinical 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)[a]	None	9	10	10	3182 (294)[a]	50.3 (1.0)[a]	33.8 (1.0)[a]
Johnson *et al.* [46]	3		1 (33%)	39–40 (39.3) 39–42 (40.3)[b]	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%)[c]	38.8			9.8		2843		
Lejeune *et al.* [65][d]		153	30 (20%)[c]	38.4			9.8		2860		
Lejeune *et al.* [66][d]		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[e]		
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[f]		
Kahila *et al.* [72]		27	3 (2%)	40 (1.6)					3640 (303)	50[f]	35[f]
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						

Table 3 *Cont.*

Author(s)	Number of buprenorphine-exposed neonates: Total sample	Subsample	Cesarean section (%)	Age at delivery (weeks) [if reported: mean ± SE or mean (SD)]	Physical anomalies	Mean Apgar scores: 1 minute	5 minutes	10 minutes	Mean birth weight (gm) [If reported: mean ± SE or mean (SD)]	Mean length (cm) [if reported: mean ± SE or mean (SD)]	Mean head circumference (cm) [if reported: mean ± SE or mean (SD)]
• 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 & Quenum [81]	1			41					3680		35
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][d]	1		0 (0%)	40	None	9	10	10	3415 (21.2)[a]	50.5 (0.7)[a]	
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][g]	3		1 (17%)[a]	271.3 (13.6) days[a]					2846.9	50.3 (1.5)	34.3 (1.0)
• Retrospective chart reviews											
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)		

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. [a]Calculated based on data reported in the paper. [b]Age at delivery was assessed by both obstetric and pediatric assessments, respectively; both are included in the table. [c]Noted as emergency cesarean section or instrumental vaginal delivery. [d]Paper not in English. [e]Only for the 15 term neonates; five born between 32–36 weeks not included. [f]Reported median only. [g]Subsample from Jones *et al.* [18] and so not included in the total sample count. SD: standard deviation; SE: standard error.

Table 4 Summary of studies examining neonatal abstinence syndrome (NAS) in neonates prenatally exposed to buprenorphine.

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: Subsample	Time to onset of NAS [if reported: mean ± SE or mean (SD)]	NAS assessment method	NAS treatment medication(s)	Mean days in treatment for NAS [if reported: mean ± SE or mean (SD)]	Mean number of days neonates in hospital [if reported: mean ± SE or mean (SD)]
• Large-scale randomized clinical trials									
Jones *et al.* [18]	58		27 (47%)			Modified-Finnegan	Morphine	4.1 ± 1.0[a]	10.0 ± 1.2
• Small-scale randomized clinical trials									
Jones *et al.* [19]	9		2 (22%)			Modified-Finnegan	Morphine		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		
Fischer *et al.* [61]		9		0		Not specified	NA	NA	NA
Ebner *et al.* [62]		14		3		Finnegan	Morphine, phenobarbital		
Fischer *et al.* [63]		15		3		Finnegan	Morphine	1.1 (2.5)	
Schindler *et al.* [51]		4		0		Finnegan	NA	NA	NA
Johnson *et al.* [46]	3		0 (0%)		'Within first 12 hours'	Modified-Finnegan; NICU Network Neurobehavioral Scale (NNNS); Infant Acoustic Cry	NA		4–5
Rohrmeister *et al.* [64]	16		3 (19%)		34.5[b] ± 16 hours	Finnegan	Phenobarbital; morphine	8.3 ± 2.6[b] days	8.0 ± 5.9[b] days
Lejeune *et al.* [41][c]	159		83		37.5 hours		Morphine hydrochloride, paregoric, morphine derivate, chlorpromazine, phenobarbital, diazepam	16.9	23[g]
Lejeune *et al.* [65][f]		153			38.5 hours	Lipsitz	paregoric elixir; phenobarbital; chloropromazine	16	23
Lejeune *et al.* [66][f]		153	52%		38.5 hours	Lipsitz			23[g]
Simmat-Durand *et al.* [67][c]		160		80 (50%)	37.5 ± 30.8 hours		Morphine hydrochloride	16.3 ± 10.5	22.6 ± 14.2
Colombini *et al.* [40]	13		13 (100%)		24–68 hours	Lipsitz	Morphine	28.2 ± 10.1	
Vert *et al.* [68]	20		12 (60%)		1–5 days	Finnegan	Morphine		16.1–20.0
Lacroix *et al.* [69]	85		20 (24%)		2.8 ± 1.9 days	Finnegan			
Lacroix *et al.* [38]		31		8	1–8 days	Finnegan	Opiates		
Lacroix *et al.* [70]		31		8	3 days	Not specified	Opiates		
Whitham *et al.* [54]		30	14 (47%)			Modified-Finnegan	Morphine; phenobarbitone		
Kahila *et al.* [52]	67		39 (58%)		2.5 days	Finnegan	Morphine; phenobarbital		18.8 (15)
Kahila *et al.* [71]		7		6		Not specified	Morphine		25 (19)
Kahila *et al.* [72]		27				Not specified	Not specified		
Hytinantti *et al.* [26]		58		38		Finnegan	Morphine; phenobarbital	20 ± 10	
Kakko *et al.* [73]	47		7 (15%)			Finnegan	Morphine		9.4 (8.4)
Binder & Vavrinkova [74]	38		33 (81%)		24–48 hours[d]	Finnegan	Opium tincture; phenobarbital		
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		
Brulet *et al.* [77]	70								
Sandtorv *et al.* [78]	4		2 (50%)				Morphine		

