

Infant developmental delays at well visit encounters in infants exposed to medications for opioid use disorder: buprenorphine or methadone

Chaitali Korgaonkar-Cherala MD, MS

Department of Obstetrics, Gynecology, and Reproductive Medicine
Renaissance School of Medicine at Stony Brook University



Stony Brook **Medicine**

OUD in Pregnancy

- OUD in pregnancy has effects on neonatal, infant, and childhood health and development
- Treatment of OUD in pregnancy improves perinatal outcomes
- MOUD during pregnancy may have risks for the neonate into childhood

Opioid use disorder (OUD) rose more than 4x among pregnant women from 1999 to 2014.



Comparison of Opioid Agonists

Buprenorphine

- **Partial agonist** at mu opioid receptor
- **Low** intrinsic activity
- Daily self-administration; can be prescribed by approved clinicians

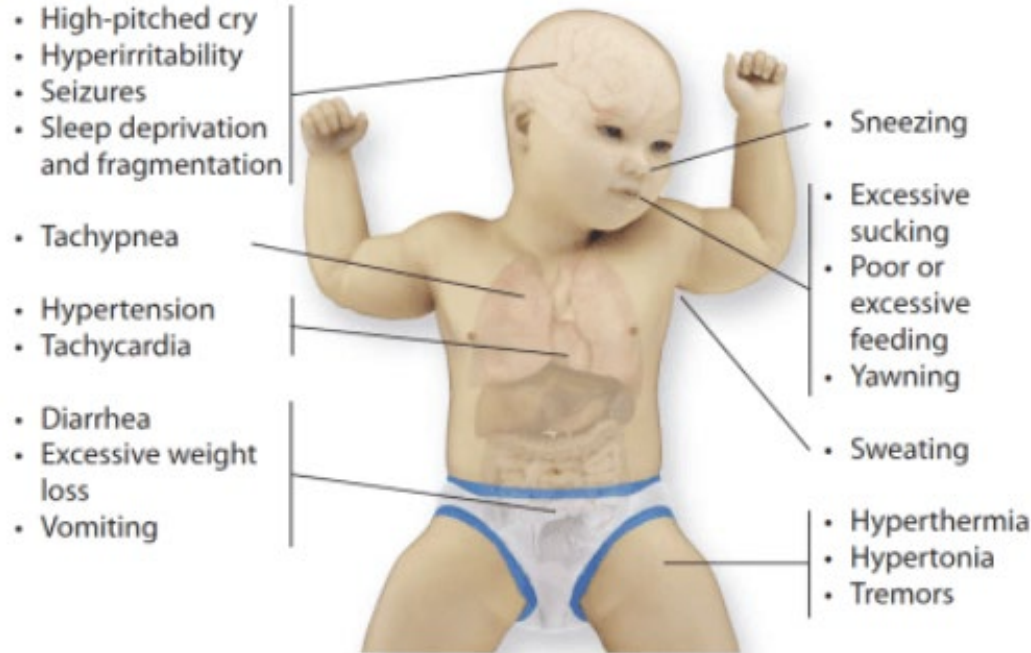
- Effective in treating OUD in pregnancy
- Lipophilic
- **Cross placenta by passive diffusion**

Methadone

- **Full agonist** at mu opioid receptor
- **High** intrinsic activity
- Daily administration at federally-regulated opioid treatment program centers
- **Higher rate of NOWS**

What is Neonatal Opioid Withdrawal Syndrome (NOWS)?

Signs of neonatal abstinence syndrome (NAS) primarily occur in the neurologic, respiratory, and GI systems.



Pediatric Developmental Milestones

Ages

1 month

2 months

3 months

4 months

6 months

7 months

9 months

12 months

18 months

2 years

3-4 years

4-5 years



GROSS MOTOR
SKILLS



FINE MOTOR
SKILLS



LANGUAGE SKILLS



COGNITIVE SKILLS



SOCIAL-EMOTIONAL
DEVELOPMENT



Stony Brook **Medicine**

Jennifer M. Zubler, Lisa D. Wiggins, Michelle M. Macias, Toni M. Whitaker, Judith S. Shaw, Jane K. Squires, Julie A. Pajek, Rebecca B. Wolf, Karnesha S. Slaughter, Amber S. Broughton, Krysta L. Gerndt, Bethany J. Mlodoch, Paul H. Lipkin; Evidence-Informed Milestones for Developmental Surveillance Tools. *Pediatrics* March 2022; 149 (3): e2021052138. 10.1542/peds.2021-052138

<https://story.motherhood.com.my/blog/children-development-milestones-the-first-five-years/>

Evaluation of Developmental Delay at Pediatric Well-Visits

Table 2. Comparison of Parent-Completed Screening Tools for Childhood Developmental Delay

