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Buprenorphine or Methadone: A Clinical Response to a Pregnancy's Dilemma

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Abstract

Background: Since the 1970s, the medical and nonmedical use of opioids has increased exponentially in women of childbearing age. Studies comparing maintenance therapies (buprenorphine and methadone) have conflicting results. These reviews also show that neonatal outcome is most often measured by duration of treatment, treatment completion rates or length of hospitalization. Patient-important clinical outcomes are more rarely evaluated and are rarely chosen as primary outcomes. However, scores used to adapt NAS therapy (such as Lipstiz or Finnegan) are based on these symptoms.

Objective(s): The aim of our study was to investigate neonatal outcome, using clinical criteria, after in utero exposure to buprenorphine or methadone.

Study Design: We conducted a retrospective study analysing data from infants admitted for NAS in two NCIU between January 2010 and December 2020. The inclusion criteria were: infants born after 37 weeks gestation, born to mothers who were treated with maintenance (buprenorphine or methadone) therapy during pregnancy and who had a Lipsitz score of 4 or higher. Statistical analysis was performed using SPSS version 25 (IBM Corporation, Armonk, NY). The groups were compared using analysis of variance for normally distributed and Kruskal– Wallis for non-normally distributed continuous variables.

Results: A total of 150 term new-borns were hospitalized for the treatment of NAS from mother substituted with buprenorphine or methadone during the study inclusion period. The repartition of NAS scores differed significantly between buprenorphine and methadone groups, with higher Lipsitz scores in the methadone group with p-value <0.003. On average, infants exposed to methadone suffered 6 more days from NAS versus buprenorphine ($p < 0,05$). They also stay 3 additional days hospitalized on average ($p < 0,05$). Infants exposed to methadone versus buprenorphine required 80% higher initial dose of morphine and 34% higher maximal dose ($p <0.05$). Less infants received Morphine therapy in buprenorphine group (55%) than in the methadone group (63%) ($p < 0,05$). No significant difference was found regarding the delay of appearance of NAS. Concerning the highest Lipsitz score obtained for each infant, scores differed significantly between both groups in favor of buprenorphine group ($p < 0,03$). On average, infants from the methadone group versus buprenorphine group had a higher appearance rate for three types of symptoms: tremor ($p = 0,018$), reflexes ($p < 0,01$) and muscle tone ($p = 0,01$).

Conclusion(s): Our study assessed the clinical differences in neonatal outcome between buprenorphine or methadone maternal maintenance therapy and found a statistically significant difference for our primary outcome in favour of buprenorphine. The number of occurrences of low Lipsitz score was higher in the buprenorphine group and the number of occurrences of high lipsitz score was higher in the methadone group. Our secondary outcome reinforces this as the methadone group had higher maximal scores and more frequent neurological symptoms such as tremor, muscle tones and reflexes.

Keywords: Neonatal Abstinence Syndrom, Buprenorphine, Methadone, Maintenance therapy, opioid, Lipsitz score

Introduction

Neonatal abstinence syndrome (NAS) is a drug withdrawal syndrome occurring mainly after in-utero opioid exposure [1,2]. Signs of NAS range from neurologic manifestations (tremors, increased muscle tone, hyperactive reflexes, seizures), to gastrointestinal manifestations (diarrhea, vomiting, uncoordinated sucking, and swallowing) and autonomic manifestations (fever, sweating, nasal stuffiness, and increased respiratory rate) [2-4]. Since the 1970s, the medical and nonmedical use of opioids has increased exponentially in women of childbearing age [5].

This has led to a growing incidence of NAS [6]. methadone has commonly been used as maintenance therapy since the 1970s [7,8] with maternal and neonatal complications [9]. Thought to be a safe alternative to morphine, many studies describe similar symptoms to NAS [1,7,10]. Nowadays, methadone is still the reference treatment for maintenance therapy in many countries like the USA [11]. In the 1990s, buprenorphine was approved as an alternative to methadone [12,13]. This partial mu-opioid receptor agonist binds to opioid receptors with higher affinity but lower activity than full agonists like methadone and Heroin [14,15]. Quickly, buprenorphine has also been proven to cause NAS-like symptoms [16].

Still, gaps persist in regards to pharmacodynamics, pharmacokinetics, and the lack of guidelines for adequate dosage during pregnancy of methadone [17] and buprenorphine [18,19]. However, methadone may interrupt neural growth and function in early brain development [20]. This theory is supported by prior studies showing exaggerated neurological manifestations in methadone-related NAS [4,21,22]. Moreover, as a long-acting opioid, methadone can delay NAS appearance causing diagnostic problems and longer symptoms [4]. Recently, studies have shown a dose effect with higher risk of NAS with higher doses of methadone maintenance therapy [23]. The properties of buprenorphine make it less likely to cross the placenta barrier and lower its impact [24]. Moreover, literature tends to show that low-dose buprenorphine gives less NAS, especially if daily doses are split as suggested by Caritis et al. [25]. These findings are confirmed by models on rodents [26,27].