Table 4 *Cont.*

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: Subsample	Time to onset of NAS [if reported: mean ± SE or mean (SD)]	NAS assessment method	NAS treatment medication(s)	Mean days in treatment for NAS [if reported: mean ± SE or mean (SD)]	Mean number of days neonates in hospital [if reported: mean ± SE or mean (SD)]
• Case reports									
Marquet *et al.* [42]	23		10 (47%)		33.1 hours	Finnegan	Morphine; chloropromazine; diazepam		16.5
Marquet *et al.* [45]		1	0 (0%)			Finnegan			6
Marquet *et al.* [79]		6	3 (50%)		2 days[i]	Finnegan	Morphine; paregoric elixir		
Regini *et al.* [80]	1		1 (100%)		2 days		Methadone		
Herve & Quenum [81]	1		1 (100%)		3 days	Finnegan	Paregoric	36[h]	
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][f]	2		0 (0%)		N/A	Finnegan	NA		
Kayemba-Kay's & Laclyde [53]	13		10 (77%)		1–5 days	Finnegan	Paregoric; morphine	21 (11.1)[e]	27.3
Siedentopf *et al.* [84]	33					Finnegan			12.2
Ross [85]	1		0 (0%)		3 days[i]	Finnegan	NA		7
Unger *et al.* [86][j]		3		2 (67%)		Modified-Finnegan	Morphine	4.7 (4.2)	
• Retrospective chart reviews									
Czerkes *et al.* [87]	68		33 (49%)						8.4
Blandthorn *et al.* [88]	20					Modified-Finnegan	Morphine; phenobarbitone		
O'Connor *et al.* [89]	23		8 (35%)		66.2 hours	Finnegan	Phenobarbital		7.7 (2.7)

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. NA 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. [a]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). [b]Reported median only. [c]Lejeune *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.* [67] report on 160 neonates exposed *in utero* to buprenorphine. [d]Reported in only 86% of the sample. [e]Calculated based on data reported in the paper. [f]Paper not in English. [g]Mean length of stay after newborn was transferred to Department of Neonatology. [h]Determined from paper narrative—neonate was treated from 6 days old to 6 weeks old. [i]Infants had NAS, but were not treated. [j]Subsample from Jones *et al.* [18] and so not included in the total sample count. SD: standard deviation; SE: standard error.

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 of 86), PROMISE retained 60% (nine of 15) and Fischer *et al*. retained 89% (eight of nine). In comparison, MOTHER retained 78% (57 of 73), PROMISE 73% (11 of 15) and Fisher *et al*. 67% (six of nine) of methadone condition participants. Jones *et al*. [18] reported that the two medications did not differ significantly in treatment completion. Neither Jones *et al*. [19] nor Fischer *et al*. [20] conducted a test for differential dropout; 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 of 58) and 18% (16 of 73) dropout rate in the buprenorphine and methadone conditions, respectively. Moreover, 29% (eight of 28) of buprenorphine condition dropouts left on the day of study entry. These findings underscore the need to examine systematically 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 reported directly in these studies, we used data that were available in the papers 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 of 15 of the independent prospective studies, 10 of 10 of the independent case reports and series and three of three of the retrospective chart reviews, with the remaining two prospective studies showing treatment retention of 93% (84 of 90) and 61% (23 of 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 notes to Table 1). Thus, these data should be interpreted with caution.

Buprenorphine treatment retention remains an important scientific question, given that a review [30] of 23 randomized clinical 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 that 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 during the last 4 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% (seven of nine) of the buprenorphine- and 73% (eight of 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% (five of 58) of the MOTHER participants and 0% (none of nine) of the PROMISE participants tested positive for illicit opioid(s) at delivery. In contrast, for methadone, 15% (11 of 73) of the MOTHER participants and 0% of the PROMISE (none of 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 nine of the 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 clinical 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 manage withdrawal symptoms effectively 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 the 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 clinical trials have been published examining pain management for opioid-dependent pregnant women during labor and delivery and postpartum. However, three retrospective analyses of data from randomized trials, 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 days 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 prescribed, significantly more often, epidural anesthesia for vaginal deliveries, non-steroidal anti-inflammatory drugs for cesarean deliveries and opioids during the first 3 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% (seven of 13) of buprenorphine-maintained pregnant women in one sample, 50% (three of six) in a second sample and 31% (49 of 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 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 50th percentile of World Health Organization (WHO) standards, and only four 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 50th 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 g), length (10 studies: 49.4 cm) and head circumference (nine studies: 34.0 cm), extracted from all such studies that reported summary data (see Table 3), suggest that most neonates were full term and within normal limits.

Neonatal abstinence syndrome (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 been utilized occasionally.

In the MOTHER study, 47% (27 of 58) of the buprenorphine-exposed neonates were treated for NAS, while 22% (two of nine) of the PROMISE study's buprenorphine-exposed neonates were treated for NAS. Fischer *et al*. reported that 63% (five of eight) of the buprenorphine-exposed neonates were treated for NAS. In contrast, 57% (41 of 73) of the methadone-exposed neonates in the MOTHER study and 46% (five of 11) in the PROMISE study were treated for NAS, while Fischer *et al*. reported that 50% (three of six) 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 three randomized clinical 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 result either 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 similarly 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 of 58)] and methadone [57% (41 of 73)] conditions were treated for NAS, would also suggest that the rates at which neonates exposed to either medication are comparable, and approximately one in two 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, available only for the three randomized clinical 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 two neonates of buprenorphine-maintained mothers treated for NAS.

