MODELING OF THE OPIOID AND NEONATAL ABSTINENCE SYNDROME CO-EPIDEMIC IN MEDICAID POPULATION OF INDIANA

by

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ABSTRACT

Background: With the onset of a second decade of opioid use creating devastating outcomes in the United States, there is value in studying the prevalence of Opioid Use Disorder (OUD) in pregnant women, a group critical to this outbreak. We used Medicaid claims 2014-2019, to analyze the medical, social and economic aspects of OUD in pregnant women and their babies.

Objectives: The research aims to study the impact of Opioid Use Disorder (OUD) in Medicaid-enrolled pregnant women and model the vertical perinatal effect of OUD, known as Neonatal Abstinence Syndrome (NAS), to the newborn baby. We also attempt to understand the effects of state legislation on doctor shopping and the role of prescribers in fraudulent solicitation of opioids.

Methods: The research uses multivariate logistic regression to create a predictive model for high-risk pregnant women based on their claims history. Doctor shopping trends pre- and post-legislation are analyzed using regression discontinuity and graph analysis of the co-prescription network of physicians. Finally, OUD and NAS are modeled together as a probabilistic Bayesian belief network to simulate the cost of interventions, namely MAT enrollment, pharmacotherapy and dyad rooming-in.

Results: Pregnant women who may have NAS offsprings are likely to have a history of nicotine addiction, alcohol use, dependence on pain medication and mental health diagnoses in the years leading up to pregnancy. State legislation is found to reduce prescription opioid shopping over the years, though the research highlights the need for policies to target complicit prescribers in addition to prescription monitoring. Finally, the compartment model calculates an incidence of 19-22% for downstream neurological delay in babies born to high-risk mothers. Lower delay rates are found to be associated with high MAT enrollment in the mother, high rooming-in of mother-infant dyad and low rate of pharmacotherapy in infants.

1. INTRODUCTION

1.1 Background

The past decade has seen an influx of opioids, both prescription and illicit in American communities that has caused devastating social, medical and economic burden. Their impact is creating an alarm to legislators, medical practitioners and general public (Chan et al., 2017) and the need for effective interventions and policies to reduce the health and economic burden of this epidemic are of increasing importance today. In the state of Indiana, drug overdose deaths involving opioids have more than quadrupled since 2010, to a staggering 1,104, of which 370 were said to be a result of prescription opioids (National Institute on Drug Abuse, 2020)

The prevalence of opioid use during pregnancy has increased by 333% from 1999 to 2014 in the United States. Among the women that were publicly insured by Medicaid during this time, approximately 1 in 4 women were prescribed opioids during their pregnancy (Anbalagan and Mendez, 2020). This has correlated with an increase in the occurrence of Neonatal Abstinence Syndrome (NAS) in babies born to opioid using mothers. Neonatal Abstinence Syndrome comprises of a collection of withdrawal symptoms that manifest as hyperactivity, tremors, tachycardia and difficulty to console (Sanlorenzo et al., 2018).

Further, adverse neurodevelopmental outcomes have been observed in infants and children exposed to opioids in-utero and it is common for them to have disruptive behavior, attention deficit disorder and poor learning outcomes (Kraft et al., 2016). Hence the study of the opioid epidemic in pregnant women is extremely relevant to addressing this crisis.

1.2 Scope

The scope of this research is limited to the Medicaid insured population of Indiana from January 2014 to March 2019. The Indiana Medicaid claims data extract comprises of approximately 1.5 million unique recipients, 247,897 of which have a diagnosis of pregnancy (list in Appendix A.). Further, the diagnosis claims for NAS (Chiang et al., 2019) yield a population of 9,124 babies that showed symptoms of withdrawal in this timeframe.

For the mother, we define a high-risk criterion which implies a pregnant woman whose substance use patterns put the fetus at high-risk of exposure to opioids in utero. The analyses done throughout this research are with the said high-risk definition for pregnant women that has been explained in Section 3.2.

Since the state is responsible for handling the protocol around mitigating the opioid issue, we intend that our research conducted at Purdue University assists the Indiana FSSA, as they work on opioid addiction treatment, the use of state INSPECT drug monitoring and maternal and child well-being in the case of pregnancy.

1.3 Abbreviations

Table 1. List of Abbreviations

Abbreviation	**Explanation**
OUD	Opioid Use Disorder
NAS	Neonatal Abstinence Syndrome
FSSA	Family and Social Services Administration
ICD	International Classification of Diseases
NDC	National Drug Code
NPI	National Provider Index
MED	Morphine Equivalent Dose
SMOTE	Synthetic Minority Oversampling Technique
ROC-AUC	Receiver Operating Characteristics - Area under Curve
RFE	Recursive Feature Elimination
PDMP	Prescription Drug Monitoring Program
BBN	Bayesian Belief Network
NICU	Neonatal Intensive Care Unit
MAT	Medication Assisted Treatment
ADHD	Attention Deficit Hyperactivity Disorder

1.4 Research Objectives

The objective of this research is to quantify the impact of Opioid Use Disorder (OUD) in Medicaid-enrolled pregnant women based on Medicaid claims for the state of Indiana (2014-2019). Further, we model the effects of OUD on the offspring, known as Neonatal Abstinence Syndrome (NAS), to understand the incremental effect of three interventions: rooming in, medication assisted treatment, and pharmacotherapy. Specifically, we will:

1. Define a criterion for opioid use in pregnancy leading to NAS to identify indicators that predict these cases of pregnant women from medical history in claims for the Medicaid-enrolled population.

2. Analyze the effects of state legislation on opioid doctor shopping in Medicaid-enrolled pregnant women and the underlying prescriber network in fraudulent solicitation of prescription opioids in Indiana.

3. Model the OUD mother-NAS infant dyad using a probabilistic network approach to compute the incidence of neurological outcomes as a result of the use of medication assisted treatment, pharmacotherapy, and rooming in.

4. Estimate the economic burden of OUD and NAS to the state of Indiana by simulating a cohort of Medicaid-enrolled pregnant women with OUD to approximate the cost incurred by Medicaid from treatment and downstream care pathways.

In summary, the research objectives collectively address aspects of prediction, legislation, treatment, and financial burden in the Indiana opioid crisis specific to Medicaid-enrolled pregnant women.

2. LITERATURE REVIEW

This chapter presents an understanding of the literature about the Opioid Use Disorder (OUD) and the factors influential to OUD in pregnant women. We study the prevalence and concerns associated with the Neonatal Abstinence Syndrome (NAS) in babies born to OUD women.

Further, this chapter studies the various definitions of doctor shopping in the literature and the success of Prescription Drug Monitoring Programs (PDMPs) implemented in the United States. We also delve into the issue of prescription drug abuse and doctor shopping from the perspective of co-prescription social networks. Finally, the section on modeling health outcomes elaborates the use of dynamic compartment models for the comparison of treatment and care interventions.

2.1 Neonatal Abstinence Syndrome

2.1.1 Definition and prevalence

Neonatal Abstinence Syndrome (NAS), as defined by Sanlorenzo et al., 2018 is “a postnatal drug withdrawal syndrome exhibited by some opioid-exposed infants that is characterized by hyperactivity of the central and autonomic nervous system and gastrointestinal tract”. It is difficult to identify which opioid-exposed infants will display symptoms of NAS.

Jansson et al., 2019 defined NAS as a “generalized multisystem disorder causing a dysregulation of the nervous system that manifests in a variety of physiologic and neurobehavioral signs, unique to each infant, in the domains of sleep-wake control, motor and/or muscle tone, autonomic functioning, and sensory processing and/or modulation.”

Leech et al., 2020 used the data from a national all-payer inpatient sample to examine the NAS trends between 2004-2016. Average incidence of NAS in the US increased from 1.6 per 1,000 hospital births in 2004 to 8.8 per 1,000 births in 2016 with region wise trends shown in Fig. 2.1.

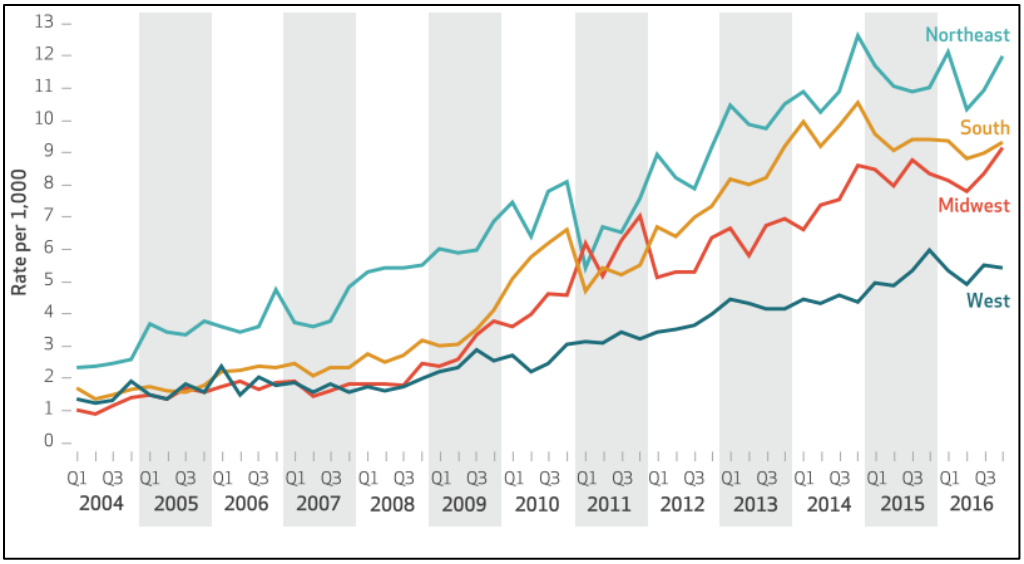


Figure 2.1. Rate of NAS per 1,000 US hospital births by region (Leech et al., 2020)

Winkelman et al., 2018 used the 2004-2014 data of a nationally representative sample of hospital discharges in the United States (N = 13102793) to study the trend in births impacted by NAS. Among Medicaid insured infants, NAS incidence increased by over five times, from 2.8 per 1000 births in 2004 (95% CI, 2.1–3.6) to 14.4 per 1000 births (95% CI, 12.9–15.8) in 2014. Infants with NAS who were covered by Medicaid were significantly more likely to be transferred to another hospital and have a longer length of stay than infants without NAS who were enrolled in Medicaid. It was observed that NAS led to complications such as long-term motor and cognitive functioning problems, and babies born with the condition have hospital costs that are five times higher than those born without NAS.

2.1.2 Treatment and care

Though medication assisted treatment given to the mother improves the outcomes of the mother-infant dyad, it did not prevent the child from being born with NAS (Kraft et al., 2016). The literature for NAS treatment and care discusses the Finnegan scoring, morphine administration and rooming-in techniques.

Kraft et al., 2016 explained the Finnegan scoring instrument, which is commonly used to monitor infants born with withdrawal symptoms. It consists of a 31-item scale to access

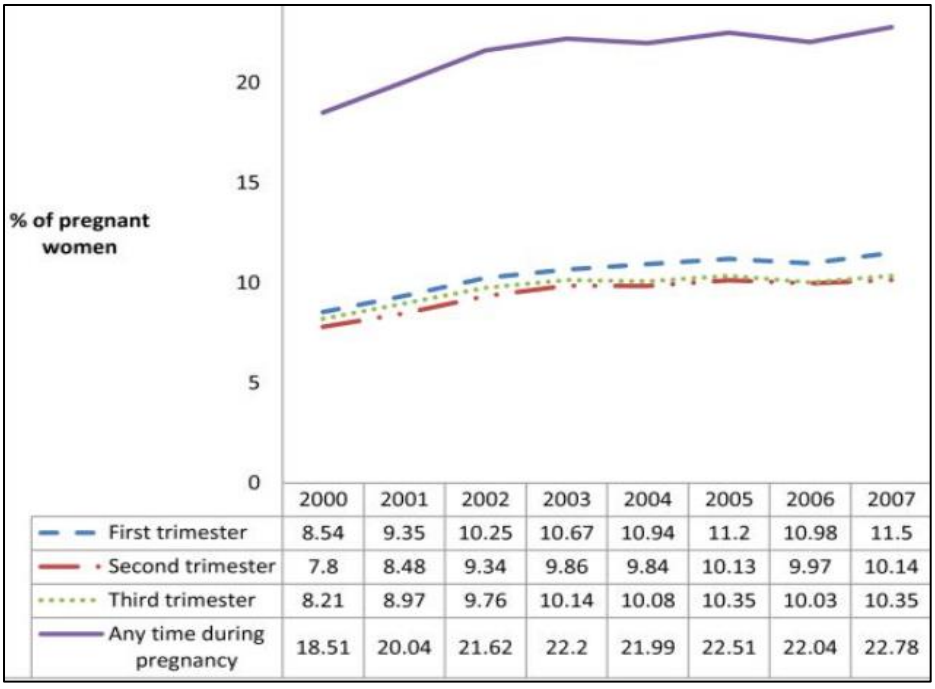
symptoms such as high-pitched crying, tremors, indigestion and sleeplessness every 3-4 hours. A score > 8 is suggestive of NAS and it helps make the decision if pharmacotherapy is required, even if the mother denies opioid use.

Jansson et al., 2019 discussed the Eat-Sleep-Console assessment tool, which is a non-pharmacological intervention that encourages maternal interaction, breastfeeding and skin-to-skin contact in timely intervals. Medication is only reserved for those infants who cannot be consoled under these criteria. The Eat-Sleep-Console tool is observed to have shorter length of hospital stay and lower risk of harm caused by medication.

