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Trends in non-medical prescription opioid and heroin co-use and medication assisted treatment utilization

By

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Trends in non-medical prescription opioid and heroin co-use and medication assisted treatment utilization

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Abstract

Trends in non-medical prescription opioid and heroin co-use and medication assisted treatment utilization

By Sasha Mital

Introduction: The rate of opioid-related overdoses more than quadrupled in the United States from 1999 to 2016. In response to the opioid epidemic, interventions emphasized reducing opioid availability rather than expanding access to medication-assisted treatment (MAT), the most effective treatment for problem opioid use. Evidence demonstrates that non-medical prescription opioid (NMPO)-only users transitioned to heroin and subsequent co-use of both opioids, which is associated with increased risk of morbidity and overdose. To better understand and inform a response to this phenomenon, this dissertation aims to 1) quantify and describe trends in co-use, 2) explore multilevel factors related to transition, and 3) examine corresponding trends in MAT enrollment and factors related to MAT completion.

Methods: We used data from the 2003-2014 National Surveys on Drug Use and Health and the 2004-2015 Treatment Episodes Datasets. Informed by trend theory, we examined trends in opioid use overall and in co-use by demographics, substance use behaviors, and mental health characteristics. We also explored the multilevel relationships between transition and access to healthcare, NMPO source, perceived opioid availability, and perceived risk of use according to the socioecological model. Guided by Andersen's Behavioral Model of Health Services, we assessed trends in MAT admissions and correlates of treatment completion by opioid use type including access to health care and demographics.

Results: While the prevalence of all opioid use decreased, co-use increased substantially. The highest prevalence of co-use was among those who lacked health insurance, were unemployed, had psychological distress, and used illicit non-opioids in the past year. These characteristics were also associated with increased risk of transition, along with earlier age of NMPO initiation, an illicit NMPO source relative to a familial source, and a lower perceived risk of trying heroin. The frequency of MAT admissions increased over time but the proportion of those enrolled for co-use remained stable. Treatment completion was less likely among co-users relative to heroin-only users. Referral source was the strongest predictor of treatment completion for co-use, while the relationship between immediate admission and treatment completion was strongest for heroin-only use, indicating differences by opioid use type.

Conclusion: Findings highlight the importance of subgroup-specific efforts to investigate and address recent shifts in opioid use and lack of treatment. Taken together, they underscore the need for targeted prevention and response interventions reaching those at risk of transition, co-users, and subgroups with disproportionately low MAT admission and completion rates.

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Table of Contents

Chapter 1: Introduction

1. The link between non-medical prescription opioid and heroin use

The United States (US) is currently facing an opioid overdose epidemic due to increased use of non-medical prescription opioids (NMPO) and heroin. Prescription opioids (POs) are synthetic and semi-synthetic substances such as oxycodone and hydrocodone that individuals can legitimately obtain through a doctor's prescription or while seeking healthcare (National Institute of Drug Abuse, 2014b). Heroin is a derivative of the opium poppy plants and referred to as the "natural" opioid. Regarding types of opioid use, NMPO use is using a PO "even once, that was not prescribed for you, or that you took only for the experience or feeling caused" (Substance Abuse and Mental Health Administration, 2002). Problem opioid use refers to abuse or dependence and generally indicates a need for response and treatment interventions (American Psychiatric Association, 2013).

Heroin's history in the US began when Bayer Pharmaceuticals introduced it in 1898 as a pain relief medication. It was banned in 1924 following acknowledgement of its addictive nature and the potential for overdose (Seppala & Rose, 2011). Heroin use became highly stigmatized and associated with marginalized populations including artists, youth with histories of delinquency, veterans, and inner-city minorities (Hughes, Barker, Crawford, & Jaffe, 1972; Jenkins, 2014). During the 1960s and 70s, prescription opioids hit the market, but prescribing was limited due to concerns stemming from prior dissemination of opioid drug formulations that included heroin (Nevius, 2016). From the 1970s to the 1990s, the prevalence of heroin use remained relatively stable at about 1% (Johnson, 1996; Johnston, 2010). Until the 1990s, the vast majority of opioid users initiated with heroin, rather than POs (Cicero, Ellis, Surratt, & Kurtz, 2014). Then, changes in opioid prescribing practices, increased NMPO use and subsequent implementation of interventions to reduce

NMPO use contributed to the reversal of the way individuals initiate heroin (Cicero et al., 2014; Compton, Jones, & Baldwin, 2016).

POs and heroin are both opioids and therefore share similarities in terms of their effects, high abuse potential, and the effective treatment options available to those who use problematically. POs and heroin act on the same brain systems and present an intrinsic abuse and dependence liability (Compton et al., 2016; Wikler, 2013). Pharmacologically, they both bind to proteins called opioid receptors, found mainly in the brain, spinal cord, and gastrointestinal tract and ultimately lead to an increase in dopamine release. This release in the critical area of the reward circuitry causes pain relief and a euphoric "high" (National Institute of Drug Abuse, 2014a; Volkow et al., 1999). Prolonged exposure to opioids in increasing doses results in structural changes to parts of the brain and inhibition of the body's own production of endogenous opioids, which account for the withdrawal symptoms experienced when use is abruptly discontinued (Kolodny et al., 2015). Withdrawal can be harsh and include pain, nausea and vomiting, and severe dehydration, which drive resumption of opioid use in an effort to avoid these symptoms (Lankenau et al., 2012; Mitchell et al., 2009; National Institute of Drug Abuse, 2014a). In terms of treating problem PO and heroin use, rigorous science conducted over the past 40 years demonstrates that medication-assisted treatment (MAT) using methadone or buprenorphine is the most effective approach (Fullerton et al., 2014; Nielsen, Larance, & Lintzeris, 2017; Thomas et al., 2014). We provide a more thorough description of MAT in relation to reducing opioid use later in this chapter.

2. **Highly dynamic patterns of opioid use**

In 2017, the US President declared a national opioid emergency caused by drastic increases in opioid use and overdose over the past two decades (Gostin,

Hodge, & Noe, 2017). Between 2002 and 2011, an estimated 25 million people initiated NMPO use and in 2014 alone, 10.3 million people reported NMPO use (Center for Behavioral Health Statistics and Quality, 2015; Manchikanti, Helm, Janata, Pampati, & Grider, 2012). Problem PO use also increased 81% from 1992 to 2003 while the population size only increased by 14% (Manchikanti, 2007). The prevalence of opioid use disorders grew 50% from 2003-2013 (Han, Compton, Jones, & Cai, 2015). Negative outcomes related to NMPO use also increased nationally. Emergency department visits related to NMPO use increased 138% between 2004 and 2011 and the rate of opioid-related overdoses more than quadrupled from 1999 to 2016 (Hedegaard, Warner, & Miniño, 2018; Substance Abuse and Mental Health Administration, 2011). By 2012, deaths involving opioids were more prevalent than motor vehicle-related death rates in many states, a historical first in the US (Rockett et al., 2012; Warner, Chen, & Makuc, 2009).

2.1. Factors related to increased NMPO use

The factors that precipitated increased NMPO use and related outcomes are varied and interrelated. An understanding of these factors informs future investigations of shifts in opioid use. In brief, the publication of several studies underscored the individual medical and social consequences of untreated pain and argued that the medical community was under-treating chronic and post-surgical pain (Brennan, Carr, & Cousins, 2007; Cousins, Brennan, & Carr, 2004; Portenoy & Foley, 1986; Verhaak, Kerssens, Dekker, Sorbi, & Bensing, 1998). These studies contended that patients with chronic pain could take opioids on a long-term basis with little risk of abuse, which led to more liberal prescribing policies (Dhalla, Persaud, & Juurlink, 2011; Porter & Jick, 1980; Zacny et al., 2003). State medical boards lessened restrictions on prescribing practices and the American Pain Society advocated for the treatment of pain as a fifth vital sign, which led to increased prescribing and greater PO availability (Hoffmann & Tarzian, 2003; Manchikanti, 2007; Mularski et al.,

2006). Following these changes, the Centers for Disease Control and Prevention (CDC) estimates that the number of prescriptions for opioids increased 10-fold in the last two decades (Centers for Disease Control and Prevention, 2012).

Healthcare access facilitated PO availability and use as many with legitimate prescriptions reported an excess of unused pills that could be diverted for misuse (Lankenau et al., 2012). In fact, studies show a parallel relationship between PO availability through legitimate channels and diversion, abuse and associated health outcomes (Dart et al., 2015; Zacny et al., 2003). In 2009-2010, 55% of NMPO users obtained POs from a friend or family member and only one in six obtained them medically through their own prescription (Substance Abuse and Mental Health Services, 2011). More opioids prescribed meant more leftover and available for dissemination through familial and peer networks, making familial and medical sources related to increased NMPO use (Compton et al., 2016; Mowbray & Quinn, 2015; Schepis & Krishnan-Sarin, 2009).

As prescribing of opioids grew and POs became more available, a favorable public perception towards PO use also grew. An analysis of mainstream news media found a negative discourse surrounding deaths caused by illegal drugs (e.g. heroin) while deaths caused by POs were framed more positively (Wood, 2011). With POs, people generally associate less harm, risk of addiction and overdose, stigma, risk of legal consequences and likelihood of adulteration (Inciardi, Surratt, Cicero, & Beard, 2009; Mateu-Gelabert, Guarino, Jessell, & Teper, 2015). This is likely because the source is a trusted medical professional, the quantity and potency is perceived as fixed within a pill, and the household is the setting where in which POs are found and consumed, as opposed to obtaining them from a dealer and finding them on the street (Compton et al., 2016; Daniulaityte, Falck, & Carlson, 2012; Frank et al., 2015).

This corresponds to previous research showing a correlation between low perceived risk of drug use and initiation of that drug (Arria, Caldeira, Vincent, O'Grady, & Wish, 2008; Daniulaityte et al., 2012).

Evidence also suggests that NMPO use and related outcomes are growing in communities historically less affected by substance use and its consequences. For example, from 1999 to 2004 opioid-related overdose deaths only increased 52% in large urban counties compared to an increase of 371% in non-urban counties (Paulozzi & Xi, 2008). Between 1993 and 2009, PO-related overdose hospital admissions among Whites increased at a rate double that of African Americans (Unick, Rosenblum, Mars, & Ciccarone, 2013).

Recent analyses of the opioid epidemic cite social and structural drivers as the root causes of increased PO use. This includes lack of economic opportunity, eroded social connections, and accompanying hopelessness during the economic decline in the early 2000s, which manifest differently by race/ethnicity, community type, socio-economic status, and access to healthcare (Dwyer-Lindgren et al., 2016; National Academies of Sciences & Medicine, 2017; Ruckert & Labonté, 2017). Thus, it is imperative to assess socio-demographic characteristics in relation to trends in opioid use and related outcomes.

2.2. Response to increased NMPO use and related outcomes

In response to increased NMPO use and related consequences, federal and state governments and other vested entities implemented interventions aimed at reducing the supply of POs to reduce NMPO use (Wakeland, Nielsen, & Geissert, 2015). For example, the Drug Enforcement Administration focused on diversion prevention while the Food and Drug Administration fast-tracked initiatives to disseminate tamper-resistant drug formulations that reduce risk of diversion and non-medical use (Kuehn, 2010; Okie, 2010). States implemented prescription drug monitoring programs (PDMPs) that allow

prescribers, pharmacists, and other officials to view opioid prescribing patterns. In turn, they can flag and cut off high volume patients and prescribers thereby reducing abuse and diversion (Brandeis, 2016; Gabay, 2015; Office of National Drug Control Policy, 2011). By 2013, 44 states implemented some type of PDMP, but states varied greatly in the data reported, who reviews it and how often, and the ability to share data between states. Criticisms of these interventions are the variation in effects by state and the fact that they only highlight potentially problematic prescribing and use, but do not necessarily link patients to drug treatment, and other services to address their demand for opioids (Davis, Pierce, & Dasgupta, 2014). Another criticism is that flagging and restricting PO access to NMPO users may also increase risk for initiation of heroin use (Cicero, Ellis, & Surratt, 2012).

2.3. Transition from NMPO-only use to heroin and co-use

Following implementation of interventions that reduce the supply of POs, reports indicate a reduction in PO prescribing and NMPO use, but also an increase in more problematic opioid use including heroin use and injection. An analysis of national data found that prevalence of NMPO use decreased from 5.4% in 2003 to 4.9% in 2013 and from 2011 to 2013, prescriptions for POs trended downward (Dart et al., 2015; Han et al., 2015). This is in contrast to more than a decade of drastic increases in NMPO use and related outcomes. However, studies also document an increase in NMPO abuse and dependence from 2003 to 2013 and a 62.5% increase in previously stable rates of heroin from 2002 to 2013. The steepest increase in heroin use was among those who reported prior NMPO use, suggesting NMPO use as a gateway to heroin use and subsequent co-use of both opioids (Jones, Logan, Gladden, & Bohm, 2015).

The literature provides additional evidence of transition from NMPO-only use to NMPO and heroin co-use. Data from national studies show that NMPO use is a robust risk factor for heroin initiation as 80% of heroin initiates from 2002 to 2011 reported previous NMPO use (Muhuri, Gfroerer, & Davies, 2013). During this period, heroin use increased among those reporting NMPO use but not among non-NMPO users (Jones, 2013). Heroin abuse or dependence is 40 times more likely with PO abuse or dependence (Jones, Logan, et al., 2015). Qualitative studies provide more context as those who transition describe heroin as less expensive, more available, and a similar but more effective high (Canfield et al., 2010; Cicero et al., 2014; Lipari & Hughes; Mars, Bourgois, Karandinos, Montero, & Ciccarone, 2014). Taken together, these studies outline an opioid use trajectory that begins with NMPO use, followed by abuse and dependence, initiation of heroin use in the face of dependency and limited PO availability, and continued use of both heroin and POs depending on availability (Inciardi et al., 2009; Levy, 2007; Siegal, Carlson, Kenne, & Swora, 2003). National studies underscore this trajectory as the growing norm; among opioid treatment enrollees, 75% reported initiating with POs instead of heroin in the 2000s, compared to only 20% in the 1960s (Cicero et al., 2014). Similarly, a study of drug injectors from 16 US cities showed that 49% of people who began injecting drugs between 2010-2015 reported previous PO use, compared to only 12% who began injecting before 1995 (Broz, Zlotorzynska, Spiller, & Paz-Bailey, 2017). While these findings indicate that transition and co-use is growing, we lack population-based estimates on the size and characteristics of co-users, which are needed to identify and serve this high-risk subgroup of opioid users.

Transition and co-use are concerning and increase risk for several reasons. First, heroin initiation is problematic due to evidence of the increased purity, the highly addictive nature of heroin and high risk of overdose and death (Drug Enforcement Administration, 2016; Pollini et al., 2011). Second, after initiation of heroin use, subsequent NMPO and

heroin co-use is associated with more severe comorbidities, a higher risk of overdose, and poorer engagement in health services compared to NMPO-only use (Al-Tayyib, Koester, & Riggs, 2017; Fischer, Patra, Cruz, Gittins, & Rehm, 2008; Rigg & Monnat, 2015; Strang et al., 1999). Third, initiation of heroin use comes with an additional layer of stigma thereby marginalizing users from social connections and access to health services (Seppala & Rose, 2011). Fourth, a shift in route of administration to injecting often occurs alongside transition to heroin, further marginalizing users and putting them at risk for HIV, Hepatitis C, and other injection-related morbidities (Cherubin & Sapira, 1993; Guarino, Marsch, Deren, Straussner, & Teper, 2015; Mars et al., 2014; Mateu-Gelabert et al., 2015; Zibbell et al., 2015). Finally, a large number of NMPO users are susceptible to transition and co-use. However, the nascent literature examining the burden of transition indicates that risk is low. In one study, incidence of transition was only 3.6% among current NMPO users with little explanation about factors that increase risk (Compton et al., 2016; Muhuri et al., 2013). This indicates that NMPO use alone does not predict transition and that a deeper understanding of this phenomenon will inform the design of interventions that identify and reach those at risk of transition.

2.4. The role of medication-assisted treatment

National strategies and policies that responded to the opioid epidemic highlighted prevention of NMPO use over effective treatment approaches for existing users (Beletsky & Davis, 2017; Kanouse & Compton, 2015; United Nations Office on Drugs and Crime, 2016; Volkow, Frieden, Hyde, & Cha, 2014). This is problematic as it fails to address current NMPO use and demand for opioids, and risks shifting one drug problem to another (Compton et al., 2016; Han et al., 2015). MAT is a comprehensive approach combining administration of pharmacotherapies,

usually methadone or buprenorphine, with additional behavioral, health, and social services (Kresina, Litwin, Marion, Lubran, & Clark, 2009). Repeated use of opioids in increasing quantities makes structural changes to the brain. This pharmacotherapy works by replacing non-medical use of an opioid with controlled use of a longer-acting one that does not produce euphoria, thus reducing withdrawal symptoms while allowing the patient to feel stable (Dole, Nyswander, & Kreek, 1966; Jaffe, 1990).

MAT treatment is the most effective treatment for problem opioid use as it reduces opioid use, injection behaviors, corresponding risk of HIV and other blood-borne infections, engagement in illegal activities, and mortality (Amato et al., 2005; Nielsen et al., 2017; Nosyk et al., 2013). A Cochrane review showed that MAT with methadone was more effective that non-pharmacological treatment approaches in terms of retaining patients on treatment and suppressing heroin use (Mattick, Breen, Kimber, & Davoli, 2009). MAT is also cost-effective as every dollar spent on treatment resulted in $38 of economic benefits when considering criminal behavior, unemployment and healthcare costs (Zarkin, Dunlap, Hicks, & Mamo, 2005).

Given the evidence of its effectiveness, leading experts call for expansion of MAT to address recent shifts in opioid use and exploding rates of overdose deaths (Blum, Gold, Clark, Dushaj, & Badgaiyan, 2016; Volkow et al., 2014). While the overall rate of treatment for problem opioid use increased steadily since 1999, a substantial gap between MAT need and capacity continues. In 2012, the rate of national opioid use exceeded the maximum treatment capacity by close to 1 million individuals (Jones, Campopiano, Baldwin, & McCance-Katz, 2015). It is unclear which populations, if any, are successfully treated by MAT. With the recent shifts in opioid use, investigations of patterns in MAT admissions are critical to highlighting gaps in access and inform targeted efforts to reach those underserved by MAT.

3. Research gaps and current research

Despite this interest in co-use and expanded treatment access, we lack generalizable findings that quantify and describe trends in co-use, explore factors related to transition and co-use, and describe corresponding trends in access to MAT and correlates of treatment success. An exploration that considers opioid use type instead of grouping all opioid use together or studying NMPO and heroin use separately will inform the development of targeted prevention and response efforts. Employing a one-size-fits-all approach may widen inequities between subgroups (Panter-Brick, Clarke, Lomas, Pinder, & Lindsay, 2006). Additionally, previous explorations of these emerging trends are largely atheoretical, making development and targeting of interventions difficult (Glanz & Bishop, 2010).

3.1. Patterns of co-use

As noted earlier, recent studies document shifts in demographic correlates of NMPO and heroin use. Evidence that NMPO-only users transition to heroin use and subsequently co-use both opioids depending on availability indicates that co-use may be growing (Church et al., 2011; Guarino et al., 2015; Inciardi et al., 2009; Jones, 2013; Mars et al., 2014). However, we lack empirical evidence of the trends in and characteristics of co-use, compared to opioid use in general.

To our knowledge, only two studies categorize NMPO and heroin co-use and find differences in characteristics of co-users relative to heroin-only users, not NMPO users (Fischer et al., 2008; Rigg & Monnat, 2015). In a study that aggregated data from 2005-2013 among problem opioid users, the prevalence of co-use was over 8% and associated with male sex relative to female, non-Hispanic White race/ethnicity relative to Hispanic, age over 18 relative to younger age, and urban residence relative to non-urban (Wu, Zhu, & Swartz, 2016). The existing literature

does not compare NMPO-only to co-users, does not examine trends over time, examines abuse and dependence but not use, and is not theoretically-framed, limiting our ability to respond systematically to shifts in opioid use.

Available theories emphasize the importance of examining trends frequently and exploring individual-level characteristics, which manifest differently due to factors at higher levels (Keyes, Cerdá, Brady, Havens, & Galea, 2014; Rhodes, 2009). Patterns in opioid use and associated harms can change quickly and are dependent on the interaction between the individual and their environment (Rhodes, 2009). Trend theory explains these trends as dynamic and a function of context, with some population segments being affected more than others. It posits that people 1) marginalized from power, 2) with access to drugs through a new delivery system, and 3) affected by changes in policies related to drug use are more likely to initiate drug use and likely share demographic characteristics (Agar & Reisinger, 2001). This provides context to increased opioid use and related outcomes in groups with historically lower rates including women relative to men, non-Hispanic Whites relative to other races/ethnicities, those with private health insurance relative to no insurance, and those residing in non-urban counties relative to urban counties (Jones, Logan, et al., 2015; Paulozzi & Xi, 2008; Unick et al., 2013). It also highlights a link between emerging types of drug use and other substance use and mental health co-morbidities.

These shifts in opioid use and trend theory's notion that certain population groups are at higher risk for initiation of drug use call for investigation of demographic, substance use, and mental health characteristics associated with co-use and changes over time. We hypothesize that co-users are a unique and growing group of interest, affecting some demographic groups, and those with substance use and mental health problems, more than others. The risks associated with co-use indicate an urgent need to quantify and describe this population. Since this subgroup may have specific service delivery needs, findings will

forecast treatment needs and inform additional prevention and response interventions (Jordan, Jarlais, & Hagan, 2014; Wu, Woody, Yang, & Blazer, 2011).

3.2. Multi-level factors related to transition

With the harms associated with transition and co-use and evidence that NMPO use alone does not indicate transition, we need a deeper understanding of factors that increase risk of transition. As discussed earlier, recent studies document an opioid use trajectory that begins with NMPO use, moves to NMPO abuse and transitions to heroin initiation when PO availability is limited (Inciardi et al., 2009; Mars et al., 2014; Mateu-Gelabert et al., 2015). There is also evidence of subsequent NMPO and heroin co-use depending on availability (Guarino et al., 2015).

Studies identifying risk factors of transition are limited. Qualitative studies link transition to an inability to obtain POs through familial or medical sources and perceived heroin availability (Inciardi et al., 2009; Siegal et al., 2003). Site-specific cross sectional and adolescent-focused research identify correlates of transition that include non-Hispanic White race relative to other race/ethnicities, non-urban residence relative to urban, lower socioeconomic status, younger age of NMPO initiation, use of non-opioids, and experiences of psychiatric comorbidities (Carlson, Nahhas, Martins, & Daniulaityte, 2016; Cerda, Santaella, Marshall, Kim, & Martins, 2015).

The interconnectedness of recent shifts in NMPO and heroin use suggests that factors related to increased NMPO use are also correlates of transition, but this requires examination. These include individual-level characteristics including access to healthcare, perceived opioid availability, and perceived risk of opioid use as well as interpersonal characteristics such as NMPO source.

Researchers highlight the importance of exploring individual-, social- and structural-level factors in relation to emerging trajectories of opioid use, but we lack population-based studies that explore macro-level factors. An understanding of macro-level factors can explain differences observed at the individual level and address the root causes of these shifts (Dasgupta, Beletsky, & Ciccarone, 2018; National Academies of Sciences & Medicine, 2017).