Fischer *et al.* reported that the mean cumulative dose of morphine needed to treat the five 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 five PROMISE neonates of methadone-maintained mothers treated for NAS. Fischer *et al.* reported that the mean cumulative dose of morphine needed by five 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, due in part probably 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 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 related significantly 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 five 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 five 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 six 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 nine 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. (Site was a blocking factor in all analyses.)] Fischer *et al.* did not report separately the 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 the wide 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]. Further, the PROMISE study [19] also found a significant difference between the buprenorphine and methadone conditions in neonatal length of hospital stay, and Fischer *et al.* [20] did not report testing this difference between medication conditions.

BUPRENORPHINE AND BREAST MILK

No randomized clinical 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, in a study of seven infants breastfed by buprenorphine-maintained mothers, Lindemalm *et al.* [44] reported 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 treated subsequently 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 breast milk 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 buprenorphine-exposed prenatally ($n = 18$) 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: anatomical and physiological studies of the brain and special senses

Magnetic resonance imaging (MRI) brain scans of seven *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 hypertonicity was reported in seven infants, with two 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 4-month-old prenatally buprenorphine-exposed infants compared to a sample of 33 control infants showed no significant differences in terms of visual maturation [54].

Sarfi *et al.* [55] examined differences in 10 measures of diurnal and nocturnal rhythmicity 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

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][a]	0	10						
Grimm *et al.* [25][b]			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[c]	Day 3 Day 6 Day 9[d]	520 g/nl 720 g/nl 230 g/nl			1.0
Lindemalm *et al.* [44]	7	6	0.06 mg/kg–0.41 mg/kg	Days 5–8	0.06–0.2 mg hour^{-1}/l	0.03–0.15 mg hour^{-1}/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		

Blank cells indicate data not reported for neonates. [a]"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 hour^{-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. [b]No infant data collected. The ingested 24-hour dose is calculated from the mother's data. [c]The paper 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. [d]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.

	Number of buprenorphine-exposed neonates included in each study		*Age of infants*			
Author(s)	*Total sample*	*Subsample*	*Total sample*	*Subsample*	*Outcome measure(s)*	*Findings*
• Neurobehavioral development						
Jones *et al.* [49][a]		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][b]		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 months		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 two children who required specialized care for peripheral hypertonia
Sarfi *et al.* [55]	35[c]		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[c]		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][d]	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 EA scales of Child Responsiveness and Involvement and the BSID-III Language scale

[a]Subsample from Jones *et al.* [19]. [b]Subsample from Jones *et al.* [18]. [c]Total sample size of agonist-exposed infants. Differences between infants exposed *in utero* to methadone and buprenorphine were not examined. [d]Mothers were out-of-treatment buprenorphine users.

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: maternal–infant interaction

Sarfi *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

Salo *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 Bayley Scales of Infant Development (BSID-III) at age 3 years. The Language Scale results remained significant following adjustment for birth weight and height, gestational age, maternal age, socio-economic 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 interpretation 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 Salo *et al*. aside for the moment, 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 methadone in terms of maternal outcomes. Buprenorphine also appears generally similar to, and in some cases superior to, methadone in terms of fetal and neonatal outcomes.

Secondly, like methadone, prenatal buprenorphine exposure appears to be associated with a clinically significant NAS requiring pharmacological intervention in approximately half the cases. However, results from the MOTHER study suggest that buprenorphine is associated with a less severe NAS than methadone. None the less, other correlates of prenatal buprenorphine exposure (e.g. its potential impact on neonatal birth weight and length and longer-term outcomes) are not understood fully and need further research.

Thirdly, 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 single 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 served optimally when a variety of medications are available, and when matching patients to pharmacotherapy is a treatment consideration.

Clinical trial registration

The clinical trial was registered with ClinicalTrials.gov (Identifier: NCT00271219; title: RCT Comparing Methadone and Buprenorphine in Pregnant Women).

Declarations of interest

MOTHER Study

All MOTHER grants are from the National Institute on Drug Abuse (NIDA) unless noted otherwise: Brown University, R01 DA 015778; Johns Hopkins University, R01 DA 015764; Medical University of Vienna, R01 DA 018417; Thomas Jefferson University, R01 DA 015738; University of Toronto, R01 DA 015741; University of Vermont, R01 DA 018410 and M01 RR 109; Vanderbilt University, R01 DA 017513 and M01 RR 00095, and Wayne State University, R01 DA 15832.

Reckitt Benckiser Healthcare, Hull, UK supplied buprenorphine tablets (and the associated placebo) via NIDA. Neither Reckitt Benckiser nor NIDA had any involvement in study design, data collection, analysis, interpretation, or manuscript preparation.

H. J. discloses that she has received reimbursement for time and travel from Reckitt Benckiser.

G. F. discloses that she has received financial support and honoraria for presentations from Reckitt Benckiser, as well as financial support and honoraria for presentations from Schering Plough.