Finally, Holmes et al., 2016 analyzed the cost associated with the treatment and care of NAS through a protocol of scoring, medications and rooming-in environments. They focused on standardizing the Finnegan scoring methodology to a more infant-centric approach where morphine was not administered solely based on the score, but on overall infant inconsolability. Rooming-in of mother and baby was advocated in 2013 and the outcomes such as cumulative morphine dose, 30-day readmission and length of stay were studied. It was reported that the newborns requiring morphine decreased by 27% by 2015 and the average length of stay decreased from 16.9 days to 12.3 days. This reduced the cost per treated infant from $19,737 to $8,755.

2.2 Opioid Use Disorder in Pregnancy

In the United States, approximately 1 in 4 Medicaid enrolled women have used opioids during pregnancy and the prevalence of OUD during pregnancy has increased by 333% from 1999 to 2014 (Anbalagan and Mendez, 2020). Desai et al., 2014 reported the prevalence of the prescription opioid use in pregnancy, shown in Fig. 2.2 using the filled prescriptions of a population of 1.1 million pregnant women in the US.



	2000	2001	2002	2003	2004	2005	2006	2007
First trimester	8.54	9.35	10.25	10.67	10.94	11.2	10.98	11.5
Second trimester	7.8	8.48	9.34	9.86	9.84	10.13	9.97	10.14
Third trimester	8.21	8.97	9.76	10.14	10.08	10.35	10.03	10.35
Any time during pregnancy	18.51	20.04	21.62	22.2	21.99	22.51	22.04	22.78

Figure 2.2. Percentage of pregnant women who filled an opioid prescription, Medicaid 2000-2007 (Desai et al., 2014)

Kennare et al., 2005 studied the risk factors associated with substance use in pregnancy in South Australia. Multivariate logistic regression was conducted using prenatal data from 1998 to 2002. Substance use was reported in 0.8% of the population and the identified women were found to be likely smokers, having underlying psychiatric conditions and dwelling in metropolitan areas in poor socio-economic conditions.

It has been analyzed by Harter 2019, that many women suffering from OUD during pregnancy are motivated to initiate treatment and abstain from prenatal use of opioids. This is to prevent the involvement of Child Protective Services (CPS) and separation from their child(ren). A pregnant woman can be treated with either methadone or buprenorphine – the two first-line approaches to treatment. The choice of medication is multifactorial, as it may depend on comorbid conditions, treatment logistics and risk of relapse. The paper explores these two approaches of MAT through a case study of a 30-year-old woman with illicit use of oxycodone during pregnancy.

2.3 Doctor Shopping

2.3.1 Definitions

Medical literature has characterized doctor shopping with different definitions. Doctor shoppers as defined in Han et al., 2014, were individuals who used more than five different prescribers for the same schedule of opioids in one calendar year. There were no restrictions on the number of pharmacies used to procure the opioids. The paper examined the age and gender traits of opioid doctor shopping among California residents and generates a trend for the use of opioids over nine years (Fig. 2.3). It was observed that the age and gender differences in doctor shoppers were relatively small, though there was growing trend in prevalence of opioid users (150% to 280% increase across different age and gender populations).

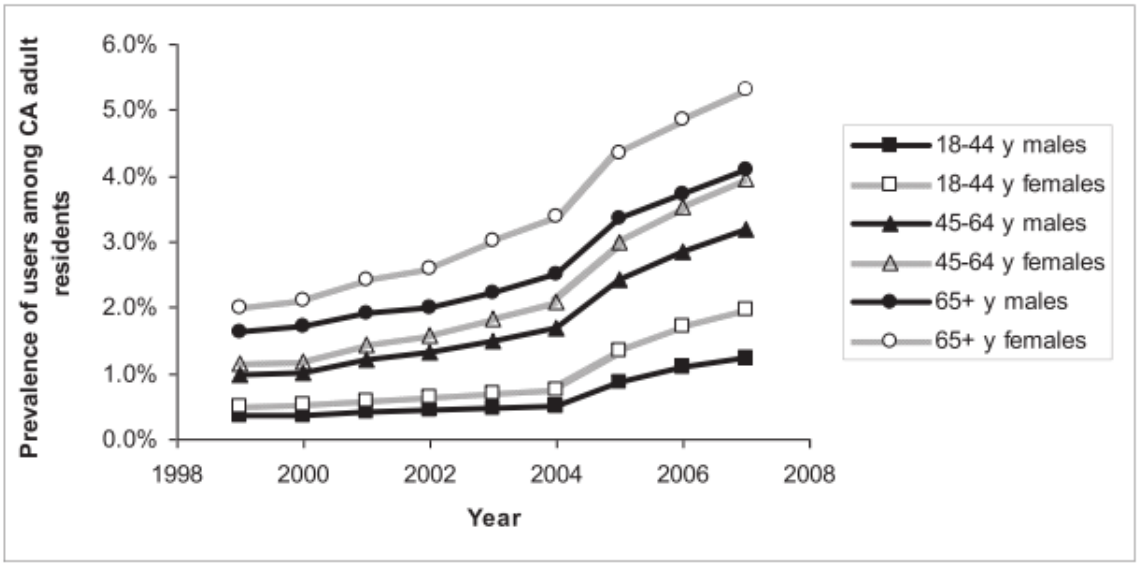


Figure 2.3. Trends in 1-year period prevalence of Schedule II opioid users among the California adult population by age and gender groups from 1999–2007 (Han et al., 2014)

Griggs et al., 2015 identifies doctor shopping through reports sent from government agencies to clinicians, surveillance of prescribing behavior to identify irresponsible prescribing and by clinician review of patient reports before prescribing. PDMP databases rely on the Drug Enforcement Administration numbers to generate data on where a prescription is filled. This may

lead to inaccurately concluding patients as doctor shoppers when they visit multiple specialists at the same hospital.

Prescription drug abuse is a serious threat to public health and is the leading cause of accidental deaths in the United States. MacDonald and Carson 2013 estimated the prevalence of doctor shopping in the US and the amounts and types of opioids involved. The sample they considered included 146.1 million opioid prescriptions dispensed during 2008 by 76% of US retail pharmacies. Prescriptions were linked to unique patients and weighted to estimate all prescriptions and patients in the nation. Longitudinal mixed models were used to study different patient populations based on age, method of payment, geographical area etc. and the count of prescribers for the models were fit to Poisson distributions. It was observed that 0.7% of purchasers obtained 32 opioid prescriptions from 10 different prescribers. This group was presumed to be doctor shopping for opioids.

Perry et al., 2019 studied the prominence of solicitors in a co-prescription network as an indicator of opioid doctor shopping. The paper is based on the prior research that doctor shopping is a social process where complicit doctors will occupy prominent positions in the network. The hypothesis is tested by calculating PageRank scores using deidentified health claims from a commercially insured population of 19 million in the Appalachian region.

A patient with a high PageRank could either visit a large number of prescribers or visit a few prescribers, that were simultaneously prescribing to several other patients; both scenarios increasing the relative importance of that patient in the social network. The paper regresses opioid outcomes such as OUD, number of prescriptions, overdose against the PageRank and it is observed that patients with higher PageRank are at greater risk of overdose and OUD. Therefore, the paper concluded that the structural position in a social network could provide insight into high risk drug soliciting.

2.3.2 Prescription Monitoring

In the attempt to curb prescription opioid overuse through policy, prescription drug monitoring programs were mandated in 22 states in the US by 2014 (Griggs et al., 2015). At the end of 2013,

Indiana implemented rules to regulate opioid prescribing and Al Achkar et al., 2018 compared the volumes of opioids prescribed before and after Indiana implemented the regulations. Time series analysis was used to measure total opioid doses dispensed per day and the population was sliced on patient's gender, age and socioeconomic status. It was observed that overall opioid use decreased post regulation, but the effects of the regulation were larger for males than females and 10 times larger for younger patients (<20 years) as compared to patients above the age of 60.

In Indiana, overdose mortality increased by 48% in 2016 and 2017. Adams et al. 2020 conducted an analysis on state level regulatory and legislative changes in five Midwestern states in order to study the increasing number of overdose deaths. Interrupted time series regression was used on data from the CDC WONDER database to yield the trends in Fig. 2.4. It was observed that Indiana had a significant increase in overdose deaths due to government involvement. However, the falling rate of opioid prescribing indicates that the deaths were a result of patients switching to illicit drugs.

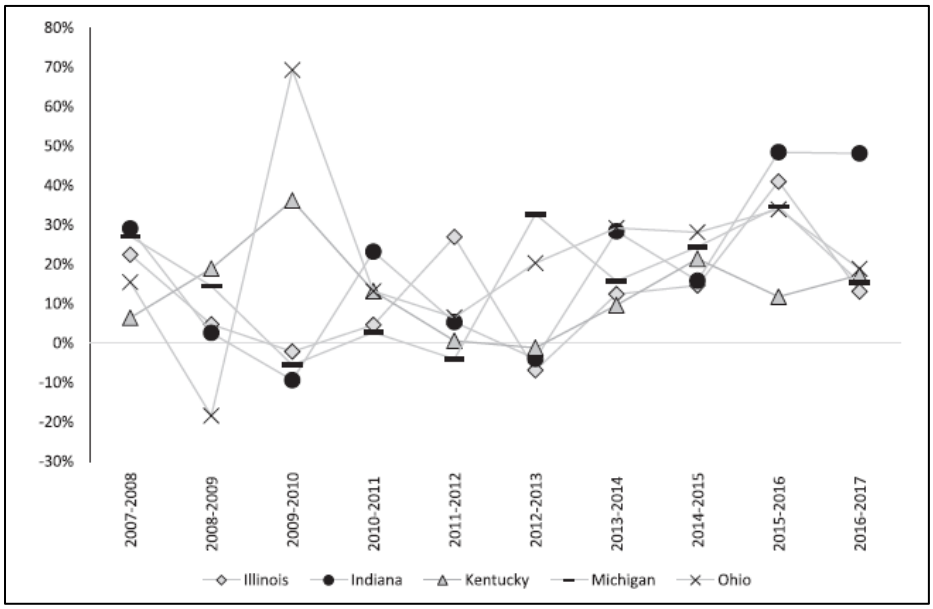


Figure 2.4. Percent changes in Opioid Overdoses 2007-20017 (Adams et al., 2020)

Further, the paper reported that overdose deaths also increased when states increased the availability of Naloxone, the emergency opioid reversing drug. This indicated the need for more education on best prescribing practices in addition to regulations and legislation.

2.4 Dynamic Compartment Modeling

Pitt et al., 2018 developed a dynamic compartmental model of pain, opioid prescribing and addiction resulting from prescription opioids in the US. The model assessed the health effects of different interventions that aim to curb opioid addiction and overdose deaths, accounting for morbidity and mortality across a five-year period (2016-2020) and a ten-year period (2016-2025) using monthly increments.

The 12 mutually exclusive and collectively exhaustive compartments represent the entire US population – Pain free nonuser, Acute pain nonuser, Chronic pain nonuser, Acute pain with Rx, Chronic pain with Rx, Chronic pain with OUD and Rx, Pain free with OUD and Rx, OUD without Rx, Heroin use disorder, Opioid use with MAT, Heroin use with MAT and Death. Initial compartment sizes and transition probabilities were derived from literature and assumptions on enrollment rates, relapses, prevalence etc. The interventions analyzed were naloxone availability, promoting needle exchange, MAT, psychosocial treatment and prescription monitoring policies among others. Finally, the outcomes measured over time were addiction deaths, life years and quality adjusted life years.

The paper reported that interventions that expanded addiction/overdose treatment were found to be uniformly beneficial over all the outcomes, However, the policies that aim to reduce prescription opioid supply produce mixed outcomes due to the implied increase in heroin use and resulting deaths. Pitt et al., 2018 provided an idea of the effectiveness of targeted policies from a compartment model approach.

Chen et. al, 2019 developed a dynamic compartment model with 3 states – those using prescription opioids without an OUD, those using prescription opioids with an OUD, and those using illicit opioids. The model simulated the non-medical opioid use since 2002, so that individual's transition in and out of the 3 states starting from initial estimates derived from the CDC's Wide-Ranging Online Data for Epidemiological Research.

The transition rates in the model were assumed to vary over time and regression analysis was used to calculate these time-dependent rates. It was reported that in the current scenario, the total

number of opioid deaths in the United States will increase by 147% from 2015 to 2025 (33,100 to 81,700). In 2025, 67,900 of the 81,700 deaths will be caused by illicit opioid use.
Further, the model predicted that the prevalence of opioid related deaths will reduce by 3.8-5.3% from 2016 to 2025 and this will be achieved by successful prevention of prescription misuse interventions. In conclusion, the dynamic model by Chen et al. emphasizes on the importance of policies addressing prevention and harm reduction in individuals that depend on illicit opioids as their incidence is expected to increase in the years to come.

Bobashev et al., 2018 developed a simulation model called ‘Pain Town’ for individual patient journeys using an agent-based dynamic model. The community simulated consists of patients that can transition from the state of being a pain patient to a user of heroin, with several intermediate steps such as prescription opioid using patient, non-compliant opioid user. The model consists of other actors in the Pain Town – physicians, pharmacy, dealer and emergency department (ED).

A five-year horizon was used and the simulation was performed for four probabilistic interventions – reducing the average initial dosage, average PDMP compliance, tamper-resistant bottles that dispense fixed quantities of pills, and naloxone availability.
The effectiveness for these interventions were measured for the outcomes – heroin users, opioid overdoses, heroin overdoses, opioid deaths and heroin deaths as shown in Fig. 2.5.

