Competition, Adherence, and Racial and Ethnic Disparities in the Medication-Assisted Treatment Market for Opioid Use Disorder

by

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DEDICATION

I dedicate my dissertation to my family. To my wife, Ciria Gibbons, I want to thank you for giving me a sense of purpose and for the motivation to get through the many challenges during my studies. You are my rock and the love of my life. Thank you to my loving parents, Carol and Robert Gibbons, whose many words of encouragement and support over the years allowed me to fulfill my maximum potential. To my uncle, Michael Homa, thank listening to my thoughts and ideas and playing monopoly with me as a child (I am sorry for cheating so much). To my sister, Julie Gibbons, her husband, Jon Klein, and my adorable nephew, Ethan Klein, thank you for always supporting my goals and aspirations.

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TABLE OF CONTENTS

LIST OF TABLES

CHAPTER I TABLES

CHAPTER II TABLES

CHAPTER III TABLES

LIST OF FIGURES

CHAPTER I FIGURES

CHAPTER II FIGURES

CHAPTER III FIGURES

LIST OF APPENDICES

ABSTRACT

Medication-Assisted Treatments (MAT) are pharmaceutical products used to treat patients' opioid use disorder and have become essential therapies in combatting the devastating effects of the United States Opioid Epidemic. However, several issues plague the MAT market, such as those related to manufacturer competition, patient adherence, and racial and ethnic treatment disparities. This dissertation studied each of these issues in individual chapters. The first chapter evaluated a defining antitrust event in the MAT market. Specifically, Reckitt Bensickler violated the Sherman Antitrust Act when they launched Suboxone Film and made false claims regarding the safety of Suboxone Tablet in order to switch patients to the film. This action, known as a product hop, allowed Reckitt to maintain high market share and prices in the MAT market for years after the expiration of their patent on Suboxone Tablet. . I determined the clinical consequences of this event by comparing observed health outcomes with predicted outcomes in a counterfactual scenario where the product hop never occurred. But for the product hop, I found that there would have been roughly 10% fewer adverse opioid events between 2010-2017 due to changes in treatment use. In response, I suggested additional scrutiny of the FDA regarding the added clinical benefit of line extensions to prevent product hops from successfully derailing generic entry. The second chapter studied the financial and clinical consequences of patient nonadherence to MATs. In particular, I estimated the effect of buprenorphine treatment gaps on adverse opioid events and monthly patient total spending, medical spending, and prescription drug spending. During months in which patients had more than half the days without MAT treatment (i.e., a "gap month"), I showed that the risk of adverse opioid events was 2.83-7.79 times higher, which translated to a $63.7-$684.6 increase in total spending in that month. I further demonstrated a large increase in medical spending in months with treatment gaps that exceeded decreases in prescription drug spending. I also found evidence of heterogeneity in effect of buprenorphine treatment gaps by dosage. Patients experienced fewer costly adverse opioid events during treatment gaps with higher dosages, likely due to protective effects of residual buprenorphine. I conclude by suggesting policymakers and practitioners

increase the rate at which patients are maintained and initiated on higher dosages of buprenorphine. The final chapter of the dissertation focused on quantifying racial and ethnic MAT treatment disparities and specifically tried to measure the effect of social versus provider factors in driving these disparities. To do so, I compared base model estimates that used only indicators for race and ethnicity with additional specifications that added social vulnerability indexes, patient-provider proximity, and provider-level fixed effects. The analyses showed evidence of significant racial and ethnic disparities in MAT access and use in Medicare. They also illustrated that provider factors, such as provider bias and practice patterns, are essential modifier of MAT use in particular. As a policy recommendation, I promoted incentivizing and educating providers to expand treatment to underserved groups as well as greater investment into culturally competent addiction treatment services by state and local governments.

CHAPTER I:

Health Consequences of Strategic Delay in the Pharmaceutical Industry: The Effect of the Suboxone Product Hop on Adverse Opioid Events

ABSTRACT

A product hop is a controversial practice in which a brand pharmaceutical manufacturer acts to transition patients to a newer and slightly modified version of one of their existing products just before generic entry. By eradicating the original product's demand, generic entrants struggle to penetrate the market, and the brand manufacturer typically maintains high market share and prices on the new product. A product hop harms patients financially by restricting the use of less expensive generic alternatives, but little is known about how it might also affect patient health. This study determined the clinical effect of the Suboxone product hop, which disrupted the market for Medication-Assisted Treatments (MAT) for opioid use disorder during a critical growth period of the U.S. Opioid Epidemic. In particular, this study estimated the effect of the Suboxone product hop on adverse opioid events (e.g., opioid abuse, overdose, and adverse effects) among Medicare beneficiaries between 2010-2017. The study used a discrete-time survival model with competing risks conditioned on predicted demand in the counterfactual absence of the product hop. Without the product hop, the analyses showed a 9.6%–10.6% reduction in the number of patients experiencing one or more adverse opioid events between 2010-2017 due to increased treatment use in the counterfactual. Regulators should therefore consider evaluating the added clinical benefit of new MAT products prior to approving them.

INTRODUCTION

Deaths from opioid overdoses currently exceed car accidents in the U.S. as the number one cause of accidental death (National Safety Council, 2018). The primary treatments used to prevent deaths from opioid overdose are Medication-Assisted Treatments (MATs). MATs are drugs that remediate cravings and mitigate symptoms of withdrawal following the long-term use of opiates. However, pharmaceutical manufacturer Reckitt Bensickler fundamentally changed the MAT market in the early 2010s by *product hopping*.

To maintain its dominance in the MAT market, Reckitt launched a film reformulation of their blockbuster MAT, Suboxone tablet, and then acted to shift patients and providers from the tablet to the film in the period just before generic entry (Carrier, 2017). By transitioning over 70% of tablet users to the film before generics could enter the market, Reckitt maintained a high market share and price for Suboxone film for years after generic Suboxone tablets had launched (Suboxone Complaint, 2015). Despite the product hop's significance in shaping MAT pricing and use, its effect on patient health is unknown.

A product hop can affect patient health by changing prices and use patterns. The primary concern antitrust regulators have with a product hop is that they can sustain high treatment prices by limiting generic entry and market penetration. The resulting lack of affordable treatment threatens population health by reducing treatment initiation and adherence (Gibson et al., 2005). However, if the innovation provides clinical benefit for at least some proportion of the population above and beyond existing treatments, its entry may be justifiable.

This study estimated the effect of the Suboxone product hop on adverse opioid events (i.e., opioid overdose, abuse, and adverse effects) using a discrete choice model linked to a discrete-time survival model under a counterfactual analysis. First, a discrete choice model estimated under mixed-effects logistic regression was used to determine empirical MAT demand. I then modified covariates and patient choice sets to reflect firm behavior in a hypothetical world where the product hop never occurred to obtain the counterfactual product choice probabilities. From there, the study used a survival model to relate time-varying treatment decisions to adverse opioid events. I then generated the approximate frequency of adverse opioid events without the product hop from this model after replacing the observed choices with counterfactual choice probabilities. In the absence of the product hop, I find a 9.6%–10.6% decrease in total adverse

opioid events between 2010-2017 relative to the observed. The analyses show that this reduction is primarily a consequence of increased MAT use in the counterfactual.

BACKGROUND

Details surrounding the role of MATs in counteracting the opioid crisis, firm incentives for strategic delay behaviors like product hopping in the pharmaceutical entry, and the Suboxone antitrust litigation inform the conceptual framework and empirical model presented in the paper. Therefore, the background section is separated into three different sections. Section 1 reviews essential considerations in the MAT product market, such as differences between MAT products and MAT use in Medicare, the study setting. Next, section 2 explains firms' motivations behind product hopping and its implications for patients. Finally, section 3 describes the primary sequence of events that represented the Suboxone product hop.

Section 1: The U.S. Opioid Crisis and Medication Assisted Therapies

Between 1999–2018, the U.S. opioid epidemic killed nearly 450,000 Americans or approximately 62 per day (Center for Disease Control, 2018). Opioid overdoses are by far the most common kind of drug overdose in the U.S. In 2018, opioid overdoses represented about 70% of all fatal overdoses (Department of Health & Human Services, 2018). This fact is particularly concerning as growth in abuse has been staggering over the last decade. For example, between July 2016 and September 2017, total emergency department visits for opioid overdoses increased by 30% (Centers for Disease Control, 2018). In 2018, 10.3 million people aged 12 or older misused opioids (Lipari and Park-Lee, 2018).

Opioid manufacturers and physicians have been the primary defendants in litigation brought by state and federal prosecutors in response to the opioid epidemic. These prosecutors have recovered billions of dollars through class action settlements with these parties following allegations that they put financial gain before their patients' lives. However, culpability may extend beyond opioid prescribers. In particular, by product hopping, Reckitt likely hindered access to one of the most vital opioid use disorder treatments during the height of the epidemic. Although Reckitt has faced legal consequences for the Suboxone product hop for antitrust and fraud violations, their role in limiting the use of generic MATs as the epidemic worsened has not yet been explored as a contributing factor to the consequences of the crisis.

MATs are critical therapies that treat opioid use disorder by reducing the risk of opioid overdose and associated mortality. Specifically, MATs dampen consumer cravings for opiates and symptoms of opioid withdrawal, making cessation easier and less risky for patients. Patients also typically receive MATs as a part of a more comprehensive treatment program, which commonly includes detoxification and counseling-based services. Treatment with MATs is often long-term, having a baseline recommendation of at least 12 months.

There are three distinct classes of MATs based on their primary active ingredient: methadone, buprenorphine, and naltrexone. Methadone is unique because it is only delivered in a controlled setting under physician supervision once per day. Physician supervision is required when prescribing methadone because it is a full opioid agonist, and can therefore be abused by patients, given its euphoric effects. Buprenorphine is a partial opioid agonist and is therefore permitted to be prescribed for use at home as its euphoric effects are moderate relative to Methadone. Unlike Buprenorphine and Methadone, Naltrexone blocks opioid receptors instead of activating them to reduce cravings. Naltrexone can be delivered either through a long-lasting injection in a physician's office once a month or daily in a tablet form at home. However, Naltrexone reduces tolerance to other opioids, and so those who discontinue Naltrexone treatment and subsequently relapse may be at higher risk of overdose.

Suboxone is a buprenorphine-based MAT, which includes Naloxone as a secondary active ingredient. Naloxone is used in conjunction with buprenorphine to dampen the euphoric effects and prevent misuse. However, the buprenorphine component remains effective in preventing withdrawal and cravings, the primary purpose of MAT. The combination of these factors is why Suboxone has become a prevalent treatment option for patients with opioid use disorder, especially in Medicare, where opioid use disorder is common.

Opioid use and opioid use disorder are common in Medicare. In 2016, providers wrote 79.4 million opioid prescriptions for Medicare beneficiaries, and around 500,000 beneficiaries were at risk of opioid use disorder due to their opioid use (Department of Health & Human Services, 2017). The high rate of opioid use disorder in conjunction with a highly vulnerable population makes Medicare beneficiaries an important population to study the health consequences stemming from the Suboxone product hop. Therefore, this study will estimate the effects of the Suboxone product hop on patient health using a population of Medicare fee-for-service (FFS) beneficiaries.

Section 2: Product Hopping

A *product hop* is when a brand pharmaceutical manufacturer develops a modified version of an existing medication that they sell (i.e., reformulation) and then acts to switch patients and prescribers to the new product just before generic entry. By the time the generics finally enter the market, most patients are already taking the new product and do not substitute again. Further, pharmacies cannot automatically replace the new product with the generic for the original product due to chemical differences (i.e., non-bioequivalent). In some cases, the reformulated product offer additional clinical benefits. However, even when clinical benefits are marginal, physicians may still prescribe the line-extended product over the generic for the originator if they are unaware of generic entry. Physicians may also be under the false impression that the reformulated product is superior due to the brand manufacturer's false marketing claims used to facilitate the product hop. Therefore, regardless of added clinical benefit of the line-extension, patients are often prescribed the reformulated product for years after the originator's generics have entered.

The most common way a brand manufacturer transitions demand in a product hop is by increasing the old product's price and investing heavily in promoting the new product. This behavior is referred to in the product hop literature as a "soft hop," which contrasts with a "hard hop," where the brand discontinues the originator entirely so that providers can no longer prescribe it (Carrier and Shadowen, 2016). In the case of Suboxone, Reckitt did both. First, Reckitt soft hopped by detailing physicians and raising the tablet price in the period before generic entry to make it less affordable relative to the film. Reckitt then “hard hopped” by discontinuing Suboxone tablet and their buprenorphine-based Subutex tablet to increase the market share of Suboxone Film further.

The particular legal antitrust justifications of product hopping vary case by case. Still, they follow the general notion that in the absence of either a hard or soft product hop that generics would enter the market unimpeded and lower market prices rapidly (Carrier and Shadowen, 2017). However, product hopping erases demand for generics of the originator and subsequently disincentivizes future generic entrants. Without additional entrants, generic price competition is limited, and market prices remain high.

Strategies that delay and hinder generic market entry (i.e., *strategic delay*) are common in the pharmaceutical industry and have profound financial implications for patients and payers

(Shapiro, 2016). Frank and Haffajee (2020) estimated a potential $200 million cost of the Suboxone product hop in Medicaid alone. Still, clinical implications of strategic delay behaviors are likely heterogeneous due to differences in treatment guidelines and outcomes across unique pharmaceutical markets. Therefore, establishing a more general framework that can be applied to study health outcomes resulting from product hops could represent a valuable contribution to policymakers and regulators.

Section 3: The Suboxone Product Hop

Reckitt took several actions to facilitate the product hop and incentivize patients and prescribers to switch to Suboxone film (see Appendix Table 1 for Timeline of Events). First, Reckitt refused to negotiate with generics to produce a Single Shared Risk Evaluation and Mitigation Strategy (SSRS). Risk Evaluation and Mitigation Strategies (REMS) are guidelines developed by pharmaceutical manufacturers to protect population health by establishing consumption, prescribing, and distribution practices for patients, physicians, and manufacturers. As a policy, the FDA requires that any originator drug with a REMS develop an SSRS with entering generics before generic approval. In anticipation, Reckitt filed for a REMS for Suboxone tablet just six months before generics entered. Reckitt then refused to cooperate with the generic Suboxone tablet manufacturers to establish an SSRS for nine months, arguing that their REMS was proprietary. In the end, generic manufacturers submitted their own REMS separately from Reckitt, which the FDA ultimately approved.

As the generic manufacturers worked to provide the FDA with a REMS, Reckitt submitted a Citizen Petition to the FDA to create an additional delay in generic competitors' approval. A Citizen Petition is a formal notice sent by any member of the public (individual or organization) to the FDA that requests their specific action regarding a raised concern. In the case of Suboxone, Reckitt claimed that it had found pediatric exposure risks with its tablet products nearly seven years after they had started selling them. They further claimed that these risks were so significant that it required the immediate discontinuation of Suboxone tablet and the rejection of all generic tablet applicants.

Note that by filing the Citizen Petition, Reckitt triggered an FDA statute that forced the FDA to investigate and respond with a detailed analysis within 150 days. Even though the FDA has rejected 92% of Citizen Petitions filed by brand pharmaceutical manufacturers in the six months before generic entry, Citizen Petition filing is typical among brand manufacturers

(Carrier, 2018). The FDA typically will not approve additional generics until it issues its investigative report, and so the mere filing guarantees at least some approval delay. The FDA reviewed Reckitt's claims for five months before rejecting them and then approved generic Suboxone tablet manufacturers for entry on the same day. By the time generics entered the market in February 2013, Reckitt had already converted over 70% of their tablet sales to film (Suboxone Complaint, 2015).

In response to the Citizen Petition, the FDA reached out to the Federal Trade Commission (FTC) to investigate potential antitrust abuses. After review, a plethora of federal and state prosecutors sued Reckitt for defrauding the FDA and violating the Sherman Antitrust Act by unduly preventing competition from generics. The resulting litigation ultimately settled for $1.4 billion in July 2019, making it one of the largest ever opioid-related settlements (Department of Justice, 2019). Still, the litigation and subsequent literature on this topic have focused primarily on the case's financial and legal implications and have not fully explored population health consequences. Filling in the knowledge gap of how the Suboxone product hop affected patient health outcomes remains essential. The Suboxone product hop and its effect on product use and pricing may be associated with the U.S. Opioid Epidemic's severity.

To summarize, the purpose of this research is to determine how the Suboxone product hop may have affected patient health during a critical period of growth in the U.S. opioid crisis between 2010–2017. This study will also guide policymakers and regulators responding to product hopping cases in other markets by establishing an empirical framework that can determine their effects on patient outcomes. The study used a population of Medicare beneficiaries to evaluate this framework and assess the Suboxone product hop's practical significance due to the high opioid use disorder rates.

ESTIMATION

The study used the following estimation framework to determine the Suboxone product hop effect on adverse opioid events (i.e., opioid overdose, abuse, and withdrawal). First, I estimated empirical demand using a mixed-effects logistic regression choice model based on Hole (2013), which uses maximum simulated likelihood estimation. I then generated counterfactual choice probabilities by modifying the covariates' coding, and the availability of the products in patient choice sets to reflect the most plausible outcome in the absence of the

product hop. In particular, I assumed that had the product hop never occurred that Brand Suboxone film would not have entered the market and that generic Suboxone tablet would have entered in May 2012. Reckitt would have also likely decided to continue selling Suboxone and Subutex tablets, which it discontinued to support a transition to Suboxone film in September 2012. However, due to the minimal use of Subutex and brand products when a generic is covered by a Part D plan (Verma, 2020), extending Suboxone and Subutex availability would not significantly impact any findings.

After generating predicted product choice probabilities under the counterfactual, I estimated a discrete-time survival model with competing risks to relate treatment use by product over time to adverse opioid events. I then replaced the observed treatment decisions with counterfactual choice probabilities to produce approximations of adverse opioid events in the counterfactual. Finally, I calculated the product hop effect by taking the difference between the total adverse opioid event probabilities in the counterfactual and the total observed adverse opioid events.

Demand

A mixed-effect logistic regression model, often referred to as a discrete choice model with random coefficients, estimated MAT demand. the discrete choice model also predicted counterfactual demand using both individual preferences and resulting changes to them due to the product hop and additional generic entry. It also captured the product's observable and unobservable aspects that affected decision-making by incorporating product fixed effects and time-varying product characteristic covariates (e.g., price). In general, discrete choice models have an advantage over more traditional multinomial logistic regression choice models. The multinomial logistic regression model can only model the contribution of subject-specific attributes to the probability of selecting a particular product, while mixed-effect logistics regression models can incorporate product characteristics and consumer characteristics. Further, mixed-effect logistics regression can accommodate random coefficients, such as a random price coefficient that can account for heterogeneity in patient price sensitivity. More generally, demand for MAT products is a function of variation in product pricing, product quality, fixed product characteristics, and shocks from new product entry and MAT policy changes. Therefore, I specified the probability a patient chose a particular MAT product *k* in month *t* as:

$$D_{ikt} = \Pr(D_{it}^{*} = k)$$
$$= \alpha_i P_{ikt} + \zeta_k + \omega_k D_{ikt-1} + \gamma_k EntryFilm_{kt} + \theta_k EntryGeneric_{kt} + Year_{kt} + x_{it}\beta + \varepsilon_{ikt} \quad [1]$$

$$where\ k = \begin{cases} 1 & if\ "Suboxone\ Tablet" \\ 2 & if\ "Suboxone\ Film" \\ 3 & if\ "Generic\ Suboxone\ Tablet" \\ 4 & if\ "Other\ Buprenorphine" \\ 5 & if\ "Naltrexone" \end{cases}$$

The outcome, D_{ikt}, was an indicator equal to one for the selected product *k* in some decision for patient *i* in month *t*. Out-of-pocket price, P_{ikt}, represented the out-of-pocket patient-specific price for a one-day supply of the medication and was estimated using a random coefficient α_i. Product-specific fixed-effects, ζ_k, captured the unobserved (to the econometrician) quality and preferences across individual products. Previous choice dummies D_{ikt-1} indicated the last product choice by a patient in the prior month. $EntryFilm_t$ identified the period after the Suboxone film entry while $EntryGeneric_t$ qualified the period after Suboxone tablet generic entry. Individual year fixed-effects, $Year_{kt}$ separately identified the effects of the event timing indicators from other MAT demand shocks that occurred over the same period. I controlled for patient characteristics x_{it}, to address demographic and health differences that affect demand across MAT products. Finally, ε_{ikt} was an extreme value type II independent and identically distrusted (iid) error term.

Mixed effect logistic discrete choice models require that independent variables vary within each choice to identify parameter estimates. However, patient characteristics and product entry do not vary within each decision. Therefore, I interacted the product hop timing and lag choice indicators with the product fixed effects, which varied within choice by construction. These interactions had the added benefit of revealing specifically how product entry and patients' previous selections shifted the demand for individual products in the current choice, in addition to controlling for patient choice inertia (i.e., persistence) and substitution patterns. I also set patient characteristics and year-fixed effects to 0 for the "No Drug" choice alternatives. This modification allowed for estimating how these factors contributed to choice at the extensive margin (i.e., the probability of selecting any drug as opposed to no drug).

Health

A discrete-time competing risk survival model (Gibbons, R.D. et al., 2003) determined the association between treatment by product and adverse opioid events. This model was

selected instead of the standard Cox proportional hazards model because it permitted the use of time-varying treatment covariates needed to connect the discrete choice model to the adverse opioid event model in the counterfactual analysis. It also had the added benefit of allowing for all-cause mortality to be estimated separately (i.e., as a competing risk), given that mortality (unrelated to overdose) potentially obfuscates the observation of future adverse opioid events. In particular, I specified the probability of experiencing an adverse opioid event as:

$$Y_{it} = Pr(Y_{it}^* = 1) = \alpha_t + \delta_1 d_{i1t} + \cdots + \delta_5 d_{i5t} + x_{it} b + v_{it} \quad [2]$$

$$where\ Y_{it}^* = \begin{cases} 0, & if\ "No\ Event" \\ 1, & if\ "Adverse\ Opioid\ Event" \\ 2, & if\ "Mortality" \end{cases}$$

The outcome, Y_{it}, a categorical variable set to zero, one, or two based on some patient *i* experiencing no event, an adverse opioid event, or mortality in month t. D_{ikt}=$\{d_{i1t}, \ldots, d_{i5t}\}$ were indicators used to represent treatment with one of the five MAT products. Patient-level control variables, x_{it}, controlled for variation in risk related to patient characteristics. The baseline hazard function was specified using month dummies, α_t, which were normalized around the index treatment month (e.g. -3, -2, -1, 0, 1, 2, 3, where 0 is the index treatment month). Finally, v_{it} was an iid error term.

Counterfactuals

I describe the counterfactual framework used to determine the Suboxone product hop's net effect on adverse opioid events below. First, I estimated empirical MAT product demand using model [1]. Covariates were then modified to mimic the counterfactual assumptions. Specifically, I assumed that the FDA blocked the product hop by rejecting the Suboxone film New Drug Application (NDA). I also assumed that without the film's approval, Reckitt would not have acted to delay generic entry by filing a Citizen Petition and refusing to negotiate an SSRS with generic manufacturers. Therefore, I made the following changes before predicting product choice probabilities from the demand model: 1) I added generic Suboxone tablet as a choice between May 2012 and February 2013, 2) I set $EntryFilm_{kt}$ set to 0 for all observations, 3) I set $EntryGeneric_{kt}$ to one for observations that occurred after the generic Suboxone tablet's earlier entry in May 2012, and 4) I removed brand Suboxone film from all beneficiary choice sets. Note that May 2012 was the expected generic entry date but for the product hop (Suboxone Complaint, 2015), while February 2013 was the observed generic entry date.

Prices also had to be imputed for the earlier entering generic Suboxone tablet in the counterfactuals. As a first attempt, I fixed the generic tablet's out-of-pocket price during its hypothetical earlier entry period to the average price in the first year of its observed entry. However, additional generic tablet manufacturers would have likely entered the market without the product hop, leading to fiercer price competition. Therefore, I conducted a second counterfactual to account for the likelihood of additional generic entry. In particular, I obtained approximations for generic price decay in the months following entry using estimates from Berndt & Aitken (2011). They found an average price decline of 23% in the first six months after generic entry, 50% at the end of the first year, and 77% after two years. Consequently, in the second counterfactual, I decreased generic prices by 4% a month until month 6, 4.5% a month between months 6 and 12, and 2.25% each month between months 12 and 24.

Next, I estimated the counterfactual adverse opioid event probabilities by replacing observed product choices with the counterfactual choice probabilities from equation [1]:

$$\hat{Y}_{it}(\widehat{D}_{ikt}) = E\left[Pr(Y_{it}=1)|\widehat{D}_{ikt}=\hat{d}_{it1},\dots,\hat{d}_{it5}\right] = \hat{\alpha}_t + \hat{\delta}_1\hat{d}_{it1} + \cdots + \hat{\delta}_5\hat{d}_{it5} + \boldsymbol{x_{it}}\hat{\boldsymbol{b}} + \hat{v}_{it} \quad [3]$$

where $\hat{Y}_{it}$ represented predictions of adverse opioid events from equation [2] after replacing D_{itk} with $\widehat{D}_{itk}$ estimated from equation [1] under each counterfactual. Aggregating the $\hat{Y}_{it}$ from equation [3] across patients and time calculated the total number of counterfactual adverse opioid events:

$$\widehat{AOE}_{Counterfactual} = \sum_{t=1}^{T}\sum_{i=1}^{I}\hat{Y}_{it}(\widehat{D}_{itk}) \quad [4]$$

Finally, the difference between observed outcomes and estimated outcomes from equation [4] determined the effect of the Suboxone product hop on adverse opioid events:

$$\Delta AOE_{Producthop} = AOE_{observed} - \widehat{AOE}_{Counterfactual} \quad [5]$$

DATA

To study the product hop effect, I needed information regarding patient MAT treatment use and related health outcomes throughout the study period.. Medicare claims data sufficiently captured this information, and in particular contained details surrounding each patient'sMAT use and opioid use disorder outcomes over time. Ideally, one would also directly observe the consumption of MATs instead of written prescriptions to ensure compliance. Further, it is possible some outcomes that did not result in a visit with physician may be unobserved.

However, The medical consequences of opioid use disorder frequently require medical attention, which reduces the likelihood that the primary outcome, adverse opioid events went unobserved.

Study Population

The study population started with a random 20% sample of patients in the universe of Medicare Fee-for-Service beneficiaries. This sample included the elderly and patients under 65 entitled to Medicare through disability or End-Stage Renal Disease (ESRD), and excluded the Medicare Advantage population due to unobserved outcomes in this population. ICD9 and ICD10 medical diagnosis codes for opioid use dependence (see Appendix Table 2) then identified a baseline sample of 325,520 individual beneficiaries between 2010–2017. There were 60,982 beneficiaries receiving MAT at some point during the study period, and 264,528 observed without treatment.