<i>Tool</i>	<i>Validated?</i>	<i>Number of items</i>	<i>Sensitivity (%)</i>	<i>Specificity (%)</i>	<i>Age range assessed</i>	<i>Time to complete; time to score*</i>
Ages and Stages Questionnaire, 3rd ed. http://agesandstages.com	Yes ²⁹	40, including 10 parental questions ¹⁸	86 ³⁰	85 ³⁰	One to 66 months ³⁰	10 to 15 minutes; One to three minutes ³⁰
Child Development Review–Parent Questionnaire http://childdevrev.com/healthcaretools/cdr-parent-questionnaire	Yes ³¹	32 questions; 99 additional items ³¹	68 ³¹	88 ³¹	18 months to five years ³¹	15 to 20 minutes total ³¹
Infant Development Inventory http://childdevrev.com/specialiststools	No ¹⁵	85 ³¹	75 to 85 ^{15,27,31}	70 to 77 ^{15,27,31}	Up to 18 months ³¹	Five to 10 minutes total ³¹
Parents' Evaluation of Developmental Status http://www.pedstest.com	Yes ¹⁵	10 ^{13,32}	74 to 80 ^{27,30}	70 to 80 ^{27,30}	Birth to seven years and 11 months ³²	Two minutes total ³²



Ages and Stages Questionnaire (ASQ-3): Examples for 12 Months

FINE MOTOR

1. After one or two tries, does your baby pick up a piece of string with his first finger and thumb? *(The string may be attached to a toy.)*



YES

SOMETIMES

NOT YET

2. Does your baby pick up a crumb or Cheerio with the tips of her thumb and a finger? She may rest her arm or hand on the table while doing it.













3. Does your baby put a small toy down, without dropping it, and then take his hand off the toy?



Why Does It Matter?

- Minimal studies addressing outcomes of pregnancies exposed to MOUD
 - MOUD may have short-term and long-term developmental sequelae on neonates into their childhood
 - Type of MOUD could influence developmental milestones
- Tracking of these milestones gives us more information to improve pregnancy and newborn care

Prenatal exposure to methadone or buprenorphine: Early childhood developmental outcomes

[Karol Kaltenbach^a](#) , [Kevin E. O'Grady^b](#) , [Sarah H. Heil^c](#) , [Amy L. Salisbury^{d e f}](#) ,
[Mara G. Coyle^e](#) , [Gabriele Fischer^g](#) , [Peter R Martin^h](#) , [Susan Stineⁱ](#) ,
[Hendrée E. Jones^{j k}](#)  

Growth and developmental outcome of infants with *in-utero* exposure to methadone vs buprenorphine

[J B Bier](#) , [A S Finger](#), [B A Bier](#), [T A Johnson](#) & [M G Coyle](#)

[Journal of Perinatology](#) 35, 656–659 (2015) | [Cite this article](#)





Objective

Primary: To assess differences between developmental milestones in infants with in-utero exposure to buprenorphine versus methadone at 2 months - 18 months of age

Secondary: To assess well infant visit compliance across groups



Study Design

- Retrospective cohort study
 - Delivered: January 2017 to December 2021
 - Infant Data through July 2023
- Inclusion criteria:
 - Patients on buprenorphine or methadone antenatally for the indication of OUD
 - Data available on maternal and neonatal outcomes
 - Delivery at Stony Brook University Hospital



Study Design

Maternal Demographics

- Parity, race/ethnicity, medical co-morbidities, psychiatric history, BMI, age, insurance type, prenatal visit compliance, MOUD and substance use

Perinatal Outcomes

- Gestational age at delivery, preterm birth rates, mode of delivery, pregnancy induced hypertension, FGR , gestational diabetes, delivery complications (e.g., PPH, transfusion)

Neonatal Outcomes

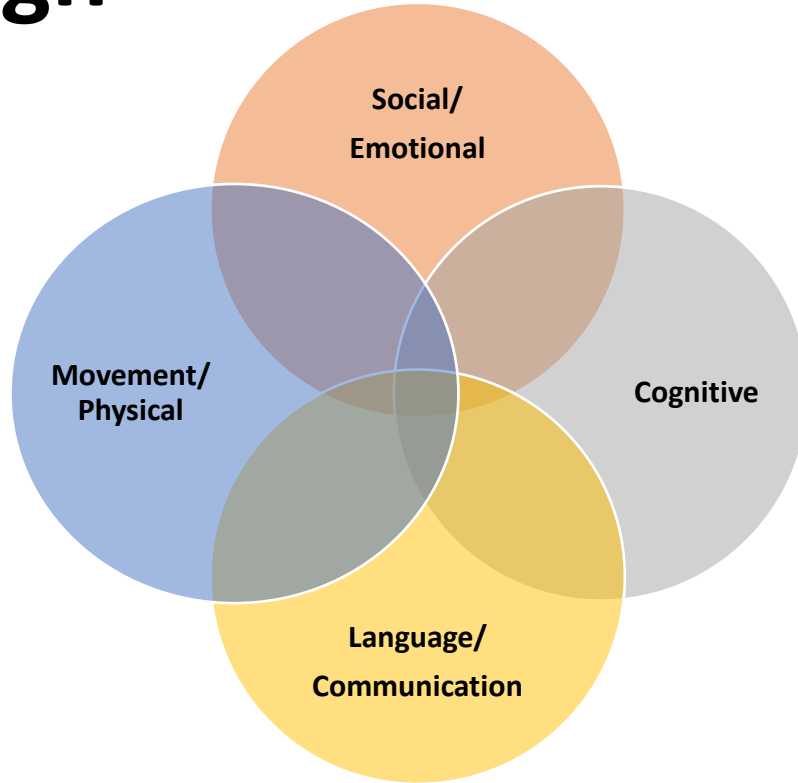
- Birth weight, birth weight category, Apgar score, NICU admission, NOWS, NOWS treatment, infant hospital length of stay