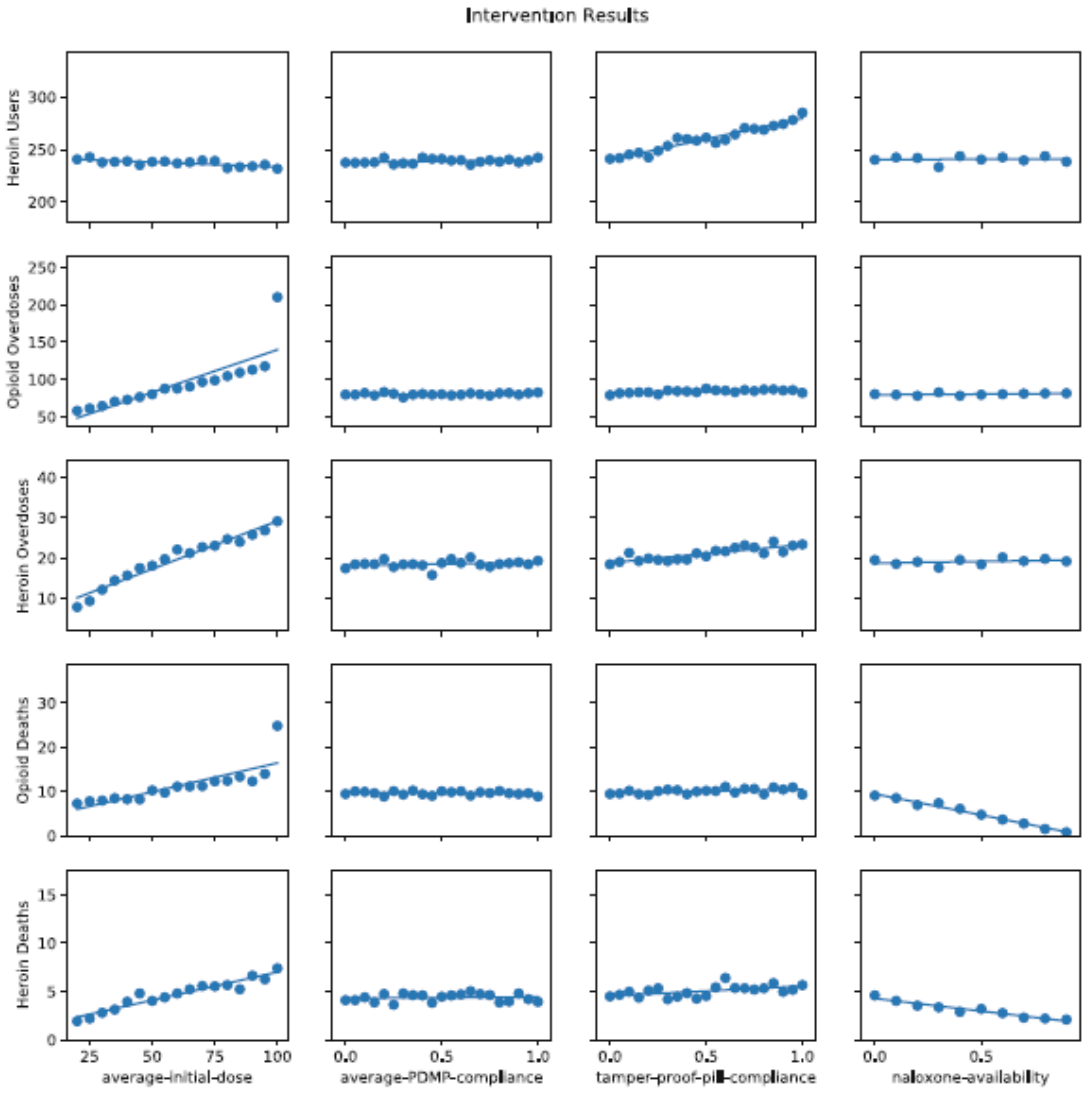


Figure 2.5. Simulation results by varied parameters (Bobashev et al., 2018)

It was observed that average PDMP compliance was not correlated with any of the outcomes. Reducing the average initial dose increased the illicit use in the heroin user pool. On the other hand, naloxone availability reduced death rates with no negative consequences.

3. OPIOID USE IN PREGNANCY: RISK FACTORS IN THE MEDICAID POPULATION OF INDIANA

3.1 Introduction

In the United States, the prevalence of opioid use during pregnancy has increased 333% from 1999 to 2014, wherein approximately 1 in 4 Medicaid enrolled women have used opioids during pregnancy (Anbalagan and Mendez, 2020). Fetal in utero opioid exposure can result in the occurrence of Neonatal Abstinence Syndrome (NAS) (Kraft et al., 2016).

In the state of Indiana, the rate of NAS was calculated to be 10.4 cases per 1000 hospital births in 2017 as compared to the national incidence of 7 cases per 1000 hospital births (National Institute on Drug Abuse, 2020). Based on claims from the Indiana State Medicaid database records, approximately 37 NAS births per 1000 live births occurred between 2014 and 2019.

The objective of this study is to predict from previous claims whether a pregnant woman will have an opioid intake pattern that may result in NAS to her child. We develop a logistic regression approach that is based on a combination of the mother's medical history and social indexes extracted from Indiana Medicaid claims. Finally, the study discusses a risk scoring system to simplify the classification in clinical practice.

3.2 Methods

We use claims from the Indiana Medicaid database consisting of roughly 1.5 million unique enrollees over the years 2014-2019. For the predictive model, we considered two types of factors, namely medical history and sociodemographic variables. The response is binary as whether the pregnant women is identified as likely to have an NAS baby (as a result of opioid intake) or not.

We developed a multivariate logistic regression model in the Scikit-learn library for the programming language Python.

Response Criteria

Women in the database with ICD 9/ICD 10 diagnosis codes for pregnancy (N = 247,897) were divided into two cohorts namely, Category 1: Risk of opioid use that leads to NAS, and Category 0: No risk of opioid use leading to NAS. These categories form the binary dependent variable for the logistic regression. Two approaches were considered to create Category 1. First was to consider in utero opioid exposure only when OUD is diagnosed at or close to the time of delivery. However, this methodology failed to account for incidence of OUD in the first and second trimesters or even before pregnancy.

Therefore, a second approach was developed that created a more robust criterion by determining the threshold number of days before and after the first diagnosis of pregnancy where an OUD diagnosis must occur. Women within the age of 13-50 years who had a minimum of one diagnosis of both opioid use and pregnancy were identified from the Medicaid claims. The difference in dates between first pregnancy diagnosis and opioid diagnosis was used to infer whether the particular recipient belonged to Category 1 or not for the purpose of the analysis.

1. When a diagnosis of opioid use occurred not more than 9 months after pregnancy detection, the recipient was classified as at risk of opioid use resulting in NAS.
2. For recipients whose last OUD diagnosis was prior to pregnancy diagnosis, a histogram of women having a complication in pregnancy due to opioid-related use based on the days between the first pregnancy diagnosis and last opioid diagnosis was made (Fig. 3.1). A total of 364 pregnant women had a diagnosis of "Drug use complicating pregnancy" in the Medicaid claims.

   It was found that after 250 days between the last opioid diagnosis and first pregnancy diagnosis, little or no residual effect was observed. Therefore, we used 250 days as the cut point in this analysis.

These criteria resulted in approximately 3% of the total population of pregnant women to belong in the 'Risk of opioid use that leads to NAS' category (Category 1).

Bin	Frequency
25	138
50	43
75	19
100	27
125	14
150	13
175	13
200	7
225	11
250	11
275	1
300	5
325	5
350	4
375	5

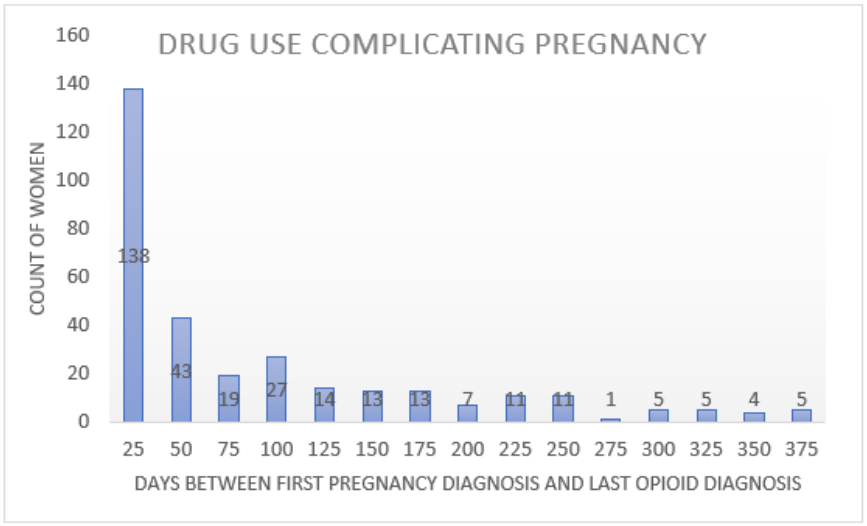


Figure 3.1. Histogram of days between first pregnancy diagnosis and last opioid diagnosis for women with 'Drug Use Complicating Pregnancy' diagnosis

Risk Factors

ICD 9/10 diagnosis were used as risk factors around patient history, while the claim itself was used to extract patient race/ethnicity, age, and 3-digit zip code. Race was defined by 5 categories – Asian (A), Black (B), Caucasian (C), Hispanic (H) and Other. We used Indiana's Public Utility Data (US Census Bureau, 2001) to determine the average high school graduation rate in the 3-digit zip code regions as a proxy measure for educational attainment.

Diagnosis codes were used to determine which women had previous diagnosis of alcohol consumption, tobacco use, prolonged steroid/pain medication, mental health issues and psychosocial issues (Table 2). For each of these parameters, we looked at the number of unique claims one year prior to pregnancy, two years prior to pregnancy and so on until the start of the data. This resulted in a total of 29 features (correlation matrix in Appendix B.) that were regressed with 95% confidence intervals. The logit regression using MLE converged to the coefficients in Table 3. (Note that the 'Tobacco dependence_2' refers to the count of tobacco dependence diagnoses cited for the recipient in year 2 prior to pregnancy detection)

Table 2. ICD (9/10) codes for risk factors

Category	**Diagnosis Code**	**ICD 9/10**	**Description**
Alcohol Consumption	F10.10 – F10.99	ICD 10	Alcohol related disorders
	O99.31	ICD 10	Alcohol use complicating pregnancy
	303.00 – 303.93	ICD 9	Alcohol dependence syndrome
	305.0	ICD 9	Non-dependent alcohol abuse
Tobacco Dependence	F17.200 – F17.299	ICD 10	Nicotine dependence
	Z72.0	ICD 10	Tobacco use
	Z87.891	ICD 10	Personal history of nicotine dependence
	O99.330 – O99.335	ICD 10	Tobacco use complicating pregnancy
	V15.82	ICD 9	Personal history of tobacco use
	305.1	ICD 9	Tobacco use disorder
	649.00 – 649.04	ICD 9	Tobacco use complicating pregnancy
Pain medication use (steroids/analgesics)	Z79.8	ICD 10	Long term drug therapy
	V58.59	ICD 9	Long term use of opiate analgesic
Mental health history	F01.50 – F09	ICD 10	Mental disorders due to known conditions
	F10.10 – F69	ICD 10	Schizophrenia, mood disorders, stress related non psychotic
	F90.0 – F98.9	ICD 10	Unspecified mental disorder
	290 – 219	ICD 9	Mental disorders
Psychosocial diagnosis	Z55.0 – Z65.9	ICD 10	Potential health hazards of socio economic or psychosocial nature
	Z69.010 – Z76.89	ICD 10	Person encountering health services in other circumstances
	V60 – V62	ICD 9	Person encountering health services in other circumstances

We observe that all but 4 features are statistically significant based on p-values. For further pruning we applied feature selection. Recursive feature elimination (RFE) retained the 10 most informative features– Recipient age at pregnancy, Tobacco dependence_1, Tobacco dependence_2, Tobacco dependence_3, Alcohol consumption_1, Mental health history_1, Pain med use_1, Pain med use_2, Pain med use_3, and Psychosocial diagnosis_1.

Table 3. Coefficients of logit regression (95% CI)

Risk Factor	Coef (95% CI)	P>|z|
Recipient Age at Pregnancy	5.48 (5.39, 5.57)	0
Educational Attainment (Zip)	-0.3 (-0.33, -0.27)	0
Tobacco dependence_1	9.24 (9.04, 9.44)	0
Tobacco dependence_2	7.56 (7.25, 7.87)	0
Tobacco dependence_3	5.66 (5.33, 5.98)	0
Tobacco dependence_4	2.57 (2.12, 3.03)	0
Tobacco dependence_5	0.73 (0.3, 1.16)	0.001
Alcohol consumption_1	8.65 (7.41, 9.88)	0
Alcohol consumption_2	2.34 (1.56, 3.13)	0
Alcohol consumption_3	4.19 (3.1, 5.27)	0
Mental health history_1	9.17 (8.74, 9.6)	0
Mental health history_2	0.3 (-0.24, 0.85)	0.275
Mental health history_3	-0.25 (-0.73, 0.23)	0.312
Mental health history_4	-0.37 (-0.95, 0.22)	0.221
Mental health history_5	-3.5 (-4.15, -2.86)	0
Pain med use_1	5.01 (4.59, 5.44)	0
Pain med use_2	2.8 (1.99, 3.6)	0
Pain med use_3	10.47 (9.4, 11.54)	0
Pain med use_4	6.79 (6.08, 7.5)	0
Pain med use_5	5.14 (4.61, 5.67)	0
Psychosocial diagnosis_1	32.39 (30.62, 34.17)	0
Psychosocial diagnosis_2	3.03 (1.86, 4.19)	0
Psychosocial diagnosis_3	-1.9 (-2.96, -0.85)	0
Psychosocial diagnosis_4	-0.9 (-2.23, 0.42)	0.181
Psychosocial diagnosis_5	-2.01 (-3.32, -0.69)	0.003
Race_Asian	-4.12 (-4.23, -4.01)	0
Race_Black	-3.22 (-3.26, -3.18)	0
Race_Caucasian	-1.85 (-1.87, -1.82)	0
Race_Hispanic	-3.97 (-4.02, -3.92)	0

Modeling Considerations

The binary logistic regression model comprises of two possible values for the dependent variable i.e. 1 or 0. We solve for a linear relationship between the predicting features and log of odds with probability p; i.e. for predictor variables x_1 and x_2:

$$\log_e \frac{p}{1-p} = \beta_0 + \beta_1 x_1 + \beta_2 x_2$$

We regressed the log odds of the risk of having opioid use resulting in NAS against the features in Table 3, to get a multivariate binary logistic regression of the nature:

$$\log_e \frac{p(\text{Risk} = 1)}{1 - p(\text{Risk} = 1)} = \beta_0 + \beta_1 * \text{Age of recipient} + \beta_2 * \text{Educational Attainment} + \beta_3 * \text{Race} + \sum_{i=1}^{5} (\beta_{4i} * \text{Tobacco dependence\_i}) + \sum_{i=1}^{5} (\beta_{5i} * \text{Alcohol consumption\_i}) + \sum_{i=1}^{5} (\beta_{6i} * \text{Mental health history\_i}) + \sum_{i=1}^{5} (\beta_{7i} * \text{Pain med use\_i}) + \sum_{i=1}^{5} (\beta_{8i} * \text{Psychosocial diagnosis\_i})$$

As multiple variables were created for each medical diagnosis type, they were tested for correlation (correlation matrix in Appendix). It was observed that features were only highly correlated with themselves, thus all 29 were used for the prediction model.