The socio-ecological model (SEM) has a long history of organizing factors beyond the individual level, including interactions between people and the broader normative environment, to explain health behaviors (Bronfenbrenner, 1979; McLeroy, Bibeau, Steckler, & Glanz, 1988; Sallis, Owen, & Fisher, 2008). While researchers have suggested a socio-ecological approach to understanding patterns in drug use, application of SEM to study these changes is limited (Dew, Elifson, & Dozier, 2007; Monnat & Rigg, 2015; Nargiso, Ballard, & Skeer, 2015). A better understanding of the relationship between multilevel factors and transition will inform interventions to identify those at risk of transitioning, reach them with effective response services, and indicate appropriate interventions at different levels of SEM.

3.2. Trends in MAT enrollment and correlates of MAT completion

Given the recent shifts in opioid use and the hypothesized emergence of co-users, we expect increases in MAT enrollment and retention. However, increasing rates of opioid-related overdose persist suggesting gaps in MAT enrollment and treatment success. Studies report use of MAT services by NMPO users and an increase in the overall rate of MAT admissions since 1999 but do not report on the characteristics of the individuals who are admitted to MAT (Brands, Blake, Sproule, Gourlay, & Busto, 2004; Jamison, Kauffman, & Katz, 2000; Jones, Campopiano, et al., 2015; Volkow et al., 2014). Additionally, the literature is not definitive when it comes to demographic correlates of MAT enrollment and has not

explored differences in MAT enrollment by opioid use type. We lack information on whether MAT admissions keep pace with changes in opioid use, namely among co-users, among non-Hispanic Whites relative to other race/ethnicities, and those in non-urban areas relative to urban areas (Jones, 2013; Paulozzi & Xi, 2008; Unick et al., 2013). Since MAT and other harm reduction interventions have historically been aimed at people who inject drugs and heroin users, access may be low among those who identify as NMPO users, even if they co-use heroin or inject. This is because they may perceive themselves differently, be outside of the networks typically reached by harm reduction services, and be unaware of this information or services (Frank et al., 2015; Mateu-Gelabert et al., 2015).

Another important but understudied indicator of MAT use is successful treatment completion. This is because dropout leads to resumption of opioid use and associated risk of morbidity and mortality. Therefore, an examination of MAT use is critical to identifying subgroups with disproportionately low rates of treatment completion. In studies of opioid users accessing buprenorphine in physicians' offices, treatment completion is less likely among co-users compared to NMPO- and heroin-only users (Moore et al., 2007; Nielsen, Hillhouse, Mooney, Ang, & Ling, 2013; Potter et al., 2013). These studies also indicate that female sex relative to male, White race relative to others, younger age, and higher socio-economic status are associated with greater likelihood of MAT completion (Moore et al., 2007; Neumann, Blondell, Azadfard, Nathan, & Homish, 2013). Office-based buprenorphine only represents a small proportion of all MAT programs (Alderks, 2017; Saloner & Karthikeyan, 2015). Therefore, information on MAT completion by these characteristics in outpatient MAT facilities, representing the majority of opioid treatment programs, will inform targeted efforts to overcome gaps in service delivery (Substance Abuse and Mental Health Administration, 2014).

Recent implementation of federal initiatives aimed at increasing access to health services overall, and substance abuse treatment specifically, calls for an examination of trends in MAT enrollment and correlates of treatment completion that considers different dimensions of healthcare access. Under the Affordable Care Act (ACA), states could opt to expand Medicaid to low-income adults under 138% of the federal poverty level, many of whom have substance use issues and previously did not qualify for coverage (Buck, 2011; Busch, Meara, Huskamp, & Barry, 2013). This may address lack of health insurance coverage as a critical financial barrier to treatment (Center for Behavioral Health Statistics and Quality, 2016; Deck & Carlson, 2004; Kwiatkowski, Booth, & Lloyd, 2000). While we expect admissions in expansion states and among those covered by health insurance to increase and to be associated with treatment success, particularly among more vulnerable opioid users, this has not been established. These initiatives also encouraged increased screening and referrals to treatment by healthcare providers and increased demand for MAT (Bao et al., 2016; Gabay, 2015). Without an increase in capacity, increased demand forces delayed treatment admissions (Albrecht, Lindsay, & Terplan, 2011; Jones, Campopiano, et al., 2015; Kaplan & Johri, 2000). While referrals from the criminal justice system are associated with treatment completion, the effect of healthcare provider referrals on MAT use requires further study (Ali, Teich, & Mutter, 2017; Arndt, Acion, & White, 2013; Gabay, 2015). Thus, national studies must examine trends in referral source and immediate admission and the relationship between these characteristics of healthcare access and treatment completion.

To examine trends in MAT enrollment and correlates of completion, Andersen's Behavioral Model of service use is a useful organizing framework (Andersen & Aday, 1978). Several researchers, even the model's developer, applied it to study health service utilization among people who use drugs (Andersen et al., 2000; Deck & Carlson, 2004; Maru

et al., 2008). It examines access to health services as a function of predisposing characteristics, enabling factors, and need for care. Exploring demographics as predisposing characteristics, dimensions of healthcare access as enabling factors, and co-use as an indicator of need would highlight subgroups in need of treatment services, strategies to make MAT more accessible to the current opioid-using population, and healthcare-related interventions to improve successful treatment completion.

3.3. Research aims

To fill these research gaps, the present research uses secondary data analysis of two national datasets related to drug and MAT use: the National Surveys on Drug Use and Health and the Treatment Episodes Datasets. Use of nationally-representative data among adults and a specific focus on differences by opioid use type enable generalizable findings that forecast needs in order to strategically plan targeted prevention and treatment interventions. This dissertation research aims to:

Aim 1: Describe current prevalence and temporal trends in opiate use in the US overall, by opiate use type (NMPO, heroin, and co-use) and demographic (sex, race, age, rurality), substance use and mental health characteristics.

Aim 2: Explore associations between multilevel factors related to increased NMPO use (e.g. healthcare access, perceived risk, availability) and transition from NMPO to heroin co-use.

Aim 3: Examine temporal trends in demographic characteristics of MAT admissions at publically-funded facilities in the US overall, and by opioid use type, demographic characteristics, and dimensions of healthcare access.

Sub-aim 3a: Explore differences in MAT completion by opiate use type, demographic characteristics, and dimensions of healthcare access (i.e. health insurance coverage and referral by care provider).

4. References

Agar, M., & Reisinger, H. S. (2001). Using trend theory to explain heroin use trends. *Journal of psychoactive drugs, 33*(3), 203-211.

Al-Tayyib, A. A., Koester, S., & Riggs, P. (2017). Prescription opioids prior to injection drug use: Comparisons and public health implications. *Addictive behaviors, 65*, 224-228.

Albrecht, J., Lindsay, B., & Terplan, M. (2011). Effect of waiting time on substance abuse treatment completion in pregnant women. *Journal of substance abuse treatment, 41*(1), 71-77.

Alderks, C. E. (2017). Trends in the use of methadone, buprenorphine, and extended-release naltrexone at substance abuse treatment facilities: 2003–2015 (update). In *The CBHSQ report: August 22, 2017*: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Rockville, MD.

Ali, M. M., Teich, J. L., & Mutter, R. (2017). Reasons for Not Seeking Substance Use Disorder Treatment: Variations by Health Insurance Coverage. *The journal of behavioral health services & research, 44*(1), 63-74.

Amato, L., Davoli, M., Perucci, C. A., Ferri, M., Faggiano, F., & Mattick, R. P. (2005). An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *Journal of substance abuse treatment, 28*(4), 321-329.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*: American Psychiatric Pub.

Andersen, R., & Aday, L. A. (1978). Access to medical care in the US: realized and potential. *Medical care*, 533-546.

Andersen, R., Bozzette, S., Shapiro, M., St Clair, P., Morton, S., Crystal, S., . . . Leibowitz, A. (2000). Access of vulnerable groups to antiretroviral therapy among persons in care for HIV disease in the United States. HCSUS Consortium. HIV Cost and Services Utilization Study. *Health Services Research, 35*(2), 389.

Arndt, S., Acion, L., & White, K. (2013). How the states stack up: Disparities in substance abuse outpatient treatment completion rates for minorities. *Drug and alcohol dependence, 132*(3), 547-554.

Arria, A. M., Caldeira, K. M., Vincent, K. B., O'Grady, K. E., & Wish, E. D. (2008). Perceived harmfulness predicts nonmedical use of prescription drugs among college students: Interactions with sensation-seeking. *Prevention Science, 9*(3), 191-201.

Bao, Y., Pan, Y., Taylor, A., Radakrishnan, S., Luo, F., Pincus, H. A., & Schackman, B. R. (2016). Prescription drug monitoring programs are associated with sustained reductions in opioid prescribing by physicians. *Health Affairs, 35*(6), 1045-1051.

Beletsky, L., & Davis, C. S. (2017). Today's fentanyl crisis: Prohibition's Iron Law, revisited. *International Journal of Drug Policy, 46*, 156-159.

Blum, K., Gold, M., Clark, H. W., Dushaj, K., & Badgaiyan, R. D. (2016). Should the United States government repeal restrictions on buprenorphine/naloxone treatment? *Substance use & misuse, 51*(12), 1674-1679.

Brandeis, P. D. M. P. C. o. E. a. (2016). *PDMP Prescriber use mandates: characteristics, current status, and outcomes in selected states*. Retrieved from Waltham, MA: http://www.pdmpassist.org/pdf/COE_documents/Add_to_TTAC/COE%20briefing%20on%20mandates%203rd%20revision.pdf

Brands, B., Blake, J., Sproule, B., Gourlay, D., & Busto, U. (2004). Prescription opioid abuse in patients presenting for methadone maintenance treatment. *Drug and alcohol dependence, 73*(2), 199-207.

Brennan, F., Carr, D. B., & Cousins, M. (2007). Pain management: a fundamental human right. *The Journal of the American Society of Anesthesiologists, 107*(1), 205-221.

Bronfenbrenner, U. (1979). The ecology of human development: Experiments by design and nature. In: Cambridge, MA: Harvard University Press.

Broz, D., Zlotorzynska, M., Spiller, M., & Paz-Bailey, G. (2017). *'Hooked on painkillers' prior to first injection among PWID in 16 US cities.* Paper presented at the Conference on Retroviruses and Opportunistic Infections, Seattle, Washington.

Buck, J. A. (2011). The looming expansion and transformation of public substance abuse treatment under the Affordable Care Act. *Health Affairs, 30*(8), 1402-1410.

Busch, S. H., Meara, E., Huskamp, H. A., & Barry, C. L. (2013). Characteristics of adults with substance use disorders expected to be eligible for Medicaid under the ACA. *Psychiatric Services, 64*(6), 520-526.

Canfield, M. C., Keller, C. E., Frydrych, L. M., Ashrafioun, L., Purdy, C. H., & Blondell, R. D. (2010). Prescription opioid use among patients seeking treatment for opioid dependence. *Journal of addiction medicine, 4*(2), 108.

Carlson, R. G., Nahhas, R. W., Martins, S. S., & Daniulaityte, R. (2016). Predictors of transition to heroin use among initially non-opioid dependent illicit pharmaceutical opioid users: A natural history study. *Drug and alcohol dependence, 160*, 127-134.

Center for Behavioral Health Statistics and Quality. (2015). *2014 National Survey on Drug Use and Health: detailed tables.* . Retrieved from Rockville, MD:

Center for Behavioral Health Statistics and Quality. (2016). *Key substance abuse and mental health indicators in the United States: Results from the 2015 National Survey on Drug Use and Health*. Retrieved from Rockville, MD:

Centers for Disease Control and Prevention. (2012). CDC grand rounds: prescription drug overdoses-a US epidemic. *MMWR Morb Mortal Wkly Rep, 61*(1), 10.

Cerda, M., Santaella, J., Marshall, B. D., Kim, J. H., & Martins, S. S. (2015). Nonmedical Prescription Opioid Use in Childhood and Early Adolescence Predicts Transitions to Heroin Use in Young Adulthood: A National Study. *J Pediatr, 167*(3), 605-612 e602. doi:10.1016/j.jpeds.2015.04.071

Cherubin, C. E., & Sapira, J. D. (1993). The medical complications of drug addiction and the medical assessment of the intravenous drug user: 25 years later. *Annals of internal medicine, 119*(10), 1017-1028.

Church, D., Barton, K., Elson, F., DeMaria, A., Cranston, K., Harris, N., . . . Holmberg, S. (2011). Risk Factors for Hepatitis C Virus Infections Among Young Adults- Massachusetts, 2010. *MMWR Morb Mortal Wkly Rep, 60*(42).

Cicero, T. J., Ellis, M. S., & Surratt, H. L. (2012). Effect of abuse-deterrent formulation of OxyContin. *New England Journal of Medicine, 367*(2), 187-189.

Cicero, T. J., Ellis, M. S., Surratt, H. L., & Kurtz, S. P. (2014). The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. *JAMA psychiatry, 71*(7), 821-826.

Compton, W. M., Jones, C. M., & Baldwin, G. T. (2016). Relationship between Nonmedical Prescription-Opioid Use and Heroin Use. *New England Journal of Medicine, 374*(2), 154-163. doi:doi:10.1056/NEJMra1508490

Cousins, M. J., Brennan, F., & Carr, D. B. (2004). Pain relief: a universal human right. *Pain, 112*(1-2), 1-4.

Daniulaityte, R., Falck, R., & Carlson, R. G. (2012). "I'm not afraid of those ones just 'cause they've been prescribed": Perceptions of risk among illicit users of pharmaceutical opioids. *International Journal of Drug Policy, 23*(5), 374-384.

Dart, R. C., Surratt, H. L., Cicero, T. J., Parrino, M. W., Severtson, S. G., Bucher-Bartelson, B., & Green, J. L. (2015). Trends in opioid analgesic abuse and mortality in the United States. *New England Journal of Medicine, 372*(3), 241-248.

Dasgupta, N., Beletsky, L., & Ciccarone, D. (2018). Opioid Crisis: No Easy Fix to Its Social and Economic Determinants. *American journal of public health, 108*(2), 182-186.

Davis, C. S., Pierce, M., & Dasgupta, N. (2014). Evolution and convergence of state laws governing controlled substance prescription monitoring programs, 1998-2011. *American journal of public health, 104*(8), 1389-1395.

Deck, D., & Carlson, M. J. (2004). Access to publicly funded methadone maintenance treatment in two western states. *The journal of behavioral health services & research, 31*(2), 164-177.

Dew, B., Elifson, K., & Dozier, M. (2007). Social and environmental factors and their influence on drug use vulnerability and resiliency in rural populations. *The Journal of Rural Health, 23*(s1), 16-21.

Dhalla, I. A., Persaud, N., & Juurlink, D. N. (2011). Facing up to the prescription opioid crisis. *BMJ, 343*, d5142.

Dole, V. P., Nyswander, M. E., & Kreek, M. J. (1966). Narcotic blockade. *Archives of internal medicine, 118*(4), 304-309.

Drug Enforcement Administration. (2016). *National Heroin Threat Assessment Summary*. Retrieved from

Dwyer-Lindgren, L., Bertozzi-Villa, A., Stubbs, R. W., Morozoff, C., Kutz, M. J., Huynh, C., . . . Van Lenthe, F. J. (2016). US county-level trends in mortality rates for major causes of death, 1980-2014. *JAMA, 316*(22), 2385-2401.

Fischer, B., Patra, J., Cruz, M. F., Gittins, J., & Rehm, J. (2008). Comparing heroin users and prescription opioid users in a Canadian multi-site population of illicit opioid users. *Drug Alcohol Rev, 27*(6), 625-632. doi:10.1080/09595230801956124

Frank, D., Mateu-Gelabert, P., Guarino, H., Bennett, A., Wendel, T., Jessell, L., & Teper, A. (2015). High risk and little knowledge: Overdose experiences and knowledge among young adult nonmedical prescription opioid users. *International Journal of Drug Policy, 26*(1), 84-91.

Fullerton, C. A., Kim, M., Thomas, C. P., Lyman, D. R., Montejano, L. B., Dougherty, R. H., . . . Delphin-Rittmon, M. E. (2014). Medication-assisted treatment with methadone: assessing the evidence. *Psychiatr Serv, 65*(2), 146-157. doi:10.1176/appi.ps.201300235

Gabay, M. (2015). Prescription Drug Monitoring Programs. *Hospital Pharmacy, 50*(4), 277-278.

Glanz, K., & Bishop, D. B. (2010). The role of behavioral science theory in development and implementation of public health interventions. *Annual review of public health, 31*, 399-418.

Gostin, L. O., Hodge, J. G., & Noe, S. A. (2017). Reframing the opioid epidemic as a national emergency. *JAMA, 318*(16), 1539-1540.

Guarino, H., Marsch, L. A., Deren, S., Straussner, S. L., & Teper, A. (2015). Opioid Use Trajectories, Injection Drug Use, and Hepatitis C Virus Risk Among Young Adult Immigrants from the Former Soviet Union Living in New York City. *J Addict Dis, 34*(2-3), 162-177. doi:10.1080/10550887.2015.1059711

Han, B., Compton, W. M., Jones, C. M., & Cai, R. (2015). Nonmedical prescription opioid use
and use disorders among adults aged 18 through 64 years in the United States,
2003-2013. *JAMA, 314*(14), 1468-1478.

Hedegaard, H., Warner, M., & Miniño, A. M. (2018). Drug overdose deaths in the United
States, 1999-2016. *NCHS data brief*(273), 1-8.

Hoffmann, D. E., & Tarzian, A. J. (2003). Achieving the right balance in oversight of physician
opioid prescribing for pain: the role of state medical boards. *The Journal of Law,
Medicine & Ethics, 31*(1), 21-40.

Hughes, P. H., Barker, N. W., Crawford, G. A., & Jaffe, J. H. (1972). The natural history of a
heroin epidemic. *American journal of public health, 62*(7), 995-1001.

Inciardi, J. A., Surratt, H. L., Cicero, T. J., & Beard, R. A. (2009). Prescription opioid abuse and
diversion in an urban community: the results of an ultrarapid assessment. *Pain
Medicine, 10*(3), 537-548.

Jaffe, J. (1990). Drug addiction and drug abuse. In A. Gilman, T. Rall, A. Nies, & T. P. (Eds.),
The pharmacological basis of therapeutics (8 ed., pp. 522-573). New York: Pergamon
Press.

Jamison, R. N., Kauffman, J., & Katz, N. P. (2000). Characteristics of methadone maintenance
patients with chronic pain. *Journal of pain and symptom management, 19*(1), 53-62.

Jenkins, P. N. (2014, February 24, 2014). Heroin addiction's fraught history. *The Atlantic*.

Johnson, R. A. (1996). *Trends in the incidence of drug use in the United States, 1919-1992*: U.S.
Dept. of Health and Human Services, Public Health Service.

Johnston, L. (2010). *Monitoring the future: National results on adolescent drug use: Overview
of key findings*: DIANE Publishing.

Jones, C. M. (2013). Heroin use and heroin use risk behaviors among nonmedical users of

    prescription opioid pain relievers–United States, 2002–2004 and 2008–2010. *Drug*

    and alcohol dependence, 132(1), 95-100.

Jones, C. M., Campopiano, M., Baldwin, G., & McCance-Katz, E. (2015). National and state

    treatment need and capacity for opioid agonist medication-assisted treatment.

    Journal Information, 105(8).

Jones, C. M., Logan, J., Gladden, R., & Bohm, M. K. (2015). Vital signs: demographic and

    substance use trends among heroin users: United States, 2002–2013. *MMWR Morb*

    Mortal Wkly Rep, 64(26), 719-725.

Jordan, A. E., Jarlais, D. D., & Hagan, H. (2014). Prescription opioid misuse and its relation to

    injection drug use and hepatitis C virus infection: protocol for a systematic review

    and meta-analysis. *Syst Rev, 3*, 95. doi:10.1186/2046-4053-3-95

Kanouse, A. B., & Compton, P. (2015). The epidemic of prescription opioid abuse, the

    subsequent rising prevalence of heroin use, and the federal response. *Journal of pain*

    & palliative care pharmacotherapy, 29(2), 102-114.

Kaplan, E. H., & Johri, M. (2000). Treatment on demand: an operational model. *Health Care*

    Manag Sci, 3(3), 171-183.

Keyes, K. M., Cerdá, M., Brady, J. E., Havens, J. R., & Galea, S. (2014). Understanding the rural–

    urban differences in nonmedical prescription opioid use and abuse in the United

    States. *American journal of public health, 104*(2), e52-e59.

Kolodny, A., Courtwright, D. T., Hwang, C. S., Kreiner, P., Eadie, J. L., Clark, T. W., & Alexander,

    G. C. (2015). The prescription opioid and heroin crisis: a public health approach to

    an epidemic of addiction. *Annual review of public health, 36*, 559-574.

24

Kresina, T. F., Litwin, A., Marion, I., Lubran, R., & Clark, H. W. (2009). United States government oversight and regulation of medication assisted treatment for the treatment of opioid dependence. *Journal of Drug Policy Analysis, 2*(1).

Kuehn, B. M. (2010). FDA opioid safety plan promotes patient, physician education to prevent abuse. *JAMA, 304*(8), 845-845.

Kwiatkowski, C. F., Booth, R. E., & Lloyd, L. V. (2000). The effects of offering free treatment to street-recruited opioid injectors. *Addiction, 95*(5), 697-704.

Lankenau, S. E., Teti, M., Silva, K., Bloom, J. J., Harocopos, A., & Treese, M. (2012). Initiation into prescription opioid misuse amongst young injection drug users. *International Journal of Drug Policy, 23*(1), 37-44.

Levy, M. S. (2007). An exploratory study of OxyContin use among individuals with substance use disorders. *Journal of psychoactive drugs, 39*(3), 271-276.

Lipari, R. N., & Hughes, A. Trends in heroin use in the United States: 2002 TO 2013.

Manchikanti. (2007). National drug control policy and prescription drug abuse: facts and fallacies. *Pain physician, 10*(3), 399.

Manchikanti, Helm, S., Janata, J. W., Pampati, V., & Grider, J. S. (2012). Opioid epidemic in the United States. *Pain physician, 15*, 2150-1149.

Mars, S. G., Bourgois, P., Karandinos, G., Montero, F., & Ciccarone, D. (2014). "Every 'never' I ever said came true": transitions from opioid pills to heroin injecting. *International Journal of Drug Policy, 25*(2), 257-266.

Maru, D. S.-R., Bruce, R. D., Walton, M., Mezger, J. A., Springer, S. A., Shield, D., & Altice, F. L. (2008). Initiation, adherence, and retention in a randomized controlled trial of directly administered antiretroviral therapy. *AIDS Behav, 12*(2), 284-293.

Mateu-Gelabert, P., Guarino, H., Jessell, L., & Teper, A. (2015). Injection and sexual HIV/HCV risk behaviors associated with nonmedical use of prescription opioids among young adults in New York City. *Journal of substance abuse treatment, 48*(1), 13-20.

Mattick, R. P., Breen, C., Kimber, J., & Davoli, M. (2009). Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev, 3*(CD002209).

McLeroy, K. R., Bibeau, D., Steckler, A., & Glanz, K. (1988). An ecological perspective on health promotion programs. *Health Education & Behavior, 15*(4), 351-377.

Mitchell, S. G., Kelly, S. M., Brown, B. S., Reisinger, H. S., Peterson, J. A., Ruhf, A., . . . Schwartz, R. P. (2009). Incarceration and opioid withdrawal: the experiences of methadone patients and out-of-treatment heroin users. *Journal of psychoactive drugs, 41*(2), 145-152.

Monnat, S. M., & Rigg, K. K. (2015). Examining rural/urban differences in prescription opioid misuse among US adolescents. *The Journal of Rural Health*.

