Maternal Exposure to Buprenorphine vs Methadone Opioid Maintenance Therapy and Risk of Neonatal Abstinence Syndrome

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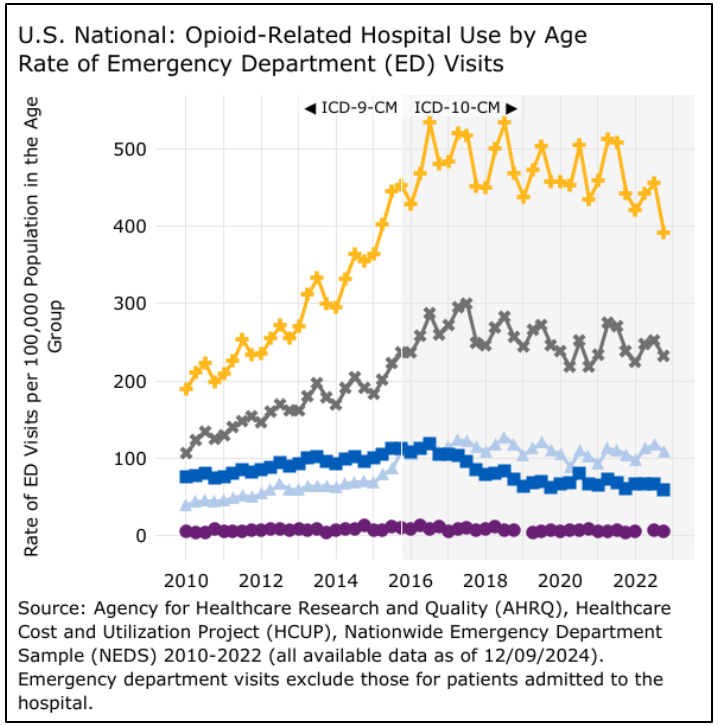
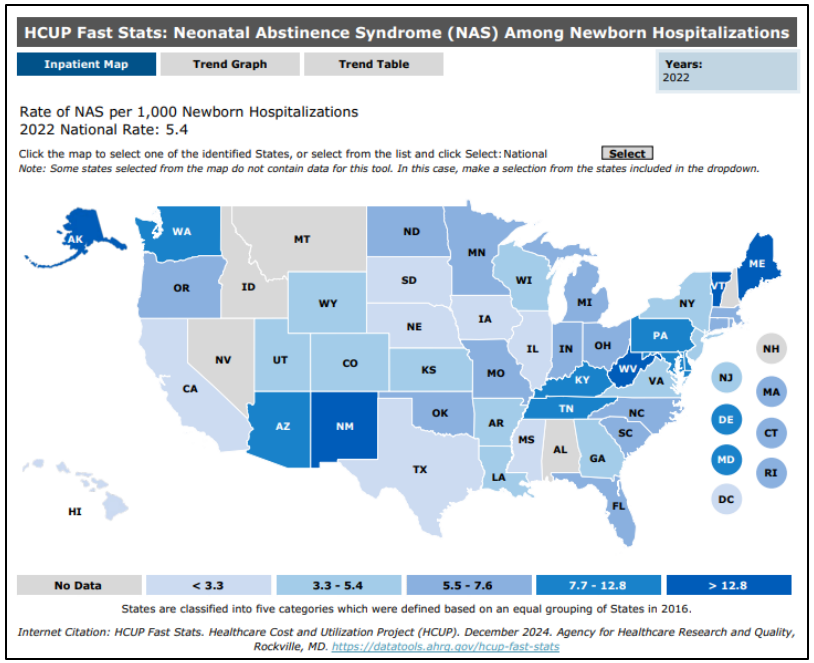
Background/Research Question

- Women at greatest risk for substance use during their reproductive years.
- NAS: neonatal abstinence syndrome has increased nationally.
- Long-term effects on neurodevelopment in neonates exposed to opioids, such as conduct disorder/emotional disturbance and ADHD.