Beneficiaries with opioid use disorder typically vary over their willingness to receive treatment and over their access to treatment. One initial concern was that individuals might select into MAT treatment based on particular innate characteristics distinct from those that abstain. Therefore, I restricted the beneficiary sample to include only beneficiaries who had at least one visit with an MAT prescribing physician. Visits with a prescribing physician could signal of an individual's willingness to initiate MAT treatment.

From this remaining sample of 60,982 MAT treated and 195,197 untreated Medicare beneficiaries, I constructed a patient-month longitudinal panel wherein every beneficiary had the option to either receive treatment with a particular product or forego treatment each month following their opioid use disorder diagnosis. In particular, a beneficiary could choose between brand Suboxone film, brand Suboxone tablet, generic Suboxone tablet, "Other" buprenorphine (e.g., Zubsolv, Subutex, Bunavail), naltrexone, or no drug. Note that methadone was excluded as a choice as it is only used in the office setting to treat opioid use disorder. Each beneficiary in the sample was then followed from their index opioid use disorder diagnosis and censored after death. In the survival model, I also censored beneficiaries after the first incidence of an adverse opioid event.

Outcomes

I measured MAT product demand using a binary choice indicator set to one for the selected alternative in each month. Note that I restricted the set of possible alternatives to only the products covered on each patient's Medicare Part D plan. In particular, I considered a

particular product covered by a patient's plan in a given year if paid for by Medicare at least once among any patient in that plan for the year of observation. I identified MAT products from the Medicare Part D claims data using NDC codes produced by the Department of Health and Human Services Office of the Assistant Secretary for Planning and Evaluation (see Appendix Table 3).

The study used two other outcomes; adverse opioid events and all-cause mortality. I estimated these outcomes simultaneously using a competing risks discrete-time survival model (Efron, 1988). I used a categorical variable representing the occurrence of no event (0), an adverse opioid event (1), or mortality (2). The Medicare Beneficiary Summary file included the exact date of death for each included beneficiary in the sample, if available. I identified adverse opioid events using a set of ICD9 and ICD10 codes for opioid poisoning (i.e., overdose), abuse, and adverse effects (see Appendix Table 4).

Covariates

The key independent variables in the product demand model captured new product entry in the MAT market. Specifically, I included indicators representing the period following the launch of Suboxone film and generic entry to estimate the effect of their entry on demand. I set the generic entry indicator to one on or after February 23, 2013, to reflect the generics' observed entry date. I then assigned the Suboxone film entry indicator to one on or after August 30, 2010, the date it entered the market. Year fixed-effects allowed for these event indicators to be separately identified from unique demand shocks over time. Demand shocks could stem from policy changes over time, such as the Comprehensive Addiction and Recovery Act of 2016 that drastically expanded the use of MATs (114^{th} U.S. Congress, 2016).

Next, I controlled for patient price sensitivity for using patient out-of-pocket price in the demand model. I calculated the patient's out-of-pocket price for a single-day supply of a selected medication by dividing the patient's paid amount for a prescription by the total days supplied on the prescription. However, I did not observe the unchosen alternative MAT prices.. To approximated these prices, I constructed a measure of patient payment liability that I multiplied by the total drug cost. Note that the patient payment liability in a given month was calculated by dividing the patient's paid amount for their observed choice by the gross cost. However, when a patient did not receive a prescription in a month, the patient payment liability was not identifiable. In these instances, I used the average out-of-pocket prices for alternatives paid by

other beneficiaries in the same plan in the same month instead. These prices reflected the marginal beneficiary's cost in the same plan at the same point in the year.

Patient demographics, ancillary treatment, and medical histories were incorporated into the empirical models to address demand heterogeneity over individual characteristics. Specific controls included age, race and ethnicity, gender, Medicaid dual eligibility status, and disability. I also added an indicator representing the presence of comorbid mental illness. It was set to one if the patient had a mood disorder, personality disorder, schizophrenia, childhood behavioral disorder, or dementia. Further, ancillary mental health and substance use disorder treatment is commonly delivered in conjunction with MAT treatment and was captured in the survival model using an indicator representing a patient receiving any of the following services in the previous three months: psychotherapy, case management, consultation, drug testing, detox, and community mental health services. I obtained all patient characteristics, treatment, and medical histories from Medicare MedPAR inpatient claim files, carrier/professional claims files, outpatient claims files, and the Medicare beneficiary summary files (MBSF).

Finally, the study modeled persistence and substitution in product demand using previous choice indicators interacted with the product fixed-effects. This framework importantly allowed for estimating how a patient's last choice shifted the choice probability for a specific alternative in the current decision. Note that demand is highly persistent in the MAT market, given that treatment gaps can lead to patient relapse and severe withdrawal symptoms.

RESULTS

The product hop enabled Reckitt to capture substantial market share for Suboxone film in Medicare between 2010-2017 (see Figure 1). The transition from brand Suboxone tablet to Suboxone film is highly apparent in the few months before generic entry, given the rate at which Suboxone tablet prescriptions fell while Suboxone film prescriptions increased. Total prescriptions for other MAT products were consistently much lower, including generic Suboxone tablet, which had comparable use with Naltrexone and all Other Buprenorphine product categories. Note further that prescriptions of all MAT products increased over time, reflecting the provider response's evolution to the growing severity of the opioid epidemic during this period.

The main results show the product hop's effect on product pricing in the MAT market between 2010-2017 (see Figure 2). The most critical finding was that while the generic

Suboxone price declined, it did so much more gradually and moderately than under traditional generic entry. The results also confirm Reckitt's scheme to make the film more economical relative to the tablet to facilitate the switch. More clearly, the price of the brand Suboxone tablet increased in the period before generic entry to be consistently higher than the price of Suboxone film. On the contrary, the total cost per day supply of the other buprenorphine product category declined over time, reflecting additional generic entry and price competition. Note further that the price of naltrexone and Suboxone film was relatively constant over the entire study period.

Characteristics varied widely between MAT treated and untreated beneficiaries in the study sample (see Table 1). Treated beneficiaries were more likely to be younger, Medicaid dual eligible, and disabled than untreated beneficiaries. They also had lower comorbid mental illness rates but received more ancillary mental health and substance use disorder treatment. Further, treated beneficiaries had lower rates of adverse opioid events, supporting MATs being efficacious therapies for opioid use disorder. There was also a noticeably lower proportion of women and black beneficiaries receiving treatment.

The study sample beneficiaries were very price-sensitive on average, given the large, negative, and statistically significant mean estimates of the random coefficient for the patient out-of-pocket price covariate (see Table 2). They also greatly varied in their degree of price sensitivity, given the large and significant estimate of the random coefficient's standard deviation. These findings were consistent with the existing literature on price sensitivity in the MAT market (McClellan, 2019).

Product entry related to the product hop also played an essential role in determining MAT demand. In particular, after Suboxone film launched, the odds a beneficiary utilized either the brand Suboxone tablet or Other Buprenorphine declined significantly. However, after generic Suboxone tablet entry, only a considerable reduction in use was observed for brand Suboxone tablet. This finding highlights the extent to which the product hop was effective in preventing generic penetration. Estimates of the product fixed effects, which capture demand across products before either generic or film entry, were primarily large, negative, and significant. These estimates likely result from the high rate of "No Drug" choices among the study sample's untreated beneficiaries.

There was heterogeneity in MAT demand across beneficiary characteristics (see Table 2). Racial disparities in MAT prescribing are well documented (Pro et al., 2020), which I attempted

to address by using race and ethnicity indicators. Beneficiaries receiving ancillary mental health and substance use disorder treatment, and beneficiaries with mental health conditions and other substance use disorders, had higher odds of MAT treatment. The more frequent encounters with providers capable of prescribing MATs among this population may explain this result. Disabled and Medicaid dual-eligible beneficiaries also had higher odds of receiving MAT treatment. This may be related to the high rates of chronic illness in the Medicare population, which often require treatment with opioids (Lauer, Henly, and Brucker, 2019). It may also be related to additional social risk factors in this population (MACPAC, 2017).

Finally, the demand model's previous choice parameter estimates confirmed strong persistence in MAT demand (see Appendix Table 5). Note that the positive, large, and statistically significant estimates suggested that beneficiaries who chose a particular product in their previous choice were much more likely to choose it again than a different product or no treatment at all. The model also correctly identified substitution as occurring primarily within the active ingredient. For example, those who chose a buprenorphine-based product in their last choice were more likely to select a buprenorphine product in their current choice than a Naltrexone product, and vice versa.

MATs are highly efficacious drugs with modest variation in their efficacy, demonstrated by the treatment effect estimates from the discrete-time survival model with competing risks (see Table 3). The log hazard estimates for each MAT product category were negative, large in magnitude, and statistically significant. However, the most crucial finding was that Suboxone tablet products were more efficacious than Suboxone film given the larger negative estimates for the brand and generic tablet indicators. Therefore, in theory, beneficiary substitution to Suboxone film due to the product hop should worsen patient health. Further, these estimates were consistent with related estimates from MAT literature (Bao et al., 2019). The complete set of results from this model are shown in the Appendix (see Appendix Tables 6.A. & 6.B).

Next, I compared counterfactual product market shares with the observed product market shares in the periods before and after generic entry (see Table 4). Note that the market share of "No Drug" was smaller in the counterfactuals after generic entry, suggesting that broader availability of the less expensive generic products motivated additional treatment initiation. The even lower share for "No Drug" in the second counterfactual where generic prices declined more steeply also supports this finding. Interestingly, the market share of "No Drug" also declined

before generic entry in the counterfactuals. This finding could be related to changes in patient and provider perceptions in the quality of the tablet after film entry due to the FDA Citizen's petition suggesting risks of pediatric exposure with the tablets. It may also relate to greater adherence to Suboxone tablet products relative to the film. This is evidenced by the higher proportion of patients switching off treatment after being prescribed Suboxone film relative to the Suboxone tablet products (see Appendix Table 7).

Finally, predicted adverse opioid events from the counterfactuals were compared with the observed (see Table 5). I observed a total of 18,932 adverse opioid events in the sample during the entire study period. Since each patient could only have one adverse opioid event in the study, 18,932 also represented the number of beneficiaries with one or more adverse opioid events. Adverse opioid events then declined to 17,112 in the first counterfactual without film entry and 16,930 in the second counterfactual without film entry and lowered generic prices. This result implies that the product hop increased the number of beneficiaries with one or more adverse opioid events by 9.6-10.6%.

DISCUSSION

The Suboxone product hop successfully delayed the entry and penetration of generic competitors. Consequently, a higher proportion of patients received treatment with Suboxone film, which is less efficacious than Suboxone tablet. It also decreased MAT treatment overall by sustaining high prices in the MAT market. Hence, had policymakers or regulators blocked the product hop, the number of patients with one or more adverse opioid events would have declined by between 9.6%-10.6% between 2010-2017. Generalizing these changes to the entire opioid use disorder population in the U.S. translates to thousands of preventable adverse opioid events. Therefore, the Suboxone product hop played an essential role in the severity of the opioid epidemic, which continues to be a top public health concern in the U.S.

The results suggest that policymakers and regulators should act swiftly to block instances of product hopping. Product hopping has significant effects on the use and pricing of products in pharmaceutical markets and can lead to the promotion and adoption of potentially worse treatment options. Frank and Haffajee (2020) provide several suggestions to reform health care policy to make product hopping less attractive and more challenging for brand manufacturers. In particular, they suggest requiring FDA review of the incremental value of product line extensions

before listing them in the FDA Orange Book. Suppose the FDA only found minimal clinical benefit associated with the new product. In that case, the FDA could withhold listing the new product in the Orange Book, which would allow automatic reformulation substitution for the originator's generic at the point of sale in the pharmacy. Frank and Haffajee (2020) also suggest requiring periods either before or after generic entry where no reformulation can receive FDA approval, removing the incentive and ability among brands to engage in product hopping. This study shows that these policies would significantly improve population health relative to the current post-hoc litigation approach to deterrence.

Despite statistically significant findings, the study design's internal validity is threatened by several factors. The first threat concerns the construction of the out-of-pocket price variable. Although I attempted to adjust out-of-pocket prices of alternatives for cost-sharing, patient payment liabilities will realistically differ by product due to their varied positions in plan formularies, which were unobserved. Similarly, using the plan average out-of-pocket price for an alternative when a patient selected no drug is problematic, given that it assumes that patients were all at the same point in their deductible in a given month. Moreover, I made several assumptions to interpolate prices in the counterfactuals instead of estimating them directly through a supply-side model that could relate product prices to use. While findings in the generic entry literature supported some of these pricing assumptions, manufacturers in the MAT market are not necessarily representative of manufacturers in the marginal pharmaceutical market. To the extent that prices suffer from measurement error, predicted choice probabilities central to recovering health effects would be more conservative.

In addition to measurement issues in the out-of-pocket price covariate, price may also be endogenous. Price is commonly endogenous in choice models due to how product quality affects both prices and demand. However, the benefit of studying pharmaceutical markets is that one can exploit price variation between subjects in different plans that charge different amounts for the same drugs. While this additional variation helps with identification, it is not entirely sufficient to ensure no price endogeneity.

There is also minimal consideration given to potential changes in plan coverage of different MAT products without the product hop. For example, I assumed that the same plans that covered the film would have covered the generic tablet in the period between the earlier counterfactual generic entry date and the observed generic entry date. This assumption is

unlikely to be completely accurate, particularly during the several months following generic entry when plan coverage will be minimal. More plans would have also covered the brand Suboxone tablet if Reckitt had not discontinued it to facilitate the product hop. Hence, counterfactual coverage in Part D Medicare Plans may bias the counterfactual choice probability estimates to favor the generic.

Although not technically a limitation, the use of adverse opioid events instead of opioid related mortality leaves additional questions surrounding the effect of this antitrust event on the severity of the US Opioid Epidemic. Given that not all adverse events are fatal, the true impact of this event on lives lost remains an important consideration. However, even if only 20% of these events ended in a fatality, the net effect of the product hop on mortality would be substantial due to the large number of opioid overdose deaths across the US during the study period. Future research should estimate this effect directly by incorporating death certificate data that specify deaths related to overdose, for example.

Finally, findings in Medicare may not generalize to patients with other insurance types. Medicare is a unique environment for substance use disorder due to many patients having chronic medical conditions requiring treatment with opiates. Medicare can also have less generous pharmaceutical coverage than other insurance programs due to the infamous coverage *donut hole* in Part D plans. Hence, demand estimates for products may not translate well to different insurance settings where coverage is more generous, and chronic illness and disability rates are lower. Still, 70% of the study population was Medicaid dual-eligible (see Table 1), making these findings relevant to Medicaid.

CONCLUSION

Reckitt's product hop of Suboxone tablet to Suboxone Film increased adverse opioid events in Medicare. This finding is due to the resulting decrease in treatment use and patient substitution from the more efficacious Suboxone tablet products to the less efficacious Suboxone film product. Specifically, without the Suboxone product hop, the estimated adverse opioid event would have declined by roughly 10%. This reduction represents tens of thousands of preventable adverse opioid events in the general opioid use disorder population. More generally, to improve population health, policymakers and regulators should act aggressively to prevent future instances of product hopping. The FDA should carefully review the added clinical benefit

of any brand line extensions seeking FDA approval in the period before generic entry or delay approval until after generics have entered for the original product. Doing so may remove the capability of and incentive for clinically harmful product hopping among brand pharmaceutical manufacturers.

REFERENCES

1. 114 US Congress. 'S.524 Comprehensive Addiction and Recovery Act of 2016', U.S. Government Publishing Office. Available at: https://www.congress.gov/bill/114th-congress/senate-bill/524/text (Accessed: October 31, 2020).

2. Berndt, E. R. and Aitken, M. L. (2011) 'Brand Loyalty, Generic Entry and Price Competition in Pharmaceuticals in the Quarter Century after the 1984 Waxman-Hatch Legislation', International Journal of the Economics of Business, 18(2), pp. 177–201.

3. Carrier, M.A. (2017) 'Five Actions to Stop Citizen Petition Abuse,' Columbia Law Review Online, 118, pp. 82–93.

4. Carrier, M.A. (2017) 'Product Hopping,' Journal of Commercial Biotechnology, 23(2).

5. Carrier, M.A. (2018), Addressing Abusive Citizen Petitions. FDA Request for Comments on Citizen Petitions, Available at SSRN: https://ssrn.com/abstract=3269498I (Accessed: October 31, 2020).

6. Carrier, M.A. and Shadowen, S. (2016) 'Product Hopping: A New Framework,' Notre Dame Law Review, 92, pp. 167-260.

7. Carrier, M.A. and Shadowen, S. (2017) 'Pharmaceutical Product Hopping: A Proposed Framework For Antitrust Analysis,' Health Affairs Blog. Available at: https://www.healthaffairs.org/do/10.1377/hblog20170601.060360/full/ (Accessed: October 25, 2020).

8. Carrier, M.A., Sooy, B. (2017) 'Five Solutions to Stop the REMS Patent Problem,' Boston University Law Review, 97(5), pp. 1661-1707.

9. Center for Disease Control and Prevention. 'Understanding the Epidemic - Drug Overdose" (2018) CDC Injury Center. Available at: https://www.cdc.gov/drugoverdose/epidemic/index.html (Accessed: October 31, 2020).

10. Center for Disease Control and Prevention. 'Vital Signs: Trends in Emergency Department Visits for Suspected Opioid Overdoses — United States, July 2016–September 2017' (2018) Morbidity and Mortality Weekly Report. Available at: https://www.cdc.gov/mmwr/volumes/67/wr/mm6709e1.htm (Accessed: October 31, 2020).

11. Department of Health & Human Services. 'Opioid Crisis Statistics' (2018). Available at: https://www.hhs.gov/opioids/about-the-epidemic/opioid-crisis-statistics/index.html (Accessed: October 31, 2020).

12. Department of Justice. 'Justice Department Obtains $1.4 Billion from Reckitt Benckiser Group in Largest Recovery in a Case Concerning an Opioid Drug in United States History' (2019) Office of Public Affairs. Available at: https://www.justice.gov/opa/pr/justice-department-obtains-14-billion-reckitt-benckiser-group-largest-recovery-case (Accessed: October 31, 2020).

13. Efron, B. (1988) 'Logistic Regression, Survival Analysis, and the Kaplan-Meier Curve,' Journal of the American Statistical Association, 83(402), pp. 414–425.

14. Feldman, R. and Wang, C. (2017) 'A Citizen Pathway Gone Astray — Delaying Competition from Generic Drugs,' New England Journal of Medicine, 376(16), pp. 1499–1501.

15. Fowler, A.C. (2017) "Pharmaceutical Line Extensions in the United States: A Primer on Definitions and Incentives," NBER White Paper. Available at: http://www2.nber.org/aging/valmed/WhitePaper-Fowler10.2017.pdf / (Accessed: 25 October 2020).

16. Gibbons, R. D. et al. (2003) 'Waiting for organ transplantation: results of an analysis by an Institute of Medicine Committee,' Biostatistics (Oxford, England), 4(2), pp. 207–222.

17. Gibson, T. B., Ozminkowski, R. J. and Goetzel, R. Z. (2005) 'The Effects of Prescription Drug Cost Sharing: A Review of the Evidence,' The American Journal of Managed Care, 11(11), p. 11.

18. Haffajee, R. L. and Frank, R. G. (2019) 'Generic Drug Policy and Suboxone to Treat Opioid Use Disorder,' The Journal of Law, Medicine & Ethics, 47(4), pp. 43–53.

19. Hole, A.R. (2007). 'Modelling heterogeneity in patients' preferences for the attributes of a general practitioner appointment,' The University of York Center for Health Economics. Available at: https://www.york.ac.uk/media/che/documents/papers/researchpapers/rp22_patients_preferences_for_the_attributes_of_a_GP_appointment.pdf (Accessed: October 31, 2020).

20. Lauer, E. A., Henly, M. and Brucker, D. L. (2019) 'Prescription opioid behaviors among adults with and without disabilities - the United States, 2015-2016', Disability and Health Journal, 12(3), pp. 519–522

21. Lipari, R.N., and Park-Lee, E. 'Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health' (2019). SAMHSA. Available at: https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHNationalFindingsReport2018/NSDUHNationalFindingsReport2018.pdf (Accessed: October 31, 2020).

22. Ma, J., Bao, Y., and Wang, R. (2019) 'Effects of medication-assisted treatment on mortality among opioids users: a systematic review and meta-analysis.' Molecular Psychiatry, 24, pp. 1868–1883.

23. MACPAC. (2017) 'Medicaid and the Opioid Epidemic,' Report to Congress on Medicaid and CHIP. Available at: https://www.macpac.gov/wp-content/uploads/2017/06/Medicaid-and-the-Opioid-Epidemic.pdf (Accessed: October 31, 2020).

24. McClellan, C., Fingar, K.R., Ali, M.M., Olesiuk, W.J., Mutter, R., Gibson, T.B. (2019) 'Price elasticity of demand for buprenorphine/naloxone prescriptions,' Journal of Substance Abuse Treatment, 106, pp. 4-11.

25. Medicare-Medicaid Coordination Office. 'People Dually Eligible for Medicare and Medicaid,' Center for Medicare & Medicaid Services. Available at: https://www.cms.gov/Medicare-Medicaid-Coordination/Medicare-and-Medicaid-Coordination/Medicare-Medicaid-Coordination-Office/Downloads/MMCO_Factsheet.pdf (Accessed: October 31, 2020).

26. National Safety Council. 'Odds of Dying' (2018) Injury Facts. Available at: https://injuryfacts.nsc.org/all-injuries/preventable-death-overview/odds-of-dying/ (Accessed: October 31 2020).

27. Office of Inspector General. 'Opioids in Medicare Part D: Concerns about Extreme Use and Questionable Prescribing' (2017). U.S. Department of Health & Human Services. Available at: https://oig.hhs.gov/oei/reports/oei-02-17-00250.pdf (Accessed: October 25, 2020).

28. Pro, G., Utter, J., Cram, J., and Baldwin, J. (2020) 'Racial/Ethnic and Gender Differences in Associations of Medication-Assisted Therapy and Reduced Opioid Use between Outpatient Treatment Admission and Discharge,' Journal of Psychoactive Drugs, 52(2), pp. 186-194.

29. SAMHSA. 'Buprenorphine' (2020). Available at: https://www.samhsa.gov/medication-assisted-treatment/medications-counseling-related-conditions/buprenorphine (Accessed: October 31, 2020).

30. SAMHSA. 'Methadone' (2020). Available at: https://www.samhsa.gov/medication-assisted-treatment/medications-counseling-related-conditions/methadone (Accessed: October 31, 2020).

31. SAMHSA. 'Naloxone' (2020). Available at: https://www.samhsa.gov/medication-assisted-treatment/medications-counseling-related-conditions/naloxone (Accessed: October 31, 2020).

32. SAMHSA. 'Naltrexone' (2020). Available at: https://www.samhsa.gov/medication-assisted-treatment/medications-counseling-related-conditions/naltrexone (Accessed: October 31, 2020).

33. Shapiro, B. (2016) 'Estimating the Cost of Strategic Entry Delay in Pharmaceuticals: The Case of Ambien C.R.' Quantitative Marketing and Economics, 14, pp. 201–231.

34. Suboxone Complaint, "In RE: Suboxone Antitrust Litigation: End Payor Plaintiffs Second Consolidated Amended Class Action Complaint." United States District Court for the Eastern District of Pennsylvania, April 2015, MDL No. 2445, Master File No. 2:13-md-02445-MSG.

35. U.S. Food and Drug Administration. 'Risk Evaluation and Mitigation Strategies' (2019). Available at: https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems (Accessed: July 28, 2020).

36. Verma, S. (2020) 'Increasing Access to Generics and Biosimilars in Medicare', Center for Medicare & Medicaid Services. Available at: https://www.cms.gov/blog/increasing-access-generics-and-biosimilars-medicare (Accessed: October 31, 2020).

37. Volkow, N.D., Frieden, T.R., Hyde, P.S., and Cha, SS. (2014) 'Medication-Assisted Therapies — Tackling the Opioid-Overdose Epidemic,' The New England Journal of Medicine, 370, pp. 2063-2066.

TABLES & FIGURES

Table 1.1. Comparison of Characteristics in Medication-Assisted Treated vs. Control Populations

Description	Treated	Control
Total Beneficiaries (N)	60,348	195,197
Abuse Rate (%)	16.2%	24.3%
Medicaid Dual Eligible (%)	52.7%	45.8%
Disabled (%)	84.8%	69.4%
Comorbid Mental Health or Substance Use Disorder (%)	88.0%	98.2%
Ancillary Mental Health or Substance Use Disorder Treatment Use (%)	71.0%	66.0%
Age (Mean)	55	63
Gender		
Male (%)	51.3%	41.4%
Female (%)	48.7%	58.6%
Race/Ethnicity		
White (%)	84.9%	81.3%
Black (%)	9.1%	13.4%
Other Race (%)	2.4%	2.5%
Hispanic (%)	3.6%	2.8%

Note: Beneficiary characteristics obtained from Medicare medical claims and beneficiary denominator files between 2010-2017.

Table 1.2. Parameter Estimates from Medication-Assisted Treatment Product Demand Model

Covariate Description	Coef.	Std. Err.	P>|z|	[95% Conf. Interval]	
Price					
Out-Of-Pocket Price (MEAN)	-9.47	0.15	0.00	-9.77	-9.18
Out-Of-Pocket Price (STDDEV)	9.15	0.15	0.00	8.86	9.44
Entry Film					
EntryFilm X Brand Suboxone Tablet FE	-1.41	0.07	0.00	-1.55	-1.28
EntryFilm X Naltrexone FE	-0.68	0.06	0.00	-0.80	-0.55
EntryFilm X Other Buprenorphine FE	-0.70	0.14	0.00	-0.97	-0.43
Entry Generic					
EntryGeneric X Suboxone Film FE	-0.45	0.19	0.02	-0.83	-0.07
EntryGeneric X Brand Suboxone Tablet FE	-2.89	0.23	0.00	-3.34	-2.44
EntryGeneric X Other Buprenorphine FE	-0.40	0.21	0.05	-0.80	0.00
EntryGeneric X Naltrexone FE	-0.59	0.19	0.00	-0.97	-0.21
Product Fixed Effects					
Suboxone Film FE	-1.33	0.13	0.00	-1.58	-1.08
Brand Suboxone Tablet FE	0.79	0.13	0.00	0.54	1.04
Generic Suboxone Tablet FE	-4.00	0.23	0.00	-4.46	-3.54
Other Buprenorphine FE	-2.93	0.17	0.00	-3.26	-2.59
Naltrexone FE	-2.25	0.13	0.00	-2.50	-2.01
Patient Characteristics					
Comorbid Mental Health Condition	-0.25	0.06	0.00	-0.36	-0.13
Age	-0.01	0.00	0.00	-0.02	-0.01
Black	-0.41	0.05	0.00	-0.51	-0.31
Hispanic	0.01	0.07	0.89	-0.12	0.14
Other Race/Ethnicity	-0.13	0.11	0.22	-0.34	0.08
Disabled	-0.06	0.05	0.23	-0.16	0.04
Dual Eligible	1.09	0.04	0.00	1.02	1.17
Female	-0.01	0.03	0.76	-0.07	0.05

Notes: Estimates are expressed as log-odds ratios. The full table of estimates is presented in Appendix Table 5 (e.g., previous choice interactions with fixed effects). Estimates were obtained using mixed-effect logistic regression. STDDEV is the standard deviation estimate from the random coefficient on the out-of-pocket price covariate.