Moore, B. A., Fiellin, D. A., Barry, D. T., Sullivan, L. E., Chawarski, M. C., O'Connor, P. G., & Schottenfeld, R. S. (2007). Primary care office-based buprenorphine treatment: comparison of heroin and prescription opioid dependent patients. *Journal of general internal medicine, 22*(4), 527-530.

Mowbray, O., & Quinn, A. (2015). Prescription pain reliever misuse prevalence, correlates, and origin of possession throughout the life course. *Addictive behaviors, 50*, 22-27.

Muhuri, P. K., Gfroerer, J. C., & Davies, M. C. (2013). Associations of nonmedical pain reliever use and initiation of heroin use in the United States. *The CBHSQ Data Review*.

Mularski, R. A., White-Chu, F., Overbay, D., Miller, L., Asch, S. M., & Ganzini, L. (2006). Measuring pain as the 5th vital sign does not improve quality of pain management. *Journal of general internal medicine, 21*(6), 607-612.

Nargiso, J. E., Ballard, E. L., & Skeer, M. R. (2015). A systematic review of risk and protective factors associated with nonmedical use of prescription drugs among youth in the United States: a social ecological perspective. *Journal of studies on alcohol and drugs, 76*(1), 5-20.

National Academies of Sciences, E., & Medicine. (2017). *Pain management and the opioid epidemic: balancing societal and individual benefits and risks of prescription opioid use*: National Academies Press.

National Institute of Drug Abuse. (2014a). *Prescription Drug Abuse*. Retrieved from Rockville, MD:

National Institute of Drug Abuse. (2014b). What are opioids? Retrieved from https://www.drugabuse.gov/publications/research-reports/prescription-drugs/opioids/what-are-opioids

Neumann, A. M., Blondell, R. D., Azadfard, M., Nathan, G., & Homish, G. G. (2013). Primary care patient characteristics associated with completion of 6-month buprenorphine treatment. *Addictive behaviors, 38*(11), 2724-2728.

Nevius, J. (2016, March 15, 2016). The strange history of opiates in America: from morphine for kids to heroin for soldiers. *The Guardian*.

Nielsen, S., Hillhouse, M., Mooney, L., Ang, A., & Ling, W. (2013). Buprenorphine pharmacotherapy and behavioral treatment: Comparison of outcomes among prescription opioid users, heroin users and combination users. *Journal of substance abuse treatment, 48*(1), 70-76. doi:10.1016/j.jsat.2014.06.006

Nielsen, S., Larance, B., & Lintzeris, N. (2017). Opioid Agonist Treatment for Patients With Dependence on Prescription Opioids. *JAMA, 317*(9), 967-968. doi:10.1001/jama.2017.0001

Nosyk, B., Anglin, M. D., Brissette, S., Kerr, T., Marsh, D. C., Schackman, B. R., . . . Montaner, J. S. (2013). A call for evidence-based medical treatment of opioid dependence in the United States and Canada. *Health Affairs, 32*(8), 1462-1469.

Office of National Drug Control Policy. (2011). Prescription Drug Monitoring Programs.

Okie, S. (2010). A flood of opioids, a rising tide of deaths. *New England Journal of Medicine, 363*(21), 1981-1985.

Panter-Brick, C., Clarke, S. E., Lomas, H., Pinder, M., & Lindsay, S. W. (2006). Culturally compelling strategies for behaviour change: a social ecology model and case study in malaria prevention. *Social Science & Medicine, 62*(11), 2810-2825.

Paulozzi, L. J., & Xi, Y. (2008). Recent changes in drug poisoning mortality in the United States by urban–rural status and by drug type. *Pharmacoepidemiology and drug safety, 17*(10), 997-1005.

Pollini, R. A., Banta-Green, C. J., Cuevas-Mota, J., Metzner, M., Teshale, E., & Garfein, R. S. (2011). Problematic use of prescription-type opioids prior to heroin use among young heroin injectors. *Substance abuse and rehabilitation, 2*(1), 173.

Portenoy, R. K., & Foley, K. M. (1986). Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain, 25*(2), 171-186.

Porter, J., & Jick, H. (1980). Addiction rare in patients treated with narcotics. *The New England journal of medicine, 302*(2), 123.

Potter, J. S., Marino, E. N., Hillhouse, M. P., Nielsen, S., Wiest, K., Canamar, C. P., . . . Saxon, A. J. (2013). Buprenorphine/naloxone and methadone maintenance treatment outcomes for opioid analgesic, heroin, and combined users: findings from starting treatment with agonist replacement therapies (START). *Journal of studies on alcohol and drugs, 74*(4), 605-613.

Rhodes, T. (2009). Risk environments and drug harms: a social science for harm reduction approach. *International Journal of Drug Policy, 20*(3), 193-201.

Rigg, K. K., & Monnat, S. M. (2015). Comparing Characteristics of Prescription Painkiller Misusers and Heroin Users in the United States. *Addictive behaviors, 51*, 106-112. doi:10.1016/j.addbeh.2015.07.013

Rockett, I. R., Regier, M. D., Kapusta, N. D., Coben, J. H., Miller, T. R., Hanzlick, R. L., . . . Kleinig, J. (2012). Leading causes of unintentional and intentional injury mortality: United States, 2000–2009. *American journal of public health, 102*(11), e84-e92.

Ruckert, A., & Labonté, R. (2017). Health inequities in the age of austerity: the need for social protection policies. *Social Science & Medicine, 187*, 306-311.

Sallis, J. F., Owen, N., & Fisher, E. B. (2008). Ecological models of health behavior. *Health behavior and health education: Theory, research, and practice, 4*, 465-486.

Saloner, B., & Karthikeyan, S. (2015). Changes in substance abuse treatment use among individuals with opioid use disorders in the United States, 2004-2013. *JAMA, 314*(14), 1515-1517.

Schepis, T. S., & Krishnan-Sarin, S. (2009). Sources of prescriptions for misuse by adolescents: differences in sex, ethnicity, and severity of misuse in a population-based study. *Journal of the American Academy of Child & Adolescent Psychiatry, 48*(8), 828-836.

Seppala, M., & Rose, M. (2011). *Prescription Painkillers: History, Pharmacology, and Treatment*: Hazelden.

Siegal, H. A., Carlson, R. G., Kenne, D. R., & Swora, M. G. (2003). Probable relationship between opioid abuse and heroin use. *American Family Physician, 67*(5), 942-945.

Strang, J., Griffiths, P., Powis, B., Fountain, J., Williamson, S., & Gossop, M. (1999). Which drugs cause overdose among opiate misusers? Study of personal and witnessed overdoses. *Drug and alcohol review, 18*(3), 253-261.

Substance Abuse and Mental Health Administration. (2002). *Results From the 2001 National Household Survey on Drug Abuse: Volume II. Technical Appendices and Selected Data Tables*. Retrieved from Rockville, MD:

Substance Abuse and Mental Health Administration. (2011). National Estimates of Drug-Related Emergency Department Visits.

Substance Abuse and Mental Health Administration. (2014). *National Survey of Substance Abuse Treatment Services (N-SSATS): 2013. Data on Substance Abuse Treatment Facilities*. Retrieved from Rockville, MD:

Substance Abuse and Mental Health Services. (2011). Results from the 2010 National Survey on Drug Use and Health: Summary of national findings. *Substance Abuse and Mental Health Services Administration: Rockville, MD, USA*.

Thomas, C. P., Fullerton, C. A., Kim, M., Montejano, L., Lyman, D. R., Dougherty, R. H., . . . Delphin-Rittmon, M. E. (2014). Medication-assisted treatment with buprenorphine: assessing the evidence. *Psychiatr Serv, 65*(2), 158-170. doi:10.1176/appi.ps.201300256

Unick, G. J., Rosenblum, D., Mars, S., & Ciccarone, D. (2013). Intertwined epidemics: national demographic trends in hospitalizations for heroin-and opioid-related overdoses, 1993–2009. *PloS one, 8*(2), e54496.

United Nations Office on Drugs and Crime. (2016). *World Drug Report 2016*. Retrieved from

Verhaak, P. F., Kerssens, J. J., Dekker, J., Sorbi, M. J., & Bensing, J. M. (1998). Prevalence of chronic benign pain disorder among adults: a review of the literature. *Pain, 77*(3), 231-239.

Volkow, N. D., Frieden, T. R., Hyde, P. S., & Cha, S. S. (2014). Medication-assisted therapies—tackling the opioid-overdose epidemic. *New England Journal of Medicine, 370*(22), 2063-2066.

Volkow, N. D., Wang, G.-J., Fowler, J. S., Logan, J., Gatley, S. J., Wong, C., . . . Pappas, N. R. (1999). Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D2receptors. *Journal of Pharmacology and Experimental Therapeutics, 291*(1), 409-415.

Wakeland, W., Nielsen, A., & Geissert, P. (2015). Dynamic model of nonmedical opioid use trajectories and potential policy interventions. *The American journal of drug and alcohol abuse*(0), 1-11.

Warner, M., Chen, L. H., & Makuc, D. M. (2009). Increase in fatal poisonings involving opioid analgesics in the United States, 1999-2006. *NCHS data brief*(22), 1-8.

Wikler, A. (2013). *Opioid dependence: Mechanisms and treatment*: Springer Science & Business Media.

Wood, M. (2011). *Media's positive and negative frames in reporting celebrity deaths from illegal drug overdoses versus prescription medication overdoses.* (M.S.), University of Kansas,

Wu, L.-T., Woody, G. E., Yang, C., & Blazer, D. G. (2011). How do prescription opioid users differ from users of heroin or other drugs in psychopathology: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of addiction medicine, 5*(1), 28.

Wu, L.-T., Zhu, H., & Swartz, M. S. (2016). Treatment utilization among persons with opioid use disorder in the United States. *Drug and alcohol dependence, 169*, 117-127.

Zacny, J., Bigelow, G., Compton, P., Foley, K., Iguchi, M., & Sannerud, C. (2003). College on Problems of Drug Dependence taskforce on prescription opioid non-medical use and abuse: position statement. *Drug and alcohol dependence, 69*(3), 215-232.

Zarkin, G. A., Dunlap, L. J., Hicks, K. A., & Mamo, D. (2005). Benefits and costs of methadone treatment: results from a lifetime simulation model. *Health economics, 14*(11), 1133-1150.

Zibbell, J. E., Iqbal, K., Patel, R., Suryaprasad, A., Sanders, K., Moore-Moravian, L., . . . Holtzman, D. (2015). Increases in hepatitis C virus infection related to injection drug use among persons aged≤ 30 years-Kentucky, Tennessee, Virginia, and West Virginia, 2006-2012. *MMWR Morb Mortal Wkly Rep, 64*(17), 453-458.

Chapter 2: Trends in non-medical prescription opioids and heroin co-use among adults, 2003-2014

Abstract

Background. Patterns in non-medical prescription opioid (NMPO) and heroin use have recently shifted, with evidence that NMPO-only users transition to NMPO and heroin co-use. Co-use is associated with increased risk of morbidity and overdose, highlighting the need for further investigation. This study aims to quantify, describe and explore trends in co-use.
Methods. Using data from the 2003-2014 National Surveys on Drug Use and Health, we compared co-use to NMPO- and heroin-only use across demographic, substance use and mental health characteristics with chi-squared tests. Logistic regression models assessed trends in opioid use overall, and stratified by co-use.
Results. From 2003 to 2014, the prevalence of all opioid use (NMPO-only, heroin-only and co-use) and NMPO-only use decreased 6.08% (p<0.01) and 4.65% (p<0.001), respectively, while prevalence of heroin-only use increased 21.32% (non-significant). Co-use increased 248.17% (p<0.001) overall, and did so in all demographic, substance use, and mental health groups. Demographic, substance use and mental health characteristics of co-users were more similar to the heroin-only group than to NMPO-only. The highest co-use prevalence was among those: without health insurance (8.72%), aged 26-34 (9.76%), reporting unemployment (12.08%), and with a major depressive episode, psychological distress, and who illicitly use or abuse drugs other than opioids or marijuana in the past year (9.33%, 10.75%, 11.87%, and 16.81%, respectively).
Discussion. The increased prevalence of co-use and differences across demographic, substance abuse and mental health characteristics highlight the need for targeted prevention and response interventions for this emerging, high-risk group.

1. Background

Patterns of non-medical prescription opioid (NMPO) and heroin use have been highly dynamic in recent years, paving the way for co-use of both opioids, given their similarities in the high potential for dependence and the euphoric high provided (Compton, Jones, & Baldwin, 2016). The rise in NMPO use and associated outcomes, evidenced by 25 million NMPO initiates between 2002 and 2011 and the quadrupling of opioid-related overdoses from 1999 to 2008, triggered implementation of various interventions aimed at reducing prescription opioid availability (Centers for Disease Control and Prevention, 2011; Dart et al., 2015; Dowell, Haegerich, & Chou, 2016; Kuehn, 2010; Office of National Drug Control Policy, 2011). Following implementation of these interventions, trends in NMPO use stabilized, but problem NMPO use, including abuse and dependence, increased (Franklin et al., 2015; Han, Compton, Jones, & Cai, 2015; Levy, Paulozzi, Mack, & Jones, 2015). Previously stable rates of heroin use also increased 63% from 2002-2013, an increase many attribute to the decreased supply of prescription opioids (POs) (Cicero, Ellis, & Surratt, 2012; Jones, Logan, Gladden, & Bohm, 2015; Unick, Rosenblum, Mars, & Ciccarone, 2013). The steepest increase in heroin use was among those who reported NMPO use, suggesting NMPO use may be a gateway to heroin use and subsequent co-use (Jones, Logan, et al., 2015).

Transitions from NMPO-only use to NMPO and heroin co-use are well-documented in the literature, but studies do not explore the size and characteristics of co-users over time. Recent national studies show that 80% of heroin initiates reported previous NMPO use and that heroin abuse or dependence is 40 times more likely with concurrent PO abuse or dependence (Jones, Logan, et al., 2015; Muhuri, Gfroerer, & Davies, 2013). NMPO users turn to heroin as a less expensive, more accessible, and similarly effective alternative when faced with opioid dependency and limited PO availability (Canfield et

al., 2010; Cicero, Ellis, Surratt, & Kurtz, 2014; Inciardi, Surratt, Cicero, & Beard, 2009; Lipari & Hughes; Mars, Bourgois, Karandinos, Montero, & Ciccarone, 2014). A shift in administration route to injection and expansion from NMPO-only use to use co-use of both opioids, depending on availability, are also reported (Guarino, Marsch, Deren, Straussner, & Teper, 2015; Kuehn, 2014; Mars et al., 2014; Mateu-Gelabert, Guarino, Jessell, & Teper, 2015). Reduced availability of POs suggests growth in co-use, but we lack empirical evidence establishing this trend.

Transition and co-use are concerning for several reasons. First, injection drug use often coincides with heroin use initiation and is more likely among co-users compared with NMPO-only users, putting co-users at higher risk for HIV and Hepatitis C. (Cherubin & Sapira, 1993; Guarino et al., 2015; Kuehn, 2014; Mars et al., 2014; Mateu-Gelabert et al., 2015; Thorpe et al., 2002; Zibbell et al., 2015). Second, co-use is associated with severe comorbidities including other substance use and mental health disorders, compared to NMPO and heroin use alone (Al-Tayyib, Koester, & Riggs, 2017; Fischer, Patra, Cruz, Gittins, & Rehm, 2008; Rigg & Monnat, 2015). Also, poly-drug use is associated with a higher risk of overdose: over half of fatal prescription opioid-related poisonings involved more than one type of drug (Fischer et al., 2008; Jones, Mack, & Paulozzi, 2013; Warner, Chen, & Makuc, 2009). Finally, a large number of NMPO users are susceptible to expanding their opioid use and may experience additional stigma and marginalization associated with heroin use if they transition (Cherubin & Sapira, 1993; Han et al., 2015). Stigma and marginalization impede health service utilization and productivity, further driving the health and social burdens related to drug use. These concerns about co-use underscore the need to identify and reach those who co-use.

The composition of populations affected by opioid use and related consequences has also evolved, particularly among demographic groups with historically lower rates of use.

For example, opioid-related overdose deaths in non-urban counties increased at a rate six-times that of urban counties from 1999 to 2004 and opioid-related hospital admissions increased among Whites at a rate double that of African Americans from 1993 to 2009 (Paulozzi & Xi, 2008; Unick et al., 2013). Heroin use increased among women at a rate double that of men, increased among non-Hispanic Whites but decreased among other race/ethnicities, and increased among those with private health insurance and those reporting other illicit substance use from 2002 to 2013 (Jones, Logan, et al., 2015). These characteristics have not been examined with trends in co-use, hindering our ability to target interventions that respond to shifts in and prevent co-use.

The goal of this study is to analyze trends in co-use and in characteristics of co-users. To our knowledge, existing studies do not explore differences between NMPO-only and co-use, are limited to cross-sectional analyses, or only focus on dependence, not use (Cicero, Ellis, & Harney, 2015; Fischer et al., 2008; Rigg & Monnat, 2015). The analysis is guided by Trend Theory. Trend theory emphasizes the importance of frequent examination of drug use trends and individual-level characteristics related to use, as trends are dynamic and incidence is likely to increase in some groups more than others (Agar & Reisinger, 2001). It posits that drug use initiation is more likely among people 1) marginalized from power, 2) with access to drugs through a new delivery system, and 3) affected by changes in policies related to drug use. This theoretical framework provides context to recent changes in the groups affected by opioid misuse and highlights a link between emerging types of drug use and other substance use and mental health co-morbidities.

We applied Trend Theory to examine 12 years of nationally representative data to (1) describe current opioid use by demographic, substance use, and mental health characteristics; (2) differences in these characteristics by opioid-use type (NMPO-only,

heroin-only and co-use) and (3) trends in (a) opioid use overall, and in (b) co-use. We

hypothesize that co-use is growing, most affecting demographic groups with historically

low rates of opioid misuse as well as those with substance use and mental health problems.

Characterizing this high-risk group will inform targeted interventions to prevent this

transition and forecast treatment needs. This investigation will also highlight the unique

needs of co-users that treatment services can address through co-location or integration of

treatment other health and social services (Wu, Woody, Yang, & Blazer, 2011).

2. Methods

2.1. Data source

We examined data from the 2003-2014 National Surveys on Drug Use and Health

(NSDUH), conducted annually by the Substance Abuse and Mental Health Administration

(SAMHSA). NSDUH provides nationally representative data regarding illicit drug use on the

civilian, non-institutionalized population. Detailed documentation of NSDUH sampling and

data collection procedures are provided elsewhere (Center for Behavioral Health Statistics

and Quality, 2016). In brief, NSDUH employs a multi-stage stratified probability sampling

design. For this study, we combined data from adults (aged 18 and older) in the 2003-2014

public-use files in six 2-year time intervals. Response rates for NSDUH ranged from 82% to

91%, depending on the year. As secondary analyses of publicly available data, this study

was exempted from Emory University's IRB approval.

2.2. Measures

We grouped respondents into four mutually exclusive outcome categories of opioid

use type: no opioid use, NMPO-only use, heroin-only use, and NMPO and heroin co-use.

NSDUH defines NMPO use as use of prescription opioids without a prescription or use only

for the feeling caused by the substance (Substance Abuse and Mental Health Administration,

2002). Consistent with the literature, current use was defined as any use within the past 12

months (Han et al., 2015; Jones, Logan, et al., 2015). Co-use is defined by the use of both heroin and NMPOs within the past 12 months (Rigg & Monnat, 2015).

We examined demographic, substance use and mental health correlates of opioid use type based on theory and literature (Agar & Reisinger, 2001; Han et al., 2015; Han, Gfroerer, & Colliver, 2010; Rigg & Monnat, 2015). Demographic characteristics included: sex (male, female), age (18-25, 26-34, 35-40, 50+), race/ethnicity (non-Hispanic White, non-Hispanic Black, non-Hispanic other, Hispanic), rurality (urban [county with city of at least 10,000], non-urban [county without city of at least 10,000]), educational attainment (less than high school, high school graduate/some college, college graduate), employment status (full time, part time, unemployed, not in labor force), marital status (married, divorced/separated/widowed, never married) and health insurance coverage (covered, not covered).

We defined all substance use and mental health measures as those experienced in the past 12 months. Specifically, we defined tobacco use as use of any of the following tobacco products: all or part of a cigarette, cigars, pipes, snuff, or chewing tobacco. We defined alcohol use as having had any drink of an alcoholic beverage. Other illicit substance use definitions included the nonmedical use of one or more of the following substances: cocaine, crack, hallucinogens, inhalants, tranquilizers, stimulants and sedatives (i.e. illicit use of drugs other than NMPO, heroin and marijuana). Abuse of alcohol and illicit substances is based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria (American Psychiatric Association, 2013). To measure psychological distress, NSDUH uses the K6 screener, which was designed to identify non-specific psychological distress with six brief questions (e.g. "How often do you feel nervous?") (Kessler et al., 2003;

Substance Abuse and Mental Health Administration, 2013). A major depressive episode

(MDE) was assessed using questions adapted from the Composite International Diagnostic

Interview (Kessler et al., 2003). Accordingly, participants were categorized as having MDE if

they met at least five of nine DSM-V criteria.

2.3.   Statistical analyses

To describe current opioid use, we used data from the most recent two-year period

(2013-2014) to compute weighted frequencies across demographic, substance use and

mental health characteristics, overall and by opioid use type. We conducted chi-squared

tests to determine differences in characteristics among co-use, compared to NMPO-only and

heroin-only use.

We used data from 2003-2014 to compute trends in opioid use overall, and by

characteristics of co-use. The prevalence of opioid use, overall and by opioid use type, was

calculated for each time interval. Prevalence estimates for each time interval, adjusting for

variables chosen a priori based on the literature including sex, age, race/ethnicity, rurality

and employment status were also calculated. To explore changes in co-use, demographic,

substance use and mental health characteristics prevalence estimates were stratified by co-

users. For all trends, percent change was modeled as the difference between the prevalence

of use between 2013-2014 and 2003-2004. Linear time trends were specified with a year

variable in logistic regression models. For all analyses, significance was determined at p

<0.05. To account for the complex survey design, all analyses were conducted in SAS-

callable SUDAAN v9.2.

3. Results

3.1.   Current prevalence of opioid use and differences by opioid use type

Descriptive analyses of opioid use from 2013-2014 showed that NMPO-only is the

most common type of opioid use with prevalence among adults of 3.76% (SE 0.09),

compared to 0.10% (SE 0.01) for heroin-only and 0.23% (SE 0.02) for co-use. Table 1 presents differences in the type of opioid used by demographic, substance use and mental health characteristics. Compared to NMPO-only, those who co-use are significantly more likely to be male, under age 34 compared to 50 and over, non-Hispanic White compared to other race/ethnicities, residing in an urban county compared to rural, and less than college educated compared to college graduates. Co-use was also more likely among those unemployed or not in the labor force compared to those with full-time employment, married compared to never married individuals, those not covered by health insurance and those reporting illicit drug use or abuse, a MDE, or psychological distress in the past year. Compared to heroin-only use, co-use is significantly more likely among 18-25 or 26-34 year olds compared to 50+ year olds, non-Hispanic Whites compared to all other race/ethnicities, the unemployed compared to those with full-time employment, and those who report illicit drug use or psychological distress in the past year. We found no differences in alcohol abuse between co-use and either NMPO-only or heroin-only use.