- Rate: 5.4 per 1,000 newborn hospitalizations



Background/Research Question

- To reduce the risk of NAS and other poor MCH outcomes, pregnant women with opioid use dependence are treated with either methadone or buprenorphine as opioid maintenance therapy.
- Literature suggests buprenorphine carries less risk of NAS than methadone
- However, unmeasured confounders in observational studies comparing the two medications has been a concern.

- **Does exposure to methadone for maternal opioid maintenance therapy have a different risk of neonatal abstinence syndrome (NAS) following delivery and up to one week postpartum, relative to buprenorphine?**

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Research Objectives

Primary Objective

- To describe the demographic and clinical characteristics of patients prescribed buprenorphine versus methadone for opioid maintenance therapy during pregnancy.

Secondary Objective (future)

- To describe the risk of neonatal abstinence syndrome in infants following delivery and up to one week postpartum who are exposed to buprenorphine versus methadone in utero for opioid maintenance therapy during pregnancy.

Primary Cohorts & Concepts

Maternal Methadone Target Cohort

1. At least one occurrence of methadone as a procedure or drug exposure where the event starts between 0 and 180 days before the index start date (singleton live birth).
    - **Procedure concepts** with descendants:
        - Supervised consumption of methadone (ID 44789507)
        - Substance Abuse Treatment @ None @ Pharmacotherapy @ Methadone Maintenance @ None @ None (ID 2900298)
        - Substance Abuse Treatment @ None @ Medication Management @Methadone Maintenance @ None @ None (ID 2854466)
        - Reintroduction to methadone maintenance therapy (ID 44791541)
        - Drug addiction therapy – methadone (ID 4149607)
    - **Drug exposure concepts** with descendants:
        - Methadone tablet for oral suspension (ID 1594129)
        - Methadone oral tablet (ID 40064071)
        - Methadone oral suspension (ID 42620946)
        - Methadone oral solution (ID 40064067)
        - Methadone oral capsule (ID 21056343)
2. No buprenorphine as a procedure or drug exposure between 0 and 180 days before the index start date.
3. Age 12-55
4. Female Gender

Maternal Buprenorphine Comparator Cohort

1. At least one occurrence of buprenorphine as a procedure or drug exposure where the event starts between 0 and 180 days before the index start date (singleton live birth).
    - **Procedure concepts** with descendants:
        - Supervised consumption of buprenorphine (ID 44804162)
        - Reinduction to buprenorphine maintenance therapy (ID 44791542)
        - Drug addiction therapy using buprenorphine (ID 37311473)
        - Buprenorphine maintenance therapy (ID 44789283)
    - **Drug exposure concepts** with descendants:
        - Buprenorphine (ID 1133201)
2. No methadone as a procedure or a drug exposure between 0 and 180 days before the index start date (singleton live birth)
3. Age 12-55
4. Female Gender

Additional Cohorts

- Maternal Singleton Live Birth Cohort (Exposure Comparison)
  - Female
  - 12-55

- **Infant NAS Outcome Cohort**
  - Neonatal abstinence syndrome diagnosis with descendants (concept ID: 4212326)
  - Age < 1 year

- Infant Non-NAS Singleton Live Births (Comparison Cohort Outcome Comparison)
  - No diagnosis of NAS following delivery = “0 occurrences between 0-7 days”
  - Age < 1 year

Patient Numbers at OMOP Institutions

Table 1. Selected OMOP CDM patient counts from condition of singleton live birth for maternal buprenorphine, maternal methadone, and infant NAS cohorts.

	Maternal Cohorts			Infant Cohorts	
	Buprenorphine	Methadone	Singleton Live Birth	NAS	Singleton Live Births w/o NAS
Institution A	178	228	56,582	762	42,512
Institution B	42	44	68,477	3	106,900
Institution C	26	93	147,332	2	31,669
Institution D	6,064	543	188,994	327	92,693

Note: Buprenorphine and Methadone are patients who exclusively used only that medicine in the 180 days before the live birth event.
Infants are not necessarily born to mothers in the maternal cohort as mother-infant linkage has not been completed.