Studies comparing both maintenance therapies have conflicting results. While some studies show that neonates exposed to maternal buprenorphine consumption have NAS symptoms of less severity [28-33] requiring less treatment [17,34,35] and with better physiological parameters [35-37] than those with maternal methadone consumption. Others concluded that the evidence was insufficient to prefer one over the other [38-42] or even that methadone could be better [43]. This is highlighted by two recent reviews concluding that current data was insufficient to determine the superiority of methadone over buprenorphine or other agents when considering patient important outcomes even if they admitted a trend in favor of buprenorphine maintenance therapy [44,45]. These reviews also show that neonatal outcome is most often measured by duration of treatment, treatment completion rates or length of hospitalization. Patient-important clinical outcomes are more rarely evaluated and are rarely chosen as primary outcomes. However, scores used to adapt NAS therapy (such as Lipstiz or Finnegan) are based on these symptoms. We did not find studies based on the analysis of these scores and the symptoms observed during NAS. To our knowledge, the results of clinical scores have never been studied to weigh buprenorphine against methadone. The aim of our study was to investigate neonatal outcome, using clinical criteria, after in utero exposure to buprenorphine or methadone.

Materials and Methods

Study Population

We conducted a retrospective study analyzing data from infants admitted for NAS in two NCIU between January 2010 and December 2020. The inclusion criteria were: infants born after 37 weeks gestation, born to mothers who were treated with maintenance (buprenorphine or methadone) therapy during pregnancy and who had a Lipsitz score of 4 or higher [3]. Signs and symptoms of NAS were objectively assessed by nurses and doctors using a Lipsitz neonatal abstinence scale. According to treatment protocoles in both NCIU, morphine was used to treat NAS if the scores were higher than 4 for two consecutive days. Any clinical history and maternal history was extracted from the neonate medical chart of the databases of both hospitals. Infants were divided into two groups according to maternal maintenance therapy. All infants were monitored for NAS including those who did not have disease severity requiring treatment.

Study Outcomes

The primary outcome was the repartition of every Lipsitz scores registered. Prespecified secondary outcome measurements were the initial and maximal dose of morphine, length of hospitalization in days, length of the syndrome and percentage of infants treated with morphine. Symptoms were also individually assessed. High score occurrence was assessed. Baseline infant and maternal characteristics including demographics and exposure to other drugs/medications were assessed using medical records.

Statistical Analysis

Statistical analysis was performed using SPSS version 25 (IBM Corporation, Armonk, NY). The groups were compared using analysis of variance for normally distributed and Kruskal– Wallis for non-normally distributed continuous variables. We used a Mann Whitney test to compare both groups' scores. A Chi^2 test was used to compare each symptom individually. The association between maternal maintenance therapy groups and continuous variables (length of syndrome in days, length of hospital stay, and the initial and maximal dose of morphine) was assessed using linear regression, adjusting for the birth weight, weight loss, day to minimum weight, day to weight gain, birth height, cranial perimeter and 5-minute Apgar score. A significant difference was defined by $p < 0.05$. Results are shown as medians [Q1; Q3].

Ethics

Before beginning our study, the French national council for data management (CNIL) was consulted. No declaration was needed for this work.

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Results

Characteristics of Study Participants

A total of 162 term new-borns were hospitalized for the treatment of NAS during the study inclusion period. Among those, 12 infants born from mothers exposed to another opioid, such as heroin, were excluded (Figure 1). The 150 remaining infants met inclusion criteria. The demographic data and clinical characteristics of infants included in our study are shown Table 1. Baseline characteristics were similar. There were no significant differences in 5-minutes Apgar score, birth weight, birth loss, birth height, cranial perimeter, sex ratio, term at birth and Intrauterine Growth Retardation among the two groups.

Table 1: Demographic data and clinical characteristics of infants and mothers.

	Criteria	Buprenorphine	Methadone	Statistical Analysis
Neonate Weight	Birth Weight (g)	2933	2935	/
	Minimal Weight (g)	2722	2710	/
	Weight Loss (g)	197	224	/
	Minimal Weight Day (days)	3,2	3,77	/
	Weight Gain Day (days)	10,2	11,3	/
Infants Criteria	Sex Ratio H/F (%)	40 / 60%	49/51%	/
	Term (SA)	39,5	39,3	/
	Height (cm)	47,5	47,4	/
	Cranial Perimeter (cm)	33,5	33,2	/
	5 Minutes APGAR	9,6	9,5	/
	IUGR (%)	28%	25%	/
Syndrome	Appearance Delay (days)	1,56	1,32	L
	Syndrome Duration (days)	9	15,3	p<0,05
	Hospitalization Duration (days)	14,3	17,5	p<0,05
Treatment	Infants Treated (%)	55%	63%	p<0,05
	Initial Dose (mg/kg/j)	0,21	0,38	p<0,05
	Maximal Dose (mg/kg/j)	0,35	0,47	p<0,05
Mother Criteria	Age (Years)	27,8	28,4	/
	Weight (kg)	55,9	61	/
	Height (cm)	165	167	/
	BMI (kg/cm2)	20,4	21,7	/
	Undernutrition (%)	49%	30%	/
	Gravidity	1,7	1,4	/
	Parity	0,68	0,71	/