3.2.   Overall trends in opioid use

From 2003-2014 (Figure 1), the prevalence of opioid use overall (NMPO, heroin and co-use combined) among all adults decreased significantly from 4.49% (SE 1.00) in 2003-2004 to 4.22% (SE 0.90) in 2013-2014 (percent change -6.08, p for linear trend <0.01). Of those reporting past year opioid use, the proportion by type of opioid used changed from 2003-2014. NMPO-only use made up 96.70% of all opioid use in 2003-2004 and 91.95% in 2013-2014, adjusting for sex, age, race/ethnicity, rurality and employment status. This represents a decline of 4.65% in the prevalence of NMPO-only use among all opioid users (p for linear trend

<0.001). On the other hand, heroin-only use increased from 1.69% of all opioid use in 2003-2004 to 2.37% in 2013-2014 (21.32% change, non-significant (NS) linear trend); and co-use increased 248.17% from 1.61% of all opioid use in 2003-2004 to 5.68% 2013-2014 (p for linear trend <0.001).

3.3.   Stratified trends in co-use

Table 2 shows stratified trends in co-use. From 2003-2014, co-use increased in every demographic, substance use and mental health category assessed with a significant linear trend among both males and females, those aged 18-25, 26-34 and 35-49, non-Hispanic Whites and non-Hispanic other, those with non-urban residence, all substance use and mental health groups, and in all categories of education status, employment status, or insurance coverage. Among all opioid users in 2013-2014, the highest prevalence of co-use was seen among those who were unemployed (12.08%), aged 26-34 (9.76%), and reported abusing (16.81%) and using (11.87) illicit drugs, psychological distress (11.87%), or a MDE (9.33%).

From 2003-2014, the growth in co-use was higher among females compared to males, among those aged 26-34 compared to other age groups, among non-Hispanic other and Hispanics compared to non-Hispanic Whites, among those with non-urban residence compared to urban residence, and among those using tobacco or illicit drugs compared to those reporting illicit drug use (Figure 2). An increased trend in co-use above the overall change in co-use (depicted by the horizontal line) was observed in the following groups: female (418%), age 26-34 (439%), non-Hispanic White (280%), non-Hispanic other (1,581%), Hispanic (523%), non-urban (302%), less than high school education (324%), college graduate (448%), married (426%), covered by health insurance (307%), any tobacco use (278%), major depressive episode (933%), psychological distress (332%), and illicit drug use other than NMPO, heroin, or marijuana (271%).

4. Discussion

Supporting our hypothesis, we found that NMPO and heroin co-use is substantial and growing. Guided by Trend Theory, we explored demographics, as well as substance use and mental health characteristics, by opioid use type. This study shows that characteristics of co-users differ from those who use NMPO or heroin only where co-users have a higher prevalence of comorbidities, highlighting the importance of independently investigating this category of opioid use.

Co-users experience a high burden of mental health problems and poly-substance use, higher than that of heroin-only users. This finding is consistent with the link between marginalization and drug use initiation proposed by Trend Theory, (Agar & Reisinger, 2001; Fischer et al., 2008; Rigg & Monnat, 2015). The growing prevalence of co-use among those with mental health and other illicit drug use highlights the need for expanded substance abuse treatment and access to mental health services. It pinpoints potential avenues to reach co-users, such as routine screening for problem drug use in primary care, emergency departments and pharmacies, potentially before transition occurs and particularly among those with histories of prescription opioid use. Screening practices that assess for more than one type of opioid will respond to the significant growth in co-use.

Co-use is increasing among groups with historically lower rates of opioid use. Similar to trends in heroin use, co-use among females is growing at a rate double that of that males (Jones, Logan, et al., 2015; Kuehn, 2014), narrowing the gap in the rate of opioid use between men and women. Compared to urban counties, prevalence of co-use in non-urban counties is almost double and growing at a much faster rate. Findings are consistent with the literature and point to delivery of harm reduction services in ways that overcome physical access and transportation issues

as barriers (Keyes, Cerdá, Brady, Havens, & Galea, 2014; Kuehn, 2014; Paulozzi & Xi, 2008).

Mobile, web-based and other platforms that make services more available in non-urban

areas are needed (Sigmon, 2014). Similar to other studies, we found the steepest increase in

prevalence of co-use among those reporting "non-Hispanic other" race/ethnicity (Han et al.,

2015; Martins, Santaella-Tenorio, Marshall, Maldonado, & Cerdá, 2015). Future studies

should specifically examine co-use and related outcomes among racial and ethnic

minorities.

We also found a greater prevalence of co-use among those without health insurance

and a greater increase in co-use among those covered, which aligns with findings that

problem NMPO use is more likely among those without health insurance and that heroin

use increased among those with private or other non-Medicaid insurance (Han et al., 2015;

Jones, Logan, et al., 2015). Increased use among those covered by insurance indicates an

opportunity to reach co-users through their access to health care, monitor NMPO use, assess

and prevent heroin use, and intervene before co-use begins. Regardless of health insurance

status, substance abuse treatment services must be accessible. Policies like Medicaid

expansion under the Affordable Care Act that aim to increase access to MAT by giving

coverage to individuals who previously did not qualify, many of whom have substance

abuse issues, are critical (Buck, 2011; Jones, Campopiano, Baldwin, & McCance-Katz, 2015).

While the overall prevalence of opioid misuse decreased slightly, it remains

substantial at just under 5% of the adult population, higher than the prevalence of stroke

and other chronic morbidities (Mozaffarian et al., 2016). Heroin-only and co-use increased,

while NMPO-only use decreased. In stratified analyses, co-use increased use among all

demographic, substance use and mental health subgroups studied. This demonstrates the

need for studies that examine gaps in treatment access given the changes in opioid use and

supply-reduction interventions, as people with problem opioid use seem to use whatever

opioids are available (Cicero et al., 2015). Additionally, interventions that merely focus on reducing the supply of opioids do not adequately address the harms associated with opioid use (Martins et al., 2015; Unick et al., 2013; Volkow, Frieden, Hyde, & Cha, 2014), as indicated by the 248% growth in co-use and high prevalence of co-morbidities among co-users found in this study after a slate of supply reduction interventions were implemented. These findings also provide context to the rise in heroin use and tripling of heroin-related overdose deaths from 2010-2015 (Centers for Disease Control and Prevention, 2017; Jones, Logan, et al., 2015). Poly-drug use is a risk factor for overdose, suggesting that the substantial increase in co-use accounts for the increased heroin-related overdose death rate. Targeting overdose-prevention interventions such as education on and distribution of naloxone at those at risk of transitioning to co-use could address the rising overdose death rate.

There are several limitations of this study. First, although NSDUH data has been shown to be reliable, particularly measures of substance use, the data are nonetheless self-reported (Kennet et al., 2010). Self-reported data are susceptible to recall and social desirability bias, as participants may have poor recall or they may be hesitant to divulge information about sensitive topics like illicit drug use. However, computer assisted self-interviewing software were used by NSDUH to enhance privacy and limit social desirability therefore, we expect this bias to be minimal (Islam et al., 2012; Substance Abuse and Mental Health Administration, 2013).

This study used serial, cross-sectional data, so we are unable to make conclusions about individual trends or within-person patterns over time. Residual confounding may also be an issue because we are limited to variables available in

NSDUH. This reliance on available variables also means we are unable to assess intermittent use of both NMPO and heroin. We explored a finite measure of co-use (past month use of NMPOs and heroin) and found similar patterns but we were unable to report findings due to the small sample sizes (Center for Behavioral Health Statistics and Quality, 2016). As cohort effects can distort population trends, we adjusted for year to limit these effects. NSDUH does not capture people who are incarcerated, homeless, or hospitalized, which may underestimate the estimates of use as these populations often have a higher likelihood of engaging in substance use (Mieczkowski, 1996). Studies enrolling those cohorts or surveillance systems where these cohorts are captured must be conducted to fill this data gap. Finally, these findings are descriptive and future studies should identify and explore additional theoretical frameworks that consider the characteristics highlighted in this study, the current socio-political context, and factors beyond the individual-level to extend our understanding of evolving patterns in opioid misuse.

Despite these limitations, this study raises important and policy-relevant points. The fact that mental health disorders and use and abuse of other illicit drugs is higher among people who co-use, compared to NMPO- and heroin-only users, indicates the co-morbidity and high risk for overdose among this cohort of opioid users. As the opioid epidemic evolves, there is a continued need to investigate sub-groups of opioid users and trends over time to determine differences in these groups, forecast future prevention and treatment needs, and inform targeted interventions and policy.

5. Tables and Figures

Table 1. Current demographic, substance use and mental health characteristics of adult opioid users, by opioid use type—NSDUH 2013-2014

	All opioids N=4,496 Wt% (SE)	NMPO-only N=4,076 Wt% (SE)	Heroin-only N=133 Wt% (SE)	NMPO heroin co-use N=287 Wt% (SE)	NMPO-only vs co-use p-value	Heroin-only vs co-use p-value
Sex						
Male	54.65 (1.15)	53.41 (1.21)	63.51 (5.67)	70.99 (3.15)	**<0.001**	0.23
Female	45.35 (1.15)	46.59 (1.21)	36.49 (5.67)	29.01 (3.15)		
Age						
18-25	30.12 (0.90)	29.93 (0.94)	27.97 (4.98)	34.12 (3.70)	**<0.001**	**<0.05**
26-34	26.06 (1.15)	24.89 (1.16)	26.62 (5.29)	44.73 (4.40)		
35-49	24.03 (0.98)	24.66 (1.04)	23.85 (5.33)	13.96 (3.04)		
50+	19.78 (1.33)	20.52 (1.38)	21.56 (5.56)	7.19 (2.57)		
Race/ethnicity						
Non-Hispanic White	66.30 (1.05)	65.42 (1.12)	67.67 (5.91)	79.96 (3.06)	**<0.01**	0.19
Non-Hispanic Black	11.51 (0.80)	11.67 (0.84)	17.81 (5.02)	6.36 (2.25)		
Non-Hispanic other	6.16 (0.56)	6.42 (0.59)	3.46 (2.21)	3.20 (1.31)		
Hispanic	16.03 (0.89)	16.50 (0.94)	11.06 (4.03)	10.48 (2.21)		
Rurality						
Non-urban	14.81 (0.95)	15.34 (1.01)	9.33 (2.82)	8.41 (1.88)	**<0.01**	0.77
Urban	85.19 (0.95)	84.66 (1.01)	90.67 (2.82)	91.59 (1.88)		
Education						
Less than HS[a]	17.65 (0.84)	17.32 (0.90)	15.34 (3.75)	24.03 (3.22)	**<0.001**	0.44
HS graduate/ Some college[a]	61.63 (1.16)	60.79 (1.21)	76.92 (5.06)	68.82 (3.51)		
College grad	20.72 (1.03)	21.89 (1.08)	7.73 (3.23)	7.15 (1.95)		
Employment status						
Full-time	50.91 (1.12)	52.19 (1.18)	39.02 (5.88)	35.15 (4.15)	**<0.001**	0.06
Part-time	17.07 (0.84)	17.01 (0.88)	18.32 (4.38)	17.57 (3.48)		
Unemployed	9.83 (0.67)	9.19 (0.71)	8.30 (2.72)	20.90 (3.18)		
Not in labor force	22.18 (0.94)	21.61 (0.99)	34.36 (6.10)	26.38 (3.57)		
Marital status						
Married	31.23 (1.26)	33.00 (1.32)	8.74 (3.62)	11.87 (0.45)	**<0.001**	0.79
Divorced/Sep/Widowed	15.99 (1.03)	16.04 (1.09)	15.88 (4.30)	15.20 (2.97)		
Never married	52.79 (0.90)	50.96 (0.94)	75.39 (4.36)	72.93 (2.96)		
Health insurance coverage						
Covered	75.46 (1.10)	76.52 (1.14)	65.51 (5.68)	62.34 (4.00)	**<0.01**	0.67
Not covered	24.54 (1.10)	23.48 (1.14)	34.49 (5.68)	37.66 (4.00)		
Substance abuse and mental health						
Any tobacco use	65.24 (1.16)	62.80 (1.27)	88.62 (4.81)	94.84 (2.33)	**<0.001**	0.26
Alcohol abuse	13.90 (0.88)	14.22 (0.93)	6.13 (2.57)	12.05 (2.56)	0.731	0.10
Major depressive episode	16.08 (0.92)	15.28 (0.91)	22.43 (4.81)	26.56 (3.54)	**<0.05**	0.48
Psychological distress	29.70 (1.10)	27.99 (1.10)	32.45 (4.82)	56.19 (4.40)	**<0.001**	**<0.01**
Illicit drug use[b]	42.68 (1.14)	39.14 (1.13)	68.43 (5.26)	89.15 (2.47)	**<0.001**	**<0.001**
Illicit drug abuse[b]	3.29 (0.33)	2.77 (0.32)	7.97 (3.27)	9.73 (2.13)	**<0.01**	0.65

Bolded values indicate statistical significance from co-use at p<0.05

[a] HS = High school; [b] Includes illicit use of drugs other than opioids and marijuana

Figure 1. Prevalence trends of opioid use, overall and by opioid use type among all opioid users, adjusted for sex, age, race, rurality and employment status—NSDUH 2003-2014
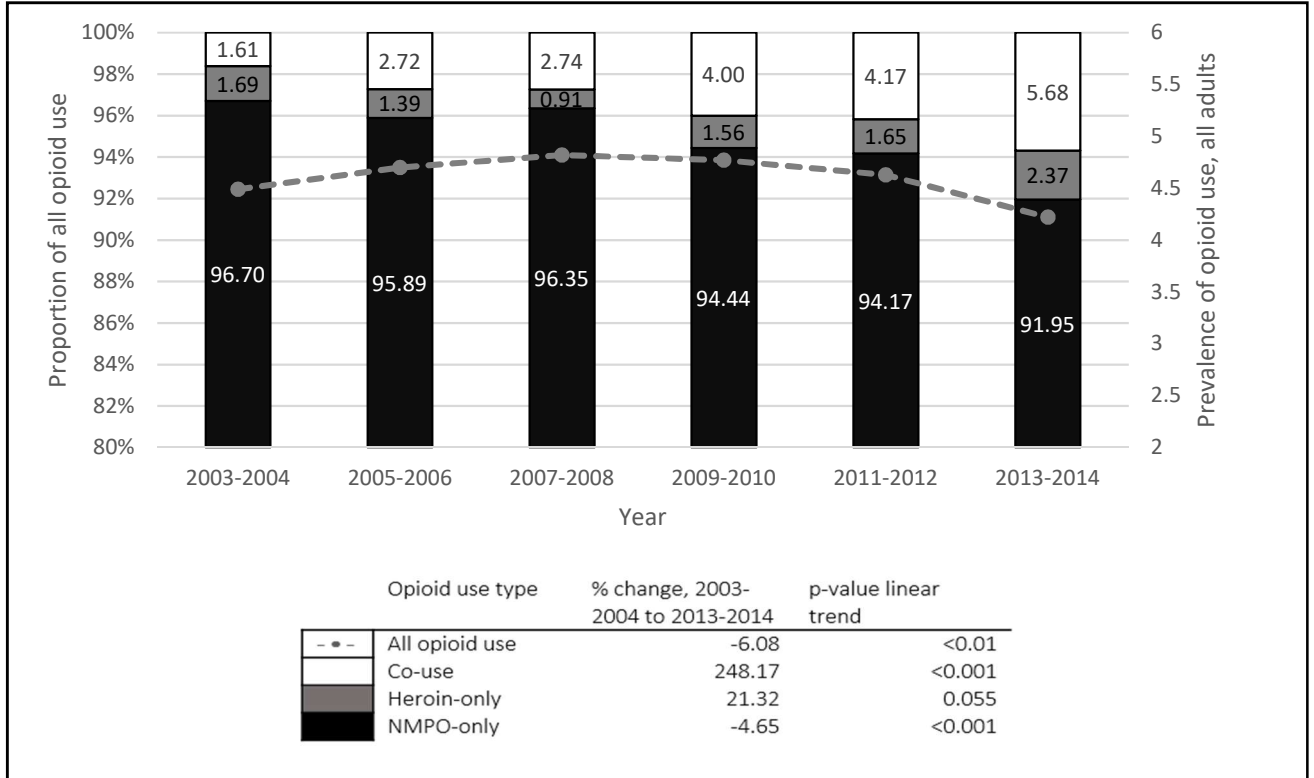

	Opioid use type	% change, 2003-2004 to 2013-2014	p-value linear trend
– • –	All opioid use	-6.08	<0.01
	Co-use	248.17	<0.001
	Heroin-only	21.32	0.055
	NMPO-only	-4.65	<0.001

Table 2. Stratified trends in prevalence of co-use—NSDUH, 2003-2014

	2003-2004 Wt.% (SE)	2005-2006 Wt.% (SE)	2007-2008 Wt.% (SE)	2009-2010 Wt.% (SE)	2011-2012 Wt.% (SE)	2013-2014 Wt.% (SE)	p-value linear trend
Sex							
Male	2.40 (0.41)	3.64 (0.61)	3.38 (0.52)	4.95 (0.71)	5.59 (0.71)	7.38 (0.70)	<0.001
Female	0.70 (0.13)	1.51 (0.27)	1.90 (0.39)	2.66 (0.46)	2.41 (0.38)	3.64 (0.49)	<0.001
Age							
18-25	2.05 (0.26)	2.90 (0.31)	3.04 (0.44)	4.13 (0.38)	5.99 (0.51)	6.44 (0.62)	<0.001
26-34	1.81 (0.65)	3.53 (1.05)	2.76 (0.72)	4.57 (0.77)	4.64 (1.06)	9.76 (1.33)	<0.001
35-49	1.32 (0.57)	1.54 (0.71)	1.99 (1.16)	3.62 (2.24)	2.83 (1.47)	3.30 (2.01)	<0.05
50+	--	3.11 (0.82)	3.43 (1.37)	3.37 (1.12)	1.83 (0.56)	2.07 (1.00)	0.65
Race/ethnicity							
NH White[a]	1.80 (0.25)	2.36 (0.30)	2.86 (0.38)	4.36 (0.53)	5.19 (0.58)	6.86 (0.56)	<0.001
NH Black[a]	2.11 (1.38)	1.36 (0.83)	3.64 (1.54)	3.76 (1.65)	2.51 (1.26)	3.14 (1.20)	0.41
NH other[a]	0.18 (0.12)	0.89 (0.43)	1.06 (0.57)	2.15 (1.00)	2.10 (1.14)	2.95 (1.14)	<0.001
Hispanic	0.60 (0.30)	6.18 (2.42)	1.96 (1.22)	2.88 (0.96)	1.51 (0.51)	3.72 (0.90)	0.07
Rurality							
Urban	2.10 (0.67)	2.07 (0.56)	2.24 (0.45)	3.16 (0.78)	2.77 (0.62)	3.23 (0.73)	0.19
Non-urban	1.52 (0.25)	2.84 (0.43)	2.84 (0.41)	4.15 (0.49)	4.40 (0.48)	6.11 (0.55)	<0.001
Education							
Less than HS[b]	1.83 (0.44)	3.26 (0.71)	5.02 (1.20)	5.96 (1.57)	3.42 (0.57)	7.74 (1.21)	<0.001
HS graduate/ Some college[b]	1.86 (0.35)	2.60 (0.40)	2.68 (0.44)	4.45 (0.43)	5.35 (0.67)	6.35 (0.61)	<0.001
College grad	0.36 (0.17)	2.49 (1.48)	0.66 (0.27)	0.90 (0.50)	1.28 (0.38)	1.96 (0.55)	<0.05
Employment status							
Full time	1.13 (0.24)	1.93 (0.42)	1.79 (0.35)	3.12 (0.56)	2.31 (0.39)	3.92 (0.52)	<0.001
Part time	1.75 (0.64)	2.42 (0.59)	2.80 (0.70)	3.69 (1.03)	5.18 (1.24)	5.85 (1.34)	<0.001
Unemployed	3.88 (1.34)	6.69 (2.46)	5.45 (1.67)	9.03 (2.44)	8.75 (1.52)	12.08 (1.77)	<0.01
Not in labor force	1.99 (0.54)	3.85 (0.93)	4.55 (1.17)	3.47 (0.81)	5.60 (1.21)	6.76 (1.18)	<0.001
Marital status							
Married	0.41 (0.19)	0.63 (0.22)	1.26 (0.50)	1.08 (0.34)	1.33 (0.48)	2.16 (0.71)	<0.001
Divorced/Sep/ Widowed	2.06 (0.71)	3.89 (0.96)	3.56 (1.15)	6.58 (1.94)	3.25 (1.00)	5.40 (1.21)	0.06
Never married	2.24 (0.39)	3.65 (0.60)	3.46 (0.49)	4.88 (0.52)	6.15 (0.64)	7.85 (0.69)	<0.001
Health insurance coverage							
Covered	1.15 (0.19)	2.14 (0.35)	2.07 (0.39)	3.58 (0.50)	3.26 (0.37)	4.70 (0.48)	<0.001
Not covered	2.94 (0.74)	4.28 (0.98)	4.51 (0.84)	5.07 (0.85)	6.60 (0.98)	8.72 (1.18)	<0.001
Substance use and mental health							
Any tobacco use	2.18 (0.18)	3.80 (0.59)	3.79 (0.50)	5.54 (0.58)	6.15 (0.64)	8.26 (0.68)	<0.001
Major depressive episode	--	--	3.68 (1.03)	6.16 (1.18)	7.79 (1.61)	9.33 (1.36)	<0.001
Psychological distress, past	2.49 (0.72)	4.17 (1.15)	4.05 (0.89)	6.41 (0.84)	8.77 (1.25)	10.75 (1.27)	<0.001
Illicit drug use[c]	3.20 (0.49)	5.42 (0.78)	4.76 (0.60)	7.83 (0.91)	7.80 (0.84)	11.87 (1.01)	<0.001
Illicit drug abuse[c]	6.21 (2.46)	10.63 (4.97)	7.64 (2.41)	14.85 (3.71)	17.38 (5.00)	16.81 (3.50)	<0.05

[a] NH = Non-Hispanic; [b] HS = High school; [c] Includes illicit use of drugs other than opioids and marijuana

Figure 2. Change in prevalence of co-use from 2003-2004 to 2013-2014, stratified trends compared to overall trend
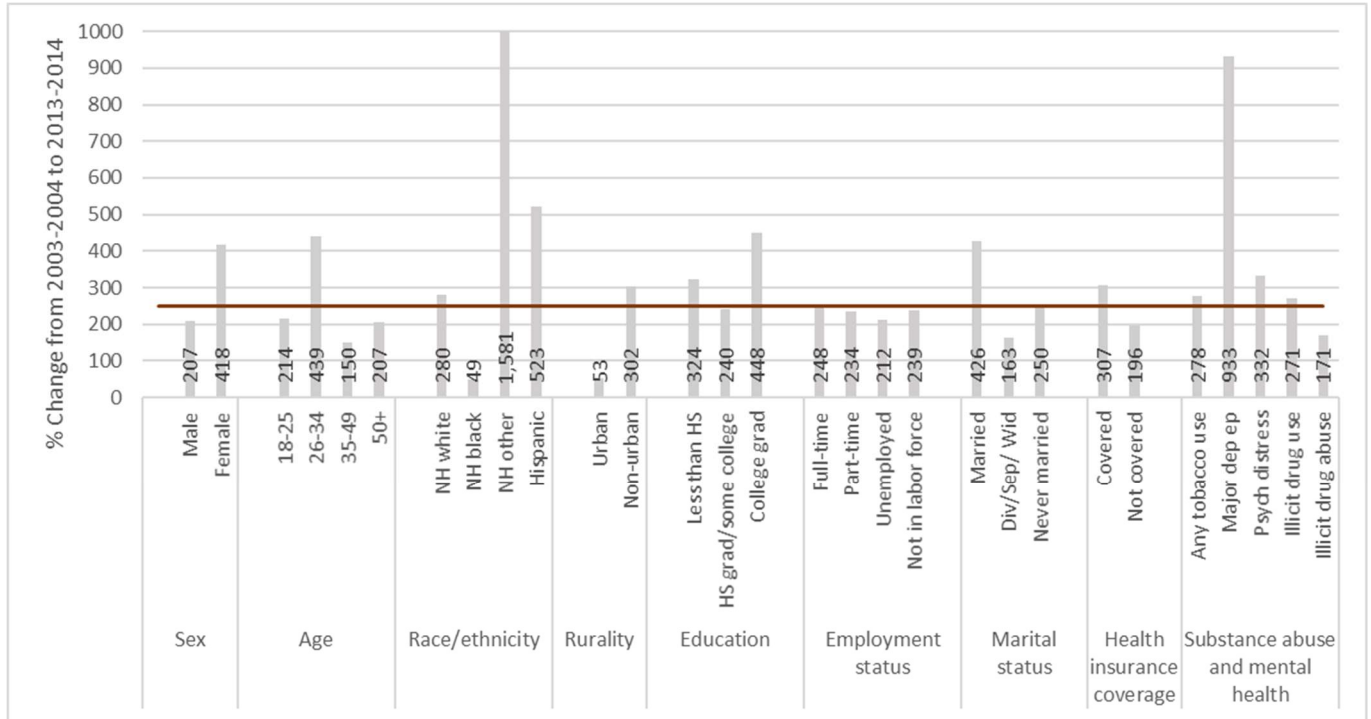
6. References

Agar, M., & Reisinger, H. S. (2001). Using trend theory to explain heroin use trends. *Journal of psychoactive drugs, 33*(3), 203-211.