Table 1.3. Effect of Medication-Assisted Treatments on Adverse Opioid Events

Covariate Description	Coef.	Std. Err.	P>|z|	[95% Conf. Interval]	
Brand Suboxone Tablet	-1.24	0.09	0.00	-1.42	-1.05
Generic Suboxone Tablet	-1.23	0.12	0.00	-1.46	-0.99
Brand Suboxone Film	-0.96	0.05	0.00	-1.05	-0.87
Other Buprenorphine	-1.02	0.12	0.00	-1.25	-0.79
Other Naltrexone	-1.96	0.12	0.00	-2.18	-1.73

Note: Coefficients are in terms of log-hazards. The model was estimated using a discrete-time survival model with competing risks, in which mortality was treated as the competing risk. Presented estimates use adverse opioid events as the outcome. See Appendix Tables 6A & 6B for the full table of parameter estimates for both outcomes.

Table 1.4. Observed vs. Counterfactual Medication-Assisted Treatment Product Market Shares before and after Generic Entry

Product Description	Pre-Generic Entry		Post-Generic Entry		
	Observed Shares	**Counterfactuals #1 & #2: Predicted Shares without Film Entry**	**Observed Shares**	***Counterfactual #1:* Predicted Shares without Film Entry**	**Counterfactual #2: Predicted Shares with Lower Generic Prices without Film Entry**
No Drug	76.11%	64.82%	66.97%	56.93%	54.33%
Brand Suboxone Film	4.03%	-	18.38%	-	-
Brand Suboxone Tablet	13.86%	26.18%	0.86%	1.22%	1.22%
Generic Suboxone Tablet	-	-	3.47%	31.41%	34.04%
Other Buprenorphine	1.19%	2.71%	3.54%	3.07%	3.01%
Naltrexone	4.79%	6.28%	6.76%	7.38%	7.39%

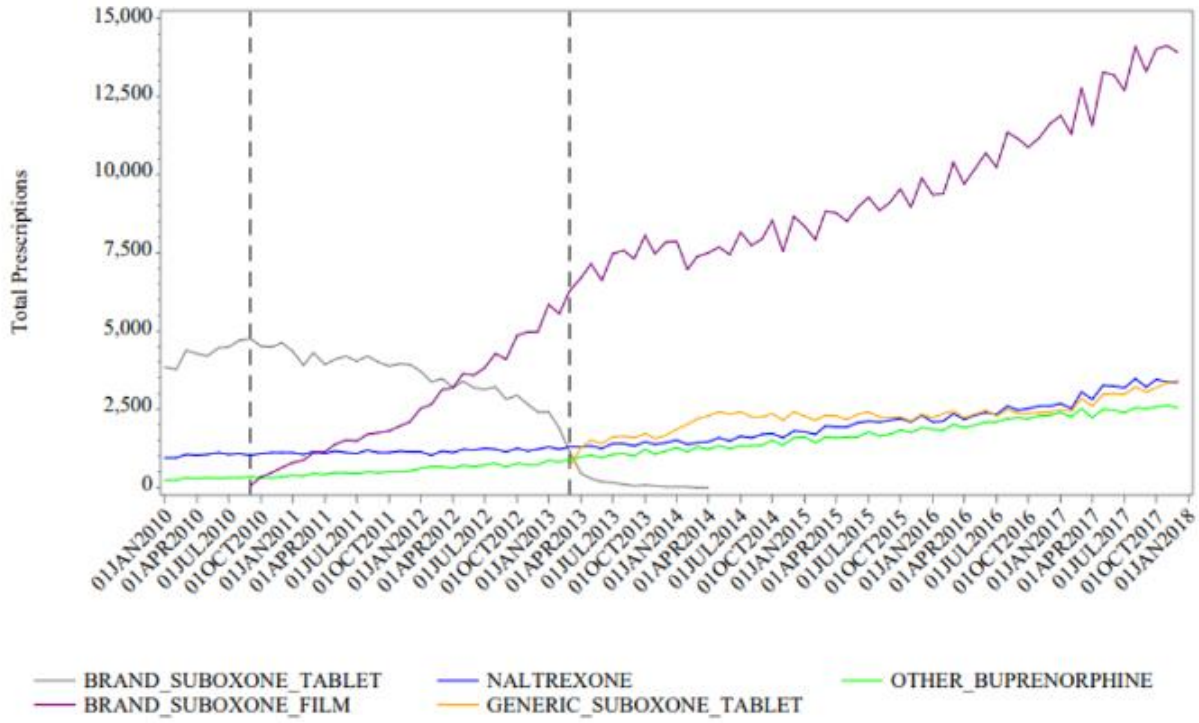
Note: Pre-generic entry reflects January 2010 – April 2012. Post Generic entry reflects May 2012 – December 2017. The "-" reflects the absence of a particular product from the market.

Table 1.5. Comparison of Observed and Counterfactual Adverse Opioid Events

Description	Adverse Opioid Events	Difference with Observed Adverse Opioid Events	Percent Change in Adverse Opioid Events
Observed	18,932	0	0.00%
Counterfactual #1: No Film Entry	17,112	1,820	-9.62%
Counterfactual #2: No Film Entry & Additional Generic Entry	16,930	2,002	-10.58%

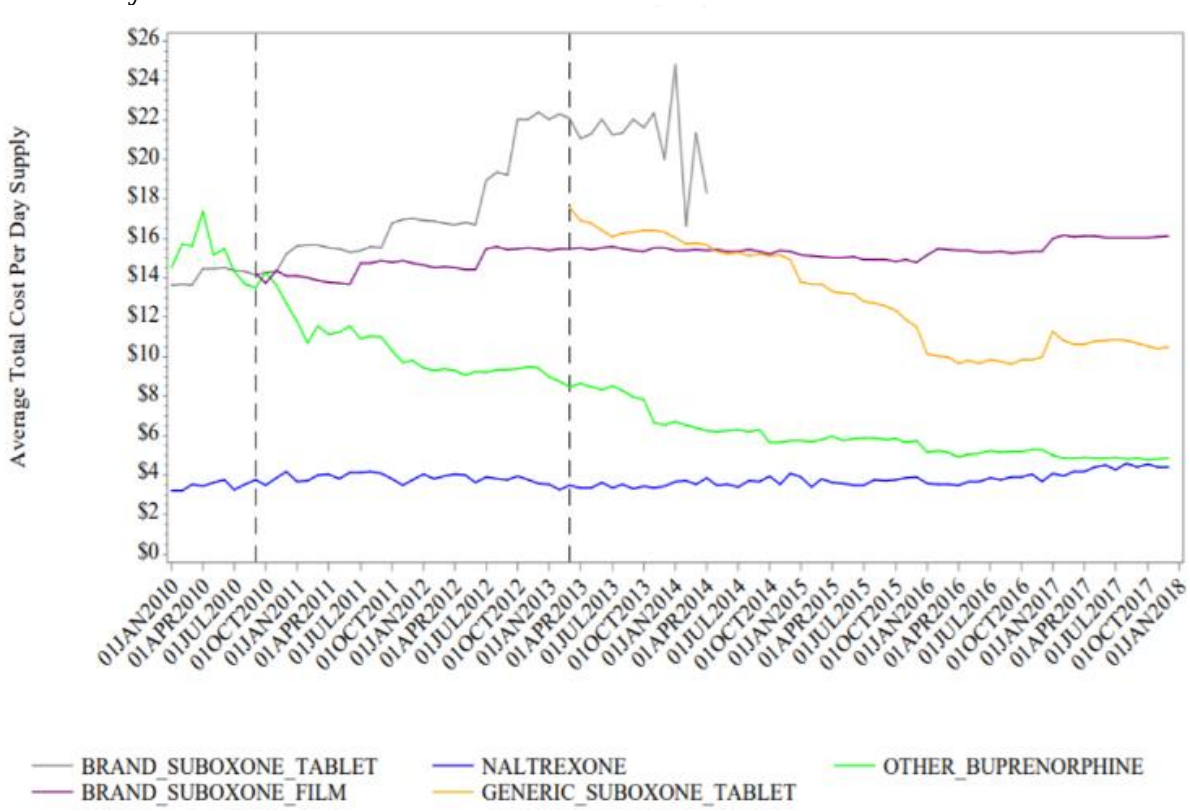
Note: Total number of first adverse opioid events among the 255,545 beneficiaries in the study sample from 2010-2017.

Figure 1.1. Total Prescriptions by Medication-Assisted Treatment Product by Month



Source: Medicare Part D Claims Data
Notes: Suboxone Generic Tablet Entry Occurred on 2/23/2013|Suboxone Brand Film Entered 8/30/2010

Figure 1.2. Average Total Cost Per Day Supplied by Medication-Assisted Treatment Product by Month



Source: Medicare Part D Claims Data
Notes: Suboxone Generic Tablet Entry Occurred on 2/23/2013|Suboxone Brand Film Entered 8/30/2010

APPENDIX

Appendix Table 1.1. Suboxone Product Hop Timeline of Key Events

Date	Event Description
10/8/2002	Suboxone (Buprenorphine/Naloxone) is granted FDA approval. It is given seven years of exclusivity as an orphan drug as patents on the active ingredients of Suboxone had previously expired.
10/21/2008	Reckitt Files its New Drug Application (NDA) for Suboxone film.
5/8/2009	Two generic manufacturers file Abbreviated New Drug Applications (ANDAs) for generic suboxone tablets
10/8/2009	Original expiration date for Suboxone tablet.
8/30/2010	FDA approves Suboxone Film.
11/1/2011	Reckitt files a Risk Evaluation and Mitigation Strategy (REMS) for Suboxone tablet.
12/22/2011	FDA approves Reckitt's REMS for Suboxone tablet.
1/6/2012	FDA advises Reckitt and impending generic manufacturers of the need for a joint REMS (Single Shared REMS (SSRS) program). FDA demands compliance of request for joint REMS by Reckitt on May 6.
5/1/2012	Reckitt refuses to cooperate with the SSRS program development, and generics call meeting with the FDA to discuss the delays. Expected Generic Entry but-for the Product Hop.
6/18/2012	Reckitt and generics meet with FDA to discuss delays.
9/25/2012	Reckitt files a Citizen Petition with the FDA arguing there existed a pediatric exposure "safety issue so severe as to require that the tablets be withdrawn from the market within the next six months."
2/22/2013	The FDA denies Reckitt's Citizen Petition. FDA waves the SSRS REMS requirement due to a lengthy negotiating period. FDA approves two generic manufacturer's Generic Suboxone Tablets.

Source: Suboxone Complaint, "In RE: Suboxone Antitrust Litigation: End Payor Plaintiffs Second Consolidated Amended Class Action Complaint." United States District Court for the Eastern District of Pennsylvania, April 2015, MDL No. 2445, Master File No. 2:13-md-02445-MSG.

Appendix Table 1.2. National Drug Codes for Medication-Assisted Treatments

NDC	Product Name	Generic Name	Form	Strength
00054-0188-13	BUPRENORPHINE-NALOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
00054-0189-13	BUPRENORPHINE-NALOXONE	Buprenorphine/Naloxone	Tablet	8-2
00093-5720-56	BUPRENORPHINE-NALOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
00093-5721-56	BUPRENORPHINE-NALOXONE	Buprenorphine/Naloxone	Tablet	8-2
00228-3154-03	BUPRENORPHINE-NALOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
00228-3154-73	BUPRENORPHINE-NALOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
00228-3155-03	BUPRENORPHINE-NALOXONE	Buprenorphine/Naloxone	Tablet	8-2
00228-3155-73	BUPRENORPHINE-NALOXONE	Buprenorphine/Naloxone	Tablet	8-2
00406-1923-03	BUPRENORPHINE-NALOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
00406-1924-03	BUPRENORPHINE-NALOXONE	Buprenorphine/Naloxone	Tablet	8-2
00490-0051-00	SUBOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
00490-0051-30	SUBOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
00490-0051-60	SUBOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
00490-0051-90	SUBOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
12496-1202-01	SUBOXONE	Buprenorphine/Naloxone	Film	2-0.5
12496-1202-03	SUBOXONE	Buprenorphine/Naloxone	Film	2-0.5
12496-1204-01	SUBOXONE	Buprenorphine/Naloxone	Film	4-1
12496-1204-03	SUBOXONE	Buprenorphine/Naloxone	Film	4-1
12496-1208-01	SUBOXONE	Buprenorphine/Naloxone	Film	8-2
12496-1208-03	SUBOXONE	Buprenorphine/Naloxone	Film	8-2
12496-1212-01	SUBOXONE	Buprenorphine/Naloxone	Film	12-3
12496-1212-03	SUBOXONE	Buprenorphine/Naloxone	Film	12-3
12496-1278-02	SUBUTEX	Buprenorphine	Tablet	2.00
12496-1283-02	SUBOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
12496-1306-02	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
12496-1310-02	SUBUTEX	Buprenorphine	Tablet	8.00
16590-0666-05	SUBOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
16590-0666-30	SUBOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
16590-0667-05	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
16590-0667-30	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
16590-0667-90	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2

23490-9270-03	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
23490-9270-06	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
23490-9270-09	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
35356-0004-07	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
35356-0004-30	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
42291-0174-30	BUPRENORPHINE-NALOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
42291-0175-30	BUPRENORPHINE-NALOXONE	Buprenorphine/Naloxone	Tablet	8-2
43063-0184-07	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
43063-0184-30	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
49999-0395-07	SUBOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
49999-0395-15	SUBOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
49999-0395-30	SUBOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
49999-0638-30	SUBUTEX	Buprenorphine	Tablet	2.00
49999-0639-30	SUBUTEX	Buprenorphine	Tablet	8.00
50383-0287-93	BUPRENORPHINE-NALOXONE	Buprenorphine/Naloxone	Tablet	8-2
50383-0294-93	BUPRENORPHINE-NALOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
52959-0304-30	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
52959-0749-30	SUBOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
53217-0138-30	BUPRENORPHINE-NALOXONE	Buprenorphine/Naloxone	Tablet	8-2
54123-0114-30	ZUBSOLV	Buprenorphine/Naloxone	Tablet	11.4-2.9
54123-0914-30	ZUBSOLV	Buprenorphine/Naloxone	Tablet	1.4-0.36
54123-0929-30	ZUBSOLV	Buprenorphine/Naloxone	Tablet	2.9-0.71
54123-0957-30	ZUBSOLV	Buprenorphine/Naloxone	Tablet	5.7-1.4
54123-0986-30	ZUBSOLV	Buprenorphine/Naloxone	Tablet	8.6-2.1
54569-5496-00	SUBOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
54569-5739-00	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
54569-5739-01	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
54569-5739-02	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
54569-6399-00	SUBOXONE	Buprenorphine/Naloxone	Film	8-2
54569-6408-00	BUPRENORPHINE-NALOXONE	Buprenorphine/Naloxone	Tablet	8-2
54868-5707-00	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
54868-5707-01	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
54868-5707-02	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
54868-5707-03	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
54868-5707-04	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
54868-5750-00	SUBOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
55045-3784-03	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
55700-0147-30	SUBOXONE	Buprenorphine/Naloxone	Film	8-2

55700-0184-30	BUPRENORPHINE-NALOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
55887-0312-04	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
55887-0312-15	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
59385-0012-01	BUNAVAIL	Buprenorphine/Naloxone	Film	2.1-0.3
59385-0012-30	BUNAVAIL	Buprenorphine/Naloxone	Film	2.1-0.3
59385-0014-01	BUNAVAIL	Buprenorphine/Naloxone	Film	4.2-0.7
59385-0014-30	BUNAVAIL	Buprenorphine/Naloxone	Film	4.2-0.7
59385-0016-01	BUNAVAIL	Buprenorphine/Naloxone	Film	6.3-1
59385-0016-30	BUNAVAIL	Buprenorphine/Naloxone	Film	6.3-1
63629-4028-01	SUBOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
63629-4034-01	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
63629-4034-02	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
63629-4034-03	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
63629-4092-01	SUBUTEX	Buprenorphine	Tablet	8.00
63874-1084-03	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
63874-1085-03	SUBOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
63874-1173-03	SUBUTEX	Buprenorphine	Tablet	8.00
63874-1174-03	SUBUTEX	Buprenorphine	Tablet	2.00
65162-0415-03	BUPRENORPHINE-NALOXONE	Buprenorphine/Naloxone	Tablet	8-2
65162-0416-03	BUPRENORPHINE-NALOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
66336-0015-30	SUBOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
66336-0016-30	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
68071-1380-03	SUBOXONE	Buprenorphine/Naloxone	Tablet	8-2
68071-1510-03	SUBOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
68258-2999-03	SUBOXONE	Buprenorphine/Naloxone	Tablet	2-0.5
63459-0300-42	VIVITROL	VIVITROL	Injection	380.00
65757-0300-01	VIVITROL	VIVITROL	Injection	380.00

Source: Office of the Assistant Secretary for Planning and Evaluation (2019) "Use of Medication Assisted Treatment for Opioid Use Disorder in Employer-Sponsored Health Insurance" U.S. Department of Health and Human Services. Available at: https://aspe.hhs.gov/system/files/pdf/260631/MATOOP.pdf. Accessed: 10/30/2020.

Appendix Table 1.3. Opioid Use Disorder ICD9 & ICD10 Codes

Adverse Opioid Event Category	ICD 9 Codes	ICD 10 Codes
Dependence	304: Opioid Dependence-Unspecified 304.01: Opioid Dependence-Continuous 304.02: Opioid Dependence-Episodic 304.03: Opioid Dependence, In Remission 304.7: Opioid Other Dep-Unspecified 304.71: Opioid Other Dep-Continuous 304.72: Opioid Other Dep-Episodic 304.73: Opioid Other Dep-In Remission	F11 series: Opioid-related disorders (except F11.21 and abuse codes)

Sources:
ICD 9 Codes obtained from Owens, PL, Barret, ML, Weiss, AJ, Washington, RE, and Kronick R, (2014) "Hospital Inpatient Utilization Related to Opioid Overuse Among Adults, 1993–2012," Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Statistical Brief #177. Available at: https://www.ncbi.nlm.nih.gov/books/NBK538344/ Accessed: October 30, 2020.

ICD 10 Codes obtained from Weiss, AJ, McDermott, KW, and Heslin, KC, (2016) "Opioid-Related Hospital Stays Among Women in the United States," Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Statistical Brief #247. Available at: https://www.ncbi.nlm.nih.gov/books/NBK246983/ Accessed: October 30, 2020.

Abbreviation:
ICD-9, International Classification of Diseases, Ninth Revision
ICD-10, International Classification of Diseases, Tenth Revision

Appendix Table 1.4. Adverse Opioid Event ICD9 & ICD10 Codes

Adverse Opioid Event Category	ICD 9 Codes	ICD 10 Codes
Abuse	305.51: Opioid Abuse-Continuous 305.52: Opioid Abuse-Episodic 305.53: Opioid Abuse-In Remission 305.5: Opioid Abuse Unspecified	F11 series: Opioid-related disorders (except F11.21 and dependence codes)
Adverse Effects	E935.2: Other opiates and related Narcotics Causing Adverse Effects in Therapeutic Use	T40.0X5: Adverse effect of opium T40.2X5: Adverse effect of other opioids T40.3X5: Adverse effect of Methadone
Overdose	965: Opium Poisoning 965.09: Poisoning by other opiates and related narcotics E850.2: Accidental poisoning by other opiates and related narcotics	T40.0X1, 0X2, 0X3, 0X4: Poisoning by opium–accidental, intentional self-harm, assault, or undetermined T40.1X1, 1X2, 1X3, 1X4: Poisoning by heroin–accidental, intentional self-harm, assault, or undetermined T40.2X1, 2X2, 2X3, 2X4: Poisoning by other opioids–accidental, intentional self-harm, assault, or undetermined T40.3X1, 3X2, 3X3, 3X4: Poisoning by Methadone–accidental, intentional self-harm, assault, or undetermined

Sources:
ICD 9 Codes obtained from Owens, PL, Barret, ML, Weiss, AJ, Washington, RE, and Kronick R, (2014) "Hospital Inpatient Utilization Related to Opioid Overuse Among Adults, 1993–2012," Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Statistical Brief #177. Available at: https://www.ncbi.nlm.nih.gov/books/NBK538344/ Accessed: October 30, 2020.

ICD 10 Codes obtained from Weiss, AJ, McDermott, KW, and Heslin, KC, (2016) "Opioid-Related Hospital Stays Among Women in the United States," Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Statistical Brief #247. Available at: https://www.ncbi.nlm.nih.gov/books/NBK246983/ Accessed: October 30, 2020.

Abbreviation:
ICD-9, International Classification of Diseases, Ninth Revision
ICD-10, International Classification of Diseases, Tenth Revision

Appendix Table 1.5. Medication-Assisted Treatment Demand Model Estimates

Covariate Description	Coef.	Std. Err.	P>|z|	[95% Conf. Interval]	
Price					
Out-Of-Pocket Price (MEAN)	-9.47	0.15	0.00	-9.77	-9.18
Out-Of-Pocket Price (STD)	9.15	0.15	0.00	8.86	9.44
Entry Film					
EntryFilm X Brand Suboxone Tablet FE	-1.41	0.07	0.00	-1.55	-1.28
EntryFilm X Naltrexone FE	-0.68	0.06	0.00	-0.80	-0.55
EntryFilm X Other Buprenorphine FE	-0.70	0.14	0.00	-0.97	-0.43
Entry Generic					
EntryGeneric X Suboxone Film FE	-0.45	0.19	0.02	-0.83	-0.07
EntryGeneric X Brand Suboxone Tablet FE	-2.89	0.23	0.00	-3.34	-2.44
EntryGeneric X Other Buprenorphine FE	-0.40	0.21	0.05	-0.80	0.00
EntryGeneric X Naltrexone FE	-0.59	0.19	0.00	-0.97	-0.21
Product Fixed Effects					
Suboxone Film FE	-1.33	0.13	0.00	-1.58	-1.08
Brand Suboxone Tablet FE	0.79	0.13	0.00	0.54	1.04
Generic Suboxone Tablet FE	-4.00	0.23	0.00	-4.46	-3.54
Other Buprenorphine FE	-2.93	0.17	0.00	-3.26	-2.59
Naltrexone FE	-2.25	0.13	0.00	-2.50	-2.01
Patient Characteristics					
Comorbid Mental Health Condition	-0.25	0.06	0.00	-0.36	-0.13
Age	-0.01	0.00	0.00	-0.02	-0.01
Black	-0.41	0.05	0.00	-0.51	-0.31
Hispanic	0.01	0.07	0.89	-0.12	0.14
Other Race/Ethnicity	-0.13	0.11	0.22	-0.34	0.08
Disabled	-0.06	0.05	0.23	-0.16	0.04
Dual Eligible	1.09	0.04	0.00	1.02	1.17
Female	-0.01	0.03	0.76	-0.07	0.05
Previous Choice Interactions					
Last Choice Suboxone Film X Suboxone Film FE	3.49	0.05	0.00	3.39	3.59
Last Choice Suboxone Film X Brand Suboxone Tablet FE	0.95	0.09	0.00	0.77	1.12
Last Choice Suboxone Film X Generic Suboxone Tablet FE	1.40	0.12	0.00	1.16	1.63
Last Choice Suboxone Film X Naltrexone FE	-1.73	0.24	0.00	-2.19	-1.26
Last Choice Suboxone Film X Other Buprenorphine FE	0.49	0.14	0.00	0.22	0.76
Last Choice Brand Suboxone Tablet X Suboxone Film FE	1.28	0.08	0.00	1.13	1.44
Last Choice Brand Suboxone Tablet X Brand Suboxone Tablet FE	3.32	0.05	0.00	3.21	3.43
Last Choice Brand Suboxone Tablet X Generic Suboxone Tablet FE	4.53	0.36	0.00	3.82	5.23
Last Choice Brand Suboxone Tablet X Naltrexone FE	-1.90	0.34	0.00	-2.56	-1.23

Last Choice Brand Suboxone Tablet X Other Buprenorphine FE	1.12	0.15	0.00	0.82	1.42
Last Choice Generic Suboxone Tablet X Suboxone Film FE	1.10	0.15	0.00	0.81	1.39
Last Choice Generic Suboxone Tablet X Brand Suboxone Tablet FE	0.68	0.73	0.35	-0.76	2.12
Last Choice Generic Suboxone Tablet X Generic Suboxone Tablet FE	5.67	0.13	0.00	5.42	5.92
Last Choice Generic Suboxone Tablet X Naltrexone FE	-2.01	0.72	0.01	-3.41	-0.60
Last Choice Generic Suboxone Tablet X Other Buprenorphine FE	1.54	0.22	0.00	1.11	1.97
Last Choice Other Buprenorphine X Suboxone Film FE	0.47	0.17	0.01	0.14	0.80
Last Choice Other Buprenorphine X Brand Suboxone Tablet FE	-0.17	0.20	0.39	-0.57	0.23
Last Choice Other Buprenorphine X Generic Suboxone Tablet FE	2.12	0.22	0.00	1.69	2.56
Last Choice Other Buprenorphine X Naltrexone FE	-2.85	1.00	0.00	-4.82	-0.89
Last Choice Other Buprenorphine X Other Buprenorphine FE	5.70	0.09	0.00	5.51	5.88
Last Choice Naltrexone X Suboxone Film FE	-3.13	0.27	0.00	-3.66	-2.59
Last Choice Naltrexone X Brand Suboxone Tablet FE	-4.09	0.34	0.00	-4.76	-3.42
Last Choice Naltrexone X Generic Suboxone Tablet FE	-3.05	1.00	0.00	-5.02	-1.09
Last Choice Naltrexone X Naltrexone FE	3.76	0.04	0.00	3.69	3.84
Last Choice Naltrexone X Other Buprenorphine FE	-2.89	0.60	0.00	-4.08	-1.71
Year					
_2011	0.28	0.05	0.00	0.19	0.38
_2012	0.40	0.06	0.00	0.29	0.52
_2013	1.51	0.19	0.00	1.14	1.88
_2014	1.77	0.20	0.00	1.37	2.17
_2015	1.64	0.20	0.00	1.24	2.03
_2016	1.92	0.20	0.00	1.53	2.31
_2017	2.37	0.20	0.00	1.98	2.76

Notes: Estimates are expressed as log-odds ratios.

