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# Prenatal buprenorphine exposure and neonatal neurobehavioral functioning

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## 1. Introduction

Medication assisted treatment (MAT) with either methadone or buprenorphine maintenance combined with comprehensive substance abuse treatment is currently the recommended standard of care for pregnant women with Opioid Use Disorder (OUD) [1,2]. I don't think these should be separate paragraphs, which would make the change in page 1 paragraph 2.

Despite the known benefits of MAT for pregnant women, the effects of methadone and buprenorphine on human infant neurodevelopment remain principally unknown. This is particularly true for buprenorphine. Animal studies suggest that buprenorphine alters critical signaling processes modulating oligodendrocyte development and myelination [3]. In rats, prenatal buprenorphine exposure is associated with alterations in offspring brain development that include reduction of the expression of nerve growth factor in the striatum [4], delay of the generation of cholinergic neurons [5], and alteration of the myelination process [3]. In addition, as the buprenorphine dose administered to pregnant rats varies, there is differential brain expression among their pups [3].

In humans, buprenorphine compared with methadone appears to result in better functioning of the fetus as indicated by less changes in fetal heart rate parameters from trough to peak levels of maternal medication measured at one time point in mid gestation [6]. In a longitudinal study, buprenorphine exposure depressed fetal heart rate and movement parameters, with increasing magnitude of effects starting at 28 weeks and progressing with gestational age [7]. Additionally, higher doses of buprenorphine appear to exert chronically depressive effects on measures of fetal heart rate [7]. While the long-term impact and clinical relevance of these changes are unknown, findings from behavioral studies in animals and humans [8] indicate the need for more research assessing different domains of the neurobehavioral functioning of the infant exposed to buprenorphine over time.

Assessment of functioning in neonates born to mothers receiving MAT for OUD is almost exclusively confined to measures of neonatal abstinence syndrome (NAS). Tools such as the Finnegan Neonatal Abstinence Scoring System [9] and modified versions [10] have been used for decades primarily to determine the need for pharmacologic treatment for NAS. In addition to the signs of NAS identified by these scales, there are other aspects of the newborn's functioning that are important in the appreciation of each opioid-exposed infant's unique neurobehavioral strengths and weaknesses. For example, infants with opiate exposure are at risk for modulation of arousal and attention that may lead to subsequent problems in other psychological domains [11]. Early detection of specific neurobehavioral challenges is needed for effective intervention and prevention of further problems [12,13]. Therefore, it is necessary to understand the individual functioning of each opioid-exposed infant beyond NAS expression for the provision of optimal non-pharmacologic care of the NAS and other neurobehavioral problems.

The NICU Network Neurobehavioral Scale (NNNS) [14] is a valid, predictive tool used during the neonatal period to evaluate infants at risk for developmental and medical problems, including infants exposed to psychoactive substances [15]. The NNNS evaluates the neurobehaviors, neurologic integrity, and stress/abstinence signs of infants during the first month of life. The NNNS has 128 items and 13 summary scales: habituation, attention, arousal, regulation, number of handling procedures, quality of movement, excitability, lethargy, number of non-optimal reflexes, hypertonicity, hypotonicity, and stress/abstinence. The exam explores sleep-wake states organization (i.e.; ranges of states of consciousness and state control), and self-regulatory capacities that

*Abbreviations:* MAT, Medication assisted Treatment; NAS, Neonatal Abstinence Syndrome; NNNS, NICU Network Neurobehavioral Scale; OUD, Opioid Use Disorder

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allow the infant to alert, locate and pay attention to auditory and visual stimuli. It also evaluates neurological integrity (i.e. neonatal reflexes, quality of movements, muscle tone and control). In addition, the NNNS evaluates infant stress/abstinence in seven categories: physiologic, autonomic, central nervous system, skin, visual, gastrointestinal and state; these categories are described elsewhere [16].

Using the NNNS, this research group previously evaluated the neurobehavior of three-day old infants born to methadone-maintained mothers. Study findings showed that this group of infants commonly displayed dysregulated behavior (e.g., motor modulation, physiologic and state control), had high levels of signs of stress/abstinence, and had difficulty modulating arousal. These disorganized neurobehaviors were significantly more present in those infants requiring pharmacologic treatment for NAS [17]. Two previous studies compared the neurobehavior of infants prenatally exposed to buprenorphine versus methadone using the NNNS [18,16]. In the first study, buprenorphine-exposed infants displayed greater arousal and excitability in the first week of life when compared to the methadone-exposed infants [18]. In the second study, buprenorphine-exposed infants had fewer stress/abstinence signs, were less excitable, less over-aroused and less hypertonic, had better self-regulation and required less handling to maintain a quiet alert state relative to in utero methadone-exposed infants [16]. Infants exposed in utero to either methadone or buprenorphine improved their neurobehavioral functioning through the first month of life. Neither study reported the role of the maternal buprenorphine dose at delivery on the neurobehavioral performance of the newborn. In humans, studies report no dose-response relationship between maternal buprenorphine dose and neonatal clinical outcomes [19,20,21], except for one study that reported that neonates with a NAS score of zero were more likely to have been exposed to a lower dose of buprenorphine during pregnancy [22].