We used the min-max scalar form of normalization to transform all features to a 0 to 1 scale. This was done so that a variable with a larger range such as ‘Age of recipient’ would not outweigh the effect of smaller range variables in the regression.

K-fold cross validation (k=5) was used to split the data into training and test sets in an 80-20% mix. For each iteration, the training data set was balanced using the SMOTE oversampling technique to address the imbalance of the NAS category in the population.

Therefore, the model was trained on five folds of data with that minority class augmented to 50%. The finalized model is an average of the performance across all folds and yields the performance metrics.

Risk Score

We developed a scoring system based on the beta coefficients of a logistic regression that was comprised of only medical history indicators selected by RFE - Tobacco dependence_1, Tobacco dependence_2, Tobacco dependence_3, Alcohol consumption_1, Mental health history_1, Pain med use_1, Pain med use_2, Pain med use_3, and Psychosocial diagnosis_1. Both Tobacco dependence and Pain med use from year 1 to year 3 were combined into single features and a score similar to the HAVOC score for Atrial Fibrillation (Kwong et al., 2017) was created by assigning points to each predictor variable. Points were obtained by dividing the beta coefficients of each of the given variables by the lowest beta coefficient and rounding up to the nearest integer, therefore creating a 10-point scale.

3.3 Results

The multivariate binary logistics regression performed with an accuracy of 76.52 % and a ROC-AUC score of 80.27% implying good separability between classes in the test set. Further, a high prediction sensitivity of 84.25% is indicative of the ability of the classification model to identify the women likely to have risky opioid intake pattern from the cohort (true positive rate).

	Predicted (Risk = 0)	Predicted (Risk = 1)
Actual (Risk = 0)	TN = 36,957	FP = 11,492
Actual (Risk = 1)	FN = 241	TP = 1,290

$$\text{Accuracy} = \frac{\text{TP} + \text{TN}}{\text{Total}} = \frac{1290 + 36957}{49980} = 76.52\%$$

$$\text{Sensitivity} = \frac{\text{TP}}{\text{TP} + \text{FN}} = \frac{1290}{1290 + 241} = 84.25\%$$

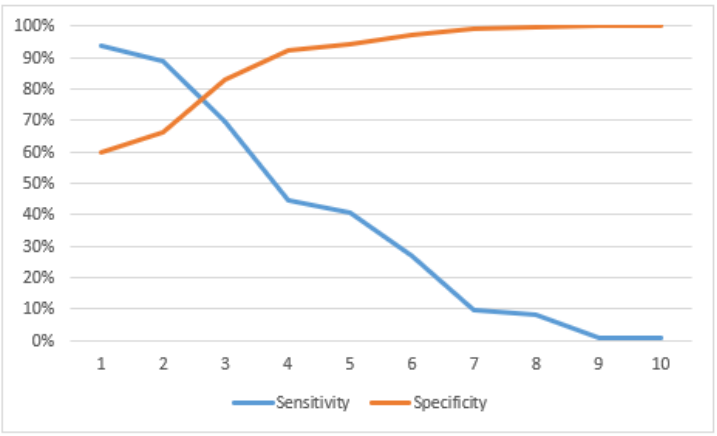
$$\text{Specificity} = \frac{\text{TN}}{\text{TN} + \text{FP}} = \frac{36957}{36957 + 11492} = 76.28\%$$

The logistic regression for the risk scoring system generated the beta coefficients and scores in Table 4. Accuracy, sensitivity and specificity for different threshold values was calculated to separate the classes and it was observed that the best trade-off between sensitivity and specificity (Fig. 3.2) was achieved at a threshold of 3. This meant that a pregnant woman who scored ≥ 3 on the 10-point scale is likely to have an opioid intake pattern resulting in the birth of a NAS baby.

Table 4. Coefficients of logistic regression for scoring system

Risk Factor	**Coef (95% CI)**	**P>|z|**	**[0.025**	**0.975]**	**Score**
Tobacco dependence (years 1-3)	8.9535	0	8.778	9.129	2
Alcohol consumption (year 1)	9.2467	0	8.209	10.284	2
Pain med use (years 1-3)	8.2193	0	7.834	8.605	2
Mental health history (year 1)	5.6714	0	5.367	5.976	1
Psychosocial diagnosis (year 1)	12.8392	0	11.856	13.822	3

For this threshold, we calculated an accuracy of 82.38%, which was higher than the accuracy of the multivariate logistic regression prediction model of 29 risk factors. This indicates that the scoring system can allow physicians to successfully classify women based on an automatic query on prior diagnosis claims and flag out recipients with a score of 3 or above.



Threshold	1	2	3	4	5	6	7	8	9	10
Accuracy	60.81%	66.86%	82.38%	90.66%	92.40%	94.88%	96.50%	96.65%	96.92%	96.92%
Sensitivity	93.78%	88.98%	69.68%	44.56%	40.76%	26.89%	9.69%	8.25%	0.71%	0.71%
Specificity	59.77%	66.16%	82.78%	92.12%	94.04%	97.04%	99.26%	99.45%	99.97%	99.98%

Figure 3.2. Sensitivity and Specificity for different threshold values of the scoring system

3.4 Discussion

The characteristics found to be most highly associated with women likely to have NAS offsprings are tobacco/nicotine use and prolonged use of pain medication. That said, alcohol, mental health and social outcomes are also indicators in the year prior to pregnancy diagnosis. The study also explores the feasibility of a scoring system in clinical practice, so that healthcare professionals can assess likelihood of NAS on a 10-point score based on the history of diagnoses for the patient.

Our findings have some limitations of the nature that women with a history of opioid dependence might avoid detection of pregnancy by opting out of medical care. The population does not account for these women and their patient journey. Further, several risk factors are subject to patient self-reporting, thus resulting in an underestimation of their incidence, which will not be systematic across all parameters.

Further a limitation of the algorithm used prevents double counting of recipients in the data, which results in the capture of only a single pregnancy for each individual woman. For a woman with more than one pregnancy during the reporting period 2014-2019, the pregnancy that is closest to a diagnosis of Opioid Use Disorder (OUD) is the one considered.

Lastly, the classification model predicts at an accuracy of 76.52% and AUC score of 80.27% which make for a good classifier. However, more advanced techniques of clustering, random forest etc. may yield a higher prediction accuracy. These methods have not been explored in the scope of this study.

4. IMPACT OF LEGISLATION ON OPIOID-BASED DOCTOR SHOPPING AMONG MEDICAID-ENROLLED PREGNANT WOMEN

4.1 Introduction

In 2019, 6.6% of pregnant women reported prescription opioid use (Ko et al., 2020), though previous studies have found that 14% to 22% of Medicaid-enrolled pregnant women filled at least one opioid prescription during pregnancy (Desai et al., 2014).

Opioid doctor shopping is the fraudulent solicitation of opioids from multiple prescribers (Perry et al., 2019). It is done by over-reporting illness or manufacturing symptoms wherein recipients go from one provider to another for concurrent prescriptions. States have developed programs and/or passed legislation in an attempt to reduce opioid prescribing, diversion, and misuse. For example, prescription drug monitoring programs (PDMP), an electronic database to track controlled substance prescriptions at the state level, have been implemented in all states. Evidence of their effectiveness, with the exception of opioid-related death rates (Patrick et al., 2016; Pardo 2017), has been weak (Finley et al., 2017; Haffajee 2019; Rhodes et al., 2019; Adams 2020).

Indiana enacted two state-based interventions, Indiana Administrative Code Title 844 in December 2013 and Indiana Public Law 194 in March 2018, which both require the use of Indiana's PDMP program INSPECT. We use a regression discontinuity model on Medicaid claims to determine if there was an associated change in the rate of opioid-based doctor shopping among Medicaid-enrolled pregnant women and the most likely associated diagnosis leading to a prescription. We also use the PageRank algorithm to determine the change in concentration of physicians that prescribe opioids to Medicaid enrolled pregnant women who doctor shop.

4.2 Methods

The state of Indiana implemented the PDMP program (INSPECT) in 2004 through the expansion of previous legislation (Norwood and Wright 2016). In 2013, Indiana enacted emergency prescribing rules, which became permanent in 2014 as the Indiana Administrative Code Title

844. This regulation triggers prescribing rules for long-term opioid users (over 60 pills a month for greater than 3 months) that advised prescribers to among other things review the patients' drug prescription history in INSPECT, schedule periodic visits for patients prescribed opioids, and obtain a signed patient agreement (Medical Licensing Board of Indiana 2014).

Morphine equivalent dose (MED) of all opioids per day per patient decreased after passage of this legislation (Al Achkar et al., 2018), though the regulation was restricted to physicians and did not directly review the prescribing habits of other healthcare professionals such as nurse practitioners. In March 2018, Indiana Public Law 194 (IN-PL-194-2018) was passed that requires physicians to review INSPECT prior to the prescribing of any opioids (Indiana General Assembly 2018). In addition, this legislation covers all medical practitioners and includes potential medical negligence penalties for non-compliance.

Table 5. Differences between Indiana Administrative Code Title 844 and Public Law 194

Indiana Administrative Code Title 844	IN-PL-194-2018 INSPECT requirements
The 2014 regulation triggers prescribing rules for long-term opioid users (more than 60 pills a month for > 3 months)	The 2018 legislation requires that physicians must check the PDMP prior to prescribing any opioids
The outcome of the regulation was that long-term existing patients could be cut off from their supply of opioids	The outcome of the law was that prescribers would have reviewed INSPECT for ongoing opioid prescriptions from another prescriber
The regulation was restricted to physicians and did not directly review prescribing habits of nurse practitioners, ER staff etc.	Legislation covered all medical practitioners and could hold them liable for negligence starting July 2018

Data

We analyzed Indiana Medicaid claims over the period of January 2014 to March 2019. The ICD9 and ICD10 codes (list in Appendix A.) were used to identify pregnant women that received an opioid prescription during pregnancy. Claims were matched to the national drug code directory (US Food & Drug Administration 2020) for prescription opiates.

The billing national provider identifiers (NPI) were used to uniquely identify prescribers. Doctor shoppers were identified as pregnant women with at least one pair of consecutive claims less than 30 days apart prescribed by different providers.

Claims that were characterized as part of an individual's doctor shopping were dated by quarter (Q1 to Q4) each year on the basis of the claim date. The quarter that a pregnant recipient procured the most prescriptions was defined as her primary doctor shopping quarter. For each quarter, we computed percent doctor shopping as 100*(number of pregnant women classified as doctor shoppers/number of pregnant women that received an opioid prescription during pregnancy).

Statistical Analysis

We used a regression model across the 21 quarters, starting at the time of passage of Indiana Administrative Code Title 844 (Q1 of 2014), to determine if there was a change in the rate of doctor shopping before and after the enactment Indiana Public Law 194 (Q1 of 2018). The regression model used is:

$$Y = a_0 + a_1 I + a_2 R + a_3 IR$$

where:
I equal 1 if observation is on or after the intervention (Q1 2018) and 0 otherwise
R is the time period minus time of the intervention, so that the intervention is scaled to 0
Y is the % doctor shopping

This results in the equation $Y = a_0 + a_2R$ pre-intervention and $Y = (a_0 + a_1) + (a_2 + a_3)R$ post-intervention. Thus, the interaction coefficient, a_3 represents the difference in slopes before and after IN-PL-194-2018 and we regressed the data in Excel to calculate the statistical significance of this coefficient.

In order to classify providers that prescribe opioids by their importance to doctor shopping we constructed a provider network where each node represented a provider and an edge was constructed between provider pairs if they were used in doctor shopping by the same individual. An illustration of the pre-enactment network is shown in Fig. 4.1.