Appendix Table 1.6A. Parameter Estimates from Discrete-Time Survival Model with Competing Risks (Outcome = Adverse Opioid Events)

Covariate Description	Coef.	Std. Err.	P>|z|	[95% Conf. Interval]	
Drug					
Brand Suboxone Tablet	-1.24	0.09	0.00	-1.42	-1.05
Generic Suboxone Tablet	-1.23	0.12	0.00	-1.46	-0.99
Brand Suboxone Film	-0.96	0.05	0.00	-1.05	-0.87
Other Buprenorphine	-1.02	0.12	0.00	-1.25	-0.79
Other Naltrexone	-1.96	0.12	0.00	-2.18	-1.73
Age	0.00	0.00	0.00	0.00	0.01
Disabled	0.28	0.03	0.00	0.22	0.35
Dual Eligible	0.10	0.02	0.00	0.06	0.13
Comorbid Mental Health or Substance Use Disorder	3.26	0.23	0.00	2.81	3.71
Ancillary Mental Health or Substance Use Disorder Treatment	2.39	0.02	0.00	2.35	2.43
Race/Ethnicity					
Black	0.02	0.03	0.47	-0.03	0.07
Hispanic	0.04	0.05	0.38	-0.05	0.14
Other Race	-0.03	0.05	0.55	-0.13	0.07
Year					
2011	0.13	0.05	0.01	0.04	0.23
2012	0.03	0.05	0.58	-0.07	0.13
2013	0.17	0.05	0.00	0.07	0.28
2014	0.06	0.05	0.28	-0.05	0.17
2015	-0.12	0.05	0.01	-0.21	-0.03
2016	-0.07	0.04	0.11	-0.16	0.02
2017	-0.16	0.05	0.00	-0.25	-0.07
Months at Risk					
1	-0.63	0.05	0.00	-0.73	-0.53
2	-0.70	0.05	0.00	-0.80	-0.59
3	-0.75	0.05	0.00	-0.85	-0.64
4	-0.77	0.05	0.00	-0.87	-0.66
5	-0.70	0.05	0.00	-0.80	-0.59
6	-0.83	0.06	0.00	-0.94	-0.71

7	-0.86	0.06	0.00	-0.98	-0.75
8	-0.84	0.06	0.00	-0.96	-0.73
9	-0.94	0.06	0.00	-1.06	-0.82
10	-0.82	0.06	0.00	-0.94	-0.70
11	-0.94	0.06	0.00	-1.07	-0.82
12	-0.82	0.06	0.00	-0.94	-0.70
13	-0.89	0.06	0.00	-1.02	-0.76
14	-0.79	0.06	0.00	-0.91	-0.66
15	-0.82	0.06	0.00	-0.95	-0.69
16	-0.95	0.07	0.00	-1.08	-0.81
17	-0.94	0.07	0.00	-1.08	-0.80
18	-0.99	0.07	0.00	-1.14	-0.85
19	-0.94	0.07	0.00	-1.08	-0.79
20	-0.94	0.07	0.00	-1.08	-0.79
21	-0.99	0.08	0.00	-1.14	-0.83
22	-0.95	0.08	0.00	-1.11	-0.80
23	-0.96	0.08	0.00	-1.12	-0.81
24	-1.20	0.09	0.00	-1.37	-1.02
25	-1.08	0.09	0.00	-1.25	-0.91
26	-1.01	0.09	0.00	-1.18	-0.84
27	-1.14	0.09	0.00	-1.32	-0.96
28	-1.06	0.09	0.00	-1.24	-0.88
29	-1.04	0.09	0.00	-1.22	-0.86
30	-1.01	0.09	0.00	-1.19	-0.83
31	-1.13	0.10	0.00	-1.32	-0.94
32	-0.95	0.09	0.00	-1.13	-0.77
33	-1.04	0.10	0.00	-1.24	-0.85
34	-1.16	0.11	0.00	-1.37	-0.95
35	-1.08	0.11	0.00	-1.29	-0.87
36	-0.95	0.10	0.00	-1.14	-0.75
37	-1.00	0.10	0.00	-1.20	-0.79
38	-1.12	0.11	0.00	-1.34	-0.90
39	-1.00	0.11	0.00	-1.21	-0.80
40	-1.08	0.11	0.00	-1.30	-0.87

41	-1.06	0.11	0.00	-1.28	-0.85
42	-1.14	0.12	0.00	-1.37	-0.91
43	-1.19	0.12	0.00	-1.42	-0.96
44	-1.10	0.12	0.00	-1.33	-0.87
45	-0.79	0.10	0.00	-0.99	-0.59
46	-0.94	0.11	0.00	-1.16	-0.73
47	-0.88	0.11	0.00	-1.09	-0.67
48	-0.83	0.11	0.00	-1.04	-0.62
49	-1.00	0.12	0.00	-1.22	-0.77
50	-0.99	0.12	0.00	-1.22	-0.76
51	-1.15	0.13	0.00	-1.40	-0.91
52	-0.95	0.11	0.00	-1.18	-0.73
53	-0.89	0.11	0.00	-1.11	-0.67
54	-1.04	0.12	0.00	-1.27	-0.80
55	-0.93	0.12	0.00	-1.16	-0.71
56	-0.95	0.12	0.00	-1.18	-0.72
57	-0.90	0.12	0.00	-1.12	-0.67
58	-0.67	0.10	0.00	-0.88	-0.46
59	-0.74	0.11	0.00	-0.95	-0.53
60	-1.03	0.12	0.00	-1.27	-0.78
61	-0.90	0.12	0.00	-1.13	-0.67
62	-0.87	0.12	0.00	-1.10	-0.64
63	-0.60	0.10	0.00	-0.80	-0.39
64	-0.59	0.11	0.00	-0.79	-0.38
65	-0.76	0.11	0.00	-0.98	-0.53
66	-0.58	0.11	0.00	-0.79	-0.38
67	-0.91	0.13	0.00	-1.16	-0.67
68	-0.90	0.13	0.00	-1.14	-0.65
69	-0.72	0.12	0.00	-0.95	-0.49
70	-0.81	0.12	0.00	-1.05	-0.57
71	-0.79	0.12	0.00	-1.03	-0.55
72	-0.75	0.12	0.00	-1.00	-0.51
73	-0.75	0.12	0.00	-1.00	-0.51
74	-0.67	0.12	0.00	-0.91	-0.42

75	-0.65	0.12	0.00	-0.89	-0.41
76	-0.57	0.12	0.00	-0.81	-0.33
77	-0.67	0.13	0.00	-0.92	-0.41
78	-0.79	0.14	0.00	-1.07	-0.51
79	-0.49	0.13	0.00	-0.74	-0.24
80	-0.80	0.15	0.00	-1.10	-0.51
81	-0.94	0.17	0.00	-1.26	-0.61
82	-0.67	0.15	0.00	-0.97	-0.38
83	-0.99	0.18	0.00	-1.35	-0.63
84	-0.83	0.18	0.00	-1.17	-0.48
85	-0.71	0.17	0.00	-1.04	-0.37
86	-0.92	0.20	0.00	-1.30	-0.53
87	-1.01	0.21	0.00	-1.42	-0.59
88	-0.64	0.19	0.00	-1.01	-0.28
89	-0.58	0.19	0.00	-0.96	-0.21
90	-1.13	0.26	0.00	-1.64	-0.62
91	-0.86	0.25	0.00	-1.34	-0.38
92	-0.90	0.27	0.00	-1.43	-0.37
93	-1.39	0.38	0.00	-2.14	-0.65
94	-1.62	0.50	0.00	-2.60	-0.63
95	-0.13	1.02	0.90	-2.13	1.87
96	-14.62	0.52	0.00	-15.63	-13.61
97	-14.67	0.71	0.00	-16.06	-13.27
98	-14.67	0.71	0.00	-16.06	-13.27
99	-14.67	0.71	0.00	-16.06	-13.27
100	-14.68	1.00	0.00	-16.64	-12.71
101	-14.68	1.00	0.00	-16.64	-12.71
102	-14.68	1.00	0.00	-16.64	-12.71
103	-17.06	1.00	0.00	-19.03	-15.10
104	-14.82	1.00	0.00	-16.79	-12.86
105	-14.82	1.00	0.00	-16.79	-12.86
106	-14.82	1.00	0.00	-16.79	-12.86
107	-14.82	1.00	0.00	-16.79	-12.86
108	-17.21	1.00	0.00	-19.17	-15.25

109	-14.82	1.00	0.00	-16.79	-12.86
110	-14.82	1.00	0.00	-16.79	-12.86
111	-14.82	1.00	0.00	-16.79	-12.86
112	-17.21	1.00	0.00	-19.17	-15.25
113	-14.82	1.00	0.00	-16.79	-12.86
114	-17.21	1.00	0.00	-19.17	-15.25
115	-14.82	1.00	0.00	-16.79	-12.86
116	-14.72	1.00	0.00	-16.68	-12.75
117	-14.72	1.00	0.00	-16.68	-12.75
118	-14.72	1.00	0.00	-16.68	-12.75
119	-14.72	1.00	0.00	-16.68	-12.75
120	-14.72	1.00	0.00	-16.68	-12.75
121	-14.72	1.00	0.00	-16.68	-12.75
122	-14.72	1.00	0.00	-16.68	-12.75
123	-14.72	1.00	0.00	-16.68	-12.75
124	-14.72	1.00	0.00	-16.68	-12.75
125	-14.72	1.00	0.00	-16.68	-12.75
126	-14.72	1.00	0.00	-16.68	-12.75
127	-14.72	1.00	0.00	-16.68	-12.75
Constant	-10.08	0.24	0.00	-10.56	-9.61

Note: Coefficients are in terms of log-hazards.

Appendix Table 1.6B. Parameter Estimates from the Discrete-Time Survival Model with Competing Risks (Outcome = All-Cause Mortality)

Covariate Description	Coef.	Std. Err.	P>|z|	[95% Conf. Interval]	
Drug					
Brand Suboxone Tablet	-1.19	0.32	0.00	-1.82	-0.56
Generic Suboxone Tablet	-0.76	0.29	0.01	-1.32	-0.19
Brand Suboxone Film	-1.03	0.16	0.00	-1.34	-0.72
Other Buprenorphine	-0.48	0.24	0.05	-0.96	-0.01
Other Naltrexone	-1.16	0.23	0.00	-1.61	-0.70
Age	0.05	0.00	0.00	0.04	0.05
Disabled	-0.04	0.05	0.35	-0.14	0.05
Dual Eligible	0.31	0.04	0.00	0.24	0.38
Comorbid Mental Health or Substance Use Disorder	1.76	0.10	0.00	1.57	1.96
Ancillary Mental Health or Substance Use Disorder Treatment	-0.61	0.05	0.00	-0.71	-0.52
Race/Ethnicity					
Black	-0.10	0.05	0.05	-0.21	0.00
Hispanic	-0.18	0.13	0.16	-0.42	0.07
Other Race	-0.03	0.10	0.78	-0.22	0.17
Year					
2011	-0.05	0.11	0.65	-0.28	0.17
2012	-0.47	0.12	0.00	-0.71	-0.24
2013	-0.37	0.12	0.00	-0.60	-0.13
2014	-0.30	0.12	0.02	-0.53	-0.06
2015	0.01	0.11	0.93	-0.20	0.22
2016	-0.05	0.10	0.65	-0.25	0.15
2017	-0.11	0.10	0.29	-0.31	0.09
Months at Risk					
1	-0.44	0.09	0.00	-0.60	-0.27
2	-0.72	0.09	0.00	-0.91	-0.54
3	-0.76	0.10	0.00	-0.96	-0.57
4	-1.03	0.11	0.00	-1.24	-0.81
5	-0.93	0.11	0.00	-1.14	-0.72
6	-0.96	0.11	0.00	-1.17	-0.74
7	-0.86	0.11	0.00	-1.07	-0.65
8	-0.88	0.11	0.00	-1.09	-0.66
9	-0.83	0.11	0.00	-1.05	-0.62
10	-0.80	0.11	0.00	-1.02	-0.58
11	-1.12	0.13	0.00	-1.38	-0.86

12	-0.95	0.12	0.00	-1.19	-0.71
13	-0.94	0.13	0.00	-1.18	-0.69
14	-1.06	0.13	0.00	-1.32	-0.79
15	-1.06	0.14	0.00	-1.33	-0.79
16	-0.94	0.13	0.00	-1.20	-0.68
17	-1.03	0.14	0.00	-1.31	-0.76
18	-0.78	0.13	0.00	-1.03	-0.53
19	-0.87	0.14	0.00	-1.14	-0.60
20	-0.82	0.14	0.00	-1.08	-0.55
21	-0.71	0.14	0.00	-0.98	-0.45
22	-0.40	0.12	0.00	-0.64	-0.15
23	-1.22	0.18	0.00	-1.56	-0.87
24	-1.13	0.18	0.00	-1.48	-0.79
25	-1.00	0.17	0.00	-1.33	-0.67
26	-1.25	0.20	0.00	-1.64	-0.87
27	-1.09	0.18	0.00	-1.45	-0.72
28	-1.08	0.19	0.00	-1.44	-0.71
29	-0.86	0.17	0.00	-1.20	-0.52
30	-0.90	0.18	0.00	-1.25	-0.55
31	-0.72	0.17	0.00	-1.05	-0.39
32	-0.74	0.18	0.00	-1.09	-0.40
33	-0.58	0.17	0.00	-0.91	-0.25
34	-0.43	0.16	0.01	-0.75	-0.10
35	-0.97	0.21	0.00	-1.39	-0.55
36	-0.88	0.21	0.00	-1.28	-0.47
37	-1.49	0.27	0.00	-2.02	-0.95
38	-0.82	0.20	0.00	-1.22	-0.43
39	-1.17	0.24	0.00	-1.63	-0.70
40	-0.93	0.21	0.00	-1.35	-0.51
41	-0.96	0.22	0.00	-1.39	-0.54
42	-1.00	0.22	0.00	-1.43	-0.57
43	-1.14	0.24	0.00	-1.60	-0.68
44	-1.04	0.23	0.00	-1.48	-0.59
45	-1.60	0.30	0.00	-2.17	-1.02
46	-0.44	0.18	0.01	-0.78	-0.09
47	-1.43	0.28	0.00	-1.97	-0.89
48	-1.49	0.28	0.00	-2.05	-0.94
49	-2.10	0.38	0.00	-2.85	-1.35
50	-1.96	0.36	0.00	-2.66	-1.25
51	-1.46	0.28	0.00	-2.02	-0.91

52	-1.02	0.23	0.00	-1.47	-0.57
53	-1.70	0.32	0.00	-2.33	-1.07
54	-1.43	0.28	0.00	-1.98	-0.87
55	-1.27	0.26	0.00	-1.79	-0.75
56	-0.92	0.23	0.00	-1.37	-0.48
57	-1.25	0.26	0.00	-1.77	-0.73
58	-0.90	0.23	0.00	-1.34	-0.46
59	-1.30	0.27	0.00	-1.84	-0.77
60	-1.04	0.24	0.00	-1.52	-0.56
61	-1.27	0.27	0.00	-1.81	-0.73
62	-1.94	0.38	0.00	-2.69	-1.19
63	-1.37	0.29	0.00	-1.95	-0.80
64	-1.27	0.28	0.00	-1.82	-0.71
65	-1.32	0.29	0.00	-1.90	-0.75
66	-1.30	0.29	0.00	-1.87	-0.72
67	-1.27	0.29	0.00	-1.85	-0.69
68	-1.02	0.26	0.00	-1.54	-0.50
69	-1.30	0.31	0.00	-1.91	-0.70
70	-0.34	0.20	0.08	-0.73	0.05
71	-0.92	0.26	0.00	-1.44	-0.40
72	-1.40	0.34	0.00	-2.06	-0.73
73	-1.24	0.32	0.00	-1.87	-0.61
74	-1.31	0.34	0.00	-1.97	-0.64
75	-0.98	0.29	0.00	-1.55	-0.40
76	-0.93	0.29	0.00	-1.50	-0.35
77	-1.16	0.34	0.00	-1.82	-0.49
78	-0.41	0.24	0.09	-0.88	0.07
79	-0.84	0.31	0.01	-1.44	-0.24
80	-0.69	0.29	0.02	-1.27	-0.11
81	-0.47	0.27	0.09	-1.01	0.07
82	-0.21	0.25	0.41	-0.70	0.29
83	-1.35	0.45	0.00	-2.23	-0.46
84	-15.23	0.06	0.00	-15.36	-15.11
85	-1.43	0.50	0.01	-2.42	-0.44
86	-1.12	0.45	0.01	-2.01	-0.24
87	-1.04	0.45	0.02	-1.92	-0.15
88	-0.60	0.38	0.12	-1.35	0.15
89	-0.25	0.34	0.46	-0.92	0.42
90	-0.52	0.41	0.21	-1.33	0.29
91	-0.57	0.45	0.21	-1.45	0.32

92	0.07	0.36	0.84	-0.63	0.77
93	0.55	0.32	0.09	-0.08	1.18
94	1.55	0.24	0.00	1.08	2.02
95	1.60	1.01	0.11	-0.37	3.58
96	-14.92	0.62	0.00	-16.14	-13.69
97	-14.84	0.93	0.00	-16.67	-13.01
98	-14.84	0.93	0.00	-16.67	-13.01
99	-14.84	0.93	0.00	-16.67	-13.01
100	-15.73	1.00	0.00	-17.70	-13.76
101	-15.73	1.00	0.00	-17.70	-13.76
102	-15.73	1.00	0.00	-17.70	-13.76
103	-15.12	1.01	0.00	-17.09	-13.15
104	-15.88	1.00	0.00	-17.85	-13.91
105	-15.88	1.00	0.00	-17.85	-13.91
106	-15.88	1.00	0.00	-17.85	-13.91
107	-15.88	1.00	0.00	-17.85	-13.91
108	-15.27	1.01	0.00	-17.24	-13.30
109	-15.88	1.00	0.00	-17.85	-13.91
110	-15.88	1.00	0.00	-17.85	-13.91
111	-15.88	1.00	0.00	-17.85	-13.91
112	-15.27	1.01	0.00	-17.24	-13.30
113	-15.88	1.00	0.00	-17.85	-13.91
114	-15.27	1.01	0.00	-17.24	-13.30
115	-15.88	1.00	0.00	-17.85	-13.91
116	-16.00	1.00	0.00	-17.97	-14.03
117	-16.00	1.00	0.00	-17.97	-14.03
118	-16.00	1.00	0.00	-17.97	-14.03
119	-16.00	1.00	0.00	-17.97	-14.03
120	-16.00	1.00	0.00	-17.97	-14.03
121	-16.00	1.00	0.00	-17.97	-14.03
122	-16.00	1.00	0.00	-17.97	-14.03
123	-16.00	1.00	0.00	-17.97	-14.03
124	-16.00	1.00	0.00	-17.97	-14.03
125	-16.00	1.00	0.00	-17.97	-14.03
126	-16.00	1.00	0.00	-17.97	-14.03
127	-16.00	1.00	0.00	-17.97	-14.03
Constant	-10.95	0.20	0.00	-11.33	-10.56

Note: Coefficients are in terms of log-hazards.

Appendix Table 1.7. Second Medication-Assisted Treatment Product Choices Conditional on First Medication-Assisted Treatment Product Choice

Choice	BRAND SUBOXONE FILM	BRAND SUBOXONE TABLET	GENERIC SUBOXONE TABLET	NONE
BRAND-SUBOXONE-FILM	81.78%	1.51%	1.84%	13.73%
BRAND-SUBOXONE-TABLET	6.66%	79.48%	0.72%	10.98%
GENERIC-SUBOXONE-TABLET	12.21%	0.12%	70.10%	16.50%

Notes: Based on first and second choices for all 255,545 beneficiaries in the patient sample between 2010-2017.

CHAPTER II:
The Effect of Nonadherence to Medication-Assisted Treatment on Patient Expenditures and Adverse Opioid Events

ABSTRACT

Medication-Assisted Treatments (MAT) are pharmaceuticals that effectively reduce the risk of an opioid overdose when taken consistently. However, studies have shown that MAT adherence is often low and that nonadherence can raise health care costs while worsening patient health. Still, little is known about the immediate effects of MAT nonadherence and product and dosage-level heterogeneity. Therefore, this study estimated the effect of MAT treatment gaps on patient health and spending. Specifically, I study buprenorphine adherence due to its ability to be prescribed for use at home, where adherence issues may particularly exacerbate outcomes. Buprenorphine was also the most commonly used MAT in Medicare where the study was set. I obtain overall estimates and product and dosage-specific estimates using a cohort of Medicare patients with opioid use disorder between 2010-2017. The study found that total patient expenditures were between $63.7-$684.6 lower in months when patients received treatment. Further, it was found that patients with buprenorphine treatment gaps were 2.83-7.79 times more likely to experience an adverse opioid event in some months than patients receiving continuous buprenorphine treatment. Most importantly, patients receiving high dosages of buprenorphine (4 MG or greater) were less likely to experience an adverse opioid event in months without treatment than patients treated with low dosages of buprenorphine (less than 4 MG). High-dosage buprenorphine patients also had more modest spending increases in the absence of treatment. Policymakers and providers should consider expanding the use of high-dosage buprenorphine treatment to reduce the risk of costly adverse opioid events.

INTRODUCTION

Medication-Assisted Treatments (MAT) are efficacious pharmaceuticals used to treat patients with opioid use disorder. When patients take their prescribed MAT consistently (i.e., without gaps between prescriptions or missing days during a prescription), their risk of opioid overdose is up to 73% lower than when their use is inconsistent (Kinksy et al., 2019). However, adherence is a common issue with MAT, with one study suggest that only 50% of patients adhere closely (Mark et al., 2020). Improving patient adherence to MATs is of critical importance to US public health in light of the devastating effects of the US Opioid Epidemic.

Despite the high rates of MAT nonadherence, there is limited research regarding the effects of MAT nonadherence on patient health and spending. While some studies have looked at adherent and nonadherent patient cohorts they have not fully explored the immediate clinical and financial consequences of treatment gaps. In theory, treatment gaps should increase patient spending and worsen health by increasing the likelihood of patient relapse with opioids due to uncontrolled cravings in the absence of treatment. However, quantifying the health and spending consequence of inconsistent MAT use remains essential to policymakers. Further, research regarding MAT adherence have primarily focused on individual active ingredients of MATs (e.g., buprenorphine, methadone, and naltrexone). Studies have not yet thoroughly examined the potential product and dosage heterogeneity within the active ingredient. Understanding potential variation in the effects of nonadherence for each MAT product is vital to providers, especially if they are faced with several treatment options. Finally, no study has looked at MAT adherence in Medicare. Medication adherence is a significant problem in Medicare, where high rates of mental and physical disability can exacerbate compliance issues (MacLaughlin et al., 2005).

This study implemented two separate analyses to estimate the association of buprenorphine nonadherence with patient spending and health in Medicare. The analyses focused on buprenorphine due to its common use in Medicare. Buprenorphine is also the most common MAT prescribed for use at home, as opposed to physician clinics, where nonadherence may pose a particular problem. To study the relationship between buprenorphine adherence and patient health, I conducted a survival analysis to relate gaps in buprenorphine treatment to the probability of experiencing an adverse opioid event in a given month. An adverse opioid event represented the presence of a diagnosis for opioid abuse, overdose, or adverse effects from opioid use and misuse (i.e., withdrawal). Second, a patient-level fixed effects regression model

estimated the association between a gap in buprenorphine treatment and medical, prescription drug, and total spending. In both the health model and spending model, I conducted subgroup analyses to determine product and dosage heterogeneity in the effects of treatment gaps. I find that patients receiving high dosages of buprenorphine (i.e., 4-8 MG) had lower costs and risk of adverse opioid events in treatment gap months than patients receiving low buprenorphine dosages (i.e., 0-4 MG).

BACKGROUND

Medication adherence has important implications for both patient health and spending. When patients do not adhere to their medications, they risk medical complications from their underlying illnesses. Complications may then require additional treatment, which raises medical expenditures. On the contrary, adhering to treatment with certain medications can be expensive, and the adverse side effects of treatment can similarly increase the need for additional care. Therefore, the extent to which treatment adherence improves patient health and reduces spending is determined by the equilibrium of these opposing effects.

Studies on nonadherence in the MAT market have shown severe effects on patient health and spending (Kinsky, 2020; Ronquest, 2019; Tkacz, 2016). Since MATs reduce opioid cravings and withdrawal symptoms, adherence is critical to reducing the likelihood of patient relapse. In Kinsky and colleagues (2020), the authors find that 3.6% of the patients who adhered to buprenorphine and methadone treatment had a nonfatal overdose relative to 13.2% of nonadherent patients. Both Ronquest and colleagues (2019) and Tkacz and colleagues (2016) noted that MAT nonadherence increased hospitalizations and emergency department visits.

MAT adherence may also reduce unnecessary health care expenditures. Kinsky and colleagues (2020) found that nonadherence with methadone was associated with significant increases in annual patient costs. Ronquest and colleagues (2019) found similar results, and in particular, showed that nonadherent patients spent up to $10,000 more on medical care than adherent patients. Tkacz and colleagues (2016) also observed significant reductions in outpatient and inpatient visits and MAT adherent patients' costs. They find that this reduction ultimately outweighed the more significant spending on prescription medications and outpatient visits among adherent patients.

Gaps in buprenorphine treatment can occur for many different reasons. Patients may experience adverse side effects of treatment that lead to nonadherence, such as opioid withdrawal. High treatment costs, both related to the treatment itself and associated costs like transportation and taking time off work to receive treatment, can also reduce compliance. Pizzicato et al. (2020) observed that younger and female patients were much more likely to adhere to treatment than older and male patients. The authors further found a strong relationship between filling a non-MAT opioid prescription during Buprenorphine treatment and lower odds of adherence, supported by Kinsky and colleagues (2020). Both Pizzicato and colleagues (2020) and Coker and colleagues (2018) showed that patients taking film buprenorphine at higher dosage were more likely to adhere than patients taking tablet buprenorphine and lower buprenorphine doses. Finally, Samples and colleagues (2019) suggest that insurance type (i.e., capitated insurance) and patient demographics are also associated with MAT adherence.

Despite a general understanding of the importance of adherence to MAT and what factors are associated with MAT adherence, more research is needed to explore the immediate consequences of MAT nonadherence and product-level heterogeneity. No study has yet compared potential variation in the effect of buprenorphine treatment gaps on patient health and spending across unique buprenorphine products or dosages. Again, this information is critical to health care providers who must balance the risks and benefits of buprenorphine treatment initiation and treatment intensity. Further, using Medicare as a setting will help determine if there are differences in the levels and effects of adherence in a predominantly elderly, disabled, and chronically ill population where treatment with opioids is standard and medication adherence is lower than in other care settings (MacLaughlin, 2005). I hypothesized that heterogeneity would primarily manifest through differences in dosages available for each product.