P. S. discloses that he has received an unrestricted educational grant from Schering Canada to provide a single training program on buprenorphine substitution treatment in 2000. His hospital receives funds from the Government of Ontario to develop and provide a training program of which he is the course director for all Ontario physicians who wish to treat opioid dependence including in pregnant women. However, the buprenorphine mono product is not available in Canada.

K. O'G. discloses that he has received reimbursement for time from Reckitt Benckiser.

All other authors declare no competing financial interests.

No contractual constraints on publishing have been imposed by any agency from which an author has received funding.

Present Paper

A. B. discloses that she has received financial support and honoraria for presentations from Reckitt Benckiser, as well as financial support and honoraria for presentations from Schering Plough.

Acknowledgements

We thank Brown University (R01 DA 015778) and Drs Barry Lester, Amy Salisbury, Suzanne Caron, Jeff Michaud, and Lawrence Novo, Katheleen Hawes, Danielle Finch, Marissa Cerrone, and the staff of the Level II Nursery at St. Luke's Hospital; Wayne State University (R01 DA 15832) and co-Investigators Drs Carl Christenson, Virginia Delaney-Black, Robert Sokol, Charles Schuster, Eugene Cepeda, and the assistance of Darlene Tansil and Mea Ebenbichler; Johns Hopkins University (R01 DA 015764) and the staff Ave Childrey, Laetitia Lemoine, Heather Fitzsimons, Julia Shadur, Michelle Tuten, Cheryl Claire, Behavioral Pharmacology Research Pharmacy and Nursing staff, Center for Addiction and Pregnancy staff, and co-Investigators Drs Donald Jasinski, Lauren Jansson, Robert Dudas, Lorraine Milio, Martha Velez, Vickie Walters, Eric Strain, and George Bigelow; Thomas Jefferson University (R01 DA 015738), Dr Amber Holbrook and the research staff, Family Center staff, OB and Pediatric nursing staff, and co-Investigators Drs Vincenzo Berghella, Jason Baxter, Jay Greenspan, and Laura McNicholas; University of Toronto (R01 DA 015741) Toronto Centre for Substance Use in Pregnancy, co-Investigators Drs Alice Ordean and Bhushan Kapur, and Ms Alla Osadchy as research coordinator and the assistance of Ms Lydia Pantea; Vanderbilt University (R01 DA 017513 and M01RR00095) and co-Investigators Drs Karen D'Apolito (co-PI), Paul Bodea-Barothi, Nancy Chescheir, Joseph Gigante, Barbara Engelhardt, nurse practitioners Michelle Collins, Mavis Schorn, and Karen Starr, as well as the assistance of Cayce Watson and Mark Nickel; University of Vermont (R01 DA 018410 and M01RR109) co-Investigators Drs John Brooklyn, Stephen Higgins, Anne Johnston, Marjorie Meyer, and Stacey Sigmon, and the staffs of the Substance Abuse Treatment Center, Chittenden Center, Comprehensive Obstetrics Service, General Clinical Research Center, Newborn Nursery, Neonatal Transitions Suite, Neonatal Intensive Care Unit, and Pharmacy at Fletcher Allen Health Care; Medical University of Vienna (R01 DA 018417) co-Investigators Drs Kenneth Thau, Bernadette Winklbaur, Nina Ebner, Klaudia Rohrmeister, Inge Frech, Martin Langer, Manfred Weninger, and Nina Kopf; Ingrid Kügler and nurses Doris Leopoldinger and Burgi Gfrerer, and Reinhold Jagsch, Verena Metz, Katrin Klebermass, Anne Unger, Andjela Baewert, Heidi Amon, Constantin Aschauer, Alexander Hecht; and Center for Substance Abuse Research Project Director Emy Nakamura (Parham); data monitors Ben Falls and Patricia Zangrillo; data preparation and analyses staff Kimberly Caldeira, Laura Dykstra, Dr Shawn Flower, Sarah Kaspersi, Gillian Pinchevsky, Lauren Stern, Kathryn Vincent, Dr Michael Wagner, Emily Winick and Elizabeth Zarate.

Notes

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

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 $P < 0.0001$.
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 $P < 0.0001$.