Al-Tayyib, A. A., Koester, S., & Riggs, P. (2017). Prescription opioids prior to injection drug use: Comparisons and public health implications. *Addictive behaviors, 65*, 224-228.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*: American Psychiatric Pub.

Buck, J. A. (2011). The looming expansion and transformation of public substance abuse treatment under the Affordable Care Act. *Health Affairs, 30*(8), 1402-1410.

Canfield, M. C., Keller, C. E., Frydrych, L. M., Ashrafioun, L., Purdy, C. H., & Blondell, R. D. (2010). Prescription opioid use among patients seeking treatment for opioid dependence. *Journal of addiction medicine, 4*(2), 108.

Center for Behavioral Health Statistics and Quality. (2016). *2015 National Survey on Drug Use and Health: Methodological summary and definitions*. Retrieved from Rockville, MD:

Centers for Disease Control and Prevention. (2011). Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. *MMWR Morb Mortal Wkly Rep, 60*(43), 1487.

Centers for Disease Control and Prevention. (2017). QuickStats: Rates of Drug Overdose Deaths Involving Heroin,* by Selected Age Groups - United States, 2006-2015. *MMWR Morb Mortal Wkly Rep, 65*(52), 1497. doi:10.15585/mmwr.mm6552a12

Cherubin, C. E., & Sapira, J. D. (1993). The medical complications of drug addiction and the medical assessment of the intravenous drug user: 25 years later. *Annals of internal medicine, 119*(10), 1017-1028.

Cicero, T. J., Ellis, M. S., & Harney, J. (2015). Shifting patterns of prescription opioid and

  heroin abuse in the United States. *New England Journal of Medicine, 373*(18), 1789-

  1790.

Cicero, T. J., Ellis, M. S., & Surratt, H. L. (2012). Effect of abuse-deterrent formulation of

  OxyContin. *New England Journal of Medicine, 367*(2), 187-189.

Cicero, T. J., Ellis, M. S., Surratt, H. L., & Kurtz, S. P. (2014). The changing face of heroin use in

  the United States: a retrospective analysis of the past 50 years. *JAMA psychiatry,*

  71(7), 821-826.

Compton, W. M., Jones, C. M., & Baldwin, G. T. (2016). Relationship between Nonmedical

  Prescription-Opioid Use and Heroin Use. *New England Journal of Medicine, 374*(2),

  154-163. doi:doi:10.1056/NEJMra1508490

Dart, R. C., Surratt, H. L., Cicero, T. J., Parrino, M. W., Severtson, S. G., Bucher-Bartelson, B., &

  Green, J. L. (2015). Trends in opioid analgesic abuse and mortality in the United

  States. *New England Journal of Medicine, 372*(3), 241-248.

Dowell, D., Haegerich, T. M., & Chou, R. (2016). CDC guideline for prescribing opioids for

  chronic pain—United States, 2016. *JAMA, 315*(15), 1624-1645.

Fischer, B., Patra, J., Cruz, M. F., Gittins, J., & Rehm, J. (2008). Comparing heroin users and

  prescription opioid users in a Canadian multi-site population of illicit opioid users.

  Drug Alcohol Rev, 27(6), 625-632. doi:10.1080/09595230801956124

Franklin, G., Sabel, J., Jones, C. M., Mai, J., Baumgartner, C., Banta-Green, C. J., . . . Tauben, D. J.

  (2015). A comprehensive approach to address the prescription opioid epidemic in

  Washington State: milestones and lessons learned. *American journal of public health,*

  105(3), 463-469.

Guarino, H., Marsch, L. A., Deren, S., Straussner, S. L., & Teper, A. (2015). Opioid Use

  Trajectories, Injection Drug Use, and Hepatitis C Virus Risk Among Young Adult

Immigrants from the Former Soviet Union Living in New York City. *J Addict Dis, 34*(2-3), 162-177. doi:10.1080/10550887.2015.1059711

Han, B., Compton, W. M., Jones, C. M., & Cai, R. (2015). Nonmedical prescription opioid use and use disorders among adults aged 18 through 64 years in the United States, 2003-2013. *JAMA, 314*(14), 1468-1478.

Han, B., Gfroerer, J. C., & Colliver, J. D. (2010). Associations between duration of illicit drug use and health conditions: results from the 2005–2007 National Surveys on Drug Use and Health. *Annals of epidemiology, 20*(4), 289-297.

Inciardi, J. A., Surratt, H. L., Cicero, T. J., & Beard, R. A. (2009). Prescription opioid abuse and diversion in an urban community: the results of an ultrarapid assessment. *Pain Medicine, 10*(3), 537-548.

Islam, M. M., Topp, L., Conigrave, K. M., van Beek, I., Maher, L., White, A., . . . Day, C. A. (2012). The reliability of sensitive information provided by injecting drug users in a clinical setting: clinician-administered versus audio computer-assisted self-interviewing (ACASI). *AIDS care, 24*(12), 1496-1503.

Jones, C. M., Campopiano, M., Baldwin, G., & McCance-Katz, E. (2015). National and state treatment need and capacity for opioid agonist medication-assisted treatment. *Journal Information, 105*(8).

Jones, C. M., Logan, J., Gladden, R., & Bohm, M. K. (2015). Vital signs: demographic and substance use trends among heroin users: United States, 2002–2013. *MMWR Morb Mortal Wkly Rep, 64*(26), 719-725.

Jones, C. M., Mack, K. A., & Paulozzi, L. J. (2013). Pharmaceutical overdose deaths, United States, 2010. *JAMA, 309*(7), 657-659.

Kennet, J., Gfroerer, J., Barker, P., Piper, L., Hirsch, E., Granger, B., & Chromy, J. R. (2010). *Reliability and Data Quality in the National Survey on Drug Use and Health*. Paper

presented at the Ninth Conference on Health Survey Research Methods, Hyattsville, MD.

Kessler, R. C., Barker, P. R., Colpe, L. J., Epstein, J. F., Gfroerer, J. C., Hiripi, E., . . . Walters, E. E. (2003). Screening for serious mental illness in the general population. *Archives of general psychiatry, 60*(2), 184-189.

Keyes, K. M., Cerdá, M., Brady, J. E., Havens, J. R., & Galea, S. (2014). Understanding the rural–urban differences in nonmedical prescription opioid use and abuse in the United States. *American journal of public health, 104*(2), e52-e59.

Kuehn, B. M. (2010). FDA opioid safety plan promotes patient, physician education to prevent abuse. *JAMA, 304*(8), 845-845.

Kuehn, B. M. (2014). Driven by prescription drug abuse, heroin use increases among suburban and rural whites. *JAMA, 312*(2), 118-119.

Levy, B., Paulozzi, L., Mack, K. A., & Jones, C. M. (2015). Trends in Opioid Analgesic–Prescribing Rates by Specialty, US, 2007–2012. *American journal of preventive medicine, 49*(3), 409-413.

Lipari, R. N., & Hughes, A. Trends in heroin use in the United States: 2002 TO 2013.

Mars, S. G., Bourgois, P., Karandinos, G., Montero, F., & Ciccarone, D. (2014). "Every 'never' I ever said came true": transitions from opioid pills to heroin injecting. *International Journal of Drug Policy, 25*(2), 257-266.

Martins, S. S., Santaella-Tenorio, J., Marshall, B. D., Maldonado, A., & Cerdá, M. (2015). Racial/ethnic differences in trends in heroin use and heroin-related risk behaviors among nonmedical prescription opioid users. *Drug and alcohol dependence, 151*, 278-283.

Mateu-Gelabert, P., Guarino, H., Jessell, L., & Teper, A. (2015). Injection and sexual HIV/HCV

    risk behaviors associated with nonmedical use of prescription opioids among young

    adults in New York City. *Journal of substance abuse treatment, 48*(1), 13-20.

Mieczkowski, T. M. (1996). The prevalence of drug use in the United States. *Crime and*

    Justice, 20, 349-414.

Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., . . . Fullerton,

    H. J. (2016). Heart disease and stroke statistics—2016 update. *Circulation, 133*(4),

    e38-e360.

Muhuri, P. K., Gfroerer, J. C., & Davies, M. C. (2013). Associations of nonmedical pain reliever

    use and initiation of heroin use in the United States. *The CBHSQ Data Review*.

Office of National Drug Control Policy. (2011). Prescription Drug Monitoring Programs.

Paulozzi, L. J., & Xi, Y. (2008). Recent changes in drug poisoning mortality in the United

    States by urban–rural status and by drug type. *Pharmacoepidemiology and drug*

    safety, 17(10), 997-1005.

Rigg, K. K., & Monnat, S. M. (2015). Comparing Characteristics of Prescription Painkiller

    Misusers and Heroin Users in the United States. *Addictive behaviors, 51*, 106-112.

    doi:10.1016/j.addbeh.2015.07.013

Sigmon, S. C. (2014). Access to treatment for opioid dependence in rural America:

    challenges and future directions. *JAMA psychiatry, 71*(4), 359-360.

Substance Abuse and Mental Health Administration. (2002). *Results From the 2001 National*

    Household Survey on Drug Abuse: Volume II. Technical Appendices and Selected Data

    Tables. Retrieved from Rockville, MD:

Substance Abuse and Mental Health Administration. (2013). *National Survey on Drug Use*

    and Health, 2013 Codebook. Retrieved from Rockville, MD:

    http://www.icpsr.umich.edu/icpsrweb/NAHDAP/studies/35509

Thorpe, L. E., Ouellet, L. J., Hershow, R., Bailey, S. L., Williams, I. T., Williamson, J., . . . Garfein, R. S. (2002). Risk of hepatitis C virus infection among young adult injection drug users who share injection equipment. *American journal of epidemiology, 155*(7), 645-653.

Unick, G. J., Rosenblum, D., Mars, S., & Ciccarone, D. (2013). Intertwined epidemics: national demographic trends in hospitalizations for heroin-and opioid-related overdoses, 1993–2009. *PloS one, 8*(2), e54496.

Volkow, N. D., Frieden, T. R., Hyde, P. S., & Cha, S. S. (2014). Medication-assisted therapies—tackling the opioid-overdose epidemic. *New England Journal of Medicine, 370*(22), 2063-2066.

Warner, M., Chen, L. H., & Makuc, D. M. (2009). Increase in fatal poisonings involving opioid analgesics in the United States, 1999-2006. *NCHS data brief*(22), 1-8.

Wu, L.-T., Woody, G. E., Yang, C., & Blazer, D. G. (2011). How do prescription opioid users differ from users of heroin or other drugs in psychopathology: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of addiction medicine, 5*(1), 28.

Zibbell, J. E., Iqbal, K., Patel, R., Suryaprasad, A., Sanders, K., Moore-Moravian, L., . . . Holtzman, D. (2015). Increases in hepatitis C virus infection related to injection drug use among persons aged≤ 30 years-Kentucky, Tennessee, Virginia, and West Virginia, 2006-2012. *MMWR Morb Mortal Wkly Rep, 64*(17), 453-458.

Chapter 3: Factors related to transition from non-medical prescription opioid use to heroin initiation and co-use of both opioids among adults, 2012-2014

Abstract

Background. The current opioid epidemic stems from increased non-medical prescription opioid (NMPO) and heroin use. Evidence suggests that greater access and more favorable perceptions drove increased NMPO use, transition from NMPO to heroin use, and subsequent co-use of both opioids when prescription opioid (PO) availability was limited. We lack an understanding of factors related to increased risk of this transition, particularly factors beyond the individual level, which is critical to addressing this phenomenon. Using the socio-ecological model as an organizing framework, this study aims to explore relationships between interpersonal-level (i.e. PO source and perceived risk of use) and individual-level factors (i.e. access to healthcare, perceived opioid availability, substance use behaviors, mental health characteristics, and demographics) with transition.
Methods. We combined cross-sectional data on adults reporting current NMPO use across three years of the National Survey on Drug Use and Health, 2012, 2013, and 2014 (N=7,045). Using chi-squared tests and multivariable logistic regression, we examined interpersonal and individual-level correlates of transition from NMPO use to heroin use.
Results. Among current NMPO users, 4.96% (95% confidence interval [CI]: 4.31, 5.71) ever transitioned to heroin and currently co-use both NMPOs and heroin. At the interpersonal level, healthcare providers as the PO source compared to an illicit source (adjusted odds ratio [AOR]: 0.34, 95% CI: 0.14, 0.80) and a lower perceived risk of trying heroin (AOR: 1.82, 95% CI: 1.16, 2.84) were associated with transition. Individual-level factors associated with transition in multivariable analysis include NMPO initiation before age 18 (AOR: 1.87, 95% CI: 1.07, 3.27), past-year illicit non-opioid drug use (AOR: 3.71 95% CI: 1.96, 7.04) and no health insurance coverage (AOR 1.93, 95% CI: 1.30, 2.88).
Conclusion. This is the first study to examine multilevel correlates of transition among a nationally representative sample of adults, and findings underscore the importance of exploring factors beyond the individual level. By identifying subgroups of NMPO users at increased risk of transition and modifiable factors associated with transition, we inform urgently needed interventions to identify and reach those at increased risk of transition.

1. **Background**

The United States is currently facing an opioid epidemic resulting from increases in the

use of both non-medical prescription opioids (NMPO) and heroin. Between 2002 and 2011,

25 million people initiated NMPO use and opioid-related overdoses more than quadrupled

from 1999 to 2016 (Hedegaard, Warner, & Miniño, 2018; Manchikanti, Helm, Janata,

Pampati, & Grider, 2012). Researchers attribute this growth to several interrelated factors

that resulted in more lenient opioid-prescribing policies (Dhalla, Persaud, & Juurlink, 2011;

Kanouse & Compton, 2015). These led to increased availability through the healthcare

system, diversion through familial networks, and changes in the public's perception of the

harms associated with opioid use (Daniulaityte, Falck, & Carlson, 2012; Kanouse &

Compton, 2015; Keyes, Cerdá, Brady, Havens, & Galea, 2014; Manchikanti et al., 2012).

Following implementation of interventions aimed at reducing PO availability, rates of NMPO

use stabilized, but NMPO abuse and heroin use increased (Han, Compton, Jones, & Cai, 2015;

Jones, Logan, Gladden, & Bohm, 2015). From 2002 to 2011, 80% of past-year heroin

initiates reported previous NMPO (Muhuri, Gfroerer, & Davies, 2013). The marked increase

in heroin use among those with a history of NMPO use suggests that the limited PO supply

precipitated transitions to heroin use and co-use of both opioids to support opioid

dependency (Cicero, Ellis, & Harney, 2015; Mars, Bourgois, Karandinos, Montero, &

Ciccarone, 2014). Qualitative studies provide further evidence of transition by documenting

an opioid use trajectory that begins with NMPO use, moves to NMPO abuse, and transitions

to heroin initiation and continued NMPO use, depending on availability (Guarino, Marsch,

Deren, Straussner, & Teper, 2015; Mars et al., 2014; Mateu-Gelabert, Guarino, Jessell, &

Teper, 2015). Those who transition describe initiating heroin when POs were less available

through familial or medical sources and heroin seemed more available (Inciardi, Surratt,

Cicero, & Beard, 2009; Siegal, Carlson, Kenne, & Swora, 2003). Studies have not quantitatively have not examined these correlates of transition.

Transition from NMPO-only use to heroin and co-use of both opioids is a public health concern in need of further investigation. Compared to NMPO-only use, co-use, and poly-drug use in general, is associated with a higher risk of mental health issues, drug dependence, and overdose (Al-Tayyib, Koester, & Riggs, 2017; Fischer, Patra, Cruz, Gittins, & Rehm, 2008; Pollini et al., 2011; Rigg & Monnat, 2015). In addition, initiation of injecting behaviors often coincides with heroin initiation, increasing risk for hepatitis C, HIV and other injection-related morbidities (Thorpe et al., 2002; Zibbell, 2015). Stigma and marginalization are also associated with heroin and injection drug use, and serve as barriers to medication-assisted treatment (MAT) and other critical health services (Cherubin & Sapira, 1993; Han, Gfroerer, & Colliver, 2010; World Health Organization, 2009). Lastly, a large number of people, all current NMPO users, are susceptible to transition although a previous study shows that only 3.6% of NMPO users actually transitioned (Compton, Jones, & Baldwin, 2016; Muhuri et al., 2013). This suggests that NMPO use alone does not predict transition and prevention efforts targeting all NMPO users are an inefficient use of resources. Thus, population-based studies identifying which subgroups of NMPO users are at risk of transitioning to heroin and co-use are needed to target prevention and treatment interventions.

Our current understanding of characteristics that increase risk of transition is limited. Qualitative research, cohort-specific cross-sectional data, and adolescent-focused research identify demographic, substance use, and mental health correlates of transition. They include non-Hispanic White race compared to other race/ethnicities, non-urban residence compared to urban, lower socio-economic status, younger age of NMPO initiation,

use of non-opioid drugs and alcohol, and experiences of psychiatric comorbidity (Carlson, Nahhas, Martins, & Daniulaityte, 2016; Cerda, Santaella, Marshall, Kim, & Martins, 2015; Guarino et al., 2015; Mars et al., 2014; Rajan, Ruggles, Guarino, & Mateu-Gelabert, 2018). However, national studies have not explored whether these factors predict transition among adults even though they represent the majority of opioid users (Muhuri et al., 2013). National studies are important as they produce generalizable results across subgroups while cohort studies produce subgroup-specific results.

In studying shifts in opioid use, researchers highlight the importance of exploring interpersonal- and structural-level factors, which can explain differences observed at the individual level, and encourage a socio-ecological approach to understand influences beyond the individual level (Dasgupta, Beletsky, & Ciccarone, 2018; Dew, Elifson, & Dozier, 2007; Keyes et al., 2014; Monnat & Rigg, 2015; National Academies of Sciences & Medicine, 2017; Ruckert & Labonté, 2017). The socio-ecological model (SEM) contextualizes a range of factors that influence health behaviors, from the individual to their relationships, community and broader environment. It also allows for consideration of the direct effect of these factors on changes in opioid use and the interplay between factors at multiple levels (Sallis, Owen, & Fisher, 2008). However, we lack empirical examinations of higher-level factors that identify and address the root causes of transition.

Given the interconnectedness of recent changes in NMPO and heroin use, and evidence that limited NMPO supply drove heroin initiation and co-use of both opioids, we hypothesize that factors related to increased NMPO use are also correlates of transition. Previous studies have not considered many of these as risk factors for transition. At the interpersonal level, qualitative research with young adults suggests that lower perceived risk of NMPO use has an inverse relationship with NMPO use (Mateu-Gelabert et al., 2015; Rhodes, 2009). Therefore, we hypothesize that lower perceived risk of heroin use will be

associated with transition. Access to POs through a healthcare-related or familial

source facilitated increased NMPO use (Bali, Raisch, Moffett, & Khan, 2013;

Mowbray & Quinn, 2015). Following implementation of interventions to limit PO

supply through these sources, we predict that turning to other sources, or an illicit

PO supply, will increase risk of transition. At the individual level, access to

healthcare, often operationalized as health insurance coverage, facilitated increased

NMPO use (Bali et al., 2013; Cicero, Surratt, Inciardi, & Munoz, 2007; Simoni-

Wastila, 2000). Therefore, we hypothesize that lack of health insurance coverage

will be associated with transition as it indicates an inability to obtain POs through a

prescription. Since past research indicates that adolescents who perceive POs as

easily available are more likely to engage in NMPO use, we predict that those who

perceive heroin as easily available will be more likely to transition, which has not

been assessed quantitatively (Cohen, Scribner, & Farley, 2000; Compton & Volkow,

2006; Young, Glover, & Havens, 2012). Lastly, we hypothesize that the substance

use behaviors, mental health characteristics, and demographics associated with

increased NMPO use and prevalent among NMPO and heroin co-users will be

associated with transition (Carlson et al., 2016; Cerda et al., 2015; Mital, Windle,

Cooper, & Crawford, 2018; Paulozzi & Xi, 2008; Unick, Rosenblum, Mars, &

Ciccarone, 2013).

   To our knowledge, this is the first study using nationally-representative data

that compares adult NMPO-only users to heroin users with a history of NMPO use to

identify multilevel factors associated with transition among adults. A better

understanding of factors across the levels of the SEM and their relationships to

transition will inform targeted interventions that both prevent transition and reach

this high-risk group of opioid users with effective treatment services. It will also indicate

interventions that may be appropriate at different levels of SEM.

2. Methods

2.1. Data sources

This study used data from the 2012-2014 National Survey on Drug Use and Health

(NSDUH), conducted annually by the Substance Abuse and Mental Health Administration

(SAMHSA). NSDUH provides serial, cross-sectional, nationally-representative data

regarding illicit drug use in the civilian, non-institutionalized population. Detailed

documentation of NSDUH sampling and data collection procedures is provided elsewhere

(Center for Behavioral Health Statistics and Quality, 2016). In brief, NSDUH employs a

multi-stage stratified probability sampling design. For this study, we combined data from

adults (aged 18 and older) for the three most recent years of data available (2012-2014) to

improve the precision of estimates as prevalence of our outcome is small (Jones, 2013).

Response rates for NSDUH ranged from 82% to 86%, depending on the year. As secondary

analyses of publicly available data, Emory University's IRB exempted this study from

approval.

2.2. Sample

This study was limited to current adult NMPO users. We defined adult as aged 18 and

above. NSDUH defines NMPO use as use of prescription opioids (POs) without a

prescription or use only for the feeling caused. Consistent with the literature, current use

was defined as any use within the past 12 months (Han et al., 2015; Jones et al., 2015).