METHODS

Data

To determine the effect of MAT gaps on patient health and spending I needed longitudinal data that captured all relevant patient diagnoses, spending, and medication use. This information was readily accessible by aggregating the Medicare MedPAR, Carrier, Outpatient, and Part D annual claims files, including all inpatient and outpatient service utilization and prescription drug use for a 20% random sample of Medicare beneficiaries. Although I would

have preferred data on observed medication use when analyzing the effect of treatment gaps, missed prescriptions observable in the claims data may signal nonadherence.

Study Population

This study used a subsample of Medicare beneficiaries treated with buprenorphine between 2010-2017. Specifically, I selected beneficiaries from an initial 20% random sample of all Medicare beneficiaries during the study period if they met two conditions: 1) a diagnosis for opioid dependence (see Appendix Table 1 for list of relevant ICD 9 & ICD 10 diagnosis codes) and 2) at least one prescription for buprenorphine. Otherwise, I excluded beneficiaries without full 12 months of enrollment in Medicare Part A & B and Medicare Part C beneficiaries to prevent potentially unobserved diagnoses and spending from biasing results. I identified beneficiaries using the Medicare Beneficiary Summary Files (MBSF), which provides monthly Medicare coverage information for each Medicare beneficiary. After applying all restrictions, I obtained an initial sample of 39,440 beneficiaries receiving buprenorphine.

Before estimating the cost and health models, I matched patients with treatment gaps 1-1 to patients without treatment gaps on their probability of having one or more buprenorphine treatment gaps. Matching was required to control for potential selection into buprenorphine gaps by patients on observables. First, I estimated a logistic regression model of "ever gap" on patient demographics (age, race, and sex), index buprenorphine product (i.e., indicators for Suboxone Film, Brand Suboxone Tablet, Generic Suboxone Tablet, and Buprenorphine HCL), index medication active ingredient dosage (0-4 MG low dosage and 4-8 MG high dosage), disability, insurance coverage (i.e., Medicaid dual eligibility), patient distance to the closest MAT provider (i.e., distance between patient residence zip code centroid and provider practice zip code centroid), and year fixed effects based on the year of buprenorphine initiation. The model estimated individual patient probabilities of "ever gap," which I used to match patients that had one or more treatment gaps to patients without treatment gaps. The matching created balance in the patient sample on characteristics likely to predict buprenorphine adherence as suggested by the existing MAT adherence literature (see Table 1). I obtained patient demographics, including patient age, race, ethnicity, gender, Medicaid dual eligibility status, and disability status, from the MBSF. The index MAT product and dosage were available in the Medicare Part D claims datafiles. The final beneficiary sample after 1-1 propensity score matching included 28,298 beneficiaries; 14,149 treated and 14,149 control beneficiaries.

Dependent Variables

The outcomes used in the analyses were the incidence of an adverse opioid event and monthly patient medical spending, drug spending, and total spending (i.e., combined medical and drug spending). An adverse opioid event was indicated in some month for a beneficiary if one of the following diagnoses was present on their medical claims: 1) opioid abuse, 2) opioid overdose, or 3) adverse opioid effects (see Appendix Table 2 for a list of relevant ICD9 and ICD10 diagnosis codes). As a composite measure, adverse opioid effects capture several critical endpoints related to failed MAT. I obtained monthly medical expenditures by aggregating the cost information provided on all inpatient, outpatient, and professional claims to the patient-month level. Similarly, I calculated patient monthly prescription drug spending by aggregating all prescription drug claim gross costs to the monthly level. Finally, total monthly spending represented the sum of monthly prescription drug spending and monthly medical spending by a patient.

Independent Variables

The key covariates used in the analyses were time-varying buprenorphine treatment gap indicators. In particular, I flagged a patient as having a gap in buprenorphine treatment in a month if they received buprenorphine fewer than 50% of the total days. The days supplied information on each prescription helped to identify net treatment days in some month. Excess treatment days were added to the following month when applicable to ensure that I did not falsely identify treated periods as untreated periods. I defined months without treatment as "gap months" as long as the total number of months before reinitiating buprenorphine treatment was three or fewer. I considered patients that had more than three months without treatment in a row as discontinued from treatment. I identified gap months separately from treatment discontinuation months to control for potentially differential effects of gaps relative to discontinuation.

The analyses also incorporated patient comorbidities associated with spending. In particular, they used Major diagnostic categories (MDC) to capture physical and mental health comorbidities across 25 unique diagnostic categories (Center for Medicare and Medicaid Services, 2019). I constructed MDCs using diagnostic-related group (DRG) codes in the Medicare inpatient claims data, which individually matched one of the 25 MDCs (see Appendix Table 3 for DRG-MDC mapping).

Statistical Analysis

To determine the association of time to first patient adverse opioid event with buprenorphine treatment gaps, I estimated a discrete-time survival model with the following complementary log-log specification:

$$AOE_{it} = +\beta_1 Gap_{it} + \sum_{t=2}^{T} \tau_t + \epsilon_{it} \quad [1]$$

The outcome, AOE_{it}, represents the probability that some patient i experienced an adverse opioid event in a month t_t conditional on survival up until that time. The key independent variable, Gap_{it}, is an indicator representing whether or not some patient had a gap in their buprenorphine treatment in month t. Next, τ_t are individual month dummy codes for each month following patient buprenorphine initiation. τ_t is also commonly known as the baseline hazard function. Finally, ϵ_{it} is the error term.

As a discrete time-to-event model, I used panel data at the patient-month level to accommodate time-varying treatment gaps. A log-log link function was used due to the small underlying patient probability of experiencing an adverse opioid event in a given month and to directly estimate parameters in terms of hazard ratios. The model used variation in each covariate over time, both within-subject and between-subject, to recover covariate parameter estimates. The model also had several key timing assumptions. In particular, the model considered patients "at-risk" of an adverse opioid event at the time of their index buprenorphine prescription. They were then followed until 1) their first adverse opioid event, 2) mortality, 3) disenrollment from Medicare parts A or B (including beneficiaries that switch to Part C), or 4) treatment discontinuation. Again, I considered a patient "discontinued" if they had more than three consecutive months without treatment, and I censored their observations after their final month of treatment. Note that using a complementary log-log link function allowed for hazard ratios to be estimated directly.

Next, to determine the effects of buprenorphine treatment gaps on spending in the gap month, I specified a patient-level fixed-effects regression model estimated under ordinary least squares:

$$\text{Cost}_{\text{it}} = \beta_0 + \beta_1 Gap_{it} + \beta_2 Gap_{it-1} + \beta_3 Gap_{it-2} + \sum_{m=1}^{25} MDC_{it}\gamma_m + \mu_i + Year_t + \eta_{it} \quad [2]$$

where Gap_{it} is a binary indicator representing the occurrence of a treatment gap for patient i in month t. The model also included two lag gap indicators, Gap_{it-1} and Gap_{it-2}, to adjust for persistent spending effects from previous gaps. Two lags were ultimately chosen given the lack

of statistical significance when three or more lags were specified. Next, MDC_{it} represents 25 MDC indicators where the absence of one or more MDCs was used as the reference group. To further control for unobserved patient factors related to spending, I added individual patient fixed effects, μ_i. Finally, $Year_t$ are year fixed effects used to control unobserved cost variation over time, and η_{it} is an i.i.d. error term.

As with the adverse opioid event model, I used patient-month panel data to estimate the cost model. However, unlike the adverse opioid event model, the cost model did not include any censoring after the initial adverse opioid event. Therefore, patients could have one or more adverse opioid events, or none at all, but the model used all of their relevant observations for estimation. Unobserved time-invariant patient cost heterogeneity was then absorbed through the patient-level fixed effects. The use of patient-level fixed effects also made this analysis within-subject, such that the model identified parameter estimates using repeated observations within patients over time.

I ran the health model and the cost model once for the entire sample, and then separately by subgroup for each buprenorphine product (i.e., Brand Suboxone Tablet, Generic Suboxone Tablet, Brand Suboxone Film, and Buprenorphine HCL) and dosage type (i.e., low, medium, and high). The subgroups were determined using each patient's index product and dosage, which may or may not have changed after that. Therefore, estimates should be interpreted as conditional on initiating a particular drug instead of consuming it in the month where a gap in treatment may have occurred. However, since most gaps in treatment occur shortly after initiation (see Appendix Figure 1), the index choice is likely to be highly predictive of the subsequent treatment decisions. Further, switching between MAT products was uncommon.

RESULTS

Balance on covariates related to treatment adherence was achieved (See Table 1 for matching results). Before matching, I found notable differences in buprenorphine product choice, initial buprenorphine dosage, distance to the nearest MAT provider, disability, and Medicaid dual eligibility. These differences disappeared after matching, with nearly all nonadherent patients finding a suitable match.

Treatment gaps were primarily observed shortly after treatment initiation (see Appendix Figure 1), with an average monthly rate of 0.4 gaps per beneficiary (see Appendix Figure 2).

This result may explain why most adverse opioid events occurred shortly after treatment initiation (see Appendix Figure 3). Average total monthly spending was also noticeably higher in months when patients experienced treatment gaps (see Appendix Figure 4).

In months with buprenorphine treatment gaps, patients were 3.47 times more likely on average to experience an adverse opioid event than patients without a treatment gap (HR, 3.47 [95% CI 2.84, 4.25], see Table 2 and Figure 1). The results provide evidence of heterogeneity in the effect of treatment gaps on health and spending by both product and dosage. In particular, generic Suboxone tablet patients were the most likely to have an adverse opioid event following a treatment gap (HR, 7.79 [95% CI 1.88, 32.23] followed by brand Suboxone tablet (HR, 4.36 [95% CI 3.23, 5.89]), and Brand Suboxone film (HR, 2.83, [95% CI 2.07, 3.87]). The association of treatment gaps with adverse opioid events after initiation with Buprenorphine HCL was positive but not statistically significant (HR, 1.32 [95% CI 0.68, 2.56]). Further, patients experiencing buprenorphine treatment gaps after initiating treatment on higher dosages of buprenorphine were less likely to experience an adverse opioid event than patients treated with lower dosages (High Dosage: HR, 3.41 [95% CI 2.77, 4.19] versus Low Dosage: HR, 5.40 [95% CI 2.19, 13.32]).

Buprenorphine treatment gaps were also associated with an overall increase in patient spending (Total Spending: $246.1 [95% CI $197.6, $294.6]). This reflects a roughly 15% increase in baseline total spending per month, given that average total spending by month by patient was $1,736 during the study period. The results show that the increase in total spending was primarily driven by a large increase in medical spending (Medical Spending: $504.4 [95% CI $463.2, $545.5]), which offset a more moderate decrease in spending on prescription drugs (Drug Spending: -$258.2 [95% CI -$284.1, -$232.4]). This finding was consistent across all buprenorphine products, although there was notable product and dosage heterogeneity. Specifically, gaps in treatment with generic Suboxone tablet led to the largest increases in total spending (Total Spending: ($684.6 [95% CI $430.9, $938.2])) followed by Buprenorphine HCL (Total Spending: ($334.5 [95% CI $202.3, $466.8])), brand Suboxone tablet (Total Spending: ($270.3 [95% CI $191.7, $294.6]), and brand Suboxone film (Total Spending: ($153.7 [95% CI $81.2, 226.2]). Further, patients treated with high buprenorphine dosages had smaller overall increases in spending in treatment gap months than patients initiated with low dosages (High

Dosage Total Spending: $241.18 [95% CI $188.0 $295.6] versus Low Dosage Total Spending: $286.3 [95% CI $169.9, $402.7]).

DISCUSSION

The study found statistically and empirically significant effects of buprenorphine treatment gaps on patient health and spending. Each treatment gap increased the risk of experiencing an adverse opioid event in a given month by between 2.83-7.79 times, depending on the particular buprenorphine product selected. Total expenditures in each treatment gap month also increased by between $64-$685 on average, representing a $368-$918 average increase in medical spending and a $182-$304 decrease in drug spending. Further, the results showed that patients treated with higher dosages of buprenorphine had lower spending and fewer adverse opioid events in treatment gap months than patients receiving lower dosages of buprenorphine.

Interestingly, gaps in treatment with generic Suboxone tablets led to more significant increases in spending and adverse opioid events than the other buprenorphine products. Given its bioequivalence with brand Suboxone tablet, this difference is likely due to patients' unique characteristics instead of actual biological differences between medications. For example, those taking generic Suboxone tablets may be more price-sensitive and have lower-incomes, which could be correlated with worse health outcomes and more frequent treatment gaps. Variation in treatment gap effects across products may further be driven by the frequency of prescriptions with specific dosages within the drug. Providers may be more likely to prescribe higher dosages for certain products, like Suboxone film, which could explain its seemingly more optimal safety profile among nonadherent patients.

The results showed that patients on higher dosages of buprenorphine typically had less costly treatment gaps in health and spending. This result is likely due to increased residual buprenorphine in the bloodstream associated with higher dosages that protected patients against adverse effects that can lead to relapse and overdose. Despite this, nearly 20% of providers in the sample initiated patients on low buprenorphine dosages (see Table 1). Given that gaps in treatment and attrition frequently happen soon after initiation (see Appendix Figure 1), initiating patients on higher dosages could reduce overdoses and health care expenditures. Further, nonadherent patients may have better outcomes if maintained on higher dosages.

It is also important to consider the underlying causes of nonadherence in the context of these results. Patients may experience gaps in treatment due to treatment side-effects, and other non-pecuniary factors like access to transportation, child-care services, and the ability to take time off from work to receive treatment with MAT at specialized facilities. Moreover, treatment side-effects that lead to treatment gaps are likely centered around a personal desire to experience the euphoria associated with opioid use, while the other factors are essentially barriers to access. Although the former issue is complicated to solve in patients with strong preferences, the latter can and should be addressed by policy reform that connects patients facing these barriers with the appropriate services that may reduce them. In particular, greater coverage of services that reduce MAT access related issues may be important for reducing nonadherence that puts patients at greater risk of overdose and death.

Limitations

There are several limitations to this study. The first limitation is that Medicare did not cover methadone during the study period. Consequently, any patient use of methadone outside of Medicare was unobserved. Unobserved treatment with methadone could potentially increase the treatment gap rate in the data for these patients, given that patients predominantly receive one MAT product at a time. However, this should make treatment gap estimates more conservative by treating a subset of the control patients (i.e., without an MAT gap) as treated (i.e., having an MAT gap). Another fundamental limitation is that patients may have switched products and dosages during the course of their treatment. Switching can potentially contaminate estimates for the dosage and product-level analyses that only consider each patient's index product and dosage. If there were substantial amounts of product or dosage switching, this would make treatment gap estimates across subgroup analyses appear closer together than in reality (i.e., underestimate actual variation across products). Although results for the product level analyses were similar to each other, receiving high dosages of buprenorphine was associated with empirically and statistically significant reductions in costly adverse opioid events relative to low dosages.

Underlying differences in the patient sample between patients that experience buprenorphine treatment gaps and patients without treatment gaps may also bias results. Specifically, the extent to which adherence is correlated with product and dosage decisions may be confound the treatment gap estimates. Propensity score matching addressed this variation on

several observable characteristics related to MAT treatment adherence in the literature, but unobserved factors remain a threat to internal validity. This bias may, for example, explain the higher costs and consequences of gaps in the generic Suboxone tablet cohort.

CONCLUSION

Buprenorphine nonadherence significantly impacts patient health and spending by increasing costly patient adverse opioid events. Specifically, the study showed a 2.83-7.79 times higher risk of experiencing an adverse opioid event in months without treatment and a $63.7-$684.6 increase in total patient expenditures between 2013-2017. Some individual buprenorphine products stand out, with generic Suboxone tablet increasing expenditures and adverse opioid events the most in months with treatment gaps, and brand Suboxone film the least. However, the results demonstrated that patients treated with higher doses of buprenorphine were less likely to have high spending and adverse opioid events in months without treatment than patients taking lower dosages. Prescribers should consider initiating and maintaining nonadherent patients on higher doses of buprenorphine.

REFERENCES

1. Adams, J. W. *et al.* (2020) 'Receipt of opioid agonist treatment halves the risk of HIV-1 RNA viral load rebound through improved ART adherence for HIV-infected women who use illicit drugs', *Drug and Alcohol Dependence*, 206, p. 107670. doi: 10.1016/j.drugalcdep.2019.107670.

2. Altice, F. L. *et al.* (2010) 'Treatment of medical, psychiatric, and substance-use comorbidities in people infected with HIV who use drugs', *The Lancet*, 376(9738), pp. 367–387. doi: 10.1016/S0140-6736(10)60829-X.

3. Center for Medicare and Medicaid Services (2019) 'Design and Development of the Diagnosis Related Group'. Available at https://www.cms.gov/icd10m/version37-fullcode-cms/fullcode_cms/Design_and_development_of_the_Diagnosis_Related_Group_(DRGs).pdf (Accessed: 5 May 2021).

4. Coker, J. L. *et al.* (2018) 'Buprenorphine medication-assisted treatment during pregnancy: An exploratory factor analysis associated with adherence', *Drug and Alcohol Dependence*, 192, pp. 146–149. doi: 10.1016/j.drugalcdep.2018.07.042.

5. 'Connery - 2015 - Medication-Assisted Treatment of Opioid Use Disord.pdf' (no date). Available at: http://ovidsp.dc2.ovid.com.proxy.lib.umich.edu/ovftpdfs/FPEBJPBFOGGDMD00/fs046/

ovft/live/gv025/00023727/00023727-201503000-00002.pdf (Accessed: 15 February 2021).

6. Connery, H. S. (2015) 'Medication-Assisted Treatment of Opioid Use Disorder: Review of the Evidence and Future Directions', *Harvard Review of Psychiatry*, 23(2), pp. 63–75. doi: 10.1097/HRP.0000000000000075.

7. Dunn, K. E., Brooner, R. K. and Stoller, K. B. (2021) 'Technology-assisted methadone take-home dosing for dispensing methadone to persons with opioid use disorder during the Covid-19 pandemic', *Journal of Substance Abuse Treatment*, 121, p. 108197. doi: 10.1016/j.jsat.2020.108197.

8. Feelemyer, J. *et al.* (2014) 'Retention of participants in medication-assisted programs in low- and middle-income countries: an international systematic review', *Addiction*, 109(1), pp. 20–32. doi: https://doi.org/10.1111/add.12303.

9. Forster, A. J. *et al.* (2015) 'Effectiveness of a computerized drug-monitoring program to detect and prevent adverse drug events and medication non-adherence in outpatient ambulatory care: study protocol of a randomized controlled trial', *Trials*, 16(1). doi: 10.1186/1745-6215-16-2.

10. 'HEAL Initiative: Behavioral Research to Improve MAT : Behavioral and Social Interventions to Improve Adherence to Medication Assisted Treatment for Opioid Use Disorders (R61/R33 Clinical Trial Optional) - Technical Assistance Videocast - NEW DATE' (2019) *US Official News*.

11. Jarvis, B. P. *et al.* (2018) 'Extended-release injectable naltrexone for opioid use disorder: a systematic review', *Addiction*, 113(7), pp. 1188–1209. doi: https://doi.org/10.1111/add.14180.

12. Kinsky, S. *et al.* (2019) 'A comparison of adherence, outcomes, and costs among opioid use disorder Medicaid patients treated with buprenorphine and methadone: A view from the payer perspective', *Journal of Substance Abuse Treatment*, 104, pp. 15–21. doi: 10.1016/j.jsat.2019.05.015.

13. Lam, W. Y. and Fresco, P. (2015) 'Medication Adherence Measures: An Overview', *BioMed Research International*, 2015. doi: 10.1155/2015/217047.

14. Ma, J. *et al.* (2019) 'Effects of medication-assisted treatment on mortality among opioids users: a systematic review and meta-analysis.', *Molecular Psychiatry*, 24(12), pp. 1868–1884. doi: 10.1038/s41380-018-0094-5.

15. MacLaughlin, E. J. *et al.* (2005) 'Assessing Medication Adherence in the Elderly', *Drugs & Aging*, 22(3), pp. 231–255. doi: 10.2165/00002512-200522030-00005.

16. Mark, T. L. *et al.* (2020) 'Adherence to buprenorphine treatment guidelines among individuals with an opioid use disorder who have private insurance', *Journal of Substance Abuse Treatment*, 116, p. 108062. doi: 10.1016/j.jsat.2020.108062.

17. McElrath, K. and Joseph, H. (2018) ‘Medication-Assisted Treatment (MAT) for Opioid Addiction: Introduction to the Special Issue’, *Substance Use & Misuse*, 53(2), pp. 177–180. doi: 10.1080/10826084.2017.1404106.

18. Pizzicato, L. N. *et al.* (2020) ‘Adherence to buprenorphine: An analysis of prescription drug monitoring program data’, *Drug and Alcohol Dependence*, 216, p. 108317. doi: 10.1016/j.drugalcdep.2020.108317.

19. Reinhart, M. *et al.* (2018) ‘The Economic Burden of Abuse of Prescription Opioids: A Systematic Literature Review from 2012 to 2017’, *Applied Health Economics and Health Policy*, 16(5), pp. 609–632. doi: 10.1007/s40258-018-0402-x.

20. Ronquest, N. A. *et al.* (2018) ‘Relationship between buprenorphine adherence and relapse, health care utilization and costs in privately and publicly insured patients with opioid use disorder’, *Substance Abuse and Rehabilitation*, 9, pp. 59–78. doi: http://dx.doi.org.proxy.lib.umich.edu/10.2147/SAR.S150253.

21. Ruetsch, C. *et al.* (2017) ‘Heterogeneity of nonadherent buprenorphine patients: subgroup characteristics and outcomes’, *The American Journal of Managed Care*, 23(6), pp. e172–e179.

22. Ruetsch, C. and Tkacz, J. (2010) ‘A Longitudinal Analysis of the Effect of Buprenorphine Medication Assisted Treatment (B MAT) and a Structured Patient Support Program on B-MAT Adherence in a National Sample of Opioid Dependent Patients’, *Value in Health*, 13(3), p. A117. doi: 10.1016/S1098-3015(10)72563-8.

23. Samples, H. *et al.* (2018) ‘Risk factors for discontinuation of buprenorphine treatment for opioid use disorders in a multi-state sample of Medicaid enrollees’, *Journal of substance abuse treatment*, 95, pp. 9–17. doi: 10.1016/j.jsat.2018.09.001.

24. Shrestha, R., Altice, F. L. and Copenhaver, M. M. (2019) ‘HIV-Related Stigma, Motivation to Adhere to Antiretroviral Therapy, and Medication Adherence Among HIV-Positive Methadone-Maintained Patients’, *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 80(2), pp. 166–173. doi: 10.1097/QAI.0000000000001891.

25. Tkacz, J. *et al.* (2016) ‘The Association Between Buprenorphine Medication-Assisted Treatment Adherence And Health Care Service Utilization And Costs’, *Value in Health*, 19(3), p. A187. doi: 10.1016/j.jval.2016.03.1371.

26. Walker, J. R. *et al.* (2019) ‘Adherence Across FDA-Approved Medications for Alcohol Use Disorder in a Veterans Administration Population’, *Journal of Studies on Alcohol and Drugs*, 80(5), pp. 572–577. doi: 10.15288/jsad.2019.80.572.

27. Zinzow, H. *et al.* (2020) ‘Study protocol for a randomized controlled trial of mindfulness-based relapse prevention for opioid use disorders’, *Contemporary Clinical Trials*, 99, p. 106182. doi: 10.1016/j.cct.2020.106182.