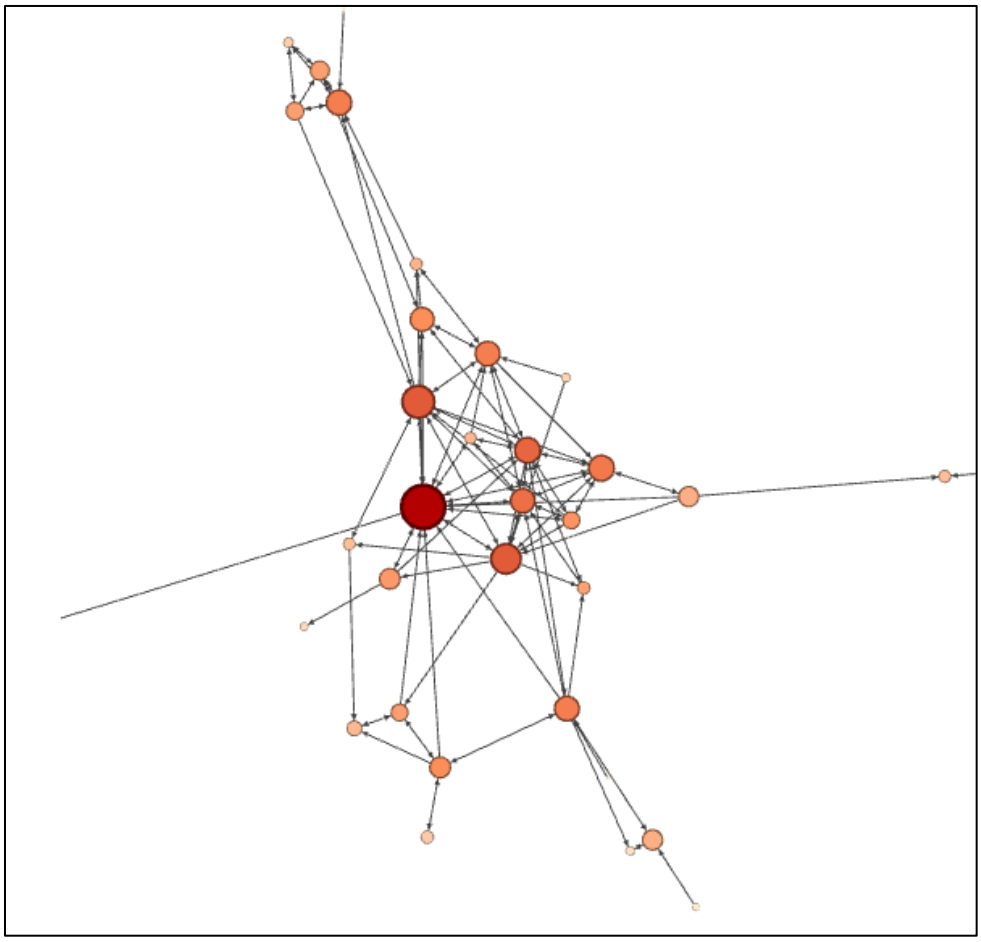


Figure 4.1. Provider network pre-enactment of IN-PL-194-2018 - size of node represents PageRank of the provider and the color represents degree of connectedness with other providers

We used the PageRank algorithm (Page et al., 1999; Xing and Ghorbani 2004) for the classification for the year prior to enactment of PL 194 (Q1 2017 to Q4 2017) and the year after enactment (Q2 2018 to Q1 2019). We included those providers that were involved with at least one case of doctor shopping and hence had a degree of at least one. We used a one-sided paired t-test to determine if there was a significant change in provider concentration based on the node degree normalized by PageRank.

4.3 Results

From the Indiana Medicaid data, 37,451 women had both pregnancy and prescription opioid claims from Q1 2014 to Q1 2019. Of these, 2,130 women met the criteria for doctor shopping. For these women, the diagnoses associated with claims of prescription opioids were primarily for abdominal pain including (in rank order): unspecified abdominal pain (ICD10 R109), right lower quadrant pain (ICD10 R1031), right upper quadrant pain (ICD10 R1011), pelvic and perineal pain (ICD10 R012) abdominal pain (ICD9 78909 and 78900), epigastric pain (ICD10 R103), lower left quadrant pain (ICD10 R1032), and lower abdominal pain unspecified (ICD10 R1030).

Fig. 4.2 shows the change in percent drug shopping among Medicaid-enrolled pregnant women over the time horizon. The regression results for the coefficients are shown in Table 5 and the output of the regression in Excel is shown in Fig. 4.3. The adjusted R^2 was 0.475 and the F statistic for the analysis of variance was significant ($p=0.003$).

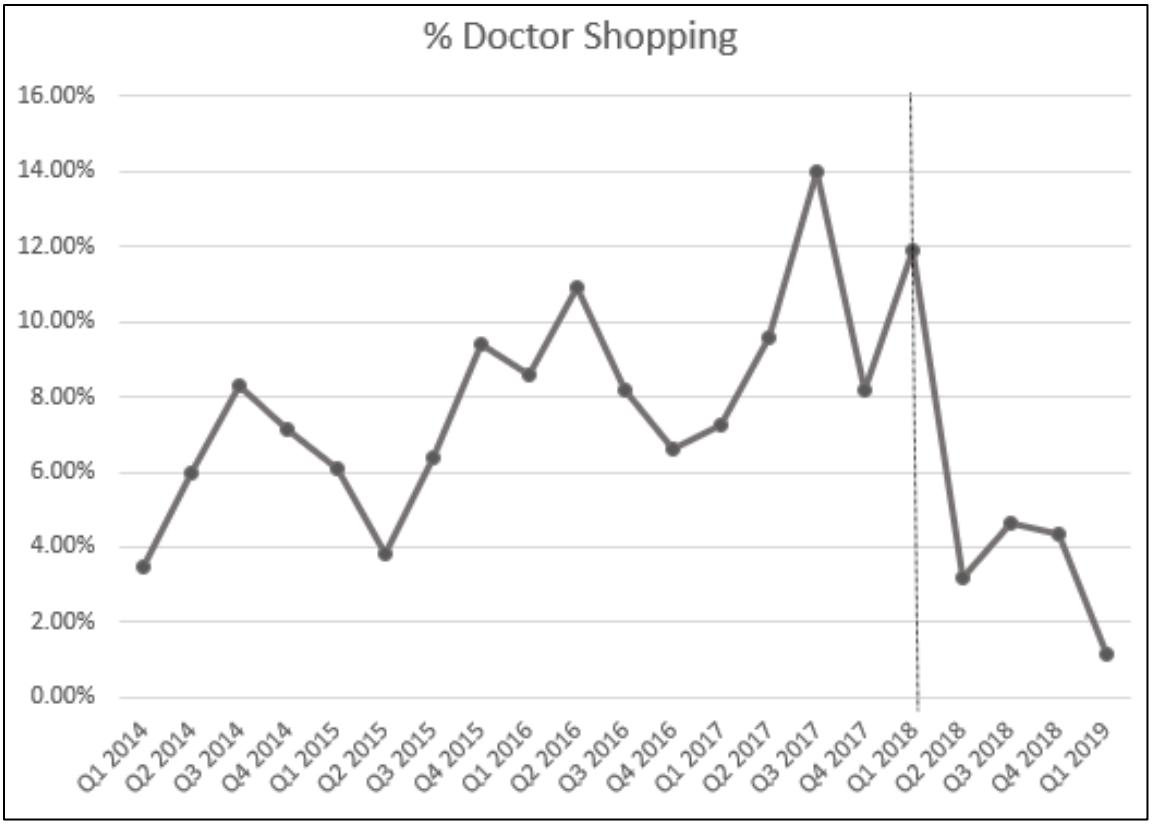


Figure 4.2. Percent of pregnant women with an opioid prescription that doctor shop over the planning horizon

Table 6. Results of the regression model for percentage of pregnant women with an opioid prescription that doctor shop over time.

Variable	**Coefficient Value**	**Standard Error**	**p-value**
Intercept	0.106	0.012	<0.000
I	-0.015	0.021	0.493
R	0.003	0.001	0.014
I*R	-0.024	0.007	0.004

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.744212216
R Square	0.553851823
Adjusted R Square	0.475119791
Standard Error	0.022526579
Observations	21

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	3	0.010709123	0.003569708	7.034644139	0.002787989
Residual	17	0.008626595	0.000507447		
Total	20	0.019335718			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	0.10581192	0.011813038	8.957214999	7.582E-08	0.080888589	0.130735252	0.080888589	0.130735252
X Variable 1	-0.014755965	0.021071686	-0.700274531	0.493229076	-0.059213335	0.029701406	-0.059213335	0.029701406
X Variable 2	0.003343743	0.001221675	2.737014667	0.014044953	0.000766234	0.005921253	0.000766234	0.005921253
X Variable 3	-0.023672134	0.007227529	-3.275273747	0.004461943	-0.038920887	-0.008423382	-0.038920887	-0.008423382

Figure 4.3. Excel output of regression model

Both the time period R and interaction term I*R were significant. The positive value of a_2 implies that the percentage of pregnant women engaging in doctor shopping increased from the time of enactment of Title 844 to the enactment of IN-PL-194-2018. The negative value of a_3 implies that the percentage of pregnant women engaging in doctor shopping decreased after enactment of PL 194. The value of a_0 implies that the overall average of percentage of pregnant women engaging in doctor shopping over the entire horizon was 10.6%.

A total of 143 providers made up the doctor shopping network. We found that the mean node degree pre-enactment was 7.22 (s.e. = 0.64; median = 4) and post-enactment was 6.77 (s.e. = 0.55; median = 5). Fig. 4.4 shows the plot of node degree of the provider versus PageRank for pre- and post-enactment. The one-sided paired t-test showed that the mean post-enactment node degree was not significantly less (p=0.12) than pre-enactment, implying that there wasn't a corresponding change in provider concentration due to legislation.

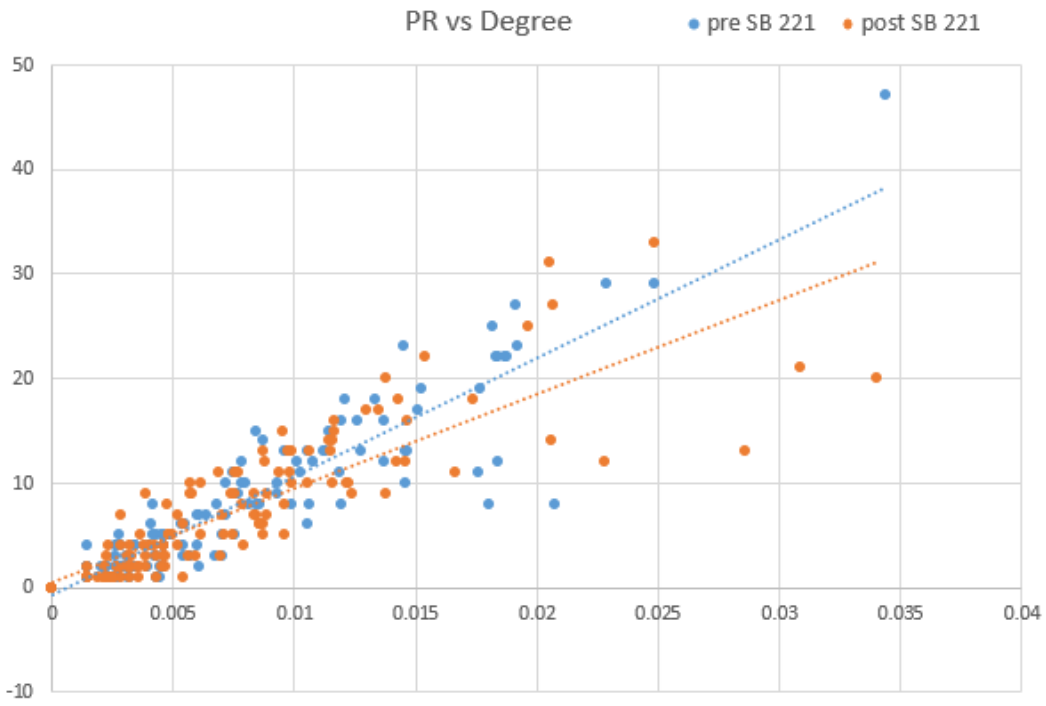


Figure 4.4. Provider PageRank versus node degree pre- and post- enactment of PL 194

4.4 Discussion

Although MEDs for all opioids per day decreased after enactment of Title 844 (Al Achkar et al., 2018), our results show that the practice of doctor shopping among Medicaid-enrolled pregnant women significantly increased. The implication is that when supply was limited, individuals with an opioid use disorder will seek alternatives (Pitt et al., 2018; Chen et al., 2018).

Doctor shopping among this group increased until the enactment of IN-PL-194-2018, after which a significant decrease followed. This points to the importance of addressing this issue from a more holistic approach since this Bill focused not just on physicians, but also a broad set of healthcare professionals including nurse practitioners and physician assistants.

It is interesting to note that although there was a decrease in doctor shopping after enactment of the public law for Medicaid-enrolled pregnant women, there was not a concurrent significant change to the underlying network structure based on the node degree of providers used for doctor shopping. This implies that the same provider set and corresponding connectedness to other

providers remained in place. Therefore, it supports the idea that doctor shopping is clustered around particular complicit prescribers that are systematically sought out by patients (Perry et al., 2019). It may be important to consider interventions that not only monitor drugs that a patient is taking but also monitoring where the prescriptions are filled in narrow time windows by the provider pairs defined by the network.

There are several limitations to our study. First, there are several alternative definitions of doctor shopping that have been used in the literature that significantly differ from ours including defining an individual who used six or more prescribers in a calendar year (Han et al., 2014). It is also possible that patients identified as “doctor shoppers” in our study instead had multiple prescribers due to poor primary care access or required visits to multiple specialists (Griggs et al., 2015).

In addition, the use of Medicaid claims limited our analysis to prescription opiates. We did not consider a possible concurrent shift to illicitly obtained opiates for this group after the enactment of IN-PL-194-2018. We also were not able to observe prescriptions filled for Medicaid-eligible patients that were not billed to Medicaid.

5. MODELING THE MOTHER-INFANT DYAD USING THE BAYESIAN BELIEF NETWORK

5.1 Introduction

Withdrawal symptoms in infants following in utero opioid exposure, also referred to as the Neonatal Abstinence Syndrome is an emerging national epidemic. Average incidence of NAS in the US increased from 1.6 per 1000 hospital births in 2004 to 8.8 per 1000 births in 2016 (Leech et al., 2020). NAS can lead to complications such as long-term motor and cognitive functioning problems, and babies born with the condition have hospital costs that are five times higher than those born without NAS (Winkelman et al., 2018). For mother-infant dyads with NAS, maternal mortality rates are 6.4 times higher and neonatal mortality and/or severe morbidity rates are 3.7 times higher than the corresponding rates of dyads without NAS (Lisonkova et al., 2019).