- Statistical analysis
 - Chi square test, student t-tests, and non-parametric tests as appropriate
 - Significance level <0.05



Study Design

Developmental data was collected at multiple infant wellness visits



Results

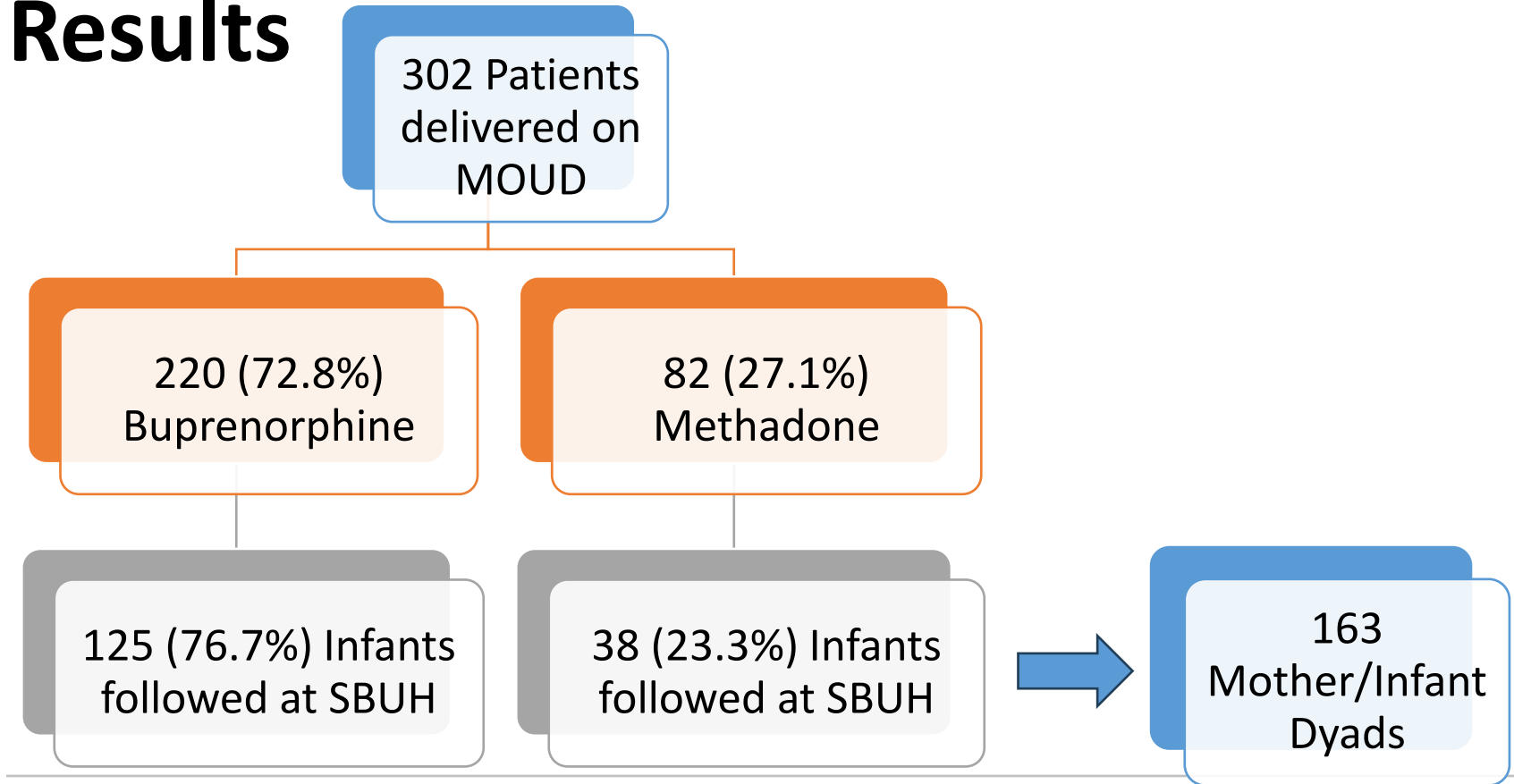


Table 1: Maternal Characteristics Across Buprenorphine and Methadone Groups

	Buprenorphine (n=125)	Methadone (n= 38)	p-value
Nulliparity	44(35.2%)	15(39.5%)	0.63
1 st trimester initiation of prenatal care (PNC)	73 (64.6%)	17 (48.6%)	0.09
Number of PNC visits	9.8 (±3.6)	7.8 (±3.1)	<0.01
Government Assisted Insurance	108 (88.5%)	35 (92.1%)	0.76
Any Co-morbidity	24 (19.4%)	4 (10.5%)	0.21
White Race	116 (92.8%)	37 (97.4%)	0.46
BMI (kg/m ²)	30.6 (±5.5)	28.1 (±7.3)	0.64
Obesity (BMI ≥30 kg/m ²)	20 (22.5%)	6 (22.2%)	0.98
Age (yrs)	30.6 (±4.4)	31.2 (±5.3)	0.49
AMA (≥35 yrs)	23 (18.5%)	10 (27.0%)	0.26
Psychiatric diagnosis	89 (71.2%)	26 (68.4%)	0.74
Psychiatric medication use	62 (49.6%)	10 (26.3%)	0.01