TABLES & FIGURES

Table 2.1. Buprenorphine Treated Beneficiary Characteristics Before and After Propensity Score Matching on the Probability of One or More Buprenorphine Treatment Gaps

Covariate	Before Matching		After Matching	
	No Treatment Gaps	One or More Treatment Gaps	No Treatment Gaps	One or More Treatment Gaps
Total Beneficiaries	35,965	16,703	11,402	11,402
Distance to Nearest Buprenorphine Prescriber	5.3	4.7	4.8	4.8
Age (Mean)	51.8	49.3	48.4	48.3
Medicaid Dual Eligibility				
Dual	66.1%	69.9%	72.4%	72.5%
Non-Dual	33.9%	30.1%	27.6%	27.5%
Disability				
Disabled	82.0%	87.1%	91.3%	91.4%
Non-Disabled	18.0%	12.9%	8.7%	8.6%
Race/Ethnicity				
White	81.3%	81.7%	82.6%	82.8%
Black	9.7%	8.9%	8.7%	8.5%
Other Race	1.8%	1.7%	1.4%	1.4%
Asian	0.6%	0.7%	0.5%	0.5%
Hispanic	6.2%	6.5%	6.2%	6.3%
Native American	0.9%	1.0%	0.9%	0.8%
Gender				
Female	48.6%	47.5%	47.1%	46.8%
Male	51.4%	52.5%	52.9%	53.2%
Index Buprenorphine Prescription Product Type				
Brand Suboxone Tablet	19.9%	36.3%	34.9%	35.1%
Brand Suboxone Film	55.8%	46.5%	47.7%	47.4%
Generic Suboxone Tablet	9.9%	6.2%	6.1%	6.3%
Buprenorphine HCL	14.4%	11.0%	11.3%	11.2%
Index Buprenorphine Prescription Dosage Type				
Low Dosage Buprenorphine	16.8%	13.8%	14.4%	14.1%
High Dosage Buprenorphine	83.2%	86.2%	85.6%	85.9%

Sources: Medicare Part D Prescription Claims Data, Medicare Beneficiary Summary File, and Medicare Carrier Claims Data

Table 2.2. Effect of Buprenorphine Treatment Gaps on the Adverse Opioid Events by Buprenorphine Product and Dosage Type

Treatment Subgroup	Complementary Log-Log Model Hazard Ratio Estimates & 95% CI
All Buprenorphine Products	3.47*** (2.84, 4.25)
Brand Suboxone Tablet	4.36*** (3.23, 5.89)
Generic Suboxone Tablet	7.79** (1.88, 32.23)
Brand Suboxone Film	2.83*** (2.07,3.87)
Buprenorphine HCL	1.32 (0.68, 2.56)
High Dose (4-8 MG Buprenorphine)	3.41 *** (2.77, 4.19)
Low Dose (0-4 MG Buprenorphine)	5.40*** (2.19, 13.32)

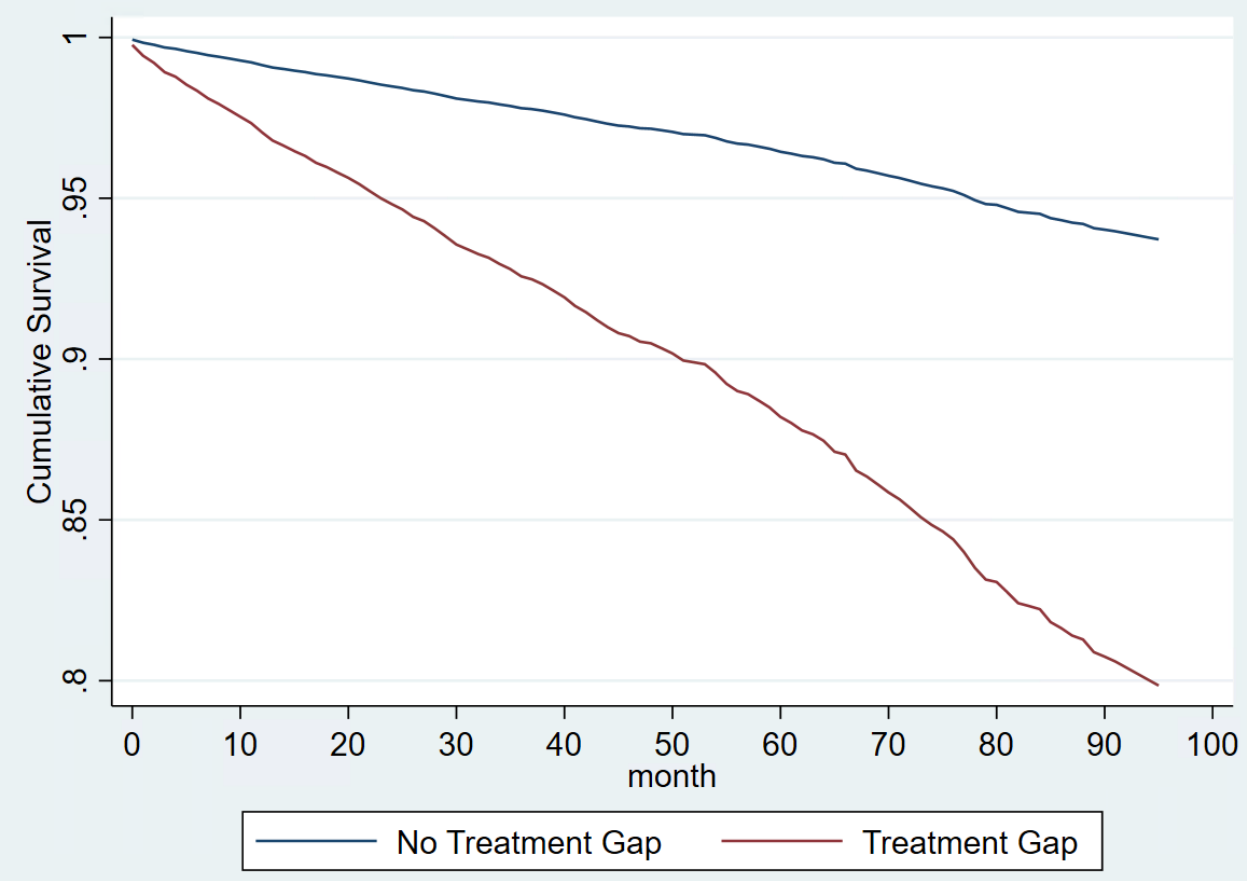
Note: Estimates are comparing months in which patients experience buprenorphine gaps to months in which patients do not experience a gap.

Table 2.3. Effect of Buprenorphine Treatment Gaps on Monthly Patient Total Spending, Medical Spending, and Drug Spending

Treatment Cohort	Total Spending	Medical Spending	Drug Spending
All Buprenorphine Products	$246.1*** ($197.6, $294.6)	$504.4*** ($463.2, $545.5)	-$258.2*** (-$284.1,-$232.4)
Brand Suboxone Tablet	$270.3*** ($191.7, $348.9)	$532.8*** ($464.9, $600.7)	-$262.6*** (-$302.2, -$222.9)
Generic Suboxone Tablet	$684.6*** ($430.9, $938.2)	$917.7*** ($709.0, $1,126.4)	-$233.2** (-$377.4,-$88.9)
Brand Suboxone Film	$153.7*** ($81.2, $226.2)	$432.8*** ($372.3, $493.2)	-$279.1*** (-$319.4, -$238.7)
Buprenorphine HCL	$334.5*** ($202.3, $466.8)	$516.49*** ($401.4, $631.5)	-$181.9*** (-$247.4, -$116.6)
High Dose (4-8 MG Buprenorphine)	$241.8*** ($188.0, $295.6)	$506.1*** ($460.7, $551.5)	-$264.3*** (-$293.2, -$235.3)
Low Dose (0-4 MG Buprenorphine)	286.3*** ($169.9, $402.7)	$510.3*** ($408.7, $611.9)	-$223.9*** (-$281.3, -$166.7)

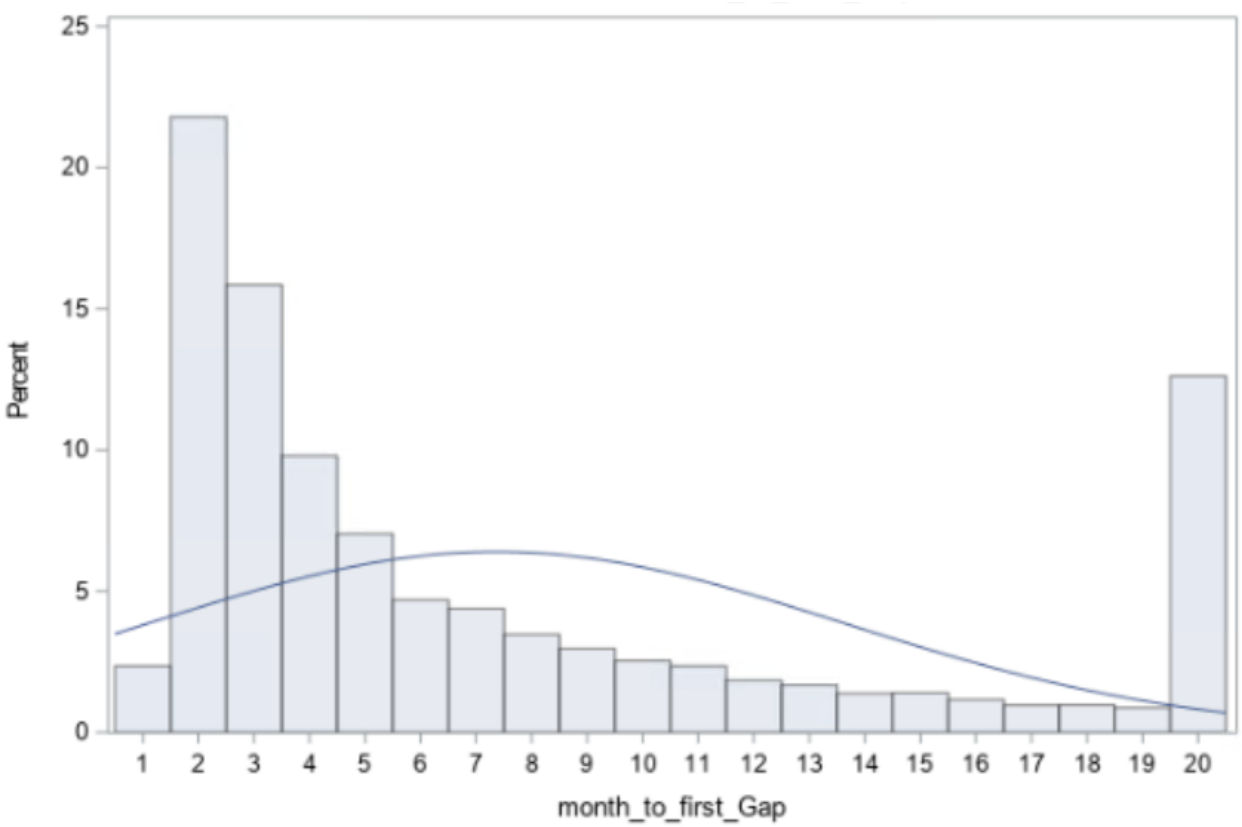
Note: Baseline Medical Spending=$983/Month | Baseline Drug Spending=$753/Month | Baseline Total Spending=$1737/Month

Figure 2.1. Association between Buprenorphine Treatment Gaps and Adverse Opioid Events – Cumulative Survival Curves for Treatment Gap versus No Treatment Gap Beneficiaries



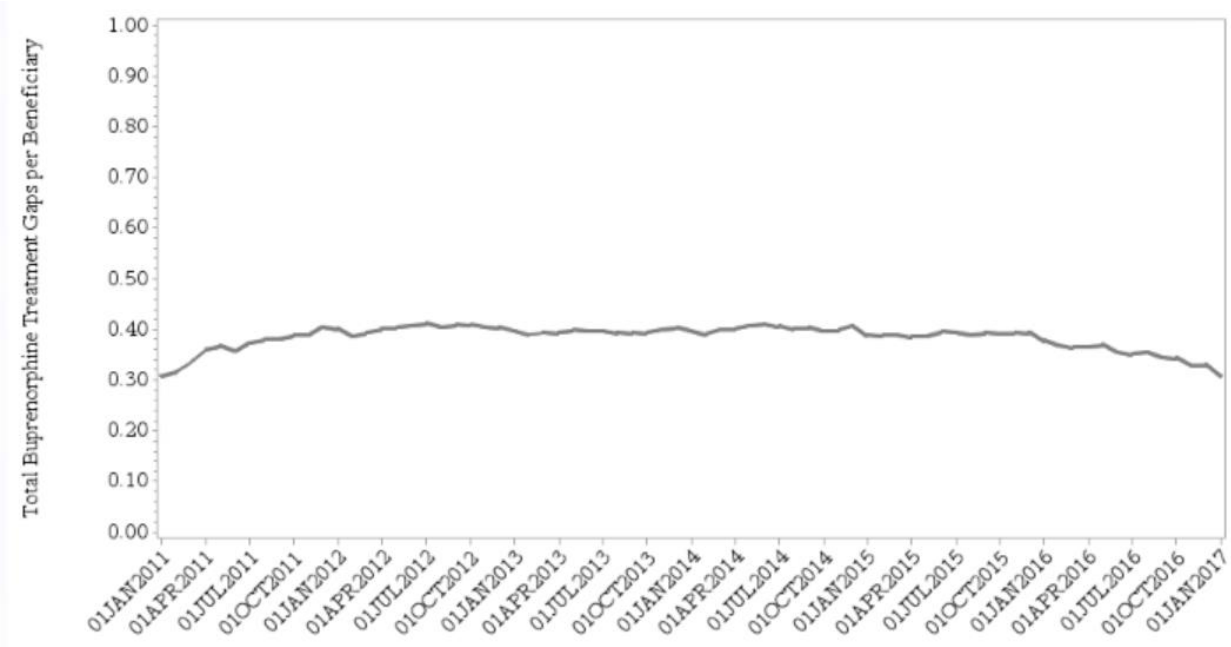
APPENDIX

Appendix Figure 2.1. Distribution of Months until First Buprenorphine Treatment Gap for Medicare Beneficiaries with one or more Buprenorphine Treatment Gaps



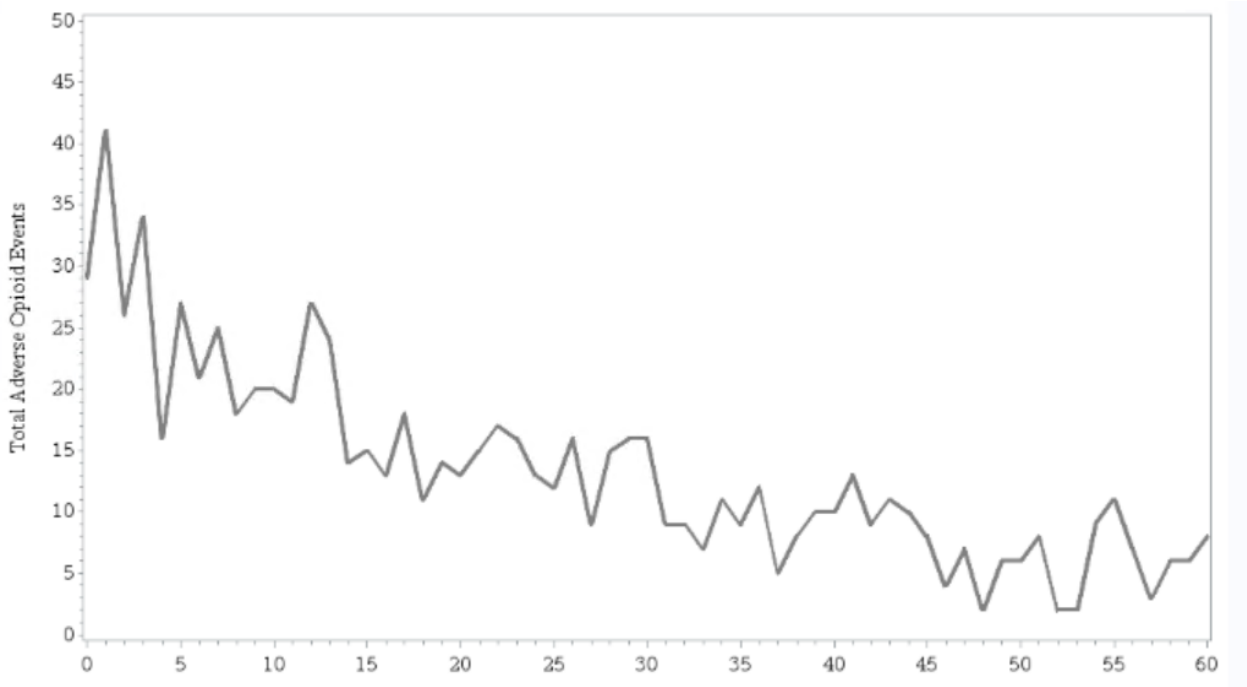
Note: The bin at 20 reflects 20 or more months until the first treatment gap following treatment initiation. Month 0 (not pictured) reflects treatment initiation while month 1 reflects the month following initiation. The blue line is the normal distribution of the data.
Source: Medicare Part D Prescription Drug Claims Data.

Appendix Figure 2.2. Total Buprenorphine Treatment Gaps per Beneficiary by Month – All Buprenorphine Products



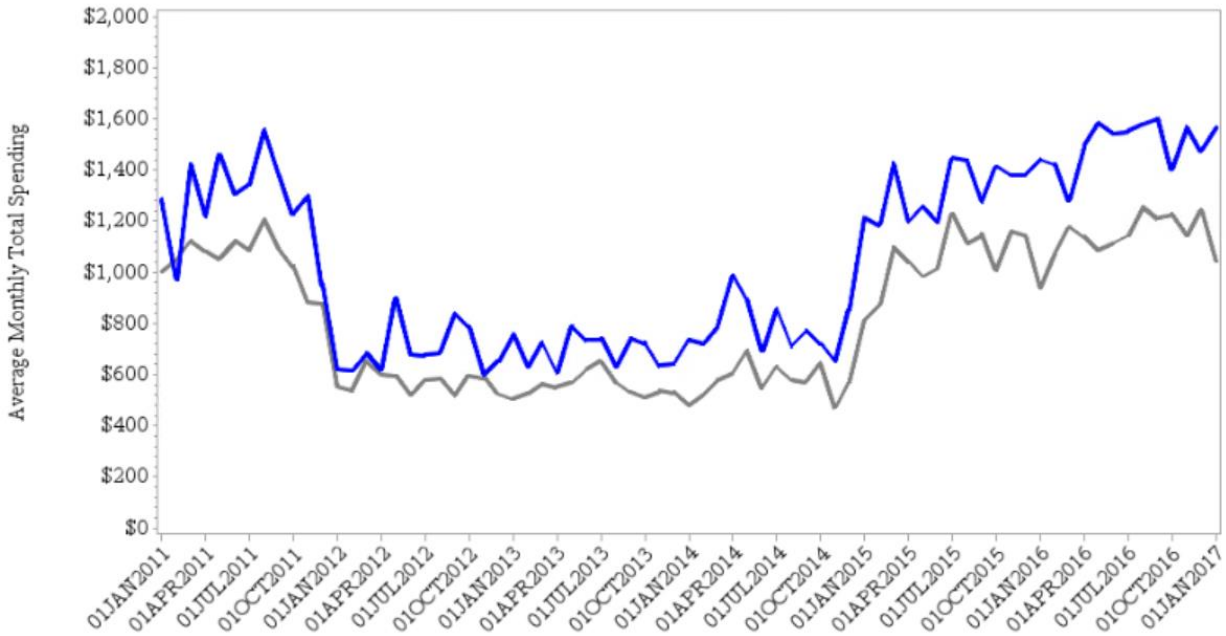
Notes: A buprenorphine treatment gap reflects a month for a patient in which 15 consecutive days there was no active buprenorphine prescription
Source: Medicare Part D Prescription Claims Data

Appendix Figure 2.3. Total Adverse Opioid Events by Month following Treatment Initiation – All Buprenorphine Products



Notes: An adverse opioid event reflects the occurrence of opioid overdose, abuse, or adverse effects from overuse. The X-Axis reflects the number of months since treatment initiation, where 0 represents the index prescription for some beneficiary. Total adverse opioid events measure all adverse opioid events in the patient sample in a particular month.
Source: Medicare Part D Prescription Claims Data

Appendix Figure 2.4. Total Health Care Expenditures by Month among Patients Treated with Buprenorphine – Treatment Gap Months versus Treated Months



[Blue: Months with Treatment Gaps | Grey: Months without Treatment Gaps]

Notes: A buprenorphine treatment gap reflects a month for a patient in which 15 consecutive days there was no active buprenorphine prescription. Average Monthly Total Spending reflects the mean of the sum of prescription and medical expenditures in the population by calendar month.
Source: Medicare Part D Prescription Claims Data, Medicare MedPAR Claims Data, Medicare Part B Claims Data, and Medicare Outpatient Claims Data

Appendix Table 2.1. Opioid Use Disorder ICD9 & ICD10 Codes

Adverse Opioid Event Category	ICD 9 Codes	ICD 10 Codes
Dependence	304: Opioid Dependence-Unspecified 304.01: Opioid Dependence-Continuous 304.02: Opioid Dependence-Episodic 304.03: Opioid Dependence, In Remission 304.7: Opioid Other Dep-Unspecified 304.71: Opioid Other Dep-Continuous 304.72: Opioid Other Dep-Episodic 304.73: Opioid Other Dep-In Remission	F11 series: Opioid-related disorders (except F11.21 and abuse codes)

Sources:
ICD 9 Codes obtained from Owens, PL, Barret, ML, Weiss, AJ, Washington, RE, and Kronick R, (2014) "Hospital Inpatient Utilization Related to Opioid Overuse Among Adults, 1993–2012," Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Statistical Brief #177. Available at: https://www.ncbi.nlm.nih.gov/books/NBK538344/ Accessed: October 30, 2020.

ICD 10 Codes obtained from Weiss, AJ, McDermott, KW, and Heslin, KC, (2016) "Opioid-Related Hospital Stays Among Women in the United States," Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Statistical Brief #247. Available at: https://www.ncbi.nlm.nih.gov/books/NBK246983/ Accessed: October 30, 2020.

Abbreviation:
ICD-9, International Classification of Diseases, Ninth Revision
ICD-10, International Classification of Diseases, Tenth Revision

Appendix Table 2.2. Adverse Opioid Event ICD9 & ICD10 Codes

Adverse Opioid Event Category	ICD 9 Codes	ICD 10 Codes
Abuse	305.51: Opioid Abuse-Continuous 305.52: Opioid Abuse-Episodic 305.53: Opioid Abuse-In Remission 305.5: Opioid Abuse Unspecified	F11 series: Opioid-related disorders (except F11.21 and dependence codes)
Adverse Effects	E935.2: Other opiates and related Narcotics Causing Adverse Effects in Therapeutic Use	T40.0X5: Adverse effect of opium T40.2X5: Adverse effect of other opioids T40.3X5: Adverse effect of Methadone
Overdose	965: Opium Poisoning 965.09: Poisoning by other opiates and related narcotics E850.2: Accidental poisoning by other opiates and related narcotics	T40.0X1, 0X2, 0X3, 0X4: Poisoning by opium–accidental, intentional self-harm, assault, or undetermined T40.1X1, 1X2, 1X3, 1X4: Poisoning by heroin–accidental, intentional self-harm, assault, or undetermined T40.2X1, 2X2, 2X3, 2X4: Poisoning by other opioids–accidental, intentional self-harm, assault, or undetermined T40.3X1, 3X2, 3X3, 3X4: Poisoning by Methadone–accidental, intentional self-harm, assault, or undetermined

Sources:
ICD 9 Codes obtained from Owens, PL, Barret, ML, Weiss, AJ, Washington, RE, and Kronick R, (2014) "Hospital Inpatient Utilization Related to Opioid Overuse Among Adults, 1993–2012," Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Statistical Brief #177. Available at: https://www.ncbi.nlm.nih.gov/books/NBK538344/ Accessed: October 30, 2020.

ICD 10 Codes obtained from Weiss, AJ, McDermott, KW, and Heslin, KC, (2016) "Opioid-Related Hospital Stays Among Women in the United States," Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Statistical Brief #247. Available at: https://www.ncbi.nlm.nih.gov/books/NBK246983/ Accessed: October 30, 2020.

Abbreviation:
ICD-9, International Classification of Diseases, Ninth Revision
ICD-10, International Classification of Diseases, Tenth Revision

Appendix Table 2.3. Mapping of Diagnostic Related Groups (DRG) to Major Diagnostic Categories (MDC)

MDC Description	DRG Range
MDC 01 Diseases & Disorders of the Nervous System	20-103
MDC 02 Diseases & Disorders of the Eye	113-125
MDC 03 Diseases & Disorders of the Ear, Nose, Mouth & Throat	129-159
MDC 04 Diseases & Disorders of the Respiratory System	163-208
MDC 05 Diseases & Disorders of the Circulatory System	215-316
MDC 06 Diseases & Disorders of the Digestive System	326-395
MDC 07 Diseases & Disorders of the Hepatobiliary System & Pancreas	405-446
MDC 08 Diseases & Disorders of the Musculoskeletal System & Connective Tissue	453-566
MDC 09 Diseases & Disorders of the Skin, Subcutaneous Tissue & Breast	573-607
MDC 10 Endocrine, Nutritional & Metabolic Diseases & Disorders	614-645
MDC 11 Diseases & Disorders of the Kidney & Urinary Tract	652-700
MDC 12 Diseases & Disorders of the Male Reproductive System	707-730
MDC 13 Diseases & Disorders of the Female Reproductive System	734-761
MDC 14 Pregnancy, Childbirth & the Puerperium	765-782
MDC 15 Newborns & Other Neonates with Conditions Originating in Perinatal Period	789-795
MDC 16 Diseases & Disorders of Blood, Blood Forming Organs, Immunologic Disorders	799-816
MDC 17 Myeloproliferative Diseases & Disorders, Poorly Differentiated Neoplasms	820-849
MDC 18 Infectious & Parasitic Diseases, Systemic or Unspecified Sites	853-872
MDC 19 Mental Diseases & Disorders	876-887
MDC 20 Alcohol/Drug Use & Alcohol/Drug Induced Organic Mental Disorders	894-897
MDC 21 Injuries, Poisonings & Toxic Effects of Drugs	901-923
MDC 22 Burns	927-935
MDC 23 Factors Influencing Health Status & Other Contacts with Health Services	939-951
MDC 24 Multiple Significant Trauma	955-965
MDC 25 Human Immunodeficiency Virus Infections	969-977

Source: CMS ICD-10-CM/PCS MS-DRG v37.0 Definitions Manual

CHAPTER III:
Racial and Ethnic Disparities in Access, Utilization, and Health Outcomes in the Medication Assisted Treatment Market for Opioid Use Disorder

ABSTRACT

Medication-Assisted Treatments (MATs) are efficacious pharmaceuticals for treating opioid use disorder. However, recent studies have shown racial and ethnic disparities in MAT that threaten to drive the opioid epidemic's severity in underserved communities. This study analyzed disparities in MAT access, use, and treatment outcomes in a population of Medicare beneficiaries with opioid use disorder. The study found significant disparities in access and treatment use, but only minor variation in treatment outcomes conditional on receiving treatment. Therefore, expanding treatment access and use will be vital to reducing racial and ethnic disparities in opioid overdose and abuse. Further, provider behavior was strongly associated with disparities in treatment use. Policymakers should consider addressing these disparities in MAT use by incentivizing and educating providers to expand culturally competent MAT services.

INTRODUCTION

Medication-Assisted Treatments (MAT) are pharmaceuticals used to curb patient addiction to opioids and prevent opioid withdrawal. Due to their efficacy, policymakers and providers have acted swiftly to increase their use in communities significantly affected by the US Opioid Epidemic. However, there remain substantial disparities in MAT access, use, and opioid related outcomes even though addiction rates are comparable by race and ethnicity (Alexander, Kiang, and Barbieri, 2018). Given the efficacy of MAT in reducing opioid overdose and related mortality, addressing racial and ethnic disparities in MAT delivery, access, and outcomes is critical. Formal policy responses are especially urgent given that recent studies have shown notable increases in non-white opioid-related overdose deaths over the last five years (Drake, Charles, Bourgeois, Daniel, and Kwende 2020). This trend has exacerbated since the start of the COVID-19 pandemic (Ghatri, Pizzicato, Viner, et al. 2020).

While many studies have identified racial and ethnic disparities in MAT, the underlying mechanisms that drive these disparities are understudied. Disparities can theoretically result from medical practitioners' inequitable treatment, social and community-level factors, provider accessibility, and patient preferences. However, the extent to which each plays a role in driving inequity is unknown. A better understanding of the root causes of disparities in MAT is needed to produce rigorously informed public health policy responses to improve addiction treatment equity.

I performed three separate analyses to estimate the magnitude of provider behavior and social vulnerability on driving MAT disparities in treatment access, use, and outcomes. The first analysis identified disparities in access by estimating the probability that patients encountered a MAT provider. The second analysis then examined disparities in receiving MAT conditional on having an encounter with a prescribing physician. Finally, I quantified disparities in adverse opioid events (e.g., overdose, abuse, and adverse effects of opioids) conditional on receiving MAT treatment. For each analysis, I estimated a base model relating race and ethnicity to the relevant outcome initially. I then modeled additional specifications that added covariates related to each root cause of MAT disparities. The study then compared marginal effects between the base model and the expanded specifications to determine the role of provider and social factors in driving disparities. In most cases, if the parameters for racial and ethnic groups decreased or became insignificant in the layered models, I attributed either provider or social factors to the

underlying disparity. The results ultimately show that provider factors are essential modifiers of MAT use, which likely explains the higher rates of adverse opioid events in racially and ethnically diverse patients.