As in the case of reducing the negative consequences of opioid use disorder (OUD) in general, addressing NAS requires the coordination and support of multiple stakeholders including hospital units (pediatrics, neonatal intensive care units, OBGyN, nursery), treatment clinics, and social services. Further, a portfolio of interventions is typically needed to mitigate the impact (Pitt et al., 2018).

Our objective is to estimate the impact of the three interventions of i) medication assisted treatment (MAT) enrollment, ii) rooming in (with and without MAT for the mother), and iii) pharmacotherapy enrollment on the incremental costs for Medicaid. The costs considered include developmental delay and neonatal intensive care unit costs for the child and MAT and pharmacotherapy costs for the mother. The time horizon was from the time of pregnancy identification until early diagnoses of neurological delay, if it occurred.

We used a Bayesian Belief Network to capture the system dynamics for Medicaid-enrolled women and their offspring. The model was parameterized using data from Indiana Medicaid claims for the years 2014 to 2019 and supplemented with estimates from the literature. Our framework is from Medicaid's perspective with the goal of helping to inform state policy.

5.2 Methods

Bayesian Belief Networks are directed acyclic graphs in which the compartments/nodes represent variables and edges signify the dependence between linked variables. The probabilistic information for the model can be derived through analysis, previously published literature, and/or expert opinions. (Tang and McCabe, 2007)

We used the Python library BBN as the environment to create the network. A combination of literature and claims from the Indiana Medicaid database (2014-2019) were used for model parameterization. In this study, we first describe the model compartments, followed by model parameters used, and then the details of simulating the interventions and corresponding financial outcomes.

Model Compartments

The mother-child universe is comprised of 8 different nodes/compartments that take binary yes/no states with probabilities that are conditioned to previous nodes. Each compartment therefore, is a Bernoulli random variable, with conditional probability calculated by assuming that the theoretical probability of success is equal to relative frequency of success for large populations (based on the Law of Large Numbers). The model compartments are: -

1. Pregnancy diagnosed (Mother) – A pregnancy is identified using claims of the ICD 9/10 diagnosis of pregnancy (list presented in the Appendix A.). There are 247,897 such women in the Indiana Medicaid database (2014-2019) and have been considered the universe for this model.

2. Opting out (Mother) – This compartment accounts for the probability of a pregnant woman opting out of prenatal and maternal care. In OUD women, this could be to avoid detection, fear of Child Protective Services or the knowledge of not being well-insured for medical services. (Jackon & Shannon, 2012; Stone 2015; Reddy et al., 2017).

Previous literature found that almost two-thirds of pregnant women covered by Medicaid receive adequate medical care during their pregnancy (MACPAC Issue Brief, 2018). We therefore used an opting out probability of 33%.

3. MAT enrollment (Mother) – MAT is the use of medications (methadone or buprenorphine) in combination with counseling and therapy to approach substance use disorders (Medication Assisted Treatment SAMHSA, 2015). The probability of a pregnant woman being enrolled into MAT is incremented by intervals of 10% in the compartment model.

4. NAS Baby (Mother+Child) – This compartment is the probability that the baby born displays symptoms of NAS. This was calculated from the diagnosis claims (Chiang et al., 2019) for NAS (list provided in Appendix A.). We found an incidence of 9,124 in 247,897 pregnancies (3.7%).
   As we did not find evidence supporting NAS risk reduction with MAT, the probability is kept constant throughout the model.

5. Room in (Mother+Child) – The traditional approach to NAS treatment involves separating the child from the mother for observation and subsequent treatment. However, minimizing this separation and allowing them to room-in together with interventions including swaddling and on-demand feeding can improve clinical outcomes. (Moore et al., 2018)
   There is evidence that these low-tech approaches have not been utilized to their full potential. However, as nursing practices do not appear as claims in Medicaid, this cannot be validated from the Medicaid data. Therefore, for the purpose of this model, room-in probabilities are varied in increments of 10% to study their effect on outcomes.

6. NICU admission (Child) – This compartment refers to the probability of a newborn being admitted to neonatal intensive care. As the data did not have specific NICU codes, we used preterm birth as a proxy for NICU admission. The probabilities associated are the

incidence of preterm birth (ICD 9: 765.1, ICD 10: P07.00-P07.39) for children with NAS in the Medicaid data.
Preterm birth in the United States is observed in 10% babies under regular circumstances (CDC Division of Reproductive Health, 2019). For an NAS child requiring NICU admission, we found 2,378 in 9,124 (26%) babies who met the criteria from the Medicaid data.

7. Pharmacotherapy (Child) – Infants with NAS are often treated pharmacologically, with morphine sulfate being the most frequently used treatment. Alternatively, Clonidine hydrochloride, Fentanyl citrate, Hydromorphone hydrochloride, Phenobarbital and benzodiazepines have been administered as seem from NDC codes in the claims.
From the Indiana Medicaid data, we observed that 11.81% of preterm babies were given pharmacotherapy. Further, we found from the literature that that rooming in is associated with a 63% reduction in the need for pharmacotherapy (The Hospitalist, 2017). For this model, the percentage of pharmacotherapy in the absence of rooming in is varied with increments of 10%.

8. Developmental Delay (Child) – Infants with in utero opioid exposure are more susceptible to neurological complications and developmental delays. The probability of developmental delay due to pharmacotherapy was derived from subsequent claims of NAS diagnosed children in the data (ICD 9: 315.0-315.9, ICD 10: F80-F89).
We found that 51.6% of the population shows diagnosis of developmental disorder of speech or language in 18-30 months of age. For the case of non-pharmacotherapy infants, an 18.81% chance of developmental outcomes was calculated from the data.

The Bayesian Belief Network model yields absolute probabilities of each state in the mother-child universe and these probabilities can be used to simulate a cohort study. Illustrations of the model are shown in Fig. 5.1 and Fig. 5.2.

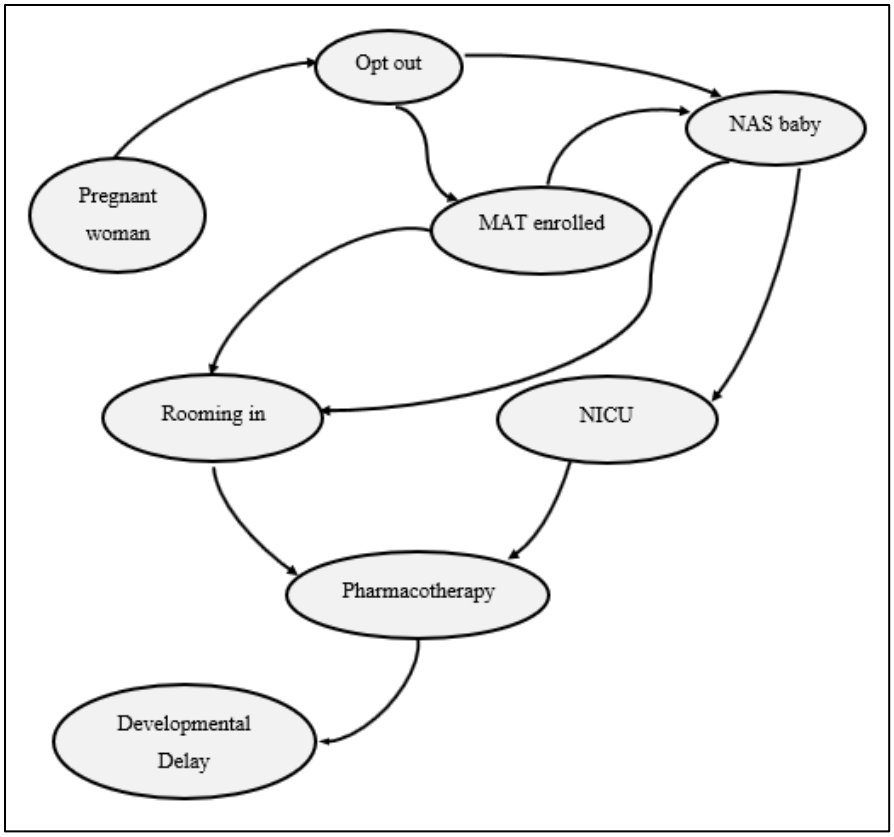


Figure 5.1. Compartment model of Mother-Infant dyad

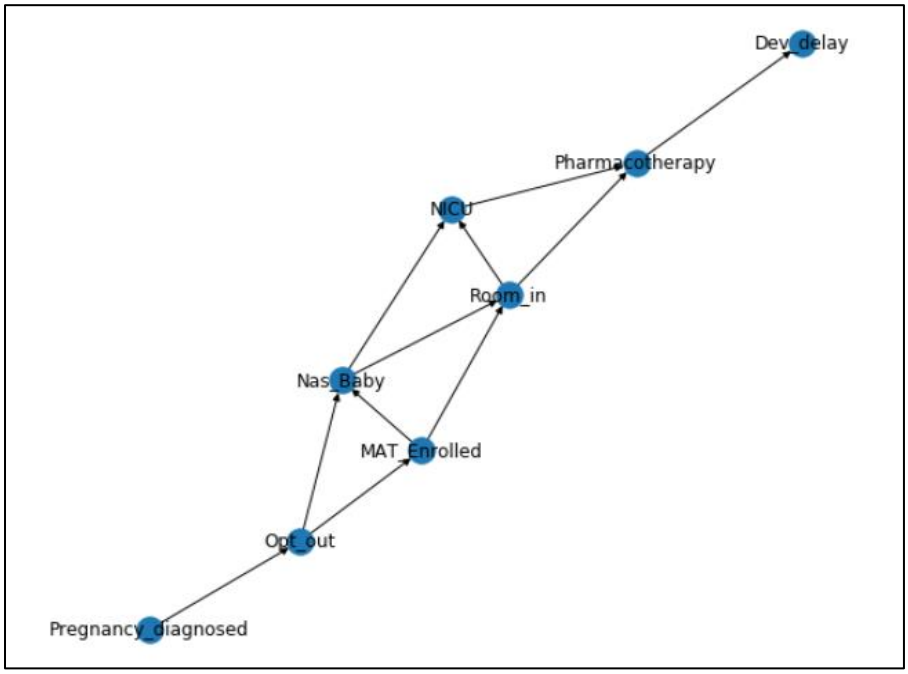


Figure 5.2. BBN of compartment model in Python library BBN

Analysis

The network is simulated by simultaneously varying parameters of MAT enrollment, Rooming in (with and without MAT for the mother) and Pharmacotherapy at increments of 10%. A constant opt-out rate of 33% is considered and the total differential cost to Medicaid for pharmacotherapy, MAT enrollment, NICU admission and developmental delay are estimated as follows.

1. Pharmacotherapy – Medicaid claims for pharmacotherapy drug codes were used to determine the distribution of a cost function for pharmacotherapy services. The goodness of fit was calculated using the Kolmogorov Smirnov test and the data fits a gamma distribution with shape 1.51629 and rate 0.0028 (p-value = 0.58; a p-value > 0.10 means that we fail to reject the null hypothesis that the gamma distribution is appropriate)

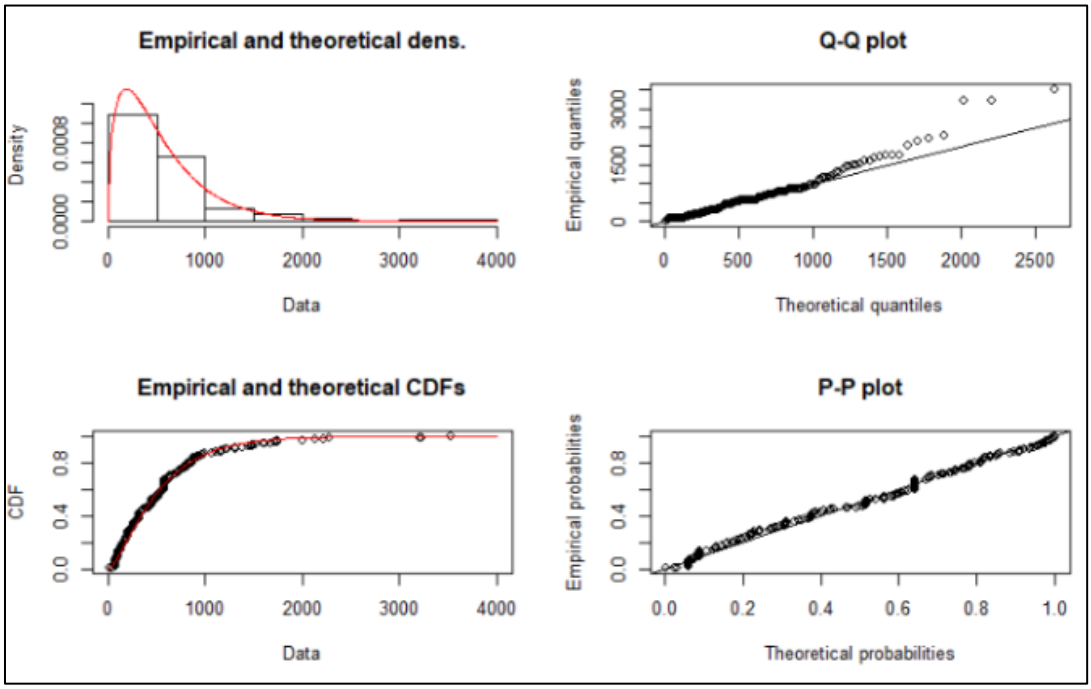


Figure 5.3. Goodness of fit test for pharmacotherapy cost with gamma distribution

2. Developmental Delay – Claims with ICD 9/10 codes for developmental delay of 1917 recipients were used to fit cost to Medicaid using the Kolmogorov Smirnov test and the data was found to fit the lognormal distribution with mean-log = 5.446, sd-log = 0.9691.