References

1. Kaltenbach K., Berghella V., Finnegan L. Opioid dependence during pregnancy. Effects and management. *Obstet Gynecol Clin North Am* 1998; **25**: 139–51.
2. Jones H. E., Tuten M., Keyser-Marcus L., Svikis D. Specialty treatment for women. In: Strain E. C., Stitzer M. L., editors. *Methadone Treatment for Opioid Dependence*. Baltimore: Johns Hopkins University Press; 2006, p. 455–84.
3. Unger A., Jung E., Winklbaur B., Fischer G. Gender issues in the pharmacotherapy of opioid-addicted women: buprenorphine. *J Addict Dis* 2010; **29**: 217–30.
4. Winklbaur B., Kopf N., Ebner N., Jung E., Thau K., Fischer G. Treating pregnant women dependent on opioids is not the same as treating pregnancy and opioid dependence: a knowledge synthesis for better treatment for women and neonates. *Addiction* 2008; **103**: 1429–40.
5. Winklbaur B., Jung E., Fischer G. Opioid dependence and pregnancy. *Curr Opin Psychiatry* 2008; **21**: 255–9.
6. Stoller K. B., Bigelow G. E., Walsh S. L., Strain E. C. Effects of buprenorphine/naloxone in opioid-dependent humans. *Psychopharmacology (Berl)* 2001; **154**: 230–42.
7. Jarvis M. A. E., Wu-Pong S., Kinseley J. S., Schnoll S. H. Alterations in methadone metabolism during late pregnancy. *J Addict Dis* 1999; **18**: 51–61.
8. Cowan A., Lewis J. W., Macfarlane I. R. Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. *Br J Pharmacol* 1977; **60**: 537–45.
9. Ariens E. J. Intrinsic activity: partial agonists and partial antagonists. *J Cardiovasc Pharmacol* 1983; **5**: S8–15.
10. Walsh S. L., Preston K. L., Stitzer M. L., Cone E. J., Bigelow G. E. Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clin Pharmacol Ther* 1994; **55**: 569–80.
11. Center for Substance Abuse Treatment. *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction*. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication no. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2004.
12. Johnson R. E., Chutuape M. A., Strain E. C., Walsh S. L., Stitzer M. L., Bigelow G. E. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *N Engl J Med* 2000; **343**: 1290–7.
13. Kamien J. B., Branstetter S. A., Amass L. Buprenorphine–naloxone versus methadone maintenance therapy: a randomised double-blind trial with opioid-dependent patients. *Heroin Addict Relat Clin Probl* 2008; **10**: 5–18.
14. Bell J. R., Butler B., Lawrance A., Batey R., Salmelainen P. Comparing overdose mortality associated with methadone and buprenorphine treatment. *Drug Alcohol Depend* 2009; **104**: 73–7.
15. Auriacombe M., Franques P., Tignol J. Deaths attributable to methadone versus buprenorphine in France. *JAMA* 2001; **285**: 45.
16. Dum J. E., Herz A. *In vivo* receptor binding of the opiate partial agonist, buprenorphine, correlated with its agonistic and antagonistic actions. *Br J Pharmacol* 1981; **74**: 627–33.
17. Kacinko S. L., Jones H. E., Johnson R. E., Choo R. E., Concheiro-Guisan M., Huestis M. A. Urinary excretion of buprenorphine, norbuprenorphine, buprenorphine–glucuronide, and norbuprenorphine–glucuronide in pregnant women receiving buprenorphine maintenance treatment. *Clin Chem* 2009; **55**: 1177–87.
18. Jones H. E., Kaltenbach K., Heil S. H., Stine S. M., Coyle M. G., Arria A. M. *et al*. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med* 2010; **363**: 2320–31.
19. Jones H. E., Johnson R. E., Jasinski D. R., O'Grady K. E., Chisholm C. A., Choo R. E. *et al*. Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. *Drug Alcohol Depend* 2005; **79**: 1–10.
20. Fischer G., Ortner R., Rohrmeister K., Jagsch R., Baewert A., Langer M. *et al*. Methadone versus buprenorphine in pregnant addicts: a double-blind, double-dummy comparison study. *Addiction* 2006; **101**: 275–81.
21. Albright B., de la Torre L., Skipper B., Price S., Abbott P., Rayburn W. Changes in methadone maintenance therapy during and after pregnancy. *J Subst Abuse Treat* 2011; **41**: 347–53.
22. Huang P., Kehner G., Cowan A., Liu-Chen L.-Y. Comparison of pharmacological activities of buprenorphine and norbuprenorphine: norbuprenorphine is a potent opioid agonist. *J Pharmacol Exp Ther* 2001; **297**: 688–95.
23. Concheiro M., Jones H., Johnson R. E., Shakleya D. M., Huestis M. A. Confirmatory analysis of buprenorphine, norbuprenorphine, and glucuronide metabolites in plasma by LCMSMS. Application to umbilical cord plasma from buprenorphine-maintained pregnant women. *J Chromatogr B Analyt Technol Biomed Life Sci* 2010; **878**: 13–20.
24. Concheiro M., Jones H. E., Johnson R. E., Choo R., Shakleya D. M., Huestis M. A. Maternal buprenorphine dose, placenta buprenorphine, and metabolite concentrations and neonatal outcomes. *Ther Drug Monit* 2010; **32**: 206–15.
25. Grimm D., Pauly E., Pöschl J., Linderkamp O., Skopp G. Buprenorphine and norbuprenorphine concentrations in human breast milk samples determined by liquid chromatography–tandem mass spectrometry. *Ther Drug Monit* 2005; **27**: 526–30.
26. Hytinantti T., Kahila H., Renlund M., Järvenpää A.-L., Halmesmäki E., Kivitie-Kallio S. Neonatal outcome of 58