2.3. Measures

2.3.1. Outcome

Our outcome was transition to heroin, defined as NMPO and heroin co-use where

NMPO use preceded heroin initiation. Since NSDUH asks participants about age of first use

for each substance, we were able to group co-users into three mutually exclusive categories: 1) NMPO use prior to heroin initiation, 2) NMPO and heroin initiation in the same year, and 3) NMPO initiation after heroin use. Since the literature indicates that the majority of recent heroin initiates have a history of NMPO use, we included categories 1 and 2 in the definition of transition (Jones, 2013; Muhuri et al., 2013). Results were virtually unchanged when we excluded category 2 (NMPO and heroin initiation in the same year) from the outcome as a sensitivity analysis; results available from the first author upon request.

2.3.2. Interpersonal factors

At the interpersonal level, we studied PO source, based on the question: "Now think about the last time you used a prescription pain reliever that was not prescribed for you or that you took only for the experience or feeling it caused. How did you get this prescription pain reliever?" Source of POs was operationalized as familial (i.e. buying, stealing or receiving it free from a friend or family member), provider (one or more doctors) or illicit/other (i.e. fake prescription, buying or stealing from a stranger, buying over the internet, or other). Perceived risk of trying heroin is based on the question: "How much do you think people risk harming themselves physically and in other ways if they try heroin once or twice?" Consistent with the literature, we examined perceived risk as great risk or none to some risk (Rigg & Monnat, 2015).

2.3.3. Individual-level factors

At the individual level, we examined access to healthcare and perceived heroin availability along with demographic, substance use and mental health characteristics. We examined health insurance coverage as an indicator of access to healthcare. Health insurance coverage was defined as current coverage by any

health insurance provider (including private, Medicare and Medicaid). We operationalized

perceived heroin availability, based on the question: "How difficult or easy would it be for

you to get some heroin if you wanted some?" as easy or difficult to impossible, which aligns

with previous investigations of perceived availability (Rigg & Monnat, 2015).

We defined all substance use and mental health measures as those experienced in

the past 12 months. Specifically, we defined tobacco use as use of any of the following

tobacco products: all or part of a cigarette, cigars, pipes, snuff, or chewing tobacco. Other

illicit substance use definitions included the non-medical use of one or more of the

following substances: cocaine, crack, hallucinogens, inhalants, tranquilizers, stimulants and

sedatives (i.e. illicit use of drugs other than opioids and marijuana). Abuse of alcohol and

illicit substances is based on the Diagnostic and Statistical Manual of Mental Disorders

(DSM-V) criteria indicating at least one of the following in the past year: 1) serious

problems at home, work, or school caused by substance use; 2) substance use in physically

dangerous situations; 3) repeated trouble with the law as a result of substance use; or 4)

problems with family or friends related to substance use and continuing to use it anyway.

(American Psychiatric Association, 2013).

To measure psychological distress, NSDUH uses the K6 screener, which was

designed to identify non-specific psychological distress with six brief questions (e.g. "How

often do you feel nervous?") (Kessler et al., 2003; Substance Abuse and Mental Health

Administration, 2013). A major depressive episode (MDE) was assessed using questions

adapted from the Composite International Diagnostic Interview and participants were

categorized as having MDE if they met at least five of nine DSM-V criteria (Kessler et al.,

2003).

Demographic characteristics included: sex (male, female), age (18-25, 26-34, 35+),

race/ethnicity (non-Hispanic White and other [non-Hispanic Black, non-Hispanic other,

Hispanic]), rurality (urban [residing in county with city of at least 10,000], non-urban [residing in county without city of at least 10,000]), marital status (ever married [divorced, separated, widowed], never married), educational attainment (less than college graduate, college graduate), and employment status (full time, under- or unemployed).

2.4. Analyses

We first conducted descriptive analyses to examine distributions across each variable. To describe current NMPO users, we computed weighted frequencies and corresponding 95% confidence intervals (CI) across all interpersonal- and individual-level factors. Using chi-squared tests, we then examined bivariate relationships between each factor and the outcome. Before conducting multivariable analysis, we examined the possibility of multicollinearity by checking for high inter-correlations between the variables, defined as a condition index greater than 30, and found none (Kleinbaum & Klein, 2010).

We conducted multivariable logistic regression with all interpersonal- and individual-level factors to produce adjusted odds ratios (AOR). Nested block regressions evaluated the combined contributions of blocks of factors on transition. We formed a total of five blocks based on the levels of the SEM and given the large number of individual-level factors, made blocks based on inherent groups (Bronfenbrenner, 1979; Hager et al., 2012). This resulted in one block of interpersonal-level access factors (perceived risk and PO source) and four blocks of individual-level factors: 1) individual-level access (health insurance and perceived availability), 2) substance use behaviors (age of first NMPO use and past year tobacco use, alcohol abuse, PO abuse, use of other illicit drugs, and abuse of other illicit drugs), 3) mental health characteristics (past year psychological distress and MDE), and 4) demographics (sex, age, race/ethnicity, rurality, marital status, education, and employment). In the full multivariable logistic regression

64

model, we removed blocks of factors one at a time and interpreted the reduction in R-squared compared to the full adjusted model and associated p-values for each factor. For all analyses, significance was determined at $p < 0.05$. To account for the complex multistage sampling design, analyses were conducted in SAS-callable SUDAAN v9.2.

3. Results

Table 1 describes current NMPO users in the 2012-2014 surveys. Our sample consists of 7,045 current NMPO users. The majority of the sample was male (54.78%), non-Hispanic White (66.49%), urban-residing (85.43%) and less than college educated (79.10%). Prevalence of illicit drug use was 41.34% but only 6.40% and 3.81% of the sample reported illicit drug abuse or PO abuse, respectively. While 75.00% had health insurance coverage, at the interpersonal-level, only 23.61% reported a provider as their source of POs. Of all current NMPO users, 5.23% (95% CI: 4.50, 5.96) co-use heroin. Almost all co-users (4.96% [95% CI: 4.31, 5.71]) transitioned from NMPO use to heroin initiation.

In bivariate analyses, we found that all factors in the interpersonal-level access, individual-level access, mental health and demographic blocks were significantly associated with transition. In the substance use block at the individual level, initiating NMPO use before the age of 18 and past year use of tobacco and illicit non-opioid drugs were also significantly associated with transition. Past year abuse of illicit non-opioids, POs, and alcohol were not associated with transition in bivariate analysis (Table 1).

Table 2 details results of multivariable logistic regression. The full model, containing all interpersonal- and individual-level factors, produced an R-squared value of 0.48, indicating that all variables included in this study explain almost half of all variance in the outcome. Removing blocks of factors from the full model one at a time resulted in R-squared reductions of 0.13 for the substance use block and 0.12 for the individual-level access block, meaning that these blocks account for the largest explained variance in transition. The R-

squared contribution of the interpersonal access (0.02 reduction), mental health (0.06 reduction), and demographic (0.08 reduction) blocks were smaller. Significance and effect sizes for factors within each block varied.

In the full model, demographic characteristics that significantly associated with transition were male sex compared to female (AOR: 3.33, 95% CI: 1.94, 5.70), non-Hispanic White compared to other race/ethnicities, (AOR: 4.11, 95% CI: 1.98, 8.53), and under- or unemployment compared to full-time, (AOR: 2.10, 95% CI: 1.22, 3.59). Initiating NMPO use before the age of 18 was associated with increased the odds of transition (AOR: 1.87, 95% CI: 1.07, 3.27), as was past-year tobacco use (AOR: 4.63, 95% CI: 1.90, 11.28) and past-year illicit drug use (AOR: 3.71, 95% CI: 1.96, 7.04). Odds of transition was lower among those reporting past-year alcohol abuse (AOR: 0.50, 95% CI: 0.27, 0.94). Other individual-level factors associated with transition were no health insurance coverage (AOR: 1.93, 95% CI: 1.30, 2.88) and perceived heroin availability as easy compared to impossible or difficult (AOR: 11.21, 95% CI: 6.76, 15.59).

At the interpersonal-level, perceiving the risk of trying heroin as less than great relative to great or more (AOR: 1.84, 95% CI: 1.17, 2.88) increased odds of transition. Compared to illicitly buying or stealing POs, a familial source (AOR: 0.34, 95% CI: 0.14, 0.80) decreased odds of transition and the relationship with a healthcare provider source was not significant.

4. Discussion

To our knowledge, this is the first study that uses nationally representative data among adults to assess multilevel factors related to transition from NMPO-only to heroin co-use. We examined factors associated with increased NMPO use, including factors beyond the individual level, and those highlighted by previous research on

transition. In our study, almost 5% of NMPO users transitioned to heroin initiation, a slightly higher estimate than other studies. This is likely because we assess past-year prevalence of transition while prospective cohort studies measure incidence (Carlson et al., 2016). Nonetheless, the low prevalence of transition underscores the need to investigate factors driving this phenomenon, including social stressors and structural inequalities not assessed in this study (Carlson et al., 2016; Dasgupta et al., 2018; Muhuri et al., 2013). Interventions to prevent transition and reach this vulnerable group of opioid users with treatment services must target those at highest risk. Aiming these interventions at all NMPO users inefficiently uses the limited resources available. These findings indicate subgroups of NMPO users at increased risk of transition and modifiable factors associated with transition, informing such interventions.

Compared to females, males were more likely to transition. Extant literature on increased drug-related risk-taking behaviors and limited healthcare utilization among males help explain this finding (Byrnes, Miller, & Schafer, 1999; Grau et al., 2007; Strathdee et al., 2001). Given our inability to report sex-specific results due to small sample size, instability of estimates and NSDUH guidelines on estimate suppression (Center for Behavioral Health Statistics and Quality, 2016), we recommend future studies examine risk perception, healthcare access and heroin availability by sex to better understand this finding. After adjusting for other factors, we found no significant difference in odds of transition between urban and non-urban residence, which adds to the overwhelming evidence that the profile of typical heroin users is no longer necessarily urban (Cerda et al., 2015; Cicero, Ellis, Surratt, & Kurtz, 2014; Mars et al., 2014; Muhuri et al., 2013; Young et al., 2012). Progress toward making harm reduction interventions accessible to rural populations, demonstrated by increased availability of MAT in non-urban areas, must continue (Dick et al., 2015).

Studies describing transition to heroin among those who previously used NMPOs indicate that problem PO use, including abuse, precedes heroin initiation after a period of NMPO use (Peavy et al., 2012; Pollini et al., 2011). In this study, PO ***abuse*** was not significantly associated with transition, showing that PO abuse does not necessarily precede transition and that risk of transition is not limited to problem PO users. Similarly, illicit use of other drugs, but not abuse, was associated with transition, suggesting additional poly-drug use and associated risk of overdose and death among those who transition. Our findings also reflect previous findings that risk of transition has an inverse relationship with age of NMPO initiation and perceived risk of heroin use (Cerda et al., 2015; Lankenau et al., 2012; Rhodes, 2009). In this study, substance use behaviors contributed the most in terms of explaining the variance in transition.

Consistent with our hypothesis, we found that obtaining POs from a friend, family member or healthcare provider was protective against transition, compared to obtaining them illicitly. Access to healthcare, indicated by health insurance coverage, was also associated with transition. Implementation of interventions aiming to reduce PO supply and limit access through a healthcare provider may have driven some users to obtain POs illicitly, including stealing them or purchasing through a dealer (Cicero, Ellis, & Surratt, 2012; Unick et al., 2013). Our findings advance the theory that a focus on supply-side interventions to reduce PO availability over public health approaches that reduce demand for opioids drives more severe opioid use when POs are unavailable through a legitimate source. We argue that reducing opioid misuse and related outcomes requires expanding access to healthcare, including greater health insurance coverage and availability of treatment services. Implementation of studies that prospectively examine changes

in PO source, health insurance coverage, MAT use, and opioid use will test these hypotheses.

Finally, perceived availability of heroin had the strongest association with transition. This is not surprising and likely due to the cross-sectional design of this study, as current co-users will know where heroin is available. It explains why the interpersonal access block, which included perceived heroin availability, contributed the least in terms of explaining transition. We were unable to truly assess perceived availability prior to transition and as a predictor of transition. Recent studies show evidence that perceived heroin access is decreasing, a finding that contradicts increased heroin use (Jones et al., 2015; Vaughn, Salas-Wright, & Oh, 2017) and highlights the need to study indicators of access and perceptions of availability in relation to heroin initiation. Clinicians, pharmacists and other public health practitioners can use messaging on harms associated with heroin use and the accessibility of evidence-based treatment interventions to counterbalance perceptions of heroin availability.

Taken together, these findings on have important practical implications. First, identifying and intervening with those misusing POs is key, before onset of abuse, which is associated with more health and social consequences than use alone (American Psychiatric Association, 2013). While increasing awareness about the risk of opioids at the population level is important (Schuchat, Houry, & Guy, 2017), targeting education efforts at those at highest risk is key to preventing transition. For patients with risk factors highlighted by this study, clinicians prescribing opioids should discuss the risks and benefits of opioid use, conduct regular follow-ups to screen for problem use, and consider the benefits of dose tapering before transition occurs. All communication campaigns should address social norms around opioid use, the risk of continued use and heroin initiation, the benefits and availability of treatment services, and approaches to improve communication between clinicians, pharmacists who are dispensing medications, and patients. Lastly, focused efforts

to intervene with adolescents prior to NMPO initiation and screening adolescents

for NMPO use, particularly those prescribed POs, will prevent both NMPO use and

more severe forms of drug use including heroin and poly-drug use.

4.1. Limitations

This study has limitations. We relied on the variables available in NSDUH and were

therefore unable to explore additional multilevel factors associated with transition,

particularly at higher levels of SEM. While NSDUH collects state codes to compute state-

level estimates, they are not available in the public-use files and the data portal to

request these variables was not functional at the time of the study. This prevented us

from examining additional structural-level factors that may influence our outcome,

including state-level heroin availability, economic deprivation, prescribing rates,

implementation of prescription drug monitoring programs and other drug policies. The

interpersonal-level variables we did study accounted for the smallest explained

variance in transition, indicating the importance of assessing additional higher-level

factors to explain transition. Researchers with access to the restricted data should

assess the role of these factors on transition and SAMHSA should prioritize resuming

functionality of the portal to enable critical public health research.

Although NSDUH produces reliable estimates of substance use behaviors,

the data are self-reported and nonetheless susceptible to recall and social

desirability bias (Kennet et al., 2010). We expect the latter to be minimal since

NSDUH uses computer assisted self-interviewing software to ensure privacy (Center

for Behavioral Health Statistics and Quality, 2016; Islam et al., 2012). NSDUH does

not capture people who are incarcerated, homeless, or hospitalized which may

underestimate use as these populations often have a higher likelihood of engaging in

substance use (49). Studies enrolling those cohorts or surveillance systems that capture these cohorts must fill this data gap.

Since this study uses cross-sectional data, we could not directly assess transition, particularly among respondents whose age (by year) of first use for both opioids is the same. However, misclassification of NMPO to heroin transition, when the order was reverse, is likely to be minimal. In recent estimates, only 1% of NMPO users reported previous heroin use, and therefore unlikely to impact overall results of our analysis (Jones, 2013; Muhuri et al., 2013). Currently, this is the best measure available to examine transition from NMPO to heroin use at a population level. Additionally, sensitivity analyses revealed no differences in findings when we removed respondents whose age of first use is the same for both NMPO and heroin from analyses (data available upon request). However, future studies specifically recruiting participants who report transitioning from NMPO to heroin use or following NMPO users prospectively to assess transition will improve measurement of this phenomenon and related factors. Lastly, due to the variables available, we may have erroneously defined co-use as intermittent use of both NMPO and heroin. We explored a more finite measure of co-use, past month use of NMPOs and heroin, and found similar patterns but we were unable to report findings due to the small sample sizes (Center for Behavioral Health Statistics and Quality, 2016).

4.2. Conclusions

Despite these limitations, this study responds to an urgent call to identify risk factors for transition from NMPO use to heroin initiation and subsequent co-use of both opioids (Jones, 2013; Pollini et al., 2011). It also expands prior research by using nationally representative data to produce findings that are generalizable to the adult population and by examining factors beyond the individual level. We identify subgroups at higher risk of transition, including males, non-Hispanic White, and those not employed full time, to inform targeted

screening and monitoring efforts. Modifiable factors related to transition, including

perceived risk of heroin use and health insurance coverage, speak to interpersonal and

structural-level interventions to prevent transition, and ultimately control the current

opioid epidemic.

5. Tables

Table 1. Descriptive statistics of current (past year) NMPO users—NSDUH 2012-2014, N=7,045

	Current NMPO use (n=7,045)		Transition (n=402)		X² p-value
	Wt%	(95% CI)	Wt%	(95% CI)	
	100	--	4.96	(4.31, 5.71)	
<u>Demographics</u>					
Sex					
Male	54.78	(52.56, 57.00)	74.02	(68.60, 78.80)	**<0.05**
Female	45.22	(43.00, 47.44)	25.98	(12.20, 31.40)	
Age					
18-25	30.43	(28.96, 31.89)	39.02	(32.46, 46.01)	**<0.05**
26-34	25.70	(23.73, 27.68)	40.42	(32.87, 48.45)	
35+	43.11	(41.74, 46.00)	20.56	(14.33, 28.60)	
Race					
Non-Hispanic White	66.49	(64.57, 68.40)	85.38	(79.84, 89.60)	**<0.05**
Other	33.51	(31.60, 35.43)	14.62	(10.40, 20.16)	
Rurality					
Urban	85.43	(83.79, 87.07)	92.04	(88.21, 94.69)	**<0.05**
Non-urban	14.57	(12.93, 16.21)	7.96	(5.31, 11.79)	
Marital status					
Never married	52.24	(50.23, 54.26)	76.55	(69.59, 82.33)	**<0.05**
Ever married	47.76	(45.74, 49.77)	23.45	(17.67, 30.41)	
Education					
Less than college grad	79.10	(77.59, 80.62)	93.22	(89.35, 95.75)	**<0.05**
College graduate	20.90	(19.04, 22.08)	6.78	(4.25, 10.65)	
Employment status					
Under/un-employed	48.18	(46.20, 50.16)	68.62	(61.57, 74.91)	**<0.05**
FT Employed	51.82	(49.84, 53.80)	31.38	(25.09, 38.43)	
<u>Substance use</u>					
Age of first NMPO use, before 18	30.61	(29.03, 32.19)	57.14	(48.76, 65.13)	**<0.05**
Any tobacco use, past year	68.88	(62.88, 66.88)	95.88	(90.50, 98.27)	**<0.05**
Illicit drug abuse, past year	6.40	(5.34, 7.47)	7.02	(4.04, 11.94)	0.76
PO abuse, past year	3.81	(2.90, 4.71)	6.60	(3.80, 11.20)	0.11
Illicit drug use, past year	41.34	(39.46, 43.23)	86.09	(81.11, 89.91)	**<0.05**
Alcohol abuse, past year	13.34	11.92, 14.76)	11.37	(7.65, 16.58)	0.36
<u>Mental health</u>					
Major depressive episode, past year	15.61	(14.17, 17.05)	26.41	(20.83, 32.87)	**<0.05**
Psychological distress, past year	29.15	(27.19, 31.12)	57.40	(49.35, 64.53)	**<0.05**
<u>Individual-level access</u>					
Health insurance coverage					
Not covered	25.00	(23.16, 26.83)	43.48	(36.81, 50.40)	**<0.05**
Covered	75.00	(73.17, 76.84)	56.52	(49.60, 63.19)	
Perceived heroin availability					
Fairly or very easy	26.78	(24.86, 28.70)	82.61	(76.49, 87.39)	**<0.05**
Impossible, very, fairly difficult	73.22	(71.30, 75.14)	17.39	(12.61, 23.51)	
<u>Interpersonal-level access</u>					
Source of POs					
Familial	67.99	(65.83, 70.16)	62.79	(51.92, 72.52)	**<0.05**
Provider	23.61	(21.45, 25.77)	12.03	(6.82, 20.37)	
Illicitly bought, stole, other	8.40	(7.10, 9.69)	25.17	(17.32, 35.08)	
Perceived risk of trying heroin					
None to moderate risk	75.41	(23.03, 26.16)	58.37	(51.77, 64.69)	**<0.05**
Great risk	24.60	(73.84, 76.97)	41.63	(35.31, 48.23)	

Bolded values indicate significance at p<0.05.

Table 2. Factors associated with transition in multivariable regression—NSDUH 2012-2014, N=7,045

	Full multivariable model	
	AOR	(95% CI)
<u>Demographics</u>		
Sex		
Male	**3.33**	**(1.94, 5.70)**
Female	REF	
Age		
18-25	1.08	(0.53, 2.20)
26-34	1.21	(0.61, 2.41)
35+	REF	
Race		
Non-Hispanic White	**4.11**	**(1.98, 8.53)**
Other	REF	
Rurality		
Urban	1.94	(0.80, 4.72)
Non-urban	REF	
Marital status		
Never married	1.21	(0.63, 2.30)
Ever married	REF	
Education		
Less than college grad	2.11	(0.92, 4.85)
College graduate	REF	
Employment status		
Under/un-employed	**2.10**	**(1.22, 3.59)**
FT Employed	REF	
<u>Substance use</u>		
Age of first NMPO use, before 18	**1.87**	**(1.07, 3.27)**
Any tobacco use, past year	**4.63**	**(1.90, 11.28)**
Illicit drug abuse, past year	0.55	(0.22, 1.38)
PO abuse, past year	2.45	(0.82, 7.31)
Illicit drug use, past year	**3.71**	**(1.96, 7.04)**
Alcohol abuse, past year	**0.50**	**(0.27, 0.94)**
<u>Mental health</u>		
Major depressive episode, past year	0.60	(0.36, 1.00)
Psychological distress, past year	**3.70**	**(2.11, 6.48)**
<u>Individual-level access</u>		
Health insurance coverage		
Not covered	**1.93**	**(1.30, 2.88)**
Covered	REF	
Perceived heroin availability		
Fairly or very easy	**11.21**	**(6.76, 15.59)**
Impossible, very, fairly difficult	REF	
<u>Interpersonal-level access</u>		
Source of POs		
Familial	**0.34**	**(0.14, 0.80)**
Provider	0.63	(0.33, 1.20)
Illicitly bought, stole, other	REF	
Perceived risk of trying heroin		
None to moderate risk	**1.84**	**(1.17, 2.88)**
Great risk	REF	

Bolded values indicate significance at $p<0.05$.

6. References

Al-Tayyib, A. A., Koester, S., & Riggs, P. (2017). Prescription opioids prior to injection drug use: Comparisons and public health implications. *Addictive behaviors, 65*, 224-228.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*: American Psychiatric Pub.

Bali, V., Raisch, D. W., Moffett, M. L., & Khan, N. (2013). Determinants of nonmedical use, abuse or dependence on prescription drugs, and use of substance abuse treatment. *Research in Social and Administrative Pharmacy, 9*(3), 276-287.

Bronfenbrenner, U. (1979). The ecology of human development: Experiments by design and nature. In: Cambridge, MA: Harvard University Press.

Byrnes, J. P., Miller, D. C., & Schafer, W. D. (1999). Gender differences in risk taking: A meta-analysis. In: American Psychological Association.

Carlson, R. G., Nahhas, R. W., Martins, S. S., & Daniulaityte, R. (2016). Predictors of transition to heroin use among initially non-opioid dependent illicit pharmaceutical opioid users: A natural history study. *Drug and alcohol dependence, 160*, 127-134.

Center for Behavioral Health Statistics and Quality. (2016). *2015 National Survey on Drug Use and Health: Methodological summary and definitions*. Retrieved from Rockville, MD:

Cerda, M., Santaella, J., Marshall, B. D., Kim, J. H., & Martins, S. S. (2015). Nonmedical Prescription Opioid Use in Childhood and Early Adolescence Predicts Transitions to Heroin Use in Young Adulthood: A National Study. *J Pediatr, 167*(3), 605-612 e602. doi:10.1016/j.jpeds.2015.04.071

Cherubin, C. E., & Sapira, J. D. (1993). The medical complications of drug addiction and the medical assessment of the intravenous drug user: 25 years later. *Annals of internal medicine, 119*(10), 1017-1028.