Selected Characterization Results: Exposure Cohorts

	Maternal OUD Singleton Live Births		All Singleton Live Births N=56,582
	Buprenorphine N=178 n(%)	Methadone N=228 n(%)	n(%)
Age			
15-19	-	-	1244(2.2)
20-24	14(7.9)	25(11.0)	4752(8.4)
25-29	51(28.7)	51(22.4)	9478(16.8)
30-34	65(36.5)	94(41.2)	20,607(36.4)
35-39	39(21.9)	46(20.2)	15,712(27.8)
40-44	9(5.1)	11(4.8)	4283(7.6)
Race*			
White	128(71.9)	173(75.9)	27,619(48.8)
Black	40(22.5)	43(18.9)	13,461(23.8)
American Indian/Alaska Native	4(2.2)	2(0.9)	165(0.3)
Asian	-	-	2380(4.2)
Asian Indian	-	-	1001(1.8)
Ethnicity*			
Hispanic/Latina	3(1.7)	3(1.3)	4283(7.6)
Not Hispanic/Latina	170(95.5)	210(92.1)	45,758(80.9)
Maternal Health			
Depression or Anxiety	16(9.0)	22(9.6)	1282(2.3)
Pregnancy Complication	173(97.2)	226(99.1)	36,268(64.1)
Delivery Outcomes			
Labor and Delivery Complication	164(92.1)	213(93.4)	48,395(85.5)
Preterm Birth	14(7.9)	57(25.0)	2177(3.8)
Severe Maternal Morbidity	19(10.7)	22(9.6)	1724(3.0)
30-day Mortality	0	0	3(0.005)
Total Mortality	2(0.05)	2(0.88)	28(0.05)

Table 2. Characteristics of maternal study patients at Johns Hopkins (N=56,988)

*Do not total to 100% due to missing/unknown

Table 3. Most Common Maternal Conditions

Buprenorphine	Condition	#	%
1.	Substance dependence in mother complicating pregnancy, childbirth and/or puerperium	156	87.64045
2.	Mental disorders during pregnancy, childbirth and the puerperium	133	74.7191
3.	Labor and delivery complicated by fetal heart rate anomaly	76	42.69663
4.	Major depression, single episode	75	42.13483
5.	Anemia of pregnancy	74	41.57303
Methadone	**Condition**	**#**	**%**
1.	Substance dependence in mother complicating pregnancy, childbirth and/or puerperium	222	97.36842
2.	Mental disorders during pregnancy, childbirth and the puerperium	170	74.5614
3.	Anemia of pregnancy	99	43.42105
4.	Major depression, single episode	93	40.78947
5.	Disease of the digestive system complicating pregnancy, childbirth and/or the puerperium	81	35.52632
Singleton Live Births	**Condition**	**#**	**%**
1.	Suspected fetal abnormality affecting management of mother	14240	25.16701
2.	Second degree perineal laceration	14185	25.06981
3.	Mental disorders during pregnancy, childbirth and the puerperium	12047	21.29122
4.	Group B streptococcus infection in mother complicating childbirth	11724	20.72037
5.	Anemia in mother complicating childbirth	11578	20.46234

Table 4. Most Common Maternal Procedures

Buprenorphine	Procedure	#	%
1.	Drug test(s), presumptive, any number of drug classes	97	54.5
2.	Substance use therapy	46	25.8
3.	Level V - Surgical pathology, gross and microscopic examination	45	25.3
4.	Immunization administration	41	23.0
5.	Electrocardiogram, routine ECG with at least 12 leads; interpretation and report only	37	20.8
Methadone	**Procedure**	**#**	**%**
1.	Drug test(s), presumptive, any number of drug classes	151	66.2
2.	Substance use therapy	118	51.8
3.	Level V - Surgical pathology, gross and microscopic examination	83	36.4
4.	Electrocardiogram, routine ECG with at least 12 leads; interpretation and report only	83	36.4
5.	Psychiatric diagnostic evaluation with medical services	61	26.8
Singleton Live Births	**Procedure**	**#**	**%**
1.	Immunization administration	14011	24.8
2.	Drug test(s), presumptive, any number of drug classes	10312	18.2
3.	Introduction of Other Hormone into Peripheral Vein, Percutaneous Approach	6909	12.2
4.	Echocardiography, fetal, cardiovascular system, real time with image documentation	6136	10.8
5.	Doppler echocardiography, fetal, pulsed wave and/or continuous wave with spectral display	6104	10.8