infants exposed to maternal buprenorphine *in utero*. *Acta Paediatr* 2008; **97**: 1040–4.
27. Jones H. E., Fischer G., Heil S. H., Martin P. R., Kaltenbach K., Coyle M. G. *et al*. Maternal Opioid Treatment: Human Experimental Research (MOTHER)—approach, issues, and lessons learned. *Addiction* 2012; **107** (Suppl. 1): 28–35.
28. Jones H. E., Martin P. R., Heil S. H., Kaltenbach K., Selby P., Coyle M. G. *et al*. Treatment of opioid-dependent pregnant women: clinical and research issues. *J Subst Abuse Treat* 2008; **35**: 245–59.
29. Rosado J., Walsh S. L., Bigelow G. E., Strain E. C. Sublingual buprenorphine/naloxone precipitated withdrawal in subjects maintained on 100 mg of daily methadone. *Drug Alcohol Depend* 2007; **90**: 261–9.
30. Mattick R. P., Kimber J., Breen C., Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2008; (2): CD002207.
31. Pond S. M., Kreek M. J., Tong T. G., Raghunath J., Benowitz N. L. Altered methadone pharmacokinetics in methadone-maintained pregnant women. *J Pharmacol Exp Ther* 1985; **233**: 1–6.
32. Jones H. E., O'Grady K., Dahne J., Johnson R., Lemoine L., Milio L. *et al*. Management of acute postpartum pain in patients maintained on methadone or buprenorphine during pregnancy. *Am J Drug Alcohol Abuse* 2009; **35**: 151–6.
33. Jones H. E., Johnson R. E., Milio L. Post-cesarean pain management of patients maintained on methadone or buprenorphine. *Am J Addict* 2006; **15**: 258–9.
34. Höflich A. S., Langer M., Jagsch R., Böert A., Winklbaur B., Fischer G. *et al*. Peripartum pain management in opioid dependent women. *Eur J Pain* 2012; **16**: 574–84.
35. Meyer M., Paranya G., Norris A. K., Howard D. Intrapartum and postpartum analgesia for women maintained on buprenorphine during pregnancy. *Eur J Pain* 2010; **14**: 939–43.
36. Jansson L. M., DiPietro J. A., Velez M., Elko A., Williams E., Milio L. *et al*. Fetal neurobehavioral effects of exposure to methadone or buprenorphine. *Neurotoxicol Teratol* 2011; **33**: 240–3.
37. Salisbury A. L., Coyle M. G., O'Grady K. E., Martin P. R., Stine S. M., Kaltenbach K. *et al*. Fetal assessment before and after dosing with buprenorphine or methadone. *Addiction* 2012; **107** (Suppl. 1): 36–44.
38. Lacroix I., Berrebi A., Chaumerliac C., Lapeyre-Mestre M., Montastruc J. L., Damase-Michel C. Buprenorphine in pregnant opioid-dependent women: first results of a prospective study. *Addiction* 2004; **99**: 209–14.
39. Jernite M., Viville B., Escande B., Brettes J., Messer J. [Buprenorphine and pregnancy. Analysis of 24 cases]. *Arch Pediatr* 1999; **6**: 1179–85.
40. Colombini N., Elias R., Busuttil M., Dubuc M., Einaudi M.-A., Bues-Charbit M. Hospital morphine preparation for abstinence syndrome in newborns exposed to buprenorphine or methadone. *Pharm World Sci* 2008; **30**: 227–34.
41. Lejeune C., Simmat-Durand L., Gourarier L., Aubisson S., Groupe d'Etudes Grossesse et Addictions (GEGA). Prospective multicenter observational study of 260 infants born to 259 opiate-dependent mothers on methadone or high-dose buprenophine substitution. *Drug Alcohol Depend* 2006; **82**: 250–7.
42. Marquet P., Lavignasse P., Gaulier J., Lachatre G. Case study of neonates born to mothers undergoing buprenorphine maintenance treatment. In: Kintz P., Marquet P., editors. *Buprenorphine Therapy of Opiate Addiction*. Totowa, NJ: Humana Press; 2002, p. 123–35.
43. Kacinko S. L., Jones H. E., Johnson R. E., Choo R. E., Huestis M. A. Correlations of maternal buprenorphine dose, buprenorphine, and metabolite concentrations in meconium with neonatal outcomes. *Clin Pharmacol Ther* 2008; **84**: 604–12.
44. Lindemalm S., Nydert P., Svensson J.-O., Stahle L., Sarman I. Transfer of buprenorphine into breast milk and calculation of infant drug dose. *J Hum Lact* 2009; **25**: 199–205.
45. Marquet P., Chevrel J., Lavignasse P., Merle L., Lachâtre G. Buprenorphine withdrawal syndrome in a newborn. *Clin Pharmacol Ther* 1997; **62**: 569–71.
46. Johnson R. E., Jones H. E., Jasinski D. R., Svikis D. S., Haug N. A., Jansson L. M. *et al*. Buprenorphine treatment of pregnant opioid-dependent women: maternal and neonatal outcomes. *Drug Alcohol Depend* 2001; **63**: 97–103.
47. Hirose M., Hosokawa T., Tanaka Y. Extradural buprenorphine suppresses breast feeding after caesarean section. *Br J Anaesth* 1997; **79**: 120–1.
48. Academy of Breastfeeding Medicine Protocol Committee. ABM Clinical Protocol #21: Guidelines for Breastfeeding and the Drug-Dependent Woman. *Breastfeed Med* 2009; **4**: 225–8.
49. Jones H. E., O'Grady K. E., Johnson R. E., Velez M., Jansson L. M. Infant neurobehavior following prenatal exposure to methadone or buprenorphine: results from the Neonatal Intensive Care Unit Network Neurobehavioral Scale. *Subst Use Misuse* 2010; **45**: 2244–57.
50. Coyle M. G., Salisbury A. S., Lester B. M., Jones H. E., Lin H., Graf-Rohrmesiter K., Fischer G. Neonatal neurobehavior effects following buprenorphine versus methadone exposure. *Addiction* 2012; **107** (Suppl. 1): 63–73.
51. Schindler S. D., Eder H., Ortner R., Rohrmeister K., Langer M., Fischer G. Neonatal outcome following buprenorphine maintenance during conception and throughout pregnancy. *Addiction* 2003; **98**: 103–10.
52. Kahila H., Kivitie-Kallio S., Halmesmäki E., Valanne L., Autti T. Brain magnetic resonance imaging of infants exposed prenatally to buprenorphine. *Acta Radiol* 2007; **48**: 228–31.
53. Kayemba-Kay's S., Laclyde J. P. Buprenorphine withdrawal syndrome in newborns: a report of 13 cases. *Addiction* 2003; **98**: 1599–604.
54. Whitham J. N., Spurrier N. J., Sawyer M. G., Baghurst P. A., Taplin J. E., White J. M. *et al*. The effects of prenatal exposure to buprenorphine or methadone on infant visual evoked potentials. *Neurotoxicol Teratol* 2010; **32**: 280–8.
55. Sarfi M., Martinsen H., Bakstad B., Røislien J., Waal H. Patterns in sleep–wakefulness in three-month old infants exposed to methadone or buprenorphine. *Early Hum Dev* 2009; **85**: 773–8.
56. Sarfi M., Smith L., Waal H., Sundet J. M. Risks and realities: dyadic interaction between 6-month-old infants and their mothers in opioid maintenance treatment. *Infant Behav Dev* 2011; **34**: 578–89.
57. Salo S., Kivistö K., Korja R., Biringen Z., Tupola S.-M., Kivitie-Kallio S. Emotional availability, parental self-efficacy beliefs, and child development in caregiver—child