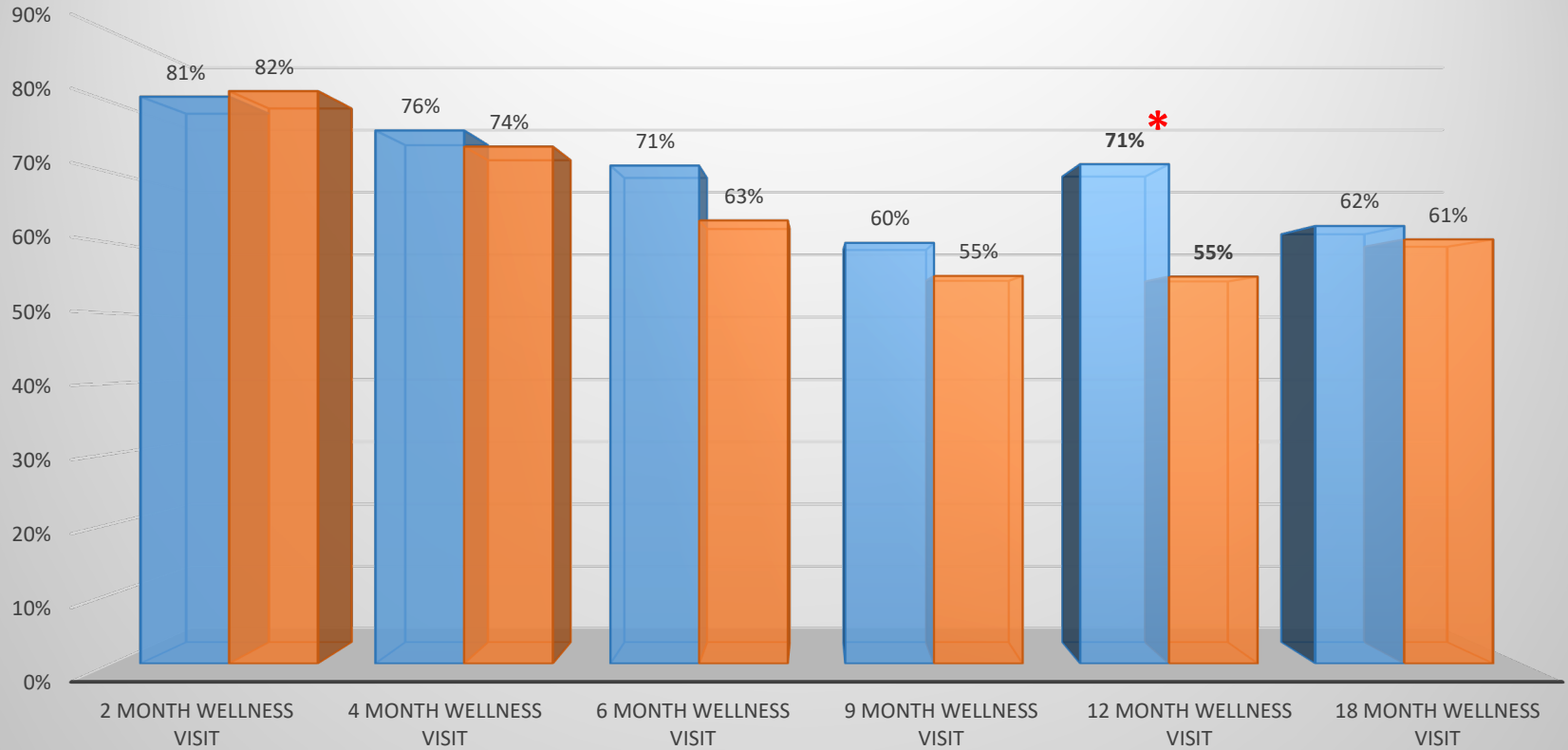
Table 2: Perinatal Outcomes Across Buprenorphine and Methadone Groups

	Buprenorphine (n=125)	Methadone (n= 38)	p-value
Pregnancy induced hypertension	18 (14.4%)	6 (16.2%)	0.79
Gestational diabetes	6 (4.8%)	1 (2.7%)	0.58
Fetal Growth Restriction	6 (4.8%)	2 (5.3%)	0.91
Any OB complication	11 (8.8%)	4 (10.5%)	0.75
Gestational age at delivery (wks)	38.2 (\pm 2.7)	37.4 (\pm 3.1)	0.11
PTB <37 weeks	14 (11.2%)	8 (21.1%)	0.12
Cesarean Delivery	57 (45.6%)	19 (50.0%)	0.63
Birth weight (g)	3003.8 (\pm595.4)	2703.6 (\pm628.5)	<0.01
Neonatal Opioid Withdrawal Syndrome	98 (80.3%)	32 (86.5%)	0.40
NOWS requiring morphine	25 (20.0%)	16 (42.1%)	<0.01
NICU Admission	80 (64.5%)	26 (70.3%)	0.52
Infant hospital LOS (days)	13.2 (\pm 25.8)	15.9 (\pm 17.4)	0.55
Maternal postpartum visit compliance	69 (55.2%)	15 (13.2%)	0.09
Relapse postpartum	5 (4.3%)	3 (9.1%)	0.38