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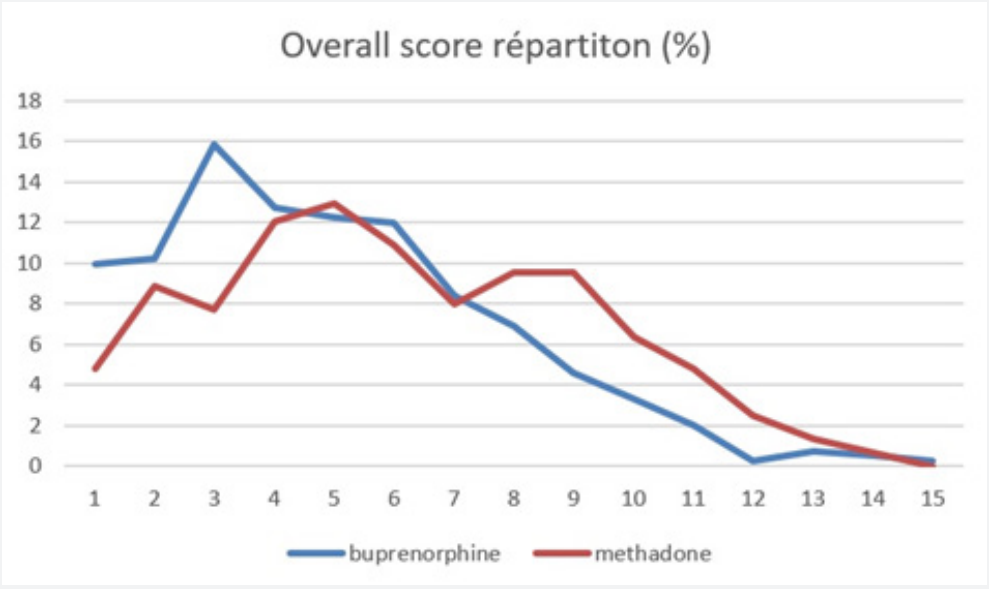

Figure 1: Overall score repartition for buprenorphine and methadone groups (%).

Primary Outcomes

The repartition of NAS scores differed significantly between buprenorphine and methadone groups, with higher Lipsitz scores in the methadone group with p-value <0.003 (Table 2 and Figure 2).

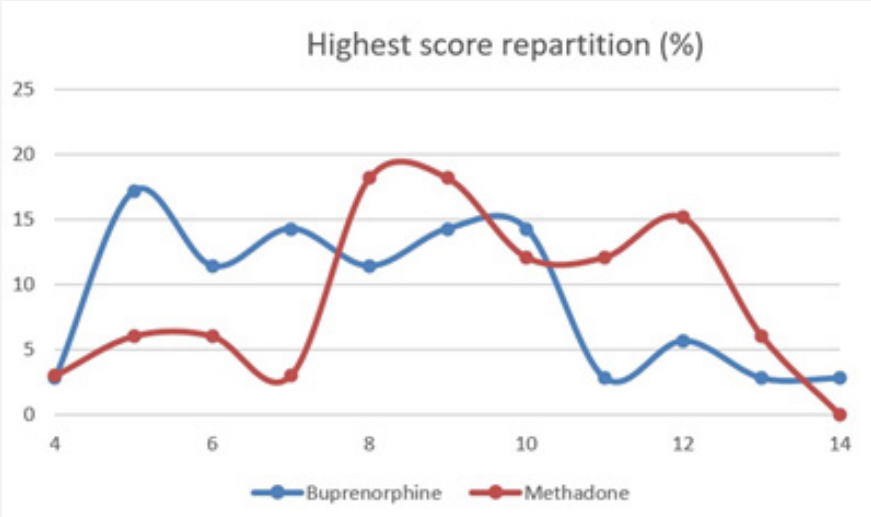

Figure 2: Highest score repartition for every infant in buprenorphine and methadone groups (%).

Table 2: Summarized Lipsitz scores for buprenorphine and methadone group (%).