The purpose of the present study is to describe the neurobehavioral functioning of buprenorphine-exposed infants during the first month of life using the NNNS. This was achieved by exploring: 1) the association between maternal characteristics, including substance use disorder variables (years of regular drug use, use/misuse of substances during treatment, nicotine exposure), and buprenorphine treatment variables (days of gestation exposed to buprenorphine, maternal buprenorphine dose during pregnancy) and functioning of the newborn on day three of life. It was hypothesized that years of drug use, other substance exposure and maternal buprenorphine dose would negatively correlate with neonatal functioning as defined by the NNNS; 2) the relationship between the NNNS scores, NAS severity and need for pharmacologic treatment for NAS. It was hypothesized that infants with more signs of physiological and neurobehavioral dysregulation per the NNNS scores on day three of life would have more severe NAS, and that infants needing pharmacologic treatment for NAS would express more neurobehavioral dysregulation than those not needing treatment; 3) the longitudinal neurobehavioral functioning of the infants exposed to buprenorphine over the first month of life. It was hypothesized that buprenorphine-exposed infants would display physiological and behavioral indicators of neurobehavioral disorganization after birth that would improve during the first month of life.

## 2. Patients and methods

The present study was one component of a larger investigation evaluating fetal and infant effects of maternal buprenorphine treatment (R01DA033689, Jansson PI). Participants were 41 buprenorphine-maintained pregnant women and their term infants. The mothers attended a comprehensive intensive outpatient treatment program for pregnant women with substance use disorders at the Center for Addiction and Pregnancy (CAP) in Baltimore, Maryland. Treatment at this center included obstetric care, and infants were delivered at an adjacent hospital. Mothers with current alcohol use disorder or more than three episodes of alcohol use during pregnancy were excluded from participation to avoid confounding with the teratogenic fetal and infant effects of alcohol exposure. Mothers with significant histories of benzodiazepine use at the time of program intake which would portend risk for seizures during inpatient induction (determined on an individual basis by the project psychiatrist) were also excluded; other substance use was not exclusionary. Other complications of pregnancy including gestational diabetes, hypertension, severe psychiatric disorder, HIV infection and/or multiple gestation were excluded due to the risk of effects in infant neurobehavior. Mothers were randomly screened weekly with urinalysis testing for opiates, cocaine, benzodiazepines, barbiturates, marijuana, phencyclidine (PCP), and alcohol.

Induction to buprenorphine treatment occurred over a three-day inpatient stay in a clinical research unit. Dosing began after subjects experienced mild withdrawal as measured by the Clinical Opiate Withdrawal Scale (COWS) [23] and was flexible. A maximal dose of 24 mg could be achieved by the third day of induction protocol and outpatient dosing after unit discharge was determined by the patient's counselor in conjunction with the center psychiatrist. The mothers received a once daily dose of sublingual buprenorphine, which was observed through tablet dissolving, with take-home dosing only for holidays, inclement weather, or for outstanding circumstance when approved by the participant's counselor based on progress in treatment.

This research was approved by the Johns Hopkins Medicine Institutional Review Board, and all subjects provided written, informed consent. The clinical trial was registered in ClinicalTrials.gov, NCT #01561079.

### 2.1. Maternal drug use, buprenorphine history, and other substance exposure

Maternal characteristics that can contribute to the diversity of the physiological and neurobehavioral functioning of each newborn were explored. Length of maternal history of substance use disorder, substances used/misused during the time in treatment with buprenorphine, violence exposure, psychiatric comorbidity and/or exposure to psychiatric medications are considered factors that may contribute to the function, organization and neurobehavioral repertoire of the newborn exposed to buprenorphine in utero and were therefore evaluated. Maternal buprenorphine treatment history (days pregnant on buprenorphine treatment; buprenorphine dose throughout treatment and at delivery) was obtained by record review during the time of treatment at the center. Maternal substance use history determined by subject report of the total years of regular (three times/week or more) substance use, and of positive urine toxicology for illicit substances or substances misused during treatment were obtained weekly by the research team. Exposure to nicotine (i.e., number of cigarettes smoked/day by patient report) was recorded for each participant at multiple points during pregnancy.

### 2.2. Infants

Infants were hospitalized for a minimum of four days postnatally for observation for signs/symptoms of NAS, as per standard care at the hospital of delivery. Infants received NAS scoring every three to four hours for their entire hospitalization, and were evaluated and treated based on a modified Finnegan algorithm described elsewhere [10]. Treatment for NAS with oral morphine sulfate, was begun with two consecutively obtained scores one hour apart greater than a defined cut-off value. NAS scores were obtained by clinical nursing staff experienced in the treatment of drug-exposed neonates. All infant hospitalization data was collected by chart review after discharge.

### 2.3. Neurobehavioral assessment

Infants were assessed using the NNNS to measure their neurologic and behavioral functioning as well as signs of stress/abstinence on days