Table 3: Comparison of ANY noted Developmental Delay at Infant Wellness Visits Across Groups

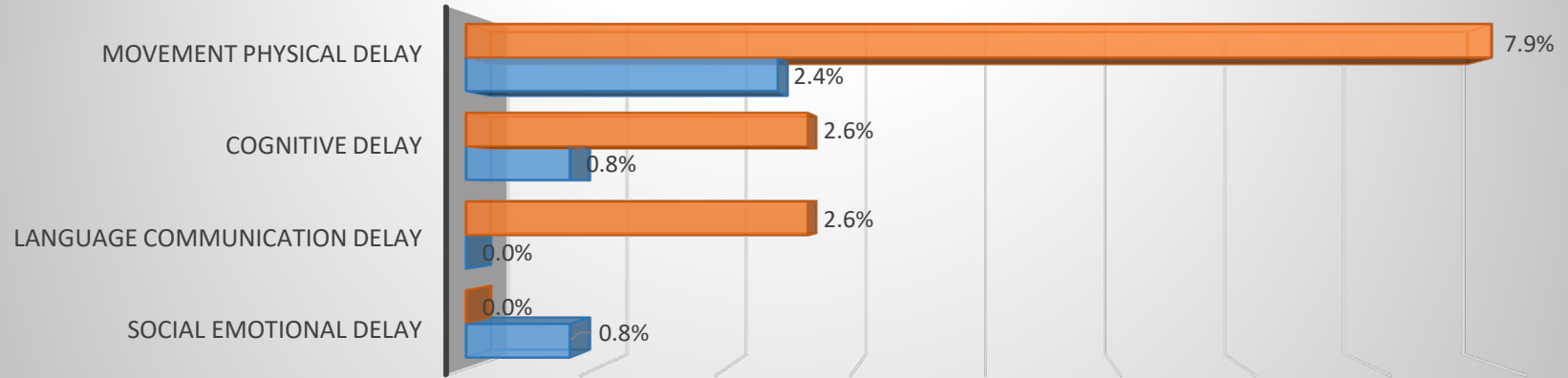
	Buprenorphine (n=125)	Methadone (n=38)	p-value
2 month (n=132)	0	0	1.00
4 month (n=123)	4 (4.2%)	3 (10.7%)	0.19
6 month (n=112)	1 (1.1%)	2 (8.3%)	0.12
9 month (n=96)	15 (20.0%)	6 (28.6%)	0.39
12 month (n=113)	9 (10.1%)	5 (20.8%)	0.17
18 month (n=101)	23 (29.5%)	6 (26.1%)	0.75