relationships with buprenorphine-exposed 3-year-olds. *Parent Sci Pract* 2009; **9**: 244–59.
58. Jones H. E., Kaltenbach K., O'Grady K. E. Methadone and the causes of maternal and perinatal complications: a response to Pinto *et al*., 'Substance abuse during pregnancy: effect on pregnancy outcomes' [*Eur J Obstet Gynecol Reprod Biol*, 2010. **150**: 137–141]. *Eur J Obstet Gynecol Reprod Biol* 2011; **158**: 116–17.
59. Jones H. E., Jansson L. M., Kaltenbach K. Methadone and perinatal outcomes: another perspective. *Am J Obstet Gynecol* 2011; **205**: e11.
60. Winklbaur B., Baewert A., Jagsch R., Rohrmeister K., Metz V., Aeschbach Jachmann C. *et al*. Association between prenatal tobacco exposure and outcome of neonates born to opioid-maintained mothers. Implications for treatment. *Eur Addict Res* 2009; **15**: 150–6.
61. Fischer G., Etzersdorfer P., Eder H., Jagsch R., Langer M., Weninger M. Buprenorphine maintenance in pregnant opiate addicts. *Eur Addict Res* 1998; **4**: 32–6.
62. Ebner N., Rohrmeister K., Winklbaur B., Baewert A., Jagsch R., Peternell A. *et al*. Management of neonatal abstinence syndrome in neonates born to opioid maintained women. *Drug Alcohol Depend* 2007; **87**: 131–8.
63. Fischer G., Johnson R. E., Eder H., Jagsch R., Peternell A., Weninger M. *et al*. Treatment of opioid-dependent pregnant women with buprenorphine. *Addiction* 2000; **95**: 239–44.
64. Rohrmeister K., Bernert G., Langer M., Fischer G., Weninger M., Pollak A. [Opiate addiction in gravidity—consequences for the newborn. Results of an interdisciplinary treatment concept]. *Z Geburtshilfe Neonatol* 2001; **205**: 224–30.
65. Lejeune C., Aubisson S., Simmat-Durand L., Cneude F., Piquet M., Gourarier L., Groupe d'Etudes Grossesse et Addictions. [Withdrawal syndromes of newborns of pregnant drug abusers maintained under methadone or high-dose buprenorphine: 246 cases]. *Ann Med Interne (Paris)* 2001; **152**: 21–7.
66. Lejeune C., Aubisson S., Simmat-Durand L., Cneude F., Piquet M. Buprenorphine and pregnancy: a comparative multi-center study of high-dose buprenorphine versus methadone maintenance. In: Kintz P., Marquet P., editors. *Buprenorphine Therapy of Opiate Addiction*. Totowa, NJ: Humana Press; 2002, p. 137–46.
67. Simmat-Durand L., Lejeune C., Gourarier L., Groupe d' Etudes Grossesse et Addictions (GEGA). Pregnancy under high-dose buprenorphine. *Eur J Obstet Gynecol Reprod Biol* 2009; **142**: 119–23.
68. Vert P., Hamon I., Hubert C., Legagneur M., Hascoet J. M. [Infants of drug-addicted mothers: pitfalls of replacement therapy]. *Bull Acad Natl Med* 2008; **192**: 961–9; discussion 969.
69. Lacroix I., Berrebi A., Garipuy D., Schmitt L., Hammou Y., Chaumerliac C. *et al*. Buprenorphine versus methadone in pregnant opioid-dependent women: a prospective multicenter study. *Eur J Clin Pharmacol* 2011; **67**: 1053–9.
70. Lacroix I., Berrebi A., Schmitt L., Garripuy D., Laperyre-Mestre M., Montastruc J. L. *et al*. High buprenorphine dosage in pregnancy: first data of a prospective study. *Drug Alcohol Depend* 2002; **66**: S97.
71. Kahila H., Saisto T., Kivitie-Kallio S., Haukkamaa M., Halmesmäki E. A prospective study on buprenorphine use during pregnancy: effects on maternal and neonatal outcome. *Acta Obstet Gynecol Scand* 2007; **86**: 185–90.
72. Kahila H., Stefanovic V., Loukovaara M., Alfthan H., Hämäläinen E., Halmesmäki E. Prenatal buprenorphine exposure: effects on biochemical markers of hypoxia and early neonatal outcome. *Acta Obstet Gynecol Scand* 2008; **87**: 1213–9.
73. Kakko J., Heilig M., Sarman I. Buprenorphine and methadone treatment of opiate dependence during pregnancy: comparison of fetal growth and neonatal outcomes in two consecutive case series. *Drug Alcohol Depend* 2008; **96**: 69–78.