Cicero, T. J., Ellis, M. S., & Harney, J. (2015). Shifting patterns of prescription opioid and heroin abuse in the United States. *New England Journal of Medicine, 373*(18), 1789-1790.

Cicero, T. J., Ellis, M. S., & Surratt, H. L. (2012). Effect of abuse-deterrent formulation of OxyContin. *New England Journal of Medicine, 367*(2), 187-189.

Cicero, T. J., Ellis, M. S., Surratt, H. L., & Kurtz, S. P. (2014). The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. *JAMA psychiatry, 71*(7), 821-826.

Cicero, T. J., Surratt, H., Inciardi, J. A., & Munoz, A. (2007). Relationship between therapeutic use and abuse of opioid analgesics in rural, suburban, and urban locations in the United States. *Pharmacoepidemiology and drug safety, 16*(8), 827-840.

Cohen, D. A., Scribner, R. A., & Farley, T. A. (2000). A structural model of health behavior: a pragmatic approach to explain and influence health behaviors at the population level. *Preventive medicine, 30*(2), 146-154.

Compton, W. M., Jones, C. M., & Baldwin, G. T. (2016). Relationship between Nonmedical Prescription-Opioid Use and Heroin Use. *New England Journal of Medicine, 374*(2), 154-163. doi:doi:10.1056/NEJMra1508490

Compton, W. M., & Volkow, N. D. (2006). Abuse of prescription drugs and the risk of addiction. *Drug and alcohol dependence, 83*, S4-S7.

Daniulaityte, R., Falck, R., & Carlson, R. G. (2012). "I'm not afraid of those ones just 'cause they've been prescribed": Perceptions of risk among illicit users of pharmaceutical opioids. *International Journal of Drug Policy, 23*(5), 374-384.

Dasgupta, N., Beletsky, L., & Ciccarone, D. (2018). Opioid Crisis: No Easy Fix to Its Social and

    Economic Determinants. *American journal of public health, 108*(2), 182-186.

Dew, B., Elifson, K., & Dozier, M. (2007). Social and environmental factors and their

    influence on drug use vulnerability and resiliency in rural populations. *The Journal*

    of Rural Health, 23(s1), 16-21.

Dhalla, I. A., Persaud, N., & Juurlink, D. N. (2011). Facing up to the prescription opioid crisis.

    BMJ, 343, d5142.

Dick, A. W., Pacula, R. L., Gordon, A. J., Sorbero, M., Burns, R. M., Leslie, D. L., & Stein, B. D.

    (2015). Increasing Potential Access to Opioid Agonist Treatment in US Treatment

    Shortage Areas. *Health affairs (Project Hope), 34*(6), 1028.

Fischer, B., Patra, J., Cruz, M. F., Gittins, J., & Rehm, J. (2008). Comparing heroin users and

    prescription opioid users in a Canadian multi-site population of illicit opioid users.

    Drug Alcohol Rev, 27(6), 625-632. doi:10.1080/09595230801956124

Grau, L. E., Dasgupta, N., Grau, L. E., Dasgupta, N., Harvey, A. P., Grau, L. E., . . . Givens‡, A.

    (2007). Illicit use of opioids: Is OxyContin® a "gateway drug"? *American Journal on*

    Addictions, 16(3), 166-173.

Guarino, H., Marsch, L. A., Deren, S., Straussner, S. L., & Teper, A. (2015). Opioid Use

    Trajectories, Injection Drug Use, and Hepatitis C Virus Risk Among Young Adult

    Immigrants from the Former Soviet Union Living in New York City. *J Addict Dis,*

    34(2-3), 162-177. doi:10.1080/10550887.2015.1059711

Hager, E. R., Candelaria, M., Latta, L. W., Hurley, K. M., Wang, Y., Caulfield, L. E., & Black, M. M.

    (2012). Maternal perceptions of toddler body size: accuracy and satisfaction differ

    by toddler weight status. *Archives of pediatrics & adolescent medicine, 166*(5), 417-

    422.

Han, B., Compton, W. M., Jones, C. M., & Cai, R. (2015). Nonmedical prescription opioid use

and use disorders among adults aged 18 through 64 years in the United States,

2003-2013. *JAMA, 314*(14), 1468-1478.

Han, B., Gfroerer, J. C., & Colliver, J. D. (2010). Associations between duration of illicit drug

use and health conditions: results from the 2005–2007 National Surveys on Drug

Use and Health. *Annals of epidemiology, 20*(4), 289-297.

Hedegaard, H., Warner, M., & Miniño, A. M. (2018). Drug overdose deaths in the United

States, 1999-2016. *NCHS data brief*(273), 1-8.

Inciardi, J. A., Surratt, H. L., Cicero, T. J., & Beard, R. A. (2009). Prescription opioid abuse and

diversion in an urban community: the results of an ultrarapid assessment. *Pain

Medicine, 10*(3), 537-548.

Islam, M. M., Topp, L., Conigrave, K. M., van Beek, I., Maher, L., White, A., . . . Day, C. A. (2012).

The reliability of sensitive information provided by injecting drug users in a clinical

setting: clinician-administered versus audio computer-assisted self-interviewing

(ACASI). *AIDS care, 24*(12), 1496-1503.

Jones, C. M. (2013). Heroin use and heroin use risk behaviors among nonmedical users of

prescription opioid pain relievers–United States, 2002–2004 and 2008–2010. *Drug

and alcohol dependence, 132*(1), 95-100.

Jones, C. M., Logan, J., Gladden, R., & Bohm, M. K. (2015). Vital signs: demographic and

substance use trends among heroin users: United States, 2002–2013. *MMWR Morb

Mortal Wkly Rep, 64*(26), 719-725.

Kanouse, A. B., & Compton, P. (2015). The epidemic of prescription opioid abuse, the

subsequent rising prevalence of heroin use, and the federal response. *Journal of pain

& palliative care pharmacotherapy, 29*(2), 102-114.

Kennet, J., Gfroerer, J., Barker, P., Piper, L., Hirsch, E., Granger, B., & Chromy, J. R. (2010). *Reliability and Data Quality in the National Survey on Drug Use and Health*. Paper presented at the Ninth Conference on Health Survey Research Methods, Hyattsville, MD.

Kessler, R. C., Barker, P. R., Colpe, L. J., Epstein, J. F., Gfroerer, J. C., Hiripi, E., . . . Walters, E. E. (2003). Screening for serious mental illness in the general population. *Archives of general psychiatry, 60*(2), 184-189.

Keyes, K. M., Cerdá, M., Brady, J. E., Havens, J. R., & Galea, S. (2014). Understanding the rural–urban differences in nonmedical prescription opioid use and abuse in the United States. *American journal of public health, 104*(2), e52-e59.

Kleinbaum, D. G., & Klein, M. (2010). *Logistic Regression: A self-learning text*. New York: Springer.

Lankenau, S. E., Teti, M., Silva, K., Bloom, J. J., Harocopos, A., & Treese, M. (2012). Initiation into prescription opioid misuse amongst young injection drug users. *International Journal of Drug Policy, 23*(1), 37-44.

Manchikanti, Helm, S., Janata, J. W., Pampati, V., & Grider, J. S. (2012). Opioid epidemic in the United States. *Pain physician, 15*, 2150-1149.

Mars, S. G., Bourgois, P., Karandinos, G., Montero, F., & Ciccarone, D. (2014). "Every 'never' I ever said came true": transitions from opioid pills to heroin injecting. *International Journal of Drug Policy, 25*(2), 257-266.

Mateu-Gelabert, P., Guarino, H., Jessell, L., & Teper, A. (2015). Injection and sexual HIV/HCV risk behaviors associated with nonmedical use of prescription opioids among young adults in New York City. *Journal of substance abuse treatment, 48*(1), 13-20.

Mital, S., Windle, M., Cooper, H. L., & Crawford, N. D. (2018). Trends in non-medical prescription opioids and heroin co-use among adults, 2003-2014. *In review*.

Monnat, S. M., & Rigg, K. K. (2015). Examining rural/urban differences in prescription opioid

    misuse among US adolescents. *The Journal of Rural Health*.

Mowbray, O., & Quinn, A. (2015). Prescription pain reliever misuse prevalence, correlates,

    and origin of possession throughout the life course. *Addictive behaviors, 50*, 22-27.

Muhuri, P. K., Gfroerer, J. C., & Davies, M. C. (2013). Associations of nonmedical pain reliever

    use and initiation of heroin use in the United States. *The CBHSQ Data Review*.

National Academies of Sciences, E., & Medicine. (2017). *Pain management and the opioid*

    epidemic: balancing societal and individual benefits and risks of prescription opioid

    use: National Academies Press.

Paulozzi, L. J., & Xi, Y. (2008). Recent changes in drug poisoning mortality in the United

    States by urban–rural status and by drug type. *Pharmacoepidemiology and drug*

    safety, 17(10), 997-1005.

Peavy, K. M., Banta-Green, C. J., Kingston, S., Hanrahan, M., Merrill, J. O., & Coffin, P. O. (2012).

    "Hooked on" prescription-type opiates prior to using heroin: results from a survey

    of syringe exchange clients. *Journal of psychoactive drugs, 44*(3), 259-265.

Pollini, R. A., Banta-Green, C. J., Cuevas-Mota, J., Metzner, M., Teshale, E., & Garfein, R. S.

    (2011). Problematic use of prescription-type opioids prior to heroin use among

    young heroin injectors. *Substance abuse and rehabilitation, 2*(1), 173.

Rajan, S., Ruggles, K. V., Guarino, H., & Mateu-Gelabert, P. (2018). Heroin Use and Drug

    Injection among Youth Also Misusing Prescription Drugs. *American Journal of Health*

    Behavior, 42(1), 144-155.

Rhodes, T. (2009). Risk environments and drug harms: a social science for harm reduction

    approach. *International Journal of Drug Policy, 20*(3), 193-201.

Rigg, K. K., & Monnat, S. M. (2015). Comparing Characteristics of Prescription Painkiller

    Misusers and Heroin Users in the United States. *Addictive behaviors, 51*, 106-112.

    doi:10.1016/j.addbeh.2015.07.013

Ruckert, A., & Labonté, R. (2017). Health inequities in the age of austerity: the need for

    social protection policies. *Social Science & Medicine, 187*, 306-311.

Sallis, J. F., Owen, N., & Fisher, E. B. (2008). Ecological models of health behavior. *Health

    behavior and health education: Theory, research, and practice, 4*, 465-486.

Schuchat, A., Houry, D., & Guy, G. P. (2017). New data on opioid use and prescribing in the

    United States. *JAMA, 318*(5), 425-426.

Siegal, H. A., Carlson, R. G., Kenne, D. R., & Swora, M. G. (2003). Probable relationship

    between opioid abuse and heroin use. *American Family Physician, 67*(5), 942-945.

Simoni-Wastila, L. (2000). The use of abusable prescription drugs: the role of gender.

    Journal of women's health & gender-based medicine, 9(3), 289-297.

Strathdee, S. A., Galai, N., Safaiean, M., Celentano, D. D., Vlahov, D., Johnson, L., & Nelson, K. E.

    (2001). Sex differences in risk factors for HIV seroconversion among injection drug

    users: a 10-year perspective. *Archives of internal medicine, 161*(10), 1281-1288.

Substance Abuse and Mental Health Administration. (2013). *National Survey on Drug Use

    and Health, 2013 Codebook*. Retrieved from Rockville, MD:

    http://www.icpsr.umich.edu/icpsrweb/NAHDAP/studies/35509

Thorpe, L. E., Ouellet, L. J., Hershow, R., Bailey, S. L., Williams, I. T., Williamson, J., . . . Garfein,

    R. S. (2002). Risk of hepatitis C virus infection among young adult injection drug

    users who share injection equipment. *American journal of epidemiology, 155*(7),

    645-653.

Unick, G. J., Rosenblum, D., Mars, S., & Ciccarone, D. (2013). Intertwined epidemics: national demographic trends in hospitalizations for heroin-and opioid-related overdoses, 1993–2009. *PloS one, 8*(2), e54496.

Vaughn, M. G., Salas-Wright, C. P., & Oh, S. (2017). Trends in heroin access among adolescents in the United States, 2002–2014. *Preventive medicine*.

World Health Organization. (2009). *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*: World Health Organization.

Young, A. M., Glover, N., & Havens, J. R. (2012). Nonmedical use of prescription medications among adolescents in the United States: a systematic review. *Journal of Adolescent Health, 51*(1), 6-17.

Zibbell, J. (2015). *National Increases in Hepatitis C Virus Infections Related to Increases in Opioid Dependency and Opioid Injections in the United States: A Syndemic Approach.* Paper presented at the American Public Health Association, Chicago, IL.

Chapter 4: Use of outpatient medication-assisted treatment by opioid use type: trends in admissions (2004-2015) and factors related to treatment completion

Abstract

Background. Medication-assisted treatment (MAT) is effective and has potential for addressing the recent growth in opioid use, including co-use of both prescription opioids (POs) and heroin, a severe but understudied type of opioid use. Federal initiatives increasing healthcare access may improve MAT enrollment and successful completion. A better understanding of MAT enrollment and completion by opioid use type (i.e. PO-only, heroin-only, co-use), dimensions of healthcare access (i.e. Medicaid expansion, health insurance coverage, provider referrals and immediate admission), and demographics would pinpoint gaps in enrollment, highlight subgroups less likely to complete treatment, and inform targeted treatment efforts.

Methods. Using the 2004-2015 Treatment Episodes Datasets, we investigated recent trends in MAT admissions overall, and across opioid use type, dimensions of access to healthcare, and demographics using the Cochran-Armitage trend test. We compared MAT admissions for co-use to those for PO- and heroin-only use across demographic characteristics and dimensions of access to healthcare using logistic regression. We also used multivariable logistic regression to examine relationships between access to healthcare characteristics and treatment completion by opioid use type.

Results. From 2004 to 2015, the frequency of MAT admissions for opioid use overall increased 143% (p<0.05). The proportion of admissions for co-use remained relatively stable (between 10-15%) during this period. Characteristics of MAT admissions changed from 2004 to 2015: female, non-urban, never married, health insured, criminal justice referred, and immediate admissions became more common (p<0.05). Demographic and healthcare access characteristics of admissions for co-use were more similar to those for PO only than heroin only. Compared to co-use, treatment completion was less likely than among heroin only (AOR 0.70, 95% CI 0.54, 0.90) and not significantly different from PO only. Referral source was the strongest predictor of treatment completion for co-use, while the relationship between immediate admission and treatment completion was strongest for heroin-only use.

Discussion. The increased frequency of MAT admissions is promising, although MAT enrollment has not kept pace with the growth in co-use. The treatment completion rate and healthcare-related facilitators of treatment completion differed by opioid use type, highlighting the need for subgroup-specific interventions to improve treatment utilization and completion.

1. Background

Tackling the current opioid epidemic requires improving access to medication-assisted treatment (MAT), the most effective treatment for problem opioid use. MAT effectively reduces opioid use and its consequences including overdose, risk of HIV and other blood-borne infections, crime, and mortality (Amato et al., 2005; Nosyk et al., 2013). The term "MAT" refers to a comprehensive therapeutic approach to treating both prescription opioid (PO) and heroin addiction through the use of pharmacotherapies, usually methadone or buprenorphine, generally layered with counseling and other health and social services (Fullerton et al., 2014; Kresina, Litwin, Marion, Lubran, & Clark, 2009; Nielsen, Larance, & Lintzeris, 2017). Compared to non-pharmacological treatments, MAT shows better outcomes and cost-effectiveness (Connock et al., 2007; Mattick, Breen, Kimber, & Davoli, 2009; Zarkin, Dunlap, Hicks, & Mamo, 2005). The current opioid epidemic is driven by increased prevalence of PO use disorders, heroin use, PO and heroin co-use, which is associated with poorer health and higher risk of overdose relative to PO- and heroin-only use (Fischer, Patra, Cruz, Gittins, & Rehm, 2008; Han, Compton, Jones, & Cai, 2015; Jones, 2013; Mital, Windle, Cooper, & Crawford, 2018; Rigg & Monnat, 2015; Strang et al., 1999). Increased growth in the rate of opioid use and overdose was observed in groups where it was historically low, including among females, among non-Hispanic Whites compared to other race/ethnicities, and in non-urban counties (Jones, 2013; Jones, Logan, Gladden, & Bohm, 2015; Paulozzi & Xi, 2008; Unick, Rosenblum, Mars, & Ciccarone, 2013). Recognizing its effectiveness, experts call for expanded MAT access in response to the growing need (Blum, Gold, Clark, Dushaj, & Badgaiyan, 2016; Volkow, Frieden, Hyde, & Cha, 2014). However, continued growth of opioid-related overdose deaths suggests that the epidemic persists, that MAT admissions do not reflect shifts in need for MAT services, and that individuals

are not fully benefiting from MAT services (Hedegaard, Warner, & Miniño, 2018; Volkow et al., 2014).

Recent implementation of initiatives aiming to enable access to health services, including substance abuse treatment, may have implications for increased MAT admissions, but further investigation is required. Under the Affordable Care Act (ACA), states opted to expand Medicaid to low-income adults under 138% of the federal poverty level (Kaiser Family Foundation, 2017). Healthcare scholars expected Medicaid expansion to increase treatment enrollment, since problem opioid use is prevalent in populations targeted by the expansion and improved health insurance coverage reduces financial barriers related to initiation of MAT (Busch, Meara, Huskamp, & Barry, 2013; McLellan & Woodworth, 2014; Volkow et al., 2014). However, studies link Medicaid expansion to an increase in MAT prescriptions, but not admissions, likely due to the time needed to see an effect (Carr et al., 2008; Maclean & Saloner, 2017; Wen, Hockenberry, Borders, & Druss, 2017). Now that several years have passed since most states expanded Medicaid (Kaiser Family Foundation, 2017), an examination of MAT admission by state expansion status and individual health insurance status will indicate the relationship between this policy and MAT admissions.

There is a lack of empirical evidence on subgroup-specific trends in MAT admissions, which hinders efforts to overcome gaps in MAT access. For example, while studies show increased frequency of MAT admissions since 1999 , they do not report on characteristics of these admissions. Moreover, studies document enrollment and retention in MAT among co-users, but they do not assess whether MAT enrollment keeps pace with the growth in co-use and shifts in characteristics of opioid users (Jones, Campopiano, Baldwin, & McCance-Katz, 2015; Sigmon, 2014; Volkow et al., 2014). Previous literature indicates that younger age, White race relative to other races, non-urban residence, lower socioeconomic status, lack of health insurance and delayed admission are associated with

greater barriers to treatment enrollment (Deck & Carlson, 2004; Kwiatkowski, Booth, & Lloyd, 2000; Peterson et al., 2010).

Treatment completion is an important but understudied indicator of effective MAT use. Completion meaningfully measures long-term treatment outcomes as those who drop out or are expelled from treatment usually relapse to opioid use and associated risks (Fullerton et al., 2014; Zhang, Friedmann, & Gerstein, 2003). Less than half of opioid users who initiate any type of treatment complete it, and MAT-specific rates are likely to be lower given the stigma associated with MAT, treatment costs, and length of treatment often required (Saloner & Cook, 2013; Substance Abuse and Mental Health Services Administration, 2014). Treatment completion rates are lower for co-use compared to PO- and heroin-only use among opioid users accessing office-based buprenorphine services, a small proportion of all MAT programs (Alderks, 2017; Moore et al., 2007; Nielsen, Hillhouse, Mooney, Ang, & Ling, 2013; Potter et al., 2013). In these studies, treatment completion is associated with female sex, White race relative to other races, younger age and higher SES (Moore et al., 2007; Neumann, Blondell, Azadfard, Nathan, & Homish, 2013). The majority of MAT clients, nearly 60%, access services in outpatient MAT programs, while the others access MAT in physicians' offices, inpatient programs, and detoxification settings. Therefore, information on completion by demographics and opioid use type in outpatient MAT programs will identify gaps in service delivery and inform targeting of efforts to overcome them (Saloner & Karthikeyan, 2015; Substance Abuse and Mental Health Administration, 2014).

Changes to healthcare access under ACA and guidelines related to provider screening and referral may influence treatment completion. By reducing the cost

associated with treatment use, these initiatives might increase the likelihood of completing treatment (Bao et al., 2016; Gabay, 2015). In light of these changes, and greater involvement with opioid-using patients, provider referrals may now be a useful strategy to improve MAT completion rates (Dowell, Haegerich, & Chou, 2016; Strathdee & Beyrer, 2015). Historically, provider referrals to MAT are not associated with treatment completion, but criminal justice referrals are (Ali, Teich, & Mutter, 2017; Arndt, Acion, & White, 2013; Brady et al., 2005; Magura, Nwakeze, & Demsky, 1998). Additionally, healthcare-related efforts to increase MAT demand may create delays in admission. Delayed admission undermines and individuals motivation for and confidence in services, therefore serving as a barrier to completion as well as enrollment (Albrecht, Lindsay, & Terplan, 2011; Kaplan & Johri, 2000). An examination of the relationship between immediate admission and treatment completion will identify subgroups that benefit from prioritized treatment on demand.

Andersen's Behavioral Model of Health Services is a useful framework for exploring subgroup-specific trends in MAT admissions and disparities in treatment completion. This model examines service use as a function of need for care, enabling factors and predisposing characteristics (Andersen & Aday, 1978; Andersen, 1995). Previous research employs the model to examine service use among people who use drugs, including MAT use (Andersen et al., 2000; Deck & Carlson, 2004; Maru et al., 2008). The demographics associated with admission and completion can be explored as predisposing characteristics, initiatives to increase access to healthcare access as enabling factors, and co-use of both POs and heroin as an indicator of need. This analysis will identify gaps in service delivery, inform strategies to increase MAT admissions among current opioid-using population and improve completion rates among those with the greatest need.

Guided by Andersen's Model, this study aims to 1) examine national trends in MAT admissions across opioid use types (i.e. PO only, heroin only, and co-use) dimensions of

healthcare access (i.e. Medicaid expansion status, health insurance coverage, referral source, and immediate admission), and demographics; and 2) assess differences in treatment completion by opioid use type and determine whether access to healthcare influences this relationship. With the recent growth in co-use, evidence of the association between co-use and poorer outcomes, and implementation of initiatives to increase access to treatment, we hypothesize that the overall increase in admissions will mask slower growth among co-users and other subgroups with growing rates of opioid use (e.g. females, non-Hispanic Whites, non-urban residence). In terms of MAT completion, we hypothesize that compared to PO-only use, treatment completion is less likely for co-use but dimensions of healthcare access, including health insurance coverage and a healthcare provider referral, strengthen treatment completion among co-users. Use of data across 12 years will provide nationally relevant information on the disparities in MAT admissions and on enabling factors that increase the likelihood of treatment completion. Findings will help target strategies to improve MAT admission and completion. This is critical and timely given the recent shifts in opioid use, access to healthcare through ACA, and policies to respond to opioid use (Buck, 2011; Compton, Jones, & Baldwin, 2016).