Infant Well Visit Compliance

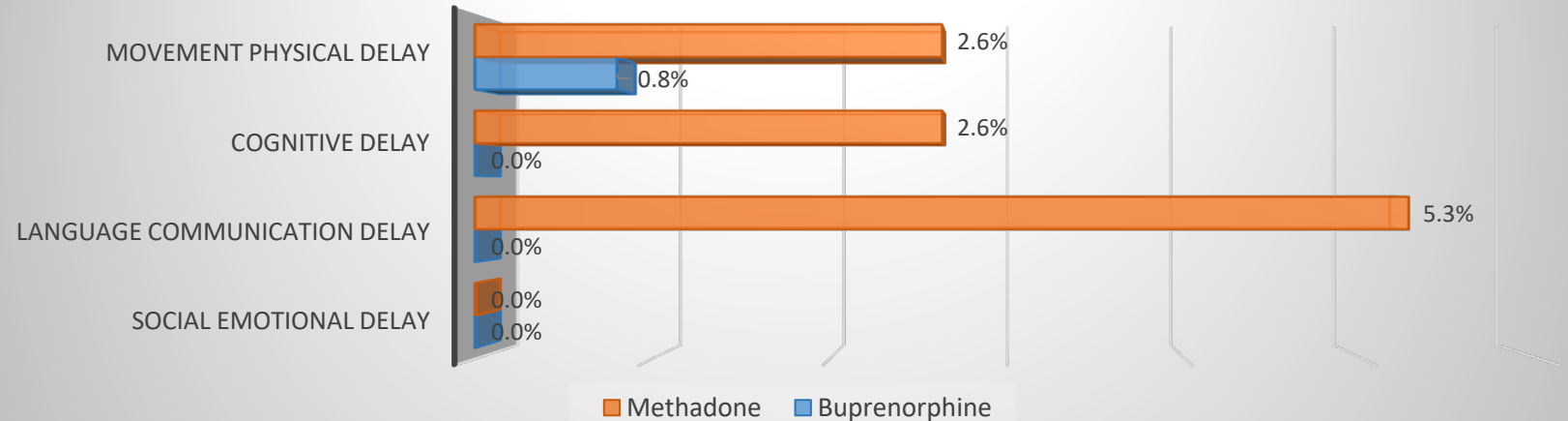


■ Buprenorphine ■ Methadone

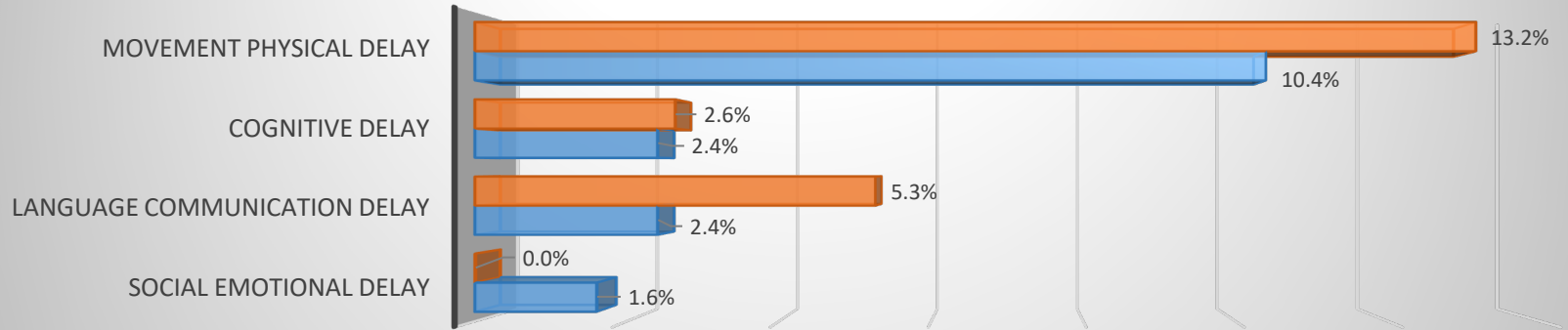
Developmental Delays 4 month Infant Well Visit



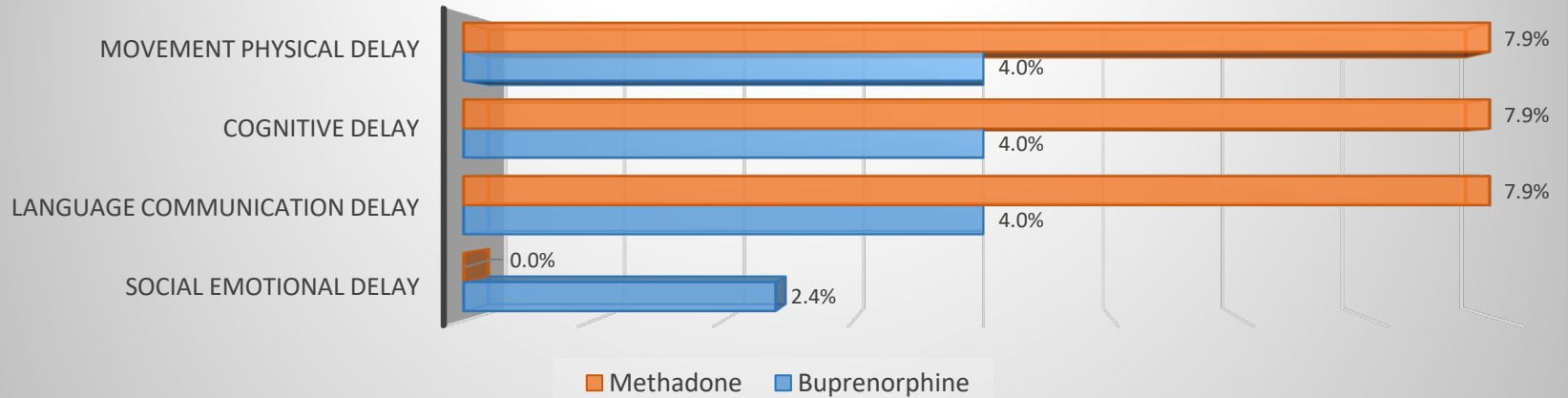
Developmental Delays 6 month Infant Well Visit