74. Binder T., Vavrinkova B. Prospective randomised comparative study of the effect of buprenorphine, methadone and heroin on the course of pregnancy, birthweight of newborns, early postpartum adaptation and course of the neonatal abstinence syndrome (NAS) in women followed up in the outpatient department. *Neuro Endocrinol Lett* 2008; **29**: 80–6.
75. Bakstad B., Sarfi M., Welle-Strand G. K., Ravndal E. Opioid maintenance treatment during pregnancy: occurrence and severity of neonatal abstinence syndrome. A national prospective study. *Eur Addict Res* 2009; **15**: 128–34.
76. Blaser A., Pulzer F., Knüpfer M., Robel-Tillig E., Vogtmann C., Nickel P. *et al*. [Drug withdrawal in newborns—clinical data of 49 infants with intrauterine drug exposure: what should be done?] *Klin Padiatr* 2008; **220**: 308–15.
77. Brulet C., Chanal C., Ravel P., Mazurier E., Boulot P., Faucherre V. [Multidisciplinary monitoring and psychosocial support reduce complications of opiate dependence in pregnant women: 114 pregnancies]. *Presse Med* 2007; **36**: 1571–80.
78. Sandtorv L., Reigstad H., Bruarøy S., Elgen I., Laegreid L. M. [Substitution treatment of drug addicts during pregnancy: consequences for the children?] *Tidsskr Nor Laegeforen* 2009; **129**: 287–90.
79. Marquet P., Delpla P. A., Kerguelen S., Bremond J., Facy F., Garnier M. *et al*. Prevalence of drugs of abuse in urine of drivers involved in road accidents in France: a collaborative study. *J Forensic Sci* 1998; **43**: 806–11.
80. Regini P., Cutrone M., Donzelli F., Flora P. G., Montesanto G. [Neonatal buprenorphine withdrawal syndrome, what is the right therapy?] *Pediatr Med Chir* 1998; **20**: 67–9.
81. Herve F., Quenum S. [Buprenorphine (Subutex) and neonatal withdrawal syndrome]. *Arch Pediatr* 1998; **5**: 206–7.
82. Auriacombe M., Afflelou S., Lavignasse P., Lafitte C., Roux D., Daulouède J. P. *et al*. [Pregnancy, abortion and delivery in a cohort of heroin dependent patients treated with drug substitution (methadone and buprenorphine) in Aquitaine]. *Presse Med* 1999; **28**: 177.
83. Eder H., Rupp I., Peternell A., Fischer G. [Buprenorphine in pregnancy]. *Psychiatr Prax* 2001; **28**: 267–9.
84. Siedentopf J., Nagel M., Eβer M., Casteleyn S., Dudenhausen J. W. Experience with buprenorphine induction and subsequent dose reduction as compared to treatment with L-methadone in pregnant opioid addicts. *Geburtshilfe Frauenheilkd* 2004; **64**: 711–8.
85. Ross D. High dose buprenorphine in pregnancy. *Aust NZ J Obstet Gynaecol* 2004; **44**: 80.
86. Unger A., Jagsch R., Jones H., Arria A., Leitich H., Rohrmeister K. *et al*. Randomized controlled trials in pregnancy: scientific and ethical aspects. Exposure to different opioid medications during pregnancy in an intra-individual comparison. *Addiction* 2011; **106**: 1355–62.

87. Czerkes M., Blackstone J., Pulvino J. *Buprenorphine versus Methadone Treatment for Opiate Addiction in Pregnancy: An Evaluation of Neonatal Outcomes*. in The American College of Obstetricians and Gynecologists. San Francisco, CA. 2010. Available at: http://www.acog.org/acm/pdf/oralTue.pdf (originally accessed 8 January 2011. Now archived at: http://web.archive.org/web/20110101092028/http://www.acog.org/acm/pdf/oralTue.pdf). (Archived at http://www.webcitation.org/6ANWQebdv on 2 September 2012).
88. Blandthorn J., Forster D. A., Love V. Neonatal and maternal outcomes following maternal use of buprenorphine or methadone during pregnancy: findings of a retrospective audit. *Women Birth* 2011; **24**: 32–9.
89. O'Connor A., Alto W., Musgrave K., Gibbons D., Llanto L., Holden S. *et al*. Observational study of buprenorphine treatment of opioid-dependent pregnant women in a family medicine residency: reports on maternal and infant outcomes. *J Am Board Fam Med* 2011; **24**: 194–201.