The goodness of fit of this test is low (p-val = 0.00407). However, the cdf plot shows that it is the best fit among other right skewed distributions, and so we chose to use the lognormal distribution anyway.

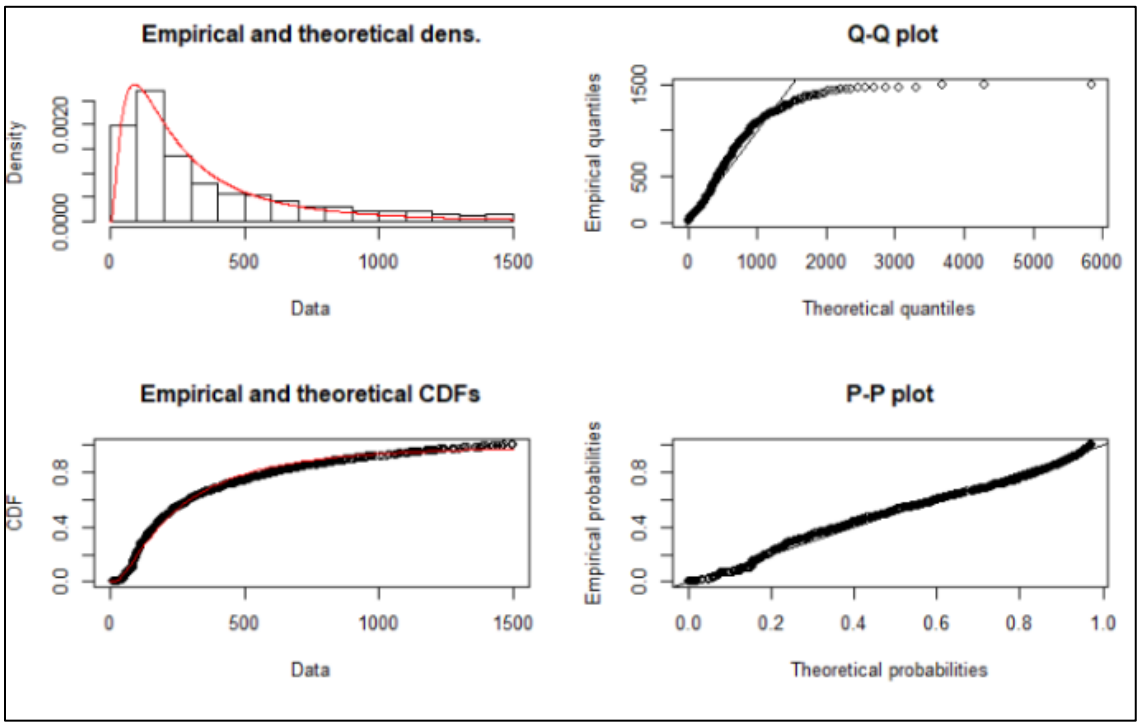


Figure 5.4. Goodness of fit test for developmental delay cost with lognormal distribution

3. MAT enrollment – Cost of MAT enrollment is approximated from the Payment Rates for Opioid Treatment Program (Centers for Medicare and Medicaid Services, 2020) in Fig. 5.5. An enrollment of 4 weeks (2 weeks of stabilization + 2 weeks taper) (National Institute on Drug Abuse, 2015) is assumed for the following costs of weekly bundles of methadone and buprenorphine.

   Thus, the cost to Medicaid is approximated as a uniform distribution with bounds (831.16, 1033.88). However, it is important to note that MAT is typically longer than 4 weeks, but for the purpose of this model we are looking at a basic enrollment cost.

Descriptor	Drug Cost	Non-Drug Cost	Total Cost
Medication assisted treatment, methadone; weekly bundle including dispensing and/or administration, substance use counseling, individual and group therapy, and toxicology testing, if performed (provision of the services by a Medicare-enrolled Opioid Treatment Program)	$35.28	$172.21	$207.49
Medication assisted treatment, buprenorphine (oral); weekly bundle including dispensing and/or administration, substance use counseling, individual and group therapy, and toxicology testing if performed (provision of the services by a Medicare-enrolled Opioid Treatment Program)	$86.26	$172.21	$258.47

Figure 5.5. Payment Rates for Opioid Treatment Program

4. NICU admission - The average length of stay in the NICU for morphine treated newborns reduces from 16.9 days to 12.3 days with the introduction of rooming in (Holmes et al., 2016). The Medicaid Fee Schedule (IHCP Fee Schedules, 2020) provides cost information for initial day NICU care (CPT code 99477) = $252.73 and neonate critical care subsequent (CPT code 99469) = $288.16. It is important to note that these amounts do not account for physician charges, hence this is the lower bound on NICU admission cost.

Cohort Simulation

We consider a cohort of N=100 pregnant women. We used 50 replications since the output parameters stabilized beyond this point. The fraction of mothers opting out of care was set to 33.33%, and for each individual and their child, we calculated the incremental costs to Medicaid as a result of the various interventions. We computed this cost for each cohort and the average and standard error across the replications.

5.3 Results and Discussion

We calculated from the BBN model that the probability of developmental delay in infants varied from 18.98% to 22.23% by changing the probabilities of MAT enrollment, rooming in and pharmacotherapy in the network. This result was found to be consistent with the literature on developmental delay that stated a maximum incidence of 19% for childhood speech and language delay (Vitrikas et al. 2017). The BBN model calculated the lowest incidence of

developmental delay for a combination of high MAT enrollment in the mother, high rooming in and low pharmacotherapy in the baby.

With regards to Medicaid-related costs incurred by the state, we derived that NICU admissions in the absence of rooming in contributed to a high financial burden ($5,123 per patient). This cost reduced to $3,798 where there was rooming in of the mother-infant dyad. These costs may differ substantially as our model considers lower bound costs for MAT and NICU enrollment.

In the cost simulation, for scenario with the highest MAT Enrollment (90%), highest rooming in (90%) and lowest pharmacotherapy without rooming in (10%), a cohort of size 100 for 50 replications resulted in an average incremental cost of $109,427 (s.e = 333).

This cost is primarily attributed to MAT enrollment for the mother; however, it has been shown that MAT is clinically effective and can help the mother sustain parental responsibilities, gain employment and maintain a self-directed life (Medication Assisted Treatment SAMHSA, 2015). These quality of life measures are not captured in our model since we are using a state Medicaid perspective.

The limitations of this model framework are due to the presence of compartments such as MAT enrollment and NICU that are difficult to quantify using diagnosis claims. The incidence of these were estimated from literature or comparative hospital studies that may not accurately represent Indiana. Further, as the Indiana Medicaid claims data is only for 5 years, we have not analyzed neurological impact that is usually observed further downstream such as ADHD and motor deficiency in young children.

Even incremental costs to Medicaid are only computed for prenatal and neonatal care practices and the future downstream costs to both mother and child are not explored in this study. Most importantly, we did not include social costs such as quality adjusted life years and employment opportunities since this analysis was done from a Medicaid cost perspective. From a social perspective, this study represents a lower bound on the value of the interventions considered.

6. CONCLUSIONS

Opioid use disorders affect women across all racial and socioeconomic groups, and pregnancy provides an opportunity for diagnosing and treating women with opioid use disorder. The study was revealing of several key results with regard to the prediction and analysis of adverse outcomes of the Opioid use and Neonatal Abstinence Syndrome co-epidemic in Indiana.

We concluded that in order to categorize an opioid using pregnant woman as capable of causing NAS to her child, there are influential risk factors such as nicotine dependence, alcohol consumption and pain medication use that care-givers can be cognizant of during diagnosis and treatment.

We studied the doctor shopping phenomenon in the state of Indiana from the lens of both patient and provider. Through a comparison of regulations by the Medical License Board in 2014 and Public Law 194 in 2018, we concluded that IN-PL-194-2018 resulted in significant decrease in doctor shopping instances. That said, legislation did not change the overall connectedness of prescribers. Further, in the context of Indiana Medicaid data recipients, the research revealed that abdominal pain was the most commonly manufactured symptoms to solicit prescriptions. These are useful insights in the direction of future policy formulation for prescription monitoring.

The research also conducted a probabilistic analysis of the OUD pregnant mother and NAS infant using a compartment model. For an NAS incidence of 37 in 1000, we observed that the developmental delay seen in infants between 18-24 months of age varies from 18-22%. This variance is observed due to interventions such as enrolling the mother into treatment, rooming in the mother and child, varying dependence on morphine and other forms of pharmacotherapy.

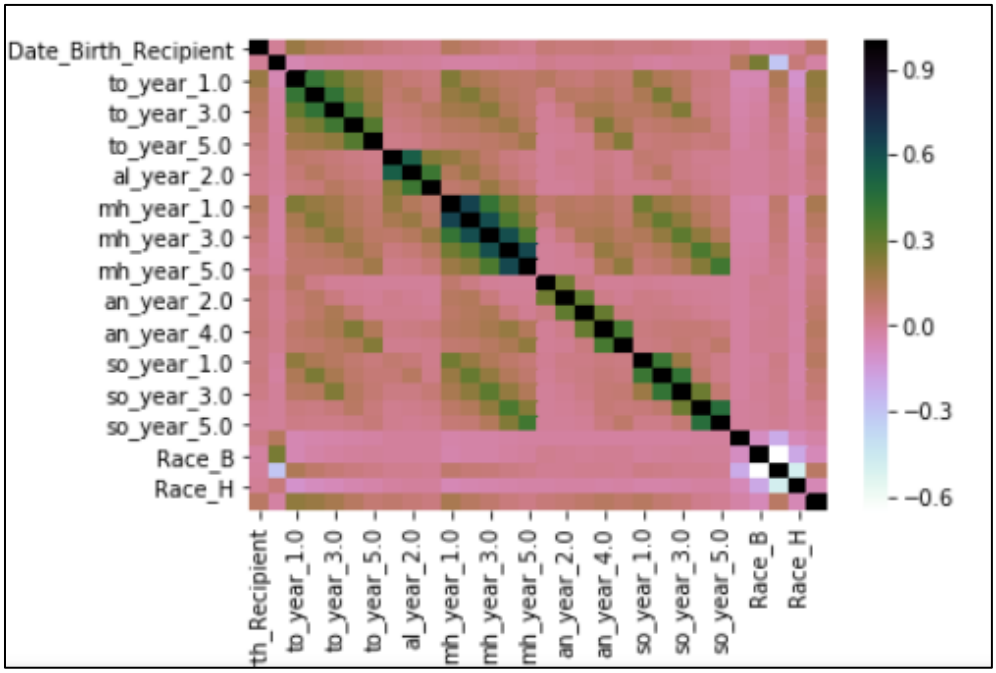
Our study helped reinforce recent literature on the benefits of rooming in for the dyad in order to lower costs to Medicaid from NICU stay and improve outcomes for both mother and child. Despite these limitations, the work is an analytical framework to further modeling and understanding of the opioid crisis in pregnant women, the cost to the state and the pathways of care that may drive recovery and alleviate some problems associated with opioid use.

APPENDIX A.

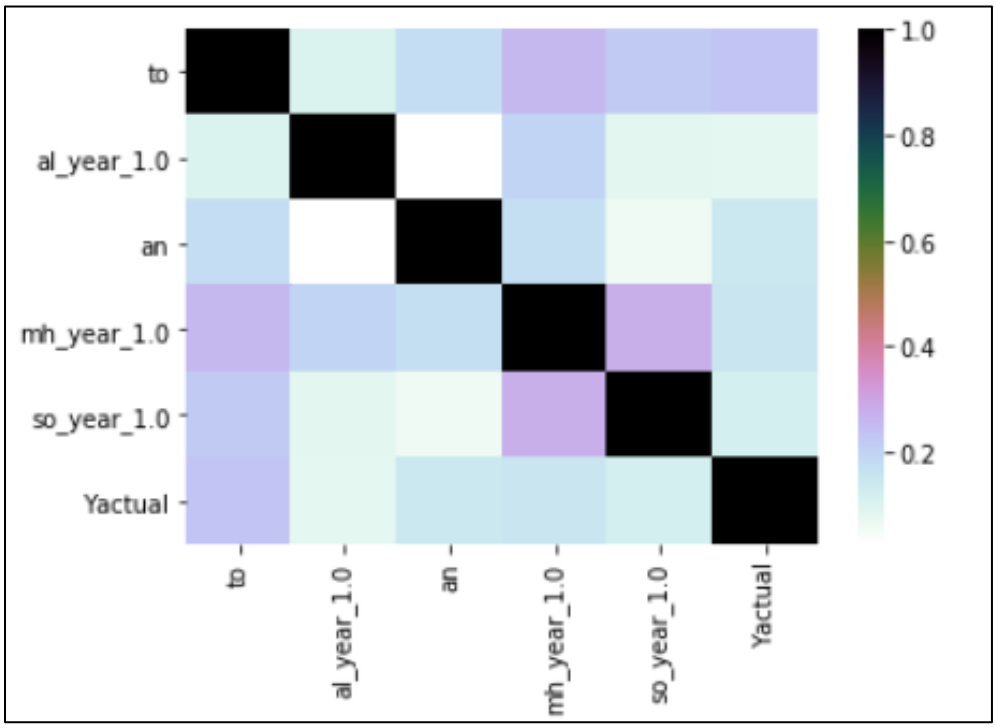
ICD 9/10 Codes

Category	Diagnosis Code	ICD 9/10	Description
Pregnancy	V22, V23	ICD 9	Pregnancy (Normal/High Risk)
	O00.00-O9A.53	ICD 10	Pregnancy, childbirth and puerperium
	Z33.1-Z33.3, Z34.00-Z34.93	ICD 10	Encounter for pregnancy
Opioid Use Disorder	292.0	ICD 9	Drug withdrawal
	304.0-304.03, 304.70-304.73	ICD 9	Opioid dependence
	305.50 - 305.53	ICD 9	Nondependent abuse of opioids
	965, 965.09	ICD 9	Poisoning by opiates and other related narcotics
	E850.2, E935.2	ICD 9	Accidental poisoning/adverse effects of other opiates
	F11.10-F11.99	ICD 10	Opioid related disorders
	T40.1X5A, T40.1X5D, T40.1X5S	ICD 10	Adverse effects of heroin
Neonatal Abstinence Syndrome	779.5	ICD 9	Drug withdrawal syndrome in newborn
	760.70-760.75	ICD 9	Alcohol/narcotics affecting fetus or newborn via placenta or breast milk
	P04.4, P04.49	ICD 10	Newborn affected by maternal use of drugs of addiction
	P96.1, P96.2	ICD 9	Neonatal withdrawal symptoms

APPENDIX B.