Summarized Overall Scores from the 75 Infants (%)															
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Buprenorphine	9,9	10,2	15,8	12,8	12,2	12	8,4	6,9	4,6	3,3	2	0,3	0,8	0,5	0,3
Methadone	4,7	8,8	7,6	11,9	13	11	8	9,6	9,6	6,4	4,8	2,5	1,4	0,7	0
Buprenorphine	61									39					
Methadone	46									54					

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Secondary Outcomes

On average, infants exposed to methadone suffered 6 more days from NAS versus buprenorphine ($p < 0,05$). They also stay 3 additional days hospitalized on average ($p < 0,05$). (Table 1) Infants exposed to methadone versus buprenorphine required 80% higher initial dose of morphine and 34% higher maximal dose ($p < 0.05$). Less infants received Morphine therapy in buprenorphine group (55%) than in the methadone group (63%) ($p < 0,05$). No significant difference was found regarding the delay of appearance of NAS. (Table 1) Concerning the highest Lipsitz score obtained for each infant, scores differed significantly between both groups in favor of buprenorphine group ($p < 0,03$). (Figure 2) On average, infants from the methadone group versus buprenorphine group had a higher appearance rate for three types of symptoms: tremor ($p = 0,018$), reflexes ($p < 0,01$) and muscle tone ($p = 0,01$) (Table 3).

Table 3: Symptom's appearance (%).

Frequency of Appearance	Total (%)	Buprenorphine %	Methadone %	Statistical Analysis	
Tremor 1	84	85	83	Khi2 = 4,12	p=0,018
Tremor 2	58	50	66		
Tremor 3	26	13	24		
Irritability 1	91	93	89	NS	
Irritability 2	74	70	74		
Irritability 3	37	25	40		
Reflexes 1	84	85	83	Khi2 = 3,86	p < 0,001
Reflexes 2	40	25	46		
Muscle Tone 1	80	75	83	Khi2 = 3,6	p = 0,001
Muscle Tone 2	54	45	57		
Stools 1	75	78	69	NS	
Stools 2	23	18	23		
Skin Abrasions 1	53	48	57		
Skin Abrasions 2	14	15	11		
Respiratory Rate 1	68	60	69		
Respiratory Rate 2	10	2,5	11		
Repetitive Sneezing	95	93	97		
Repetitive Yawning	49	43	51		
Forceful Vomiting	42	30	46		
Fever	27	28	26		

Discussion

a) Principal Findings

Our study assessed the clinical differences in neonatal outcome between buprenorphine or methadone maternal maintenance therapy and found a statistically significant difference for our primary outcome in favour of buprenorphine.

b) Results

The number of occurrences of low Lipsitz score was higher in the buprenorphine group and the number of occurrences of high lipsitz score was higher in the methadone group. Our secondary outcome reinforces this as the methadone group had higher maximal scores and more frequent neurological symptoms such as tremor, muscle tones and reflexes. This study also confirmed previous results as we found longer NAS and longer hospitalization in the methadone group. More children received Morphine therapy, with higher initial doses and higher maximal doses in the methadone group. Though our findings must be interpreted within the context of our study design, these results should weigh in the balance when discussing maintenance therapy with pregnant or soon-to-be-pregnant women.

c) Clinical Implications

Nowadays the use of buprenorphine has spread around the world [46]. In some countries like France, buprenorphine is the most commonly used maintenance therapy [47]. In many countries, buprenorphine is mostly prescribed by licensed physicians or general practitioners [48]. As women take buprenorphine on their own, there are higher dropout rates with an increasing risk of misuse of other opioids [49]. On the contrary, methadone is initiated in specialized centers and women must attend daily

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for treatment delivery. This allows for more social support and counselling [50]. These differences cause a social bias concerning the severity of maternal opioid dependence which can lead to an influence in clinical prescribing. buprenorphine would be used to treat more stable opioid-dependent pregnant women who do not need the structure of observed daily dosing [11,37,51]. However, studies have shown that well-followed mothers have easier access to buprenorphine maintenance therapy [52] and have less misuse compared with women taking methadone [53]. Moreover, a French study argued that free prescription by a trusted physician creates a better bond between prescriber and patient and is linked to less dropout and a better follow-up for these patients [54,55]. Focusing on the behavior that initiates and maintains this consumption is an urgent priority [39] as relapse is still a cause of maternal mortality [56,57].

d) **Research Implications**

Our study shows the necessity to focus more on Neonates symptoms to witness NAS severity. Prospective studies could lead to a better understanding of how scoring could lead to a better choice between buprenorphine and methadone concerning substitution therapy.

e) **Strengths and Limitations**

The primary limitation is the observational and retrospective nature of the study. Moreover, the limited cohort of our study is of concern though similar studies (ref) also had small cohorts.

Conclusion

When hesitating between buprenorphine and methadone, our study tends to tip the balance in favor of buprenorphine. A prospective study with a larger cohort is needed to validate these results to better care for mothers-to-be who need maintenance therapy. Indeed, less misuse and better management of NAS could better the neurological development of neonates.

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