Selected Characterization Results: Outcome Cohorts

		NAS N=762 n(%)	Infants w/o NAS N=38,592 n(%)
Race*	White	489(64.2)	15,943(41.3)
	Black	197(25.9)	10,903(28.3)
	American Indian/Alaska Native	12(1.6)	129(0.3)
	Asian	2(0.3)	1168(3.0)
	Asian Indian	0	1576(1.5)
Ethnicity*	Hispanic/Latina	10(1.3)	1986(5.1)
	Not Hispanic/Latina	640(84.0)	27,419(71.0)
Gender	Male	407(53.4)	20,407(52.9)
	Female	355(46.6)	18,185(47.1)
Most Common Medications			
	Glucose Injection	275(36.1)	5470(14.2)
	Ampicillin Injection	227(29.8)	2675(6.9)
	Hepatitis B vaccine	222(29.1)	9384(24.3)
	Gentamicin	217(28.5)	2388(6.2)
	Morphine sulfate oral solution	42(5.5)	10(0.03)
Most Common Conditions			
	Neonatal jaundice	332(43.6)	12,901(33.4)
	Fetal disorder caused by chemicals	313(41.1)	189(0.5)
	Respiratory distress syndrome	240(31.5)	4710(12.2)
	Low birth weight	233(30.6)	3790(9.8)
Most Common Procedures			
	Radiologic examination, chest	186(24.4)	3227(8.4)
	Assistance with Respiratory Ventilation	90(11.8)	2226(5.8)
	Introduction of Serum, Toxoid and Vaccine into Muscle	46(6.0)	2815(7.3)
Mortality			
	30-day Mortality	0	57(0.1)
	Total Mortality	5(0.7)	164(0.4)

Table 5. Characteristics of infant study patients at Johns Hopkins (N=39,354)

*Do not total to 100% due to missing/unknown

Lessons Learned

- Need to specify age and gender criteria when defining cohorts
- Check totals for covariates
- Check variation in estimated counts across institutions; investigate if needed

	Analysis name	Cohort ID	Cohort name	Covariate	Covariate name	Count	Percent
3	DemographicsRace	717	[MHF] Buprenorphine in Pregnancy (SLB)	8657004	race = American Indian or Alaska Native	4	2.247191
4	DemographicsRace	717	[MHF] Buprenorphine in Pregnancy (SLB)	8527004	race = White	128	71.91011
5	DemographicsRace	717	[MHF] Buprenorphine in Pregnancy (SLB)	8516004	race = Black or African American	40	22.47191
6						Total	96.62921
7	DemographicsRace	718	[MHF] Methadone in Pregnancy (SLB)	8657004	race = American Indian or Alaska Native	3	1.234568
8	DemographicsRace	718	[MHF] Methadone in Pregnancy (SLB)	8527004	race = White	179	73.66255
9	DemographicsRace	718	[MHF] Methadone in Pregnancy (SLB)	8516004	race = Black or African American	48	19.75309
0						Total	94.65021

Next Steps

- Identify additional data partners, especially those with a claims database, and/or linked mother-infant data.
- Complete meta-analysis for descriptive analysis of MOUD population of interested partner sites (Objective 1)
- Upon completion of mother-baby linkage, complete population-level effect estimation of treatment exposure to buprenorphine versus methadone and risk of NAS (Objective 2)
- Interested in being a data partner? Please email me!

Email: elizabeth.howardmoehlen@ochsner.org

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