2. Methods

2.1. Data sources

The Treatment Episodes Data Set (TEDS) is the Substance Abuse and Mental Health Services Administration's (SAMHSA) national census data system of annual admissions to public and private substance abuse treatment facilities receiving funds from the state or federal government and state-certification to provide treatment (Substance Abuse and Mental Health Administration, 2013). TEDS does not include treatment received in private physicians' offices, facilities that do not receive public funds, or emergency departments. At intake, treatment programs

record the demographic, substance use, and treatment characteristics of each admission, which SAMHSA made available as Treatment Episodes Dataset-Admissions (TEDS-A) from 1992 to 2015. Beginning in 2006, SAMHSA linked admissions data to discharge data, included discharge information, and made the data available as Treatment Episodes Dataset-Discharges (TEDS-D). Facilities in all 50 states and Washington, DC submit this data to the federal government on a yearly basis. This study combined TEDS-A admission data from 2004-2015 and TEDS-D discharge data from 2013, the last year available at the time of submission.

2.2. Measures

2.2.1. Outcomes: MAT use

We examined MAT use in two ways. First, we examined frequency of MAT admissions. We restricted analyses to admissions 1) among adults (aged 18 and older), 2) where use of opioid medications was part of the treatment plan, 3) for use of opioids (i.e. heroin and/or POs) and 4) in outpatient treatment settings. Outpatient settings constitute over 90% of all opioid treatment programs (Substance Abuse and Mental Health Administration, 2014). Although there is substantive interest in repeated treatment admissions, this study is limited to first-time admissions only to maintain independence of observations. Previous studies indicate similar treatment outcomes between first timers and repeaters, suggesting generalizability to all treatment admissions (Cacciola, Dugosh, & Camilleri, 2009; Magura et al., 1998).

Second, we examined MAT use as successful treatment completion. Discharge due to treatment completion was compared to treatment dropout (i.e. patient left against professional advice, was terminated by the facility or was incarcerated).

2.2.2. Exposure variables: Need, enabling factors and predisposing factors

Indicator of need: Opioid use type. Clients self-report primary, secondary and tertiary problem substance use at admission. We categorized opioid use type as PO and heroin co-use when a client indicated both POs (e.g. non-prescription methadone, buprenorphine, codeine, hydrocodone, hydromorphone, meperidine, morphine, opium, oxycodone, pentazocine, propoxyphene, tramadol, and any other drug with morphine-like effects) and heroin as a primary, secondary, or tertiary problem substance. We defined heroin-only and PO-only opioid use where heroin and POs, respectively, were the only opioids indicated at admission.

Enabling factors: Access to healthcare. We examined health insurance coverage as covered (i.e. admissions with private or public [Medicaid, Medicare] insurance) and not covered (i.e. clients reporting no health insurance coverage).

We relied on data from the Kaiser Family Foundation to construct our Medicaid expansion variable. Variation in state-level expansion of Medicaid allowed us to study patterns in treatment use by adoption status. Based on the location of the MAT facility, Medicaid expansion indicates an admission or discharge in one of the 25 states or Washington, DC where Medicaid expanded by the start of 2014 (Kaiser Family Foundation, 2017). This also includes states with approved Section 1115 waivers to implement Medicaid expansion (Kaiser Family Foundation, 2018).

We categorized referral to MAT as healthcare provider (referral from a community program, alcohol/drug abuse care provider, or other healthcare provider), court or criminal justice referral, or self/other referral (self, individual, school, employer, or other).

Facilities report the number of days waiting from first contact or request for service to provision of first clinical service. We defined immediate MAT access as waiting zero days and delayed access as waiting one or more days. We classified

delayed admission as waiting one or more days since it is associated with failing to initiate or complete treatment and indicates that treatment demand exceeds capacity (Kaplan & Johri, 2000).

Predisposing characteristics: Demographics. We included the following demographic characteristics assessed at the time of admission: sex (male or female); age (18-25, 26-34, 35-49, and 50+); race (non-Hispanic White, non-Hispanic Black, non-Hispanic other, and Hispanic); highest level of education (less than high school, high school graduate, college graduate); employment status (employed, unemployed, not in labor force); and rurality (non-urban, urban) of the treatment facility. To measure rurality, TEDS indicates whether a treatment facility is located in a core-based statistical area (CBSA) with a population of at least 10,000 people. Following the US Census Bureau definition (Ratcliffe, Burd, Holder, & Fields, 2016), we define rurality as urban for admissions located in a CBSA and non-urban for those not located in a CBSA.

2.3. Statistical analyses

We began the analyses with descriptive characteristics of the study population and examined distributions across each exposure and outcome variable. We used data from 2004-2015 to compute trends in MAT admissions overall, and in each opioid use type, access to healthcare, and demographic category. We examined the 12-year trends for each variable and modeled percent change as the difference between the frequency of admissions between 2015 and 2004. Using the Cochran-Armitage trend test (one-sided), we tested linear change in frequency of admissions across time (Agresti, 2003). After examining 12-year trends across each variable, we summarized using four-year intervals and the last year of data available (2004, 2008, 2012 and 2015). This approach best captured the major changes in admissions over time and synthesized the abundance of data. To characterize MAT admissions by opioid use type, we used data from 2015 to compute

frequencies across demographic and access to healthcare characteristics overall, and by opioid use type. We used bivariate logistic regression models to assess the odds of admission for co-use, compared to NMPO- and heroin-only use, across dimensions of healthcare access and demographic characteristics.

We also used discharge data from 2013 TEDS-D to examine successful MAT completion and began by removing observations discharged for another reason (i.e. transferred to another facility, death, other), representing 1,333 (8.76%) discharges. Bivariate analyses using chi-square tests assessed the relationship between treatment completion and opioid use type, access to healthcare, and demographic characteristics. To produce adjusted odds ratios for opioid use type and demographic variables, we used multivariable logistic regression models that included all demographic, access to healthcare, and opioid use type variables found significant in the bivariate analysis. For each access to healthcare variable, we assessed the interaction between multivariable opioid use type and healthcare access to determine whether the relationship between treatment completion and healthcare access differed by opioid use type. The omnibus test identified significant interaction terms and the simple slopes approach to probing interactions produced stratified estimates at each level of opioid use type (Cohen, Cohen, West, & Aiken, 2013). We did not use a multi-level modeling approach since our data represent a census of states and admissions that meet TEDS criteria, rather than a sample, and there was no substantive rationale for modeling random state-level effects (Greenland, 2000; West, 2016). Significance was determined at p<0.05, and we performed all analyses using SAS version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. MAT admissions

Overall, there were 299,833 first time, outpatient MAT admissions among individuals reporting opioid use from 2004 to 2015. The number of admissions increased 143% from 18,141 in 2004 to 44,086 in 2015, with the largest increase occurring from 2014 to 2015. The proportion of all first time, outpatient treatment admissions that used MAT as part of the plan also increased 122% from 6.17% in 2004 to 13.69% in 2015.

Need. The number of admissions increased in every category of opioid use type, but the greatest increase was among PO-only (287%; p for linear trend <0.001), followed by PO and heroin co-use (128%; p for linear trend <0.001) and heroin-only use (117%; p for linear trend <0.001). Most MAT admissions were for heroin-only use (Figure 1). The proportion of MAT admissions for heroin-only use decreased 8% from 2004 to 2015, while it increased 8% for PO-only use, and remained stable (between 10-15%) in the co-use group.

Enabling factors. In 2004, MAT admissions were roughly split by health insurance coverage status but among those with health insurance, admissions grew 419% and made up 88% of all admissions by 2015. Individuals without health insurance were the only group with decreased MAT admissions. The frequency of MAT admissions rose 161% in states that adopted Medicaid expansion and stayed stable in states without expansion. From 2004-2015, the majority of admissions were among those in Medicaid expansion states (81-95%), those with self or other referrals (78-82%). Admissions referred by healthcare providers grew 139%, compared to a 48% and 155% growth in criminal justice and self/other referral, respectively. The frequency of immediate and delayed admissions

increased 852% and 180%, respectively, and 83% of admissions experienced

treatment on demand in 2015.

Predisposing characteristics. Non-urban admissions constituted 5% of all

admissions in 2004 and grew 2,112% to make up just under half of all admissions

by 2015. In terms of age, MAT admissions grew the most (223%) among 26-34 year

olds to constitute 37% of all admissions by 2015 while the proportion of admissions

either decreased or remained stable among the other age groups (18-23, 35-49 and

50+). From 2004 to 2015, most MAT admissions were among males (56-64%), non-

Hispanic whites (60-70%), those with high school diplomas/some college education

(45-52%), never married individuals (55-68%), and those not employed or in the

labor force (66%-73%). The only group without a significant linear trend in

frequency was those not in labor force. (Table 1).

Table 2 details differences in predisposing characteristics and enabling factors of

2015 MAT admissions by type of opioid use. Compared to PO- and heroin-only use, MAT

admissions for co-use are significantly less likely to be in Medicaid expansion states,

covered by health insurance, and experience immediate admission. Referrals from

healthcare providers and the criminal justice system were more likely among

admissions for co-use, compared to heroin-only use. Admissions for co-use significantly

differed from those for PO- and heroin-only use according to sex, age, race/ethnicity,

rurality, and employment status. Compared to PO-only and heroin-only use, admissions

for co-use were more likely to be under age 50 (compared to age 50+), non-Hispanic

White (compared to non-Hispanic Black), in urban facilities (compared to non-urban),

and unemployed (compared to employed). With regard to sex, compared to co-use

admissions, those for PO-only use were more likely to be female and those for heroin-

only were more likely to be male. Compared to heroin-only use admissions, co-use

admissions were more likely to be college graduates, compared to less educational attainment.

3.2. Successful treatment completion

In 2013, there were 13,883 first-time admissions discharged from MAT, representing 22.79% of discharges. In analyses adjusting for predisposing, enabling and need factors, odds of MAT completion were significantly lower for heroin-only use (AOR 0.70, 95% CI 0.54, 0.90) but not significantly different for PO-only use, compared to discharges for co-use. Healthcare (AOR 1.37, 95% CI 1.26, 1.48) and criminal justice referrals (AOR 2.27, 95% CI 1.96, 2.63), compared to self/other referral, were significantly associated with increased odds of treatment completion. Medicaid expansion (AOR 0.48, 95% CI 0.39, 0.59) was associated with decreased odds of treatment completion overall. In terms of predisposing factors, age was the only demographic characteristic not associated with treatment completion while odds of completion were significantly higher among female, non-Hispanic white (compared to non-Hispanic blacks), urban, college educated (compared to less than high school graduated), and employed (compared to unemployed) admissions (Table 3).

Opioid use type significantly moderated the relationship between treatment completion and Medicaid expansion, referral source and immediate admission (Table 4). In states with Medicaid expansion, treatment completion was less likely overall (AOR 0.53, 95% CI 0.37, 0.74), but Medicaid expansion was not significantly associated with completion for PO-only and co-use. For both PO-only and heroin-only use, healthcare referrals (PO-only: AOR 2.64, 95% CI 1.90, 3.67; heroin-only: AOR 2.53, 95% CI 1.72, 3.73) were most predictive of treatment completion. For co-use, criminal justice referral (AOR 5.36, 95% CI 4.01, 7.16) was the greatest predictor of treatment completion. The relationship between health insurance coverage and treatment completion was not significant overall, or for any

category or opioid use. Immediate admission was associated with completion among for heroin-only use (AOR 1.33, 95% CI 1.04, 1.72) but not for other types of opioid use.

4. Discussion

From 2004-2015, enrollment in outpatient MAT services increased substantially, with notable differences by opioid use type. Guided by the Behavioral Model of Health Services, we explored trends in MAT admissions and factors related to successful MAT completion, compared to dropout. Per the model, we explored these outcomes with demographics as predisposing factors, type of opioid use as an indicator of need, and dimensions of healthcare access as enabling factors (Andersen & Aday, 1978; Deck & Carlson, 2004).

4.1. Predisposing factors

Admissions in rural areas grew more than any other subgroup, which is consistent with facility-level data regarding the reduced shortage of MAT facilities in non-urban counties (Dick et al., 2015) and shows progress toward meeting the need for improved treatment availability in rural areas. Barriers to providing those services include physical access and transportation issues and this increase may signal that efforts to overcome these barriers are starting to work (Keyes, Cerdá, Brady, Havens, & Galea, 2014; Kuehn, 2014; Paulozzi & Xi, 2008). However, the odds of successful treatment completion were significantly higher in urban settings, calling for additional measures to address barriers to retention in non-urban settings. These may include reducing travel time and the frequency of visits by providing take-home dosing and integrating mobile technologies that provide psychosocial and adherence support at a distance (Hall et al., 2014; Sigmon, 2014). These findings highlight a need to evaluate barriers to MAT completion in non-urban settings and strategies to address them.

Our findings were also consistent with past literature on differences in demographic characteristics of admissions by opioid use type. The majority of MAT admissions are among non-Hispanic Whites and admissions for co-use were more likely to be non-Hispanic White, compared to heroin- and PO-only, aligning with dynamic patterns in use (Pouget, Fong, & Rosenblum, 2017). Findings regarding sex aligned with previous work; compared to admissions for co-use, those for PO-only use are more likely to be female and those for heroin-only use are more likely to be male (McCabe et al., 2013; Potter et al., 2013). Diverging from previous studies, we found that males were less likely than females to complete treatment (Gundel, Allen III, Osborne, & Shwayhat, 2017). Sex-disaggregated analyses by opioid use type are required to distill sex-specific disparities and to target services that improve treatment outcomes. We also demonstrate the importance of education and employment for treatment completion, particularly among those accessing publicly funded treatment facilities. These factors are dimensions of socioeconomic status, which is associated with facilitators of treatment retention, including treatment costs, transportation and a support network (Albrecht et al., 2011).

4.2. Need

In response to growing rates in PO abuse and heroin use, the increasing trend in MAT admissions from 2004 to 2015 demonstrates headway in fighting the opioid epidemic. Policies and programs that expand access must continue. The overall positive trend masks slower growth in some subgroups, underscoring the importance of subgroup-specific analyses. We observed the largest growth in MAT admissions among those reporting PO-only use. Both the frequency and proportion of admissions among co-users grew, but at a slower rate. Co-users are the fastest growing subgroup of opioid users, so strategies to improve MAT access should make concerted efforts to focus on those who co-use (Mital et al., 2018). Compared to co-users, heroin-only users are more likely to enroll in MAT and

dropout, while PO-only users have higher odds of treatment completion, highlighting

the need for different strategies to improve treatment use for different groups of opioid

users (Gundel et al., 2017).

4.3. Enabling factors

These analyses with data through 2015 confirm that it takes time to see changes in

MAT enrollment as a function of Medicaid expansion (Carr et al., 2008; Maclean &

Saloner, 2017). Our findings show that growth in MAT admissions occurred in tandem

with an increase in the number of facilities providing MAT, growth in funding for MAT

prescriptions, and implementation of federal initiatives to improve healthcare access

(Alderks, 2017; Clemans-Cope, Epstein, & Kenney, 2017). This is particularly evident in

the substantial increase from 2014 to 2015, which parallels adoption of Medicaid

expansion by 25 states and Washington, DC by the start of 2014 (Kaiser Family

Foundation, 2017). We found that MAT admissions grew among those with health

insurance coverage. This complements increased prevalence of health insurance

coverage among those with substance abuse issues, including heroin abuse, a likely

effect of Medicaid expansion (Jones, Logan, et al., 2015; McLellan & Woodworth, 2014;

Volkow et al., 2014). The decline in admissions among those not covered by health

insurance highlights an emerging gap in access for the uninsured (Barry & Huskamp

2011; Feder et al., 2017). Continued systems-level initiatives to make evidence-based

treatment of problem opioid use at low or no cost would further expand access

(D'Onofrio et al., 2015). We found no association between insurance status and

successful MAT completion. Use of data from publicly funded treatment facilities may

have muted the effect, as private insurance is associated with treatment success in prior

research, likely because subsidized cost is associated with retention and publicly funded

treatment programs offer services at a subsidized rate (Maclean & Saloner, 2017).

Finally, findings related to referral source and immediate admission are consistent with previous studies and have important public health implications. The small proportion of MAT admissions referred from healthcare providers in our sample may be due to provider preference to refer patients to detoxification or rehabilitation services or to substance use treatment programs integrated into general healthcare (Gryczynski, Schwartz, Salkever, Mitchell, & Jaffe, 2011). The latter was part of ACA efforts to improve availability of treatment, including office-based buprenorphine, which TEDS does not capture (Maclean & Saloner, 2017). While referrals from healthcare providers are less likely among admissions for co-use, compared to PO-only admissions, the relationship between referrals from healthcare providers and treatment completion is strongest for co-use, compared to PO- and heroin only-use. These findings point to the importance of screening for use of multiple substances in healthcare settings and referring those with poly-substance use problems to treatment. Facility-level data on increased capacity of MAT underscore our results related to the increased number and proportion of MAT admissions immediately admitted (Alderks, 2017). These findings are encouraging, as treatment on demand predicts treatment success, particularly for co-use. The higher likelihood of delayed admission among co-users compared to PO and heroin only use, found here and in previous studies (Gryczynski et al., 2011), requires further investigation. We found that immediate admission positively affects treatment completion among heroin-only, so treatment programs and referral sources should prioritize this group for treatment on demand.

4.4. Limitations

This study has several limitations. Although we used a large, national survey of annual admissions and discharges, state-level reporting was incomplete and 5.76% of admissions did not indicate whether use of opioid medications were part of the treatment plan. Only substance abuse treatment facilities receiving public funds and state certification to provide

treatment are required to submit data to TEDS. Therefore, findings do not include all

MAT use. The inability to describe admissions in private treatment facilities and

determine any differences from those accessing publicly funded MAT is a significant

limitation to generalizability. In 2002, FDA began permitting physicians who obtain

specialized training and a waiver to prescribe buprenorphine outside of substance

abuse treatment facilities and in take-away doses, which is associated with improved

retention. Therefore, these findings underestimate new MAT admissions and the

relationship with access to healthcare, as those with access to healthcare through

insurance may be more likely to initiate MAT in a physician's office. Future research

should explore the relevancy of findings to clients who access MAT outside of publicly

funded facilities.

The variables available in TEDS served as another limitation. According to

Andersen's model, systems- and facility-level characteristics influence use of health

services (Andersen, 1995). However, factors such as facility size, patient-to-provider

ratio, and service offerings are not included in TEDS. Variables such as length of

retention in MAT and outcomes of treatment including reduced opioid use may be

better measures of MAT success, but are not available in TEDS. We could only assess

whether health insurance covered the individual admitted, not necessarily the

treatment admission, highlighting the need to compare our findings against studies

that directly assess use of health insurance to access MAT. Residual confounding

may also be an issue as we are limited to variables available in these data sources. In

the future, variables available from other data sources may improve exploration of

additional predisposing, enabling and need factors associated with treatment use.

Use of serial, cross-sectional data limits our ability to make conclusions about

individual trends or within-person patterns over time.

Finally, states are encouraged, but not required, to report the number of days between first patient contact and delivery of the first clinical service following admission. Therefore, it is possible that programs with long waiting lists were less likely to report this information resulting in findings that represent a subset of treatment programs. Requiring reporting of admission delays would improve generalizability.

4.5. Conclusion

Despite these limitations, this study makes a meaningful contribution by describing recent trends in MAT enrollment and completion and establishing relationships between improved access to healthcare and these indicators of MAT use. Trends in opioid use are dynamic. MAT is a valuable component of a more comprehensive approach to prevent and respond to increased problem use and related outcomes. These findings highlight gaps in service delivery, including the need to improve MAT access among people who co-use POs and heroin, a growing and understudied group of opioid users. Findings point to policies and interventions with potential to tackle the opioid epidemic.

5. Tables and Figures

Figure 1. MAT admissions overall and by problem opioid use type—2004-2015, TEDS-A
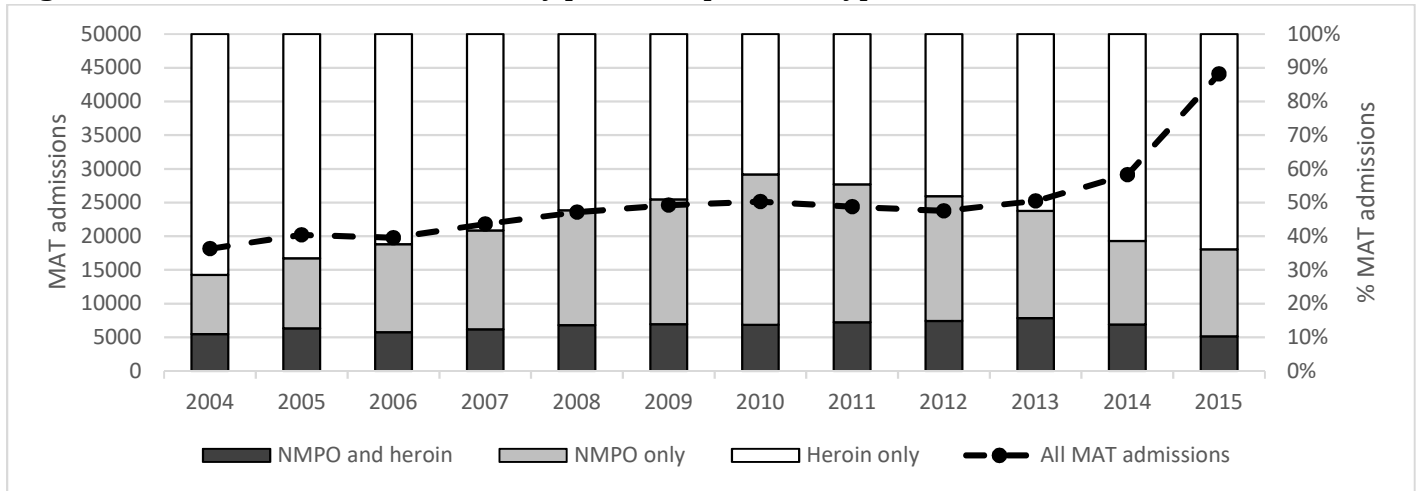
Table 1. Problem opioid use type, demographic, and access to healthcare characteristics among MAT admissions—2004-2015, TEDS-A

	2004		2008		2012		2015		% change 2004 to 2015	p-value trend
	N	(%)	N	(%)	N	(%)	N	(%)		
All MAT admissions	18,141		23,581		23,742		44,086		143%	<0.001
Need: Problem opioid use type										
PO only	3,178	(18)	8,035	(34)	8,789	(37)	11,367	(26)	258%	<0.001
Heroin only	12,973	(72)	12,330	(49)	11,432	(48)	28,173	(64)	117%	<0.001
PO and heroin	1,990	(11)	3,216	(14)	3,521	(15)	4,546	(10)	128%	<0.01
Predisposing characteristics										
Sex										
Male	11,159	(62)	14,047	(60)	13,387	(56)	24,566	(56)	120%	<0.001
Female	6,978	(38)	9,528	(40)	10,355	(44)	19,514	(44)	180%	<0.001
Age										
18-25	2,836	(16)	4,812	(20)	4,798	(20)	5,710	(13)	101%	<0.001
26-34	5,017	(28)	7,718	(33)	9,114	(38)	16,194	(37)	223%	<0.001
35-49	5,281	(29)	5,217	(22)	4,440	(19)	8,976	(20)	70%	<0.001
50+	5,007	(28)	5,834	(25)	5,390	(23)	13,206	(30)	164%	<0.01
Race/ethnicity										
NH white	10,810	(60)	15,680	(67)	16,569	(70)	26,983	(64)	150%	<0.001
NH black	3,579	(20)	2,886	(12)	2,553	(11)	8,235	(19)	130%	<0.001
NH other	645	(4)	883	(4)	981	(4)	1,486	(4)	130%	<0.001
Hispanic	3,073	(17)	3,979	(17)	3,559	(15)	5,542	(13)	80%	<0.001
Rurality										
Non-