BACKGROUND

The literature on racial and ethnic disparities in MAT has identified severe MAT access, use, and subsequent health outcome issues. The underlying drivers of these disparities have been primarily linked to provider factors and social determinants of health.

Providers treating non-white patients are more likely to under-prescribe and fail to adhere to treatment guidelines. This notion is evidenced in particular by D'Aunno and Pollack (2002), who showed that African American heroin users are more likely than white heroin users to receive inadequate doses of Methadone. Further, Schiff and colleagues (2020) observed that African American and Hispanic pregnant women were much less likely to receive buprenorphine than white women. Pregnant women with opioid use disorder are strongly recommended to use buprenorphine to prevent relapse with more potent opioids. MAT prescribers have also been less likely to locate near or provide care for patients in non-white neighborhoods. Hansen and colleagues (2016) noted that buprenorphine prescribing in New York City increased the most in neighborhoods with the lowest proportion of African Americans and Hispanic residents between 2004 and 2013. Stein and colleagues (2018) found that in 2009, counties with the highest proportions of African American and Hispanic residents had the lowest MAT use rates in Medicaid. Further, Goedel and colleagues (2020) observed that for every 1% decrease in the probability of interaction between African American and white residents in a community, the number of methadone facilities increased by 0.6 facilities. Treatment with Methadone occurs only in highly regulated systems, creating additional time and access burdens for patients.

Social determinants also play an essential role in driving MAT disparities. There are substantial disparities in access to affordable transportation, child care, and the ability to take time off from work to receive treatment that limits MAT accessibility in underserved areas. These burdens are exacerbated by the fact that non-white patients are far more likely to receive Methadone, which requires patients to take daily trips to clinics. The additional burdens faced by non-white patients then reduce treatment adherence and increase the rate of early MAT discontinuation. For example, Samples and colleagues (2018) find that African American and

Hispanic patients are 1.24-1.31 times more likely than white patients to discontinue MAT within 180 days after initiation. Most patients also either use self-pay and private insurance for buprenorphine treatment, which Lagisetty and colleagues (2019) identified. This result suggests disparities in insurance coverage type and generosity and income drive MAT disparities.

The purpose of this study was to quantify the role of providers and social determinants in driving disparities in MAT access, use, and health outcomes. Specifically, the focus was to estimate the effects of race and ethnicity on the probability of seeing a prescribing physician, obtaining treatment conditional on a visit, and having good health outcomes conditional on treatment while controlling for provider-level factors and social vulnerability. These additional controls will make it possible to study the impact of ecological circumstances and provider behavior on existing disparities identified in the models without their inclusion. More generally, addressing the knowledge gap concerning the underlying causes of MAT disparities is essential to policymakers and providers seeking to make MAT more equitable.

METHODS

Study Population

The study used a population of Medicare beneficiaries diagnosed with opioid use disorder between 2013-2017 to determine the association of provider behavior and social determinants with MAT disparities in access, use, and treatment outcomes. Many Medicare beneficiaries suffer from opioid use disorder due to chronic illnesses that require treatment with opioids that can lead to addiction. In response, coverage of MAT has been increasing in Medicare, and more providers have started prescribing MAT to their Medicare patients. However, there is limited research concerning potential variation in these services' diffusion by race and ethnicity. Given the growing evidence of disparities in other health care programs like Medicaid, it is vital to determine the extent to which MAT disparities exist in one of the nation's most vulnerable populations.

Starting with an initial sample of 10,241,222 Fee-for-Service Medicare beneficiaries enrolled for at least one year between 2013-2017, I obtained a cohort of 325,520 beneficiaries who had at least one diagnosis for opioid use disorder during the entire study period (see Appendix Table 1 for list of included ICD9 and ICD10 diagnoses codes). Their relevant medical

and prescription drug claims were then extracted from the Medicare Carrier, MedPAR, and Part D claims data.

Dependent Variables

The study focused on three different outcomes. First, to proxy beneficiary access to treatment, I used the presence of a patient encounter with an MAT prescriber. I identified visits using Medicare Part B carrier claims data, which contain all claims billed by Medicare physicians (i.e., professional claims). I considered any visit with a MAT prescriber an encounter even if the actual reason for the visit was unrelated to the patient's opioid use disorder. A provider also had to have one or more MAT prescriptions in the year of the encounter to qualify as an MAT prescriber. I identified MAT prescribers using the Medicare Part D claims data which indicated the prescriber national provider identifier (NPI) on each prescription.

The subsequent outcome, MAT use, reflected whether a patient received one or more MAT prescriptions conditional on an initial encounter with a prescribing physician. Any prescription MAT fill qualified a patient as receiving MAT treatment regardless of MAT product type or if the initial encounter physician was the index prescriber.

The last outcome was the presence of an adverse opioid event conditional on treatment. An adverse opioid event reflects the occurrence of one or more of the following in some months: opioid abuse, overdose, or adverse effects (i.e., opioid withdrawal). I developed this measure using a set of ICD9 and ICD10 diagnosis codes identified in the Medicare medical claims data (see Appendix Table 2 for list of ICD codes).

Independent Variables

The first set of covariates used in the statistical models included a combination of beneficiary demographics and county-level social determinants of health (SDOH). I obtained beneficiary characteristics from the Medicare Beneficiary Summary Files (MBSF). They included age, race (i.e., African American, Asian, Native American, or Other/Unknown Race), ethnicity (i.e., Hispanic), gender, Medicaid dual eligibility status, and disability. I used county-level SDOH variables from the Agency for Healthcare Research and Quality (AHRQ) Social Determinants of Health (SDOH) Database files (2013-2017). The AHRQ SDOH files contain measures corresponding to five key SDOH domains: 1) social context, 2) economic context, 3) education, 4) physical infrastructure, and 5) healthcare. In addition to individual factors, AHRQ provides specialized social vulnerability indexes by 1) socioeconomics, 2) household

composition and disability, 3) minority status/language, 4) housing/transportation, and 5) overall social vulnerability. These indexes reflect each county's percentile rank concerning a weighted average of the individual measures in each group. Note that the analyses only used the socioeconomic, household composition, and housing/transportation domains. I excluded the minority/language and overall index due to their correlation with beneficiary race.

I also incorporated several provider-level factors into the analyses. The first provider measure reflected the distance between a beneficiary's residence and the nearest MAT prescriber. I constructed this measure by calculating the distance between the beneficiary residence zip code and the closest MAT provider's practice zip code using the haversine formula (i.e., distance as the crow flies). Each beneficiary's zip code was reported annually in the MBSF. However, to determine a provider's zip code, each provider had to be assigned to a unique practice. Provider practice assignment was determined using the plurality of each provider's charges at the Tax Identification Number (TIN) level, where the resulting TIN assignment identified the provider's zip code. Further, in addition to distance, provider-level fixed effects were used to control for time-invariant unobserved provider characteristics potentially associated with treatment disparities.

The final covariate was an indicator representing a patient MAT gap in a given month. In particular, a patient was said to experience a gap in MAT if there were 15 or more days in some month where they were not receiving MAT. The duration of each MAT prescription was determined by adding the days supplied on the prescription to the prescription fill date. The days between MAT windows then identified months where patients were not on treatment for the plurality of days in that month.

Models

I used Logistic regression to relate the probability of encountering a MAT prescriber to patient demographics, social determinants, and provider proximity:

$$E_i = Pr(E_i^* = 1)$$

$$= RaceEthnicity_i\alpha + X_i\beta + SDOH_{c(i)}\gamma + \omega Distance_i + Year_{t(i)} + \epsilon_i \quad [2]$$

$$E_i^* = \begin{cases} 0, & if\ "No\ Visits\ w/\ MAT\ Prescriber" \\ 1, & if\ "One\ or\ More\ Visits\ w/\ MAT\ Prescriber" \end{cases}$$

On the left-hand side of the equation, there is E_i, which is a binary indicator set to 1 if a patient i ever had a visit with a MAT prescriber. On the right-hand side, there is $RaceEthnicity_i$, which

correspond to indicators for each race and ethnicity among African American, Asian, Hispanic, Native American, other/unknown race, and White. Next, I included patient demographics with the exclusion of race and ethnicity in X_i (i.e., age, gender, Medicaid dual eligibility, and disability). County-level social vulnerability index scores from patient i residing in county c were captured by $SDOH_{c(i)}$ (i.e., housing and transportation vulnerability index, socioeconomic vulnerability index, and housing composition and disability vulnerability index). Patient distance in miles to the nearest MAT prescriber $Distance_i$, and year fixed effects, $Year_{t(i)}$, were incorporated to control for provider proximity and encounter variation over time. Note that the year used in the year fixed effects for each beneficiary was the year of the diagnosis for opioid use disorder. Finally, ϵ_i is a fixed error term with variance $\frac{\pi^2}{3}$.

After estimating the MAT encounter model, I estimate a second logistic regression model that relates the probability of receiving MAT conditional on an encounter to demographics, social determinants, and provider factors:

$$T_i = \Pr(T_i^* = 1 | E_i^* = 1)$$
$$= \beta_0 + RaceEthnicity_i\alpha + X_i\beta + SDOH_{c(i)}\gamma + Provider_i + Year_{t(i)} + \theta_i \quad [3]$$

$$T_i^* = \begin{cases} 0, & if\ "Never\ Treated\ w/\ MAT" \\ 1, & if\ "Treated\ at\ Least\ Once\ w/\ MAT" \end{cases}$$

The outcome, T_i, reflects the probability that a patient received treatment conditional on an encounter with a MAT prescriber. Note that I reused the independent variables from Equation 1, except for distance which I omitted and provider level fixed effects, $Provider_i$, which I added. Further, θ_i is the new error term.

The addition of provider level fixed effects controlled for fixed unobserved provider factors correlated with the decision to initiate a patient on MAT. The use of provider fixed effects also created a within-provider interpretation for the estimates. This means that the estimates reflected actual differences in treatment given to patients of different races and ethnicities by the same provider.

Finally, to evaluate disparities in MAT outcomes, a mixed effect logistic regression model was used to estimate the probability of experiencing an adverse opioid event by patient race and ethnicity:

$$AOE_{it} = pr(AOE_{it}^* = 1 | T_i^* = 1)$$
$$= \beta_0 + RaceEthnicity_i\alpha + X_i\beta + SDOH_{c(i)}\gamma + \delta Gap_{it} + Provider_i + Year_t + \eta_{it} \quad [4]$$

$$AOE_{it}^{*} = \begin{cases} 0, & if\ "No\ Event" \\ 1, & if\ "Adverse\ Opioid\ Event" \end{cases}$$

The dependent variable, AOE_{it}, is a binary indicator set to 1 in any month t that some beneficiary i experienced an adverse opioid event. Novel covariates include Gap_{it}, which indicated MAT gaps and was set to one in each month where a patient received MAT less than 50% of the days in that month, and the error term $\eta_{ict} = \eta \sim N(0, \frac{\pi^2}{3})$. Unlike the previous models, the data used to estimate this equation was at the patient month panel level (i.e., one observation per patient per month), which permitted the estimation of a discrete time-to-event model. The data were also censored following the first instance of an adverse opioid event, making it a time-to-event analysis. This limited the persistence of previous adverse opioid events from biasing estimates for patients experiencing multiple adverse opioid events. It also changed the interpretation of parameter estimates to be relative to experiencing one or more adverse opioid events in a given month following treatment initiation. I additionally censored patients after death or disenrollment from Medicare (including a transition to Medicare managed care plans where claims will be unobserved).

Since the purpose of the study was to understand how different provider and SDOH factors modified disparities, I compared a base model using only beneficiary characteristics to additional specifications that incorporated SDOH and provider-level covariates. Specifically, I first estimated each of the three models using only demographics $RaceEthnicity_i$ and X_i (i.e., the "base model"), and then re-estimated the models with the inclusion of SDOH and provider covariates (i.e., $Provider_i$ fixed effects, $Distance_i$). I then compared differences in parameter estimates for race and ethnicity across the base model and the additional specifications to see how SDOH and provider factors changed estimates relative to the base model. Note that before comparing estimates across models, I transformed them into marginal effects (ME). Adding covariates to a logistic regression model changes the standard deviation of the error term, which Norton and Dowd (2018) show prevent comparisons of odds ratios across different specifications. Marginal effects permit cross-specification comparisons by comparing predicted probabilities with and without treatment assignment in the same population.

RESULTS

Descriptive statistics of covariates comparing beneficiaries across each outcome can be found in Table 1. Relative to beneficiaries with no encounters with MAT prescribers, beneficiaries with encounters were more likely to be disabled, younger, Medicaid dual eligible, and to reside in communities with lower (i.e., worse) social vulnerability index scores. Differences by race, ethnicity, and gender were modest, with more diversity in the no encounter group. However, race, ethnicity, and gender differences were substantial across beneficiaries with and without treatment and adverse opioid events. Specifically, non-white beneficiaries were less likely to receive treatment conditional on a MAT prescriber encounter and more likely to experience an adverse opioid event conditional on treatment. Further, beneficiaries receiving treatment and not experiencing adverse opioid events had lower social vulnerability index scores.

Results from the MAT prescriber encounter model (i.e., equation [1]) show that white beneficiaries were more likely than African American, Asian, Hispanic, and other/unknown race beneficiaries to have an encounter with a MAT prescriber (see Table 2). In the base model without social vulnerability and provider factors, the most pronounced effects were seen in Asian beneficiaries (ME, -0.106 [95% CI: -0.126, -0.086]), followed by Native American (ME, -0.083 [95% CI: -0.100, -0.065]), African American (ME, -0.061 [95% CI: -0.067, -0.056]), Hispanic (ME, -0.065 [95% CI: -0.073, -0.057]), and other/unknown race beneficiaries (ME, -0.015 [95% CI: -0.031, 0.002]). In the following specifications, parameter estimates for race and ethnicity covariates became more negative (i.e., disparities increased), except for Native American patients whose estimates increased when adding social vulnerability indexes (ME, -0.077 [95% CI: -0.097, -0.056]) and distance to the nearest MAT prescriber (ME, -0.063 [95% CI: -0.084, -0.042]).

Estimates from the MAT utilization model also show substantial MAT use disparities by race and ethnicity (see Table 3). As with the encounter model, the base model estimates for race and ethnicity were all negative (see Table 3 column 1). In particular, conditional on having a MAT prescriber visit, non-white beneficiaries were 2.1%-8.6% percentage points less likely to receive MAT than white beneficiaries. After adding social vulnerability indexes and provider fixed effects to the base model, the estimates became more negative. This is in exception of Native American beneficiaries who again had larger estimates after controlling for social and

provider factors (Base Model w/ SDOH: ME, -0.033 [95% CI: -0.051, -0.015]; Base Model w/ SDOH & Provider Factors: ME, 0.028 [95% CI: -0.010, 0.066]).

The final set of results show that conditional on MAT, disparities in resulting adverse opioid events (i.e., treatment outcomes) were limited. This result is evidenced by the empirically small and statistically insignificant marginal effects for nearly all racial and ethnic groups in the base model, the base model with social vulnerability index controls, and the base model with social vulnerability index controls and treatment provider-level fixed effects. The one exception was Asian patients, who had positive and statistically significant parameter estimates in the final specification (ME, 0.5673 [95% CI: 0.1213, 1.0132]).

DISCUSSION

Together, the results illustrate the severity of MAT disparities by race and ethnicity. First, the MAT access model showed that non-white beneficiaries were much less likely to have any encounter with MAT prescribers. This finding held even after controlling for provider proximity and social vulnerability. Disparities even increased after controlling for distance to the nearest MAT provider, suggesting that closer proximity among non-white patients may be masking an even more significant disparity in access. The likelihood that non-white beneficiaries then received MAT conditional on an encounter was also much lower. The social vulnerability indexes had only minor impacts on treatment use disparities, suggesting that other factors may better explain the original disparities. One likely source is provider bias, given the fact that I observed more considerable disparities for African American, Asian, and Hispanic patients after incorporating encounter provider fixed effects. More clearly, conditional on visiting the same MAT prescriber, white patients had an increased likelihood of receiving treatment than patients in other racial and ethnic groups.

One interesting finding was that MAT access and use disparities for Native Americans decreased in the models with social and provider factors. This decrease suggests that provider proximity, provider practice, and social vulnerability are highly associated with disparities in MAT access and use among Native Americans with opioid use disorder, given that they explained the original variation in the base model.

Once treated, beneficiaries of all races experienced similar treatment outcomes. This result is evidenced by the generally statistically insignificant race and ethnicity parameter

estimates in all of the specifications. Although the estimate for Asian patients became positive and significant after incorporating treatment provider fixed-effects, this might be explained by the limited number of Asian patients receiving MAT from prescribers treating multiple opioid use disorder patients. Otherwise, Medicaid Dual Eligible status and MAT gaps were the most significant predictors of future adverse opioid events.

All findings stress the need for policy reform. National programs aimed, in particular, at educating prescribers about existing MAT access and use disparities while encouraging and incentivizing them to expand treatment to vulnerable populations should be considered. This policy is especially pertinent given the finding of increased disparities after controlling for encounter provider fixed effects in the treatment use model; clinics seeing multiple patients of potentially different races were even less likely to treat African American and Hispanic patients than smaller practices with less racial diversity. The treatment access and use results also illustrate that other factors, such as beneficiary preferences, could be significantly related to disparities. Resources allocated to improving culturally competent addiction services might increase the rate at which individuals in underserved groups seek and accept MAT. Qualitative research has pointed to differential experiences of BIPOC patients in treatment programs as driving hesitancy.

Limitations

There are several limitations to the study design that limit generalizability and threaten internal validity. The first is that Medicare did not cover Methadone during the study period. Therefore, there may be unobserved use of Methadone use in the beneficiary sample, which may inflate estimates of disparities in the MAT use model in particular. However, given the advantages of buprenorphine relative to Methadone, this model still captures key MAT use disparities. The second issue is that the selected social and provider factors may not fully capture all relevant confounders in these domains. If many unobserved factors related to provider behavior and patient environments were not addressed, then the disparities estimates will be biased. Regardless, I was able to make meaningful inferences by exploring how parameters change after incorporating social vulnerability and provider factors across the different models.

Another potential limitation to the generalizability of this study is that MAT prescribing in Medicare is unique, given the high rates of opioid use to treat pain from chronic conditions

common among Medicare beneficiaries. Disparities in other insurance programs may therefore manifest differently. One could imagine, for example, that patients in Medicaid may experience even greater disparities in access and use due to their more limited income relative to Medicare patients. Specifically, barriers to access and use such as limited transportation, access to child care services, and the ability to take time off from work will therefore be exacerbated in Medicaid. With that said, there is a vast population of Medicaid dual-eligible beneficiaries, and under 65 beneficiaries who qualify for Medicare due to End-Stage Renal Disease and Disability, in the patient sample who may face somewhat similar MAT access and use barriers. Still, future work should consider alternative insurance programs to ensure the generalizability of my findings in Medicare.

One final limitation is that it is not clear from this research how reducing MAT access and use will ultimately effect disparities in adverse opioid events. I found that conditional on receiving treatment that disparities are minimal, but Table 1 confirms that adverse opioid event rates are generally higher in the non-white subgroups. Understanding the effect of access and use disparities on differences in adverse opioid events rates by race and ethnicity remains an essential research question, and is left for future research.

CONCLUSION

The study found substantial disparities in MAT access and use in a population of US Medicare beneficiaries between 2013-2017. In particular, non-white beneficiaries were significantly less likely to have encounters with MAT prescribing physicians or to go on to receive MAT. However, after initiating treatment, beneficiaries of different races and ethnicities had similar likelihoods of experiencing an adverse opioid event. Hence, increasing treatment access and use could reduce the underlying differences in adverse opioid event rates in the general population. In particular, the findings show that policy reform aimed at increasing MAT use might consider focusing on carefully addressing MAT prescriber bias. Further, expanding access to culturally competent addiction treatment may increase the rate at which racially and ethnically diverse patients seek treatment. Future research should consider the effect of treatment and use disparities on differences in overdose and abuse rates by race and ethnicity.

REFERENCES

1. Abraham, A. J. *et al.* (2019) 'County-level access to opioid use disorder medications in medicare Part D (2010-2015)', *Health Services Research*, 54(2), pp. 390–398. doi: 10.1111/1475-6773.13113.

2. Alexander, M. J., Kiang, M. V. and Barbieri, M. (2018) 'Trends in Black and White Opioid Mortality in the United States, 1979–2015', *Epidemiology*, 29(5), pp. 707–715. doi: 10.1097/EDE.0000000000000858.

3. Andrews, C. M. *et al.* (2018) 'Medicaid Benefits For Addiction Treatment Expanded After Implementation Of The Affordable Care Act', *Health Affairs*, 37(8), pp. 1216–1222. doi: 10.1377/hlthaff.2018.0272.

4. Andrilla, C. H. A. and Patterson, D. G. (no date) 'Tracking the geographic distribution and growth of clinicians with a DEA waiver to prescribe buprenorphine to treat opioid use disorder', *The Journal of Rural Health*, n/a(n/a). doi: https://doi.org/10.1111/jrh.12569.

5. Breen, C. T. and Fiellin, D. A. (2018) 'Buprenorphine Supply, Access, and Quality: Where We Have Come and the Path Forward', *Journal of Law, Medicine & Ethics*, 46(2), pp. 272–278. doi: 10.1177/1073110518782934.

6. D'Aunno, T. and Pollack, H. A. (2002) 'Changes in methadone treatment practices: results from a national panel study, 1988-2000', *JAMA*, 288(7), pp. 850–856. doi: 10.1001/jama.288.7.850.

7. Dayton, L. *et al.* (2020) 'Racial Disparities in Overdose Prevention among People Who Inject Drugs', *Journal of Urban Health*, 97(6), pp. 823–830. doi: 10.1007/s11524-020-00439-5.

8. 'Disparities in Health Care Hinder Access to MAT' (no date) *Psychiatric News*. Available at: https://psychnews-psychiatryonline-org.proxy.lib.umich.edu/doi/abs/10.1176/appi.pn.2019.10b1 (Accessed: 26 January 2021).

9. Essien, U. R. *et al.* (2020) 'Racial/Ethnic Differences in the Medical Treatment of Opioid Use Disorders Within the VA Healthcare System Following Non-Fatal Opioid Overdose', *Journal of General Internal Medicine*, 35(5), pp. 1537–1544. doi: 10.1007/s11606-020-05645-0.

10. Gryczynski, J. *et al.* (2011) 'Patterns in admission delays to outpatient methadone treatment in the United States', *Journal of Substance Abuse Treatment*, 41(4), pp. 431–439. doi: 10.1016/j.jsat.2011.06.005.

11. Guerrero, E. G. *et al.* (2017) 'Does the implementation of evidence-based and culturally competent practices reduce disparities in addiction treatment outcomes?', *Addictive Behaviors*, 73, pp. 119–123. doi: 10.1016/j.addbeh.2017.05.006.

12. Hansen, H. *et al.* (2016) 'Buprenorphine and methadone treatment for opioid dependence by income, ethnicity and race of neighborhoods in New York City', *Drug and Alcohol Dependence*, 164, pp. 14–21. doi: 10.1016/j.drugalcdep.2016.03.028.

13. Hansen, H. B. *et al.* (2013) 'Variation in Use of Buprenorphine and Methadone Treatment by Racial, Ethnic, and Income Characteristics of Residential Social Areas in New York City', *The Journal of Behavioral Health Services & Research*, 40(3), pp. 367–377. doi: 10.1007/s11414-013-9341-3.

14. Howard, D. L., Barrett, N. J. and Holmes, D. N. (2010) 'Can Cultural Competency Speak to the Race Disparities in Methadone Dosage Levels?', *The Review of Black Political Economy*, 37(1), pp. 7–23. doi: 10.1007/s12114-009-9052-4.

15. James, K. and Jordan, A. (2018) 'The Opioid Crisis in Black Communities', *The Journal of Law, Medicine & Ethics: A Journal of the American Society of Law, Medicine & Ethics*, 46(2), pp. 404–421. doi: 10.1177/1073110518782949.

16. King, Z. *et al.* (2021) 'Access to treatment for pregnant incarcerated people with opioid use disorder: Perspectives from community opioid treatment providers', *Journal of Substance Abuse Treatment*, 126, p. 108338. doi: 10.1016/j.jsat.2021.108338.

17. Krawczyk, N. *et al.* (2017) 'Only One In Twenty Justice-Referred Adults In Specialty Treatment For Opioid Use Receive Methadone Or Buprenorphine', *Health Affairs*, 36(12), pp. 2046–2053. doi: http://dx.doi.org.proxy.lib.umich.edu/10.1377/hlthaff.2017.0890.

18. Lagisetty, P. A. *et al.* (2019) 'Buprenorphine Treatment Divide by Race/Ethnicity and Payment', *JAMA Psychiatry*, 76(9), p. 979. doi: 10.1001/jamapsychiatry.2019.0876.

19. Lowder, E. M., Amlung, J. and Ray, B. R. (2020) 'Individual and county-level variation in outcomes following non-fatal opioid-involved overdose', *J Epidemiol Community Health*, 74(4), pp. 369–376. doi: 10.1136/jech-2019-212915.

20. Mallow, P. J., Mercado, M. and Topmiller, M. (2020) 'Disparities in Opioid Use Disorder Treatment Admissions in the United States', *Journal of Health Economics and Outcomes Research*, 7(1), pp. 85–93. doi: 10.36469/jheor.2020.13266.

21. Nguemeni Tiako, M. J. (2021) 'Addressing racial & socioeconomic disparities in access to medications for opioid use disorder amid COVID-19', *Journal of Substance Abuse Treatment*, 122, p. 108214. doi: 10.1016/j.jsat.2020.108214.

22. Nunes, E. V. *et al.* (2021) 'Medication treatment for opioid use disorder in the age of COVID-19: Can new regulations modify the opioid cascade?', *Journal of Substance Abuse Treatment*, 122, p. 108196. doi: 10.1016/j.jsat.2020.108196.

23. 'Patterns of clinic switching and continuity of medication for opioid use disorder in a Medicaid-enrolled population' (2021) *Drug and Alcohol Dependence*, 221, p. 108633. doi: 10.1016/j.drugalcdep.2021.108633.

24. Peeler, M. *et al.* (2020) 'Racial and Ethnic Disparities in Maternal and Infant Outcomes Among Opioid-Exposed Mother–Infant Dyads in Massachusetts (2017–2019)', *American Journal of Public Health*, 110(12), pp. 1828–1836. doi: 10.2105/AJPH.2020.305888.

25. Pro, G., Utter, J., Haberstroh, S., *et al.* (2020) 'Dual mental health diagnoses predict the receipt of medication-assisted opioid treatment: Associations moderated by state Medicaid expansion status, race/ethnicity and gender, and year', *Drug and Alcohol Dependence*, 209, p. 107952. doi: 10.1016/j.drugalcdep.2020.107952.