Correlation Matrix of 29 risk factors for causing NAS



Correlation Matrix of most informative features with binary dependent variable

APPENDIX C.

Prescription Opiates from the National Drug Code Directory, US Food & Drug Administration:

ACETAMINOPHEN; HYDROCODONE BITARTRATE
ACETAMINOPHEN; OXYCODONE HYDROCHLORIDE
BENZHYDROCODONE HYDROCHLORIDE; ACETAMINOPHEN
BUPRENORPHINE
BUPRENORPHINE HYDROCHLORIDE
BUPRENORPHINE HYDROCHLORIDE; NALOXONE
BUPRENORPHINE HYDROCHLORIDE; NALOXONE HYDROCHLORIDE
BUPRENORPHINE; NALOXONE
FENTANYL, FENTANYL CITRATE
HYDROCODONE BITARTRATE
HYDROCODONE BITARTRATE; ACETAMINOPHEN
HYDROCODONE BITARTRATE; CHLORPHENIRAMINE MALEATE
HYDROCODONE BITARTRATE; HOMATROPINE METHYLBROMIDE
HYDROCODONE BITARTRATE; IBUPROFEN
HYDROCODONE; CHLORPHENIRAMINE
HYDROMORPHONE HYDROCHLORIDE
MEPERIDINE HYDROCHLORIDE
METHADONE HYDROCHLORIDE
MORPHINE SULFATE
MORPHINE SULFATE; NALTREXONE HYDROCHLORIDE
OXYCODONE
OXYCODONE HYDROCHLORIDE
OXYCODONE HYDROCHLORIDE; ACETAMINOPHEN
OXYCODONE HYDROCHLORIDE; ASPIRIN
OXYCODONE HYDROCHLORIDE; IBUPROFEN
OXYCODONE; ACETAMINOPHEN
TAPENTADOL HYDROCHLORIDE

REFERENCES

Chan WKV, D'Ambrogio A, Zacharewicz G, Mustafee N, Wainer G, and Page E. Modeling approaches, challenges, and preliminary results for the opioid and heroin co-epidemic crisis. *IEEE*. 2017; 978-1-5386-3428-8.

National Institute on Drug Abuse. Indiana, Opioid-Involved Deaths and Related Harms. 2020. Available at: https://www.drugabuse.gov/drug-topics/opioids/opioid-summaries-by-state/indiana-opioid-involved-deaths-related-harms. Accessed December 30, 2019.

Anbalagan S, Mendez MD. Neonatal Abstinence Syndrome. *StatPearls Publishing*. 2020.

Sanlorenzo LA, Stark AR, Patrick SW. Neonatal abstinence syndrome: an update. *Current opinion in pediatrics*. 2018; 30(2), 182–186.

Kraft WK, Stover MW, Davis JM. Neonatal abstinence syndrome: Pharmacologic strategies for the mother and infant. *Seminars in perinatology*. 2016; 40(3), 203–212.

Chiang KV, Okoroh EM, Kasehagen LJ, Garcia-Saavedra LF, Ko JY. Standardization of state definitions for neonatal abstinence syndrome surveillance and the opioid crisis. *The Americal Journal of Public Health*. 2019; 109(9):1193-1197.

Jansson LM, Velez ML. Optimal Care for NAS: Are We Moving in the Wrong Direction?. *Hospital pediatrics*. 2019; 9(8), 655–658.

Leech AA, Cooper WO, McNeer E, Schoot TA, Patrick SW. Neonatal abstinence syndrome in the United States, 2004-16. *Health Affairs*. 2020; 39: 764-767.

Winkelman, T. N. A., Villapiano, N., Kozhimannil, K. B., Davis, M. M., & Patrick, S. W. (2018) Incidence and costs of neonatal abstinence syndrome among infants with Medicaid: 2004-2014. *Pediatrics*, 141(4), e20173520.

Holmes AV, Atwood EC, Whalen B, Beliveau J, Jarvis JD, Matulis JC, Ralston SL. Rooming-In to Treat Neonatal Abstinence Syndrome: Improved Family-Centered Care at Lower Cost. *Pediatrics*. 2016; 137(6):e20152929.

Desai RJ, Hernandez-Diaz S, Bateman BT, Huybrechts KF. Increase in prescription opioid use during pregnancy among Medicaid-enrolled women. *Obstet Gynecol*. 2014; 123:997–1002.

Kennare R, Heard A, Chan A. Substance use during pregnancy: risk factors and obstetric and perinatal outcomes in South Australia. *The Australian and New Zealand Journal of Obstetrics and Gynaecology (ANZJOG)*. 2005.

Harter K. Opioid use disorder in pregnancy. *The mental health clinician*. 2019; 9(6), 359–372.

Han H, Kass PH, Wilsey BL, Li CS. Increasing trends in Schedule II opioid use and doctor shopping during 1999–2007 in California. *Pharmacoepidemiology and Drug Safety*. 2014; 23:26-35.

Griggs CA, Weiner SG, Feldman JA. Prescription drug monitoring programs: examining limitations and future approaches. *Western Journal of Emergency Medicine*. 2015; 16(1):67.
McDonald DC, Carlson KE. Estimating the prevalence of opioid diversion by "doctor shoppers" in the United States. *PloS one*. 2013; 8:e69241.

Perry BL, Yang KC, Kaminski P, Odabas M, Park J, Martel M, et al. Co-prescription network reveals social dynamics of opioid doctor shopping. *PLoS ONE*. 2019; 14(10): e0223849.

Al Achkar M, Grannis S, Revere D, MacKie P, Howard M, Gupta S. The effects of state rules on opioid prescribing in Indiana. *BMC Health Services Research*. 2018; 18:1-7.

Adams N, Gundlach E, Cheng CW. An Analysis of State-Level Policies and Opioid Overdose Deaths. *Western Journal of Nursing Research*. 2020 Jan 16:0193945919897538.

Pitt, A.L., Humphreys, K., & Brandeau, M.L. (2018). Modelling health benefits and harms of public policy responses to the US opioid epidemic. *American Journal of Public Health*, 108(10), 1394-1400.

Chen Q, Larochelle MR, Weaver DT, Lietz AP, Mueller PP, Mercaldo S, Wakeman SE, Freedberg KA, Raphel TJ, Knudsen AB, Pandharipande PV, Chhatwal J. Prevention of Prescription Opioid Misuse and Projected Overdose Deaths in the United States. *JAMA Network Open*. 2019; 2(2):e187621.

Bobashev G, Goree S, Frank J, Zule W. Pain Town, an Agent-Based Model of Opioid Use Trajectories in a Small Community. *In: Thomson R., Dancy C., Hyder A., Bisgin H. (eds) Social, Cultural, and Behavioral Modeling. SBP-BRiMS 2018.*

US Census Bureau, High School Graduate Higher and Bachelor's Degree or Higher by Indiana County, 1990 and 2000. 2001. Available at: http://www.stats.indiana.edu/web/county/edattain00.asp. Accessed September 23, 2019.

Kwong C, Ling AY, Crawford MH, Zhao SX, Shah NH. A Clinical Score for Predicting Atrial Fibrillation in Patients with Cryptogenic Stroke or Transient Ischemic Attack. *Cardiology*. 2017; 138(3):133-140.

Ko JY, D'Angelo DV, Haight SC, Morrow B, Cox S, von Essen BS, Strahan AE, Harrison L, Tevendale HD, Warner L, Kroelinger CD. Vital signs: Prescription opioid pain reliever use during pregnancy—34 US Jurisdictions, 2019. *MMWR Morb Mortal Wkly Rep*. 2020; 69:897.

Patrick SW, Fry CE, Jones TF, Buntin MB. Implementation of prescription drug monitoring programs associated with reductions in opioid-related death rates. *Health Affairs*. 2016; 35(7):1324-32.

Pardo B. Do more robust prescription drug monitoring programs reduce prescription opioid overdose?. *Addiction*. 2017; 112(10):1773-1783.

Finley EP, Garcia A, Rosen K, McGeary D, Pugh MJ, Potter JS. Evaluating the impact of prescription drug monitoring program implementation: a scoping review. *BMC Health Services Research*. 2017; 17(1):420.

Haffajee RL. Prescription drug monitoring programs—friend or folly in addressing the opioid-overdose crisis?. *New Engl J Med*. 2019; 381(8):699.

Rhodes E, Wilson M, Robinson A, Hayden JA, Asbridge M. The effectiveness of prescription drug monitoring programs at reducing opioid-related harms and consequences: a systematic review. *BMC Health Services Research*. 2019; 19(1):784.

Norwood CW, Wright ER. Integration of prescription drug monitoring programs (PDMP) in pharmacy practice: Improving clinical decision-making and supporting a pharmacist's professional judgment. *Research in Social and Administrative Pharmacy*. 2016; 12:257-266.

Indiana General Assembly. Indiana Administrative Code Title 844 Medical Licensing Board of Indiana. 2015. Available at: http://iac.iga.in.gov/iac/iac_title?iact=844&iacv=iac2015 Accessed October 13, 2020.

Indiana General Assembly. Senate Enrolled Act No. 221. 2018. Available at: http://iga.in.gov/legislative/2018/bills/senate/221#document-879a0ea2 Accessed October 13, 2020.

US Food and Drug Administration. National Drug Code Directory. 2020. Available at: https://www.fda.gov/drugs/drug-approvals-and-databases/national-drug-code-directory Accessed September 24, 2020.

Xing W, Ghorbani A. Weighted pagerank algorithm. In Proceedings Second Annual Conference on Communication Networks and Services Research, 2004. 2004 May 21 (pp. 305-314). IEEE.

Lisonkova, S., Richter, L.L., Ting, J., et al. (2019). Neonatal abstinence syndrome and associated neonatal and maternal mortality and morbidity. *Pediatrics*, 144(2), e20183664.

Tang Z, McCabe BY. Developing Complete Conditional Probability Tables from Fractional Data for Bayesian Belief Networks. *Journal for Computing in Civil Engineering*. 2007; 21(4):265-276.

Jackson, A. & Shannon, L. (2012). Barriers to receiving substance abuse treatment among rural pregnant women in Kentucky. *Maternal and Child Health Journal*, 2012, vol. 16(9), 1762-1770.

Reddy, U. M., Davis, J. M., Ren, Z., & Greene, M. F. (2017). Opioid Use in Pregnancy, Neonatal Abstinence Syndrome, and Childhood Outcomes: Executive Summary of a Joint Workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, American Congress of Obstetricians and Gynecologists, American Academy of Pediatrics, Society for Maternal-Fetal Medicine, Centers for Disease Control and Prevention, and the March of Dimes Foundation. *Obstetrics and Gynecology*, 130(1), 10.

Stone, R. (2015). Pregnant women and substance use: fear, stigma, and barriers to care. *Health & Justice*, 2015, 3(1), 2.

Medicaid and CHIP Payment and Access Commission. Access in Brief: Pregnant Women and Medicaid. 2018. Available at: https://www.macpac.gov/wp-content/uploads/2018/11/Pregnant-Women-and-Medicaid.pdf Accessed May 21, 2020.

Substance Abuse and Mental Health Services Administration. Medication-Assisted Treatment (MAT). Available at: https://www.samhsa.gov/medication-assisted-treatment. Accessed June 5, 2020.

Health Affairs Blog. Opioid Crisis In Medicaid: Saving Mothers And Babies. Available at: https://www.healthaffairs.org/do/10.1377/hblog20180426.63403/full/. Accessed June 3,2020.

Centre for Disease Control and Prevention. Division of Reproductive Health. Preterm Birth. Available at: https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm. Accessed May 30, 2020.

The Hospitalist. Study: Don't separate NAS infants from moms. Available at: https://www.the-hospitalist.org/hospitalist/article/146401/pediatrics/study-dont-separate-nas-infants-moms. Accessed May 30, 2020.

National Institute on Drug Abuse. Long-Term Follow-Up of Medication-Assisted Treatment for Addiction to Pain Relievers Yields "Cause for Optimism". 2015. Available at: https://archives.drugabuse.gov/news-events/nida-notes/2015/11/long-term-follow-up-medication-assisted-treatment-addiction-to-pain-relievers-yields-cause-optimism. Accessed April 20, 2020.

Centers for Medicare and Medicaid Services. CY2020 Final Payment Rates for Opioid Treatment Program (OTP). 2020. Available at: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/Opioid-Treatment-Program/Downloads/CY2020-OTP-Payment-Rates.pdf. Accessed September 16, 2020.

Indiana Medicaid. IHCP Fee Schedules- Copyright Agreement. 2020. Available at: http://provider.indianamedicaid.com/ihcp/Publications/MaxFee/fee_home.asp. Accessed September 18, 2020.

Vitrikas K, Savard D, Bucaj M. Developmental Delay: When and How to Screen. *Am Fam Physician*. 2017; 96(1):36-43. PMID: 28671370.