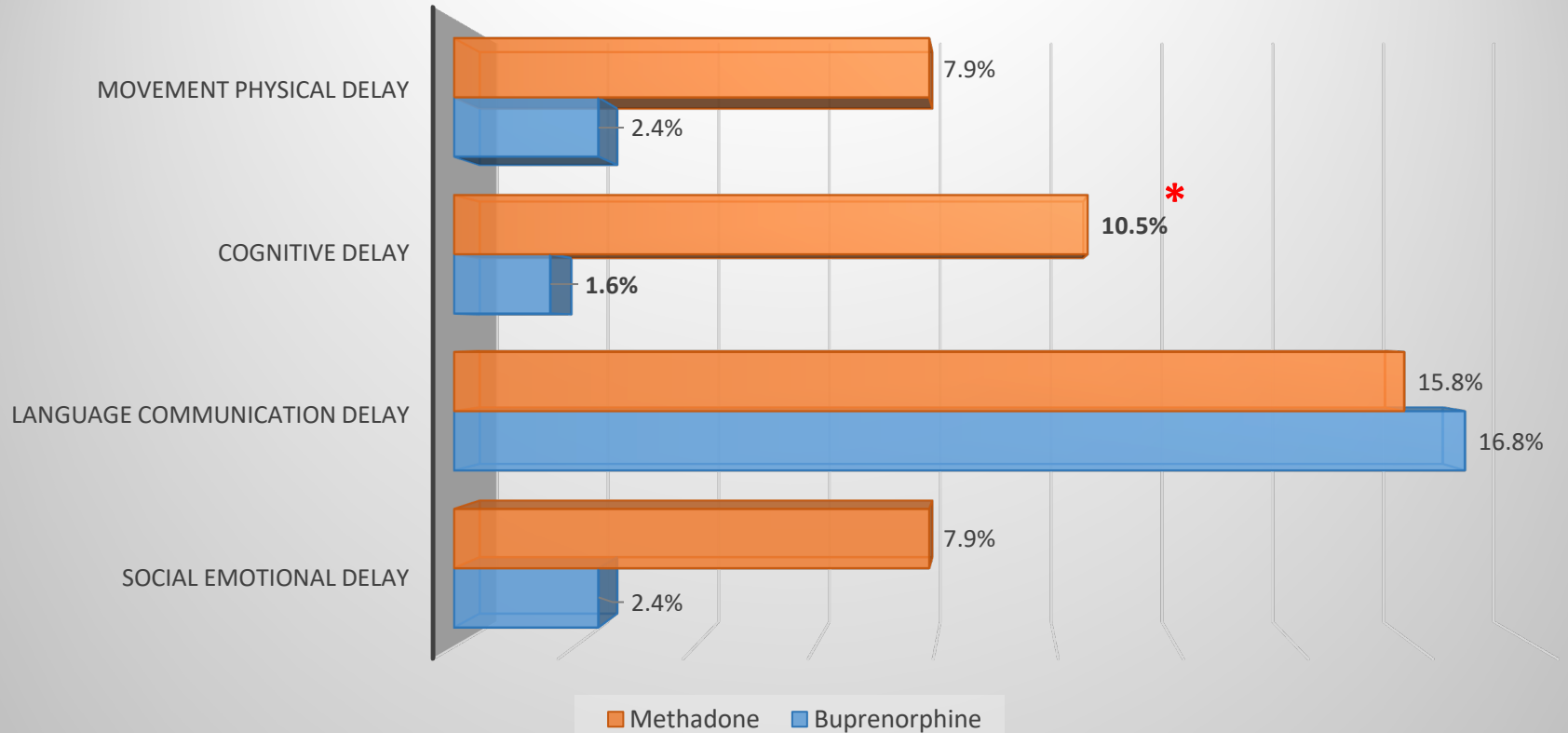
Developmental Delays 9 month Infant Well Visit



Developmental Delays 12 month Infant Well Visit



Developmental Delays 18 month Infant Well Visit



Conclusions

- **When comparing outcomes of gestations exposed to methadone and buprenorphine:**
 - **Similar developmental outcomes to 18 months**
 - **Possible cognitive delay at the 18-month mark with methadone**
 - **Similar newborn visit compliance**



Discussion

Strengths

- Stratifies developmental outcomes individually at multiple time points: 2, 4, 6, 9, 12, and 18-month wellness visits
- Standardized developmental milestone assessment at one institution
- Assesses visit compliance at multiple time points

- Confounding social and environmental factors
- Variance in attendance at prenatal visits, may impact the metrics studied
- Does not take into account dose response
- Small number of patients in methadone group

Limitations

Summary

- **Developmental milestones did not differ between buprenorphine and methadone groups, except for a small difference in cognitive delay at 18 months**
- **Long-term outcomes of infants exposed to different MOUD agents in-utero should be assessed through larger studies with a longer follow-up period**



Acknowledgements

Maternal Opioid Management Support Team:

Co-authors:

Emily Stetler MD
Lauren Stewart MD
Oladunni Ogundipe MD
Julia Kim MD
Rakasa Pattanaik
David Garry DO
Kimberly Herrera MD
Diana Garretto MD
Cassandra Heiselman DO

- OBGYN
 - David Garry DO
 - Diana Garretto MD
 - Kimberly Herrera MD
 - Cassandra Heiselman DO
 - Nancy Bowden CNM PMHNP
 - Kristen Alarcon NP
- Nursing
 - Wanda Davila RNC
 - Sabine Sterlin RNC
 - Wanda Ivette Davila RNC
 - Susan Little RNC RN, WHNP, NEA-BC
 - Kaitlin M Scherer RN
 - Antonietta Lynch RNC
 - Elizabeth C Mullady RNC
- Regional Perinatal Center
 - Marianna Lawrence RN
 - Keisha M. Butler
 - AnnMarie E Kotarba RNC
- Social work
 - Susan McCarthy LCSW, MS, CCM
 - Zarie Lisa Sedigh LMSW
 - Stephanie Rued LMSW
 - Fatima M Calle LMSW
- IT Support
 - Mindy G Lawrence RN
- Inpatient pharmacy
 - Marie Varela PharmD
- Outpatient office
 - Nichole Seda
- Anesthesia
 - Irina Lokshina MD
- Pediatrics
 - Lisa Clark DNP CPNP-AC/PC
 - Shanthi Sridhar MD FAAP