26. Pro, G., Utter, J., Cram, J., *et al.* (2020) 'Racial/Ethnic and Gender Differences in Associations of Medication-Assisted Therapy and Reduced Opioid Use between Outpatient Treatment Admission and Discharge', *Journal of Psychoactive Drugs*, 52(2), pp. 186–194. doi: 10.1080/02791072.2020.1717685.

27. Pro, G. and Zaller, N. (2020) 'Interaction effects in the association between methadone maintenance therapy and experiences of racial discrimination in U.S. healthcare settings', *PLoS One*, 15(2), p. e0228755. doi: http://dx.doi.org.proxy.lib.umich.edu/10.1371/journal.pone.0228755.

28. Rieckmann, T. *et al.* (2017) 'National Overview of Medication-Assisted Treatment for American Indians and Alaska Natives With Substance Use Disorders', *Psychiatric Services*, 68(11), pp. 1136–1143. doi: 10.1176/appi.ps.201600397.

29. Samples, H. *et al.* (2018) 'Risk factors for discontinuation of buprenorphine treatment for opioid use disorders in a multi-state sample of Medicaid enrollees', *Journal of Substance Abuse Treatment*, 95, pp. 9–17. doi: 10.1016/j.jsat.2018.09.001.

30. Saxon, A. J. *et al.* (2013) 'Medication-assisted treatment for opioid addiction: methadone and buprenorphine', *Journal of food and drug analysis*, 21(4), pp. S69–S72. doi: 10.1016/j.jfda.2013.09.037.

31. Schiff, D. M. *et al.* (2020) 'Assessment of Racial and Ethnic Disparities in the Use of Medication to Treat Opioid Use Disorder Among Pregnant Women in Massachusetts', *JAMA Network Open*, 3(5), p. e205734. doi: 10.1001/jamanetworkopen.2020.5734.

32. Schuler, M. S., Dick, A. W. and Stein, B. D. (2021) ‘Growing racial/ethnic disparities in buprenorphine distribution in the United States, 2007-2017’, *Drug and Alcohol Dependence*, 223, p. 108710. doi: 10.1016/j.drugalcdep.2021.108710.

33. Stein, B. D. *et al.* (2018) ‘A population-based examination of trends and disparities in medication treatment for opioid use disorders among Medicaid enrollees’, *Substance Abuse*, 39(4), pp. 419–425. doi: 10.1080/08897077.2018.1449166.

34. Venner, K. L. *et al.* (2018) ‘Future directions for medication assisted treatment for opioid use disorder with American Indian/Alaska Natives’, *Addictive Behaviors*, 86, pp. 111–117. doi: 10.1016/j.addbeh.2018.05.017.

35. Zaller, N. D. *et al.* (2009) ‘Attitudes toward Methadone among Out-of-Treatment Minority Injection Drug Users: Implications for Health Disparities’, *International Journal of Environmental Research and Public Health*, 6(2), pp. 787–797. doi: 10.3390/ijerph6020787.

TABLES & FIGURES

Table 3.1. Descriptive Statistics of Patient Sample by Primary Outcome

Covariate	No Encounter	Encounter	No Treatment	Treatment	No Adverse Opioid Event	Adverse Opioid Event
Total Beneficiaries	107,578	155,949	129,824	26,125	22,037	2,102
Race/Ethnicity						
African American	12.7%	12.6%	13.3%	9.1%	8.2%	10.5%
Asian	1.0%	0.6%	0.7%	0.4%	0.5%	0.4%
Hispanic	5.9%	5.6%	5.5%	6.1%	6.2%	7.6%
Native American	1.1%	1.0%	1.0%	1.0%	0.9%	0.5%
Other Race	1.2%	1.2%	1.1%	1.4%	1.3%	1.3%
White	78.0%	79.0%	78.3%	82.0%	83.0%	79.7%
Gender						
Female	56.9%	56.0%	57.7%	48.0%	48.4%	43.9%
Male	43.1%	44.0%	42.3%	52.0%	51.6%	56.1%
Medicaid Dual Eligible	35.5%	53.2%	49.8%	70.0%	71.0%	79.8%
Disability	52.8%	74.1%	70.6%	91.5%	93.8%	96.0%
Age (Mean)	67.20	60.36	62.23	51.09	50.71	48.08
MAT Gap	-	-	-	-	54.2%	74.0%
Miles to Nearest MAT Prescriber (Mean)	6.6	4.9	5.0	4.1	-	-
Social Determinants of Health						
Socioeconomic Index	0.47	0.46	0.46	0.45	0.44	0.42
Disability Index	0.40	0.39	0.39	0.37	0.36	0.32
Transportation Index	0.61	0.61	0.61	0.62	0.64	0.63

Note: Percentages are inclusive by column (e.g., all race and ethnicity percentages add up to one within each column).

Table 3.2. Marginal Effect Estimates from a Logistic Regression of the Probability of Medication-Assisted Treatment Prescriber Encounter on Race/Ethnicity

Covariate	Base Model	Base Model w/ SDOH	Base Model w/ SDOH & Provider Factors
African American	-0.061 (-0.067, -0.056)	-0.066 (-0.072, -0.06)	-0.073 (-0.08, -0.067)
Asian	-0.106 (-0.126, -0.086)	-0.125 (-0.147, -0.103)	-0.128 (-0.15, -0.107)
Hispanic	-0.065 (-0.073, -0.057)	-0.066 (-0.075, -0.058)	-0.068 (-0.077, -0.059)
Native American	-0.083 (-0.1, -0.065)	-0.077 (-0.097, -0.056)	-0.063 (-0.084, -0.042)
Other Race	-0.015 (-0.031, 0.002)	-0.024 (-0.042, -0.005)	-0.025 (-0.044, -0.007)
Female	0.002 (-0.002, 0.006)	0.004 (0, 0.008)	0.004 (0, 0.008)
Medicaid Dual Eligible	0.121 (0.117, 0.124)	0.121 (0.117, 0.126)	0.121 (0.117, 0.125)
Disability	0.177 (0.173, 0.18)	0.177 (0.173, 0.181)	0.177 (0.172, 0.181)
Socioeconomic Vulnerability Index	-	-0.012 (-0.026, 0.002)	0.004 (-0.01, 0.018)
Household Composition and Disability Vulnerability Index	-	-0.059 (-0.071, -0.048)	-0.037 (-0.049, -0.025)
Transportation and Housing Vulnerability Index	-	0.019 (0.009, 0.029)	-0.003 (-0.013, 0.007)
Distance to Nearest MAT Prescriber	-	-	-0.004 (-0.005, -0.004)
2014	0.005 (-0.012, 0.022)	0.0005 (-0.017, 0.018)	0.008 (-0.009, 0.026)
2015	-0.1 (-0.115, -0.086)	-0.097 (-0.113, -0.081)	-0.099 (-0.116, -0.083)
2016	-0.129 (-0.142, -0.116)	-0.134 (-0.148, -0.119)	-0.133 (-0.147, -0.118)
2017	-0.123 (-0.135, -0.111)	-0.118 (-0.131, -0.105)	-0.124 (-0.138, -0.111)

Note: 2013 is the reference group for the year fixed effects. White is the reference group for the race and ethnicity estimates.

Table 3.3. Marginal Effect Estimates from a Logistic Regression of Race/Ethnicity on the Probability of Medication-Assisted Treatment - Conditional on a Prescriber Encounter

Covariate	Base Model	Base Model w/ SDOH	Base Model w/ SDOH & Provider Factors
African American	-0.086 (-0.092, -0.08)	-0.084 (-0.091, -0.078)	-0.117 (-0.131, -0.103)
Asian	-0.058 (-0.085, -0.031)	-0.068 (-0.098, -0.038)	-0.075 (-0.127, -0.023)
Hispanic	-0.021 (-0.028, -0.013)	-0.024 (-0.032, -0.016)	-0.03 (-0.046, -0.014)
Native American	-0.033 (-0.051, -0.015)	-0.025 (-0.045, -0.004)	0.028 (-0.01, 0.066)
Other Race	0.016 (0, 0.031)	0.008 (-0.01, 0.026)	-0.02 (-0.051, 0.011)
Female	-0.05 (-0.054, -0.047)	-0.052 (-0.056, -0.048)	-0.047 (-0.055, -0.039)
Medicaid Dual Eligible	0.092 (0.088, 0.096)	0.092 (0.088, 0.097)	0.119 (0.109, 0.129)
Disability	0.168 (0.162, 0.174)	0.169 (0.162, 0.176)	0.175 (0.162, 0.187)
Socioeconomic Vulnerability Index	-	-0.047 (-0.06, -0.033)	-0.007 (-0.04, 0.026)
Household Composition and Disability Vulnerability Index	-	-0.019 (-0.03, -0.007)	0.003 (-0.024, 0.029)
Transportation and Housing Vulnerability Index	-	0.042 (0.033, 0.052)	0.025 (0.003, 0.047)
2014	0.001 (-0.014, 0.015)	-0.005 (-0.02, 0.01)	-0.01 (-0.04, 0.02)
2015	0.024 (0.011, 0.037)	0.021 (0.006, 0.035)	0.026 (0.001, 0.052)
2016	0.013 (0.002, 0.025)	0.007 (-0.006, 0.02)	0.028 (0.005, 0.051)
2017	0.017 (0.007, 0.028)	0.013 (0.001, 0.025)	0.029 (0.008, 0.05)
Provider Fixed Effects	NO	NO	YES

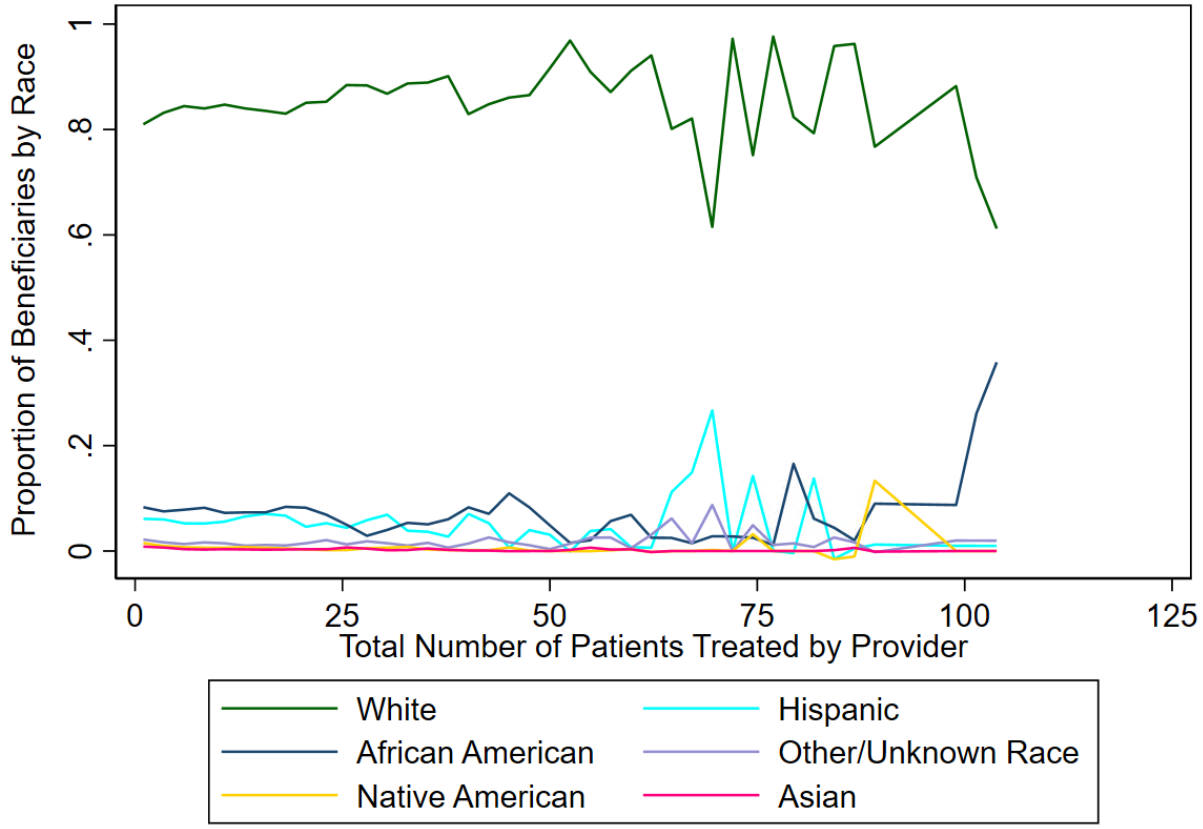
Note: 2013 is the reference group for the year fixed effects. White is the reference group for the race and ethnicity estimates.

Table 3.4. Marginal Effect Estimates of a Logistic Regression of Race/Ethnicity on the Probability of One or More Adverse Opioid Events - Conditional on a Medication-Assisted Treatment Prescription

Covariate	Base Model	Base Model w/ SDOH	Base Model w/ SDOH & Provider Factors
African American	0.0001 (-0.0002, 0.0004)	-0.0001 (-0.0007, 0.0004)	-0.0452 (-0.1314, 0.041)
Asian	-0.0001 (-0.0014, 0.0013)	0.0006 (-0.0018, 0.0029)	0.5673 (0.1213, 1.0132)
Hispanic	0.0001 (-0.0003, 0.0004)	-0.0006 (-0.0012, 0.0001)	-0.0763 (-0.1811, 0.0286)
Native American	-0.0006 (-0.0017, 0.0004)	0.0004 (-0.0014, 0.0022)	0.0021 (-0.3859, 0.39)
Other Race	0.0001 (-0.0007, 0.0009)	0.00003 (-0.0014, 0.0015)	-0.0426 (-0.2655, 0.1802)
Female	-0.0004 (-0.0006, -0.0002)	-0.0005 (-0.0008, -0.0002)	-0.0478 (-0.1008, 0.0053)
Medicaid Dual Eligible	0.001 (0.0008, 0.0012)	0.0009 (0.0005, 0.0013)	0.1613 (0.09, 0.2325)
Disability	0.0003 (-0.0001, 0.0007)	-0.0002 (-0.001, 0.0005)	-0.0328 (-0.1465, 0.081)
MAT Treatment Gap	0.0016 (0.0014, 0.0018)	0.0015 (0.0012, 0.0019)	0.1771 (0.1184, 0.2358)
Socioeconomic Vulnerability Index	-	-0.0002 (-0.0013, 0.001)	0.1027 (-0.1409, 0.3463)
Household Composition and Disability Vulnerability Index	-	-0.0007 (-0.0018, 0.0003)	-0.0973 (-0.312, 0.1175)
Transportation and Housing Vulnerability Index	-	0.0003 (-0.0005, 0.0011)	-0.1506 (-0.3438, 0.0427)
2014	0.00049 (-0.0003, 0.0012)	0.0005 (-0.0005, 0.0016)	0.0974 (-0.0786, 0.2733)
2015	0.0002 (-0.0004, 0.0008)	0.0002 (-0.0009, 0.0014)	0.0357 (-0.165, 0.2364)
2016	0.0006 (0, 0.0012)	0.0006 (-0.0004, 0.0015)	0.1057 (-0.0525, 0.264)
2017	0 (-0.0006, 0.0005)	0.0003 (-0.0007, 0.0012)	0.0711 (-0.0888, 0.2311)
Provider Fixed Effects	NO	NO	YES

Note: 2013 is the reference group for the year fixed effects. White is the reference group for the race and ethnicity estimates.

Figure 3.1. Proportion of Beneficiaries Treated by Race by the Total Number of Treated Patients per Prescriber



APPENDIX

Appendix Table 3.1. Opioid Use Disorder ICD9 & ICD10 Codes

Adverse Opioid Event Category	ICD 9 Codes	ICD 10 Codes
Dependence	304: Opioid Dependence-Unspecified 304.01: Opioid Dependence-Continuous 304.02: Opioid Dependence-Episodic 304.03: Opioid Dependence, In Remission 304.7: Opioid Other Dep-Unspecified 304.71: Opioid Other Dep-Continuous 304.72: Opioid Other Dep-Episodic 304.73: Opioid Other Dep-In Remission	F11 series: Opioid-related disorders (except F11.21 and abuse codes)

Sources:
ICD 9 Codes obtained from Owens, PL, Barret, ML, Weiss, AJ, Washington, RE, and Kronick R, (2014) "Hospital Inpatient Utilization Related to Opioid Overuse Among Adults, 1993–2012," Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Statistical Brief #177. Available at: https://www.ncbi.nlm.nih.gov/books/NBK538344/ Accessed: October 30, 2020.

ICD 10 Codes obtained from Weiss, AJ, McDermott, KW, and Heslin, KC, (2016) "Opioid-Related Hospital Stays Among Women in the United States," Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Statistical Brief #247. Available at: https://www.ncbi.nlm.nih.gov/books/NBK246983/ Accessed: October 30, 2020.

Abbreviation:
ICD-9, International Classification of Diseases, Ninth Revision
ICD-10, International Classification of Diseases, Tenth Revision

Appendix Table 3.2. Adverse Opioid Event ICD9 & ICD10 Codes

Adverse Opioid Event Category	ICD 9 Codes	ICD 10 Codes
Abuse	305.51: Opioid Abuse-Continuous 305.52: Opioid Abuse-Episodic 305.53: Opioid Abuse-In Remission 305.5: Opioid Abuse Unspecified	F11 series: Opioid-related disorders (except F11.21 and dependence codes)
Adverse Effects	E935.2: Other opiates and related Narcotics Causing Adverse Effects in Therapeutic Use	T40.0X5: Adverse effect of opium T40.2X5: Adverse effect of other opioids T40.3X5: Adverse effect of Methadone
Overdose	965: Opium Poisoning 965.09: Poisoning by other opiates and related narcotics E850.2: Accidental poisoning by other opiates and related narcotics	T40.0X1, 0X2, 0X3, 0X4: Poisoning by opium–accidental, intentional self-harm, assault, or undetermined T40.1X1, 1X2, 1X3, 1X4: Poisoning by heroin–accidental, intentional self-harm, assault, or undetermined T40.2X1, 2X2, 2X3, 2X4: Poisoning by other opioids–accidental, intentional self-harm, assault, or undetermined T40.3X1, 3X2, 3X3, 3X4: Poisoning by Methadone–accidental, intentional self-harm, assault, or undetermined

Sources:

ICD 9 Codes obtained from Owens, PL, Barret, ML, Weiss, AJ, Washington, RE, and Kronick R, (2014) "Hospital Inpatient Utilization Related to Opioid Overuse Among Adults, 1993–2012," Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Statistical Brief #177. Available at: https://www.ncbi.nlm.nih.gov/books/NBK538344/ Accessed: October 30, 2020.

ICD 10 Codes obtained from Weiss, AJ, McDermott, KW, and Heslin, KC, (2016) "Opioid-Related Hospital Stays Among Women in the United States," Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Statistical Brief #247. Available at: https://www.ncbi.nlm.nih.gov/books/NBK246983/ Accessed: October 30, 2020.

Abbreviation:

ICD-9, International Classification of Diseases, Ninth Revision

ICD-10, International Classification of Diseases, Tenth Revision

Appendix Table 3.3. Frequency and Proportion of MAT Prescriptions and Beneficiaries by Race

Race/Ethnicity Description	Total Claims	Total Beneficiaries	Average Claims per Beneficiary	Proportion of Claims	Proportion of Beneficiaries
AFRICAN AMERICAN	45,160	3,148	14.3	6.6%	8.5%
ASIAN	3,050	234	13.0	0.4%	0.6%
HISPANIC	35,468	2,097	16.9	5.2%	5.7%
NATIVE AMERICAN	6,420	363	17.7	0.9%	1.0%
OTHER RACE	9,874	662	14.9	1.4%	1.8%
WHITE	583,013	30,320	19.2	85.4%	82.3%

Source: Medicare Part D Prescription Drug Claims Data and Medicare Beneficiary Summary Files (MBSF)

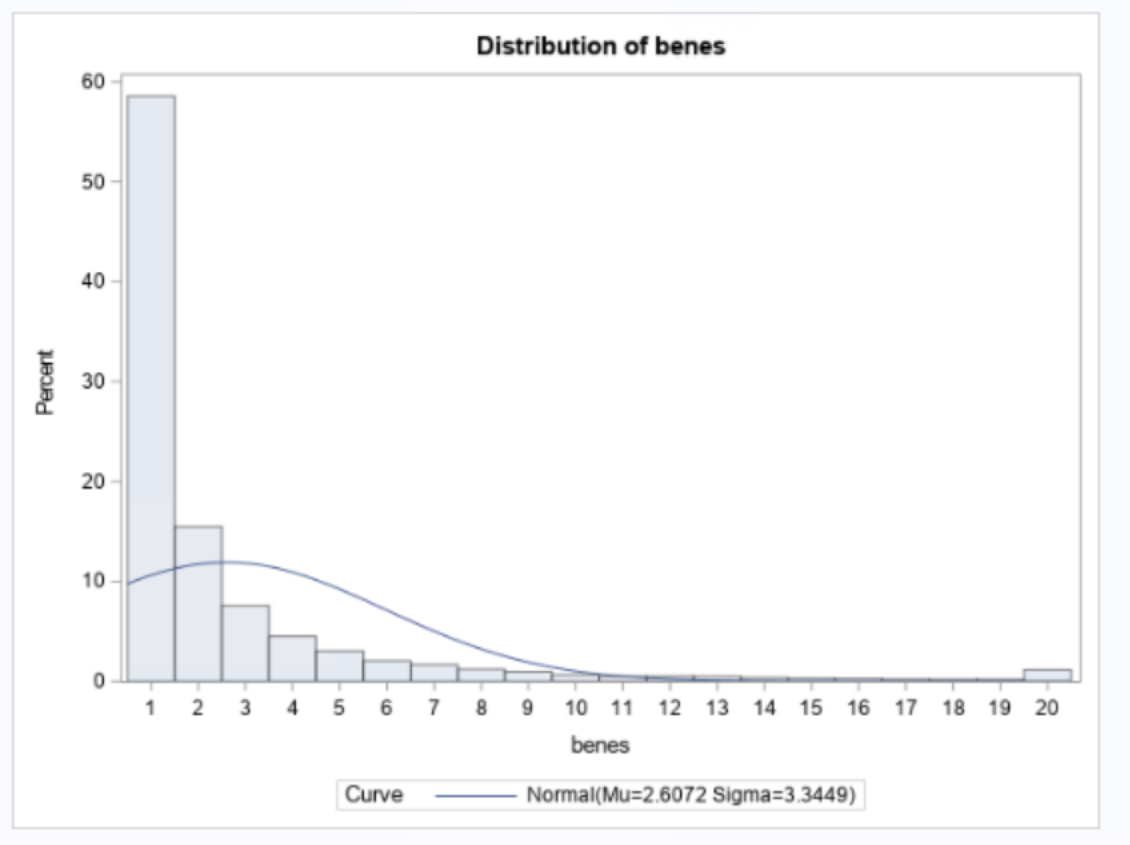
Appendix Table 3.4. Frequency of MAT Beneficiaries and MAT Prescriptions by Buprenorphine & Naltrexone Dosage and Race/Ethnicity

Race/Ethnicity Description	Dosage Description	Total Claims	Total Beneficiaries	Average Claims per Beneficiary	Proportion of Claims by Dosage	Proportion of Beneficiaries by Dosage
AFRICAN AMERICAN	LOW DOSE BUPRENORPHINE	2,552	430	5.9	5.8%	8.3%
ASIAN	LOW DOSE BUPRENORPHINE	241	31	7.8	0.6%	0.6%
HISPANIC	LOW DOSE BUPRENORPHINE	2,439	286	8.5	5.6%	5.5%
NATIVE AMERICAN	LOW DOSE BUPRENORPHINE	402	56	7.2	0.9%	1.1%
OTHER RACE	LOW DOSE BUPRENORPHINE	804	85	9.5	1.8%	1.6%
WHITE	LOW DOSE BUPRENORPHINE	37,207	4,275	8.7	85.2%	82.8%
AFRICAN AMERICAN	MEDIUM DOSE BUPRENORPHINE	966	272	3.6	5.4%	10.3%
ASIAN	MEDIUM DOSE BUPRENORPHINE	31	11	2.8	0.2%	0.4%
HISPANIC	MEDIUM DOSE BUPRENORPHINE	1,233	157	7.9	6.9%	5.9%
NATIVE AMERICAN	MEDIUM DOSE BUPRENORPHINE	265	28	9.5	1.5%	1.1%
OTHER RACE	MEDIUM DOSE BUPRENORPHINE	409	46	8.9	2.3%	1.7%
WHITE	MEDIUM DOSE BUPRENORPHINE	14,868	2,136	7.0	83.7%	80.6%
AFRICAN AMERICAN	HIGH DOSE BUPRENORPHINE	33,326	1,731	19.3	6.3%	8.0%

ASIAN	HIGH DOSE BUPRENORPHINE	1,865	92	20.3	0.4%	0.4%
HISPANIC	HIGH DOSE BUPRENORPHINE	26,815	1,220	22.0	5.1%	5.6%
NATIVE AMERICAN	HIGH DOSE BUPRENORPHINE	4,310	186	23.2	0.8%	0.9%
OTHER RACE	HIGH DOSE BUPRENORPHINE	6,702	298	22.5	1.3%	1.4%
WHITE	HIGH DOSE BUPRENORPHINE	454,077	18,146	25.0	86.1%	83.7%
AFRICAN AMERICAN	LOW DOSE NALTREXONE	7,890	1,203	6.6	8.9%	9.1%
ASIAN	LOW DOSE NALTREXONE	893	126	7.1	1.0%	1.0%
HISPANIC	LOW DOSE NALTREXONE	4,532	779	5.8	5.1%	5.9%
NATIVE AMERICAN	LOW DOSE NALTREXONE	1,376	163	8.4	1.5%	1.2%
OTHER RACE	LOW DOSE NALTREXONE	1,842	330	5.6	2.1%	2.5%
WHITE	LOW DOSE NALTREXONE	72,511	10,616	6.8	81.4%	80.3%
AFRICAN AMERICAN	HIGH DOSE NALTREXONE	426	97	4.4	7.8%	9.7%
ASIAN	HIGH DOSE NALTREXONE	20	6	3.3	0.4%	0.6%
HISPANIC	HIGH DOSE NALTREXONE	449	74	6.1	8.3%	7.4%
NATIVE AMERICAN	HIGH DOSE NALTREXONE	67	16	4.2	1.2%	1.6%
OTHER RACE	HIGH DOSE NALTREXONE	117	25	4.7	2.2%	2.5%
WHITE	HIGH DOSE NALTREXONE	4,350	778	5.6	80.1%	78.1%

Source: Medicare Part D Prescription Drug Claims Data and Medicare Beneficiary Summary Files (MBS

Appendix Figure 3.1. Distribution of MAT Beneficiaries by Provider



Source: Medicare Part D Prescription Drug Claims Data