Additional Slides



Psychiatric Medication Usage Between Groups

	Buprenorphine (n=125)	Methadone (n=38)	p-value
Fluoxetine (Prozac)	5 (4.0%)	0 (0.0%)	0.59
Alprazolam (Xanax)	11 (8.8%)	4 (10.5%)	0.75
Venlafaxine (Effexor)	0 (0%)	1 (2.6%)	0.23
Sertraline (Zoloft)	15 (12.0%)	2 (5.3%)	0.36
Escitalopram (Lexapro)	5 (4.0%)	1 (2.6%)	1.00
Bupropion (Wellbutrin)	4 (3.2%)	2 (5.3%)	0.62
Gabapentin (Neurontin)	11 (8.8%)	3 (7.9%)	1.00
Duloxetine (Cymbalta)	2 (1.6%)	0 (0.0%)	1.00
Bupirone (Buspar)	4 (3.2%)	1 (2.6%)	1.00
Quetiapine (Seroquel)	9 (7.2%)	1 (2.6%)	0.46
Clonazepam (Klonopin)	7 (5.6%)	0 (0.0%)	0.20
Lamotrigine (Lamictal)	3 (2.4%)	0 (0.0%)	1.00
Citalopram (Celexa)	3 (2.4%)	0 (0.0%)	1.00
Other	20 (16.0%)	2 (5.3%)	0.09
ANY Psych Meds	62 (49.6%)	10 (26.3%)	0.01

Buprenorphine Dosing at Delivery & Developmental Delay

	High Dose (>16mg)	P	Higher Dose (>12mg)	P
Any delay at 4 months	2 (15.4%)	0.09	2 (6.1%)	0.61
Any delay at 6 months	0 (0.0%)	1.00	0 (0.0%)	1.00
Any delay at 9 months	3 (42.9%)	0.15	6 (25.0%)	0.55
Any delay at 12 months	1 (9.1%)	1.00	5 (15.6%)	0.28
Any delay at 18 months	3 (37.5%)	0.69	10 (38.5%)	0.26
Cumulative delay at 12 months	5 (35.7%)	0.14	10 (24.4%)	0.30
Cumulative delay at 18 months	7 (50.0%)	0.22	19 (45.2%)	0.04

Range of Buprenorphine dose at delivery

- 0.5 mg to 30 mg
- Median 10mg
- Mean 11 mg
- High does (>16mg) n=15
- Higher dose (>12mg) n=45

Methadone Dosing at Delivery & Developmental Delay

	High Dose (>100mg)		P
	Yes	No	
Any delay at 4 months	3 (18.8%)	0 (0.0%)	0.24
Any delay at 6 months	2 (15.4%)	0 (0.0%)	0.48
Any delay at 9 months	4 (44.4%)	2 (16.7%)	0.33
Any delay at 12 months	3 (25%)	2 (16.7%)	1.00
Any delay at 18 months	3 (27.3%)	3 (25%)	0.90
Cumulative delay at 12 months	6 (30.0%)	4 (28.6%)	0.93
Cumulative delay at 18 months	8 (38.1%)	6 (35.3%)	0.86

Range of Methadone dose at delivery

- 20mg to 220mg
- Median 110mg
- Mean 106mg
- High dose (>100mg) n=21

Infant Developmental Delays 2 months through 6 months

	Buprenorphine (n=125)	Methadone (n=38)	p-value
2 month wellness visit (n=132)			
Any delay	0	0	1.00
4 month wellness visit (n=123)			
Any delay	4 (4.2%)	3 (10.7%)	0.19
Social Emotional Delay	1	0	1.00
Language Communication Delay	0	1	0.23
Cognitive Delay	1	1	0.41
Movement Physical Delay	3	3	0.31
6 month wellness visit (n=112)			
Any delay	1 (1.1%)	2 (8.3%)	0.12
Social Emotional Delay	0	0	1.00
Language Communication Delay	0	2	0.05
Cognitive Delay	0	1	0.21
Movement Physical Delay	1	1	0.38

Infant Developmental Delays 9 months through 18 months

	Buprenorphine (n=125)	Methadone (n=38)	p-value
9 month wellness visit (n=96)			
Any delay	15 (20.0%)	6 (28.6%)	0.39
Social Emotional Delay	2	0	1.00
Language Communication Delay	3	2	0.30
Cognitive Delay	3	1	1.00
Movement Physical Delay	13	5	0.53
12 month wellness visit (n=113)			
Any delay	9 (10.1%)	5 (20.8%)	0.17
Social Emotional Delay	3	0	1.00
Language Communication Delay	5	3	0.36
Cognitive Delay	5	3	0.36
Movement Physical Delay	5	3	0.36
Any delay at any wellness visit up to 12 months	22 (19.0%)	10 (29.4%)	0.19
18 month wellness visit (n=101)			
Any delay	23 (29.5%)	6 (26.1%)	0.75
Social Emotional Delay	3	3	0.13
Language Communication Delay	21	6	1.00
Cognitive Delay	2	4	0.02
Movement Physical Delay	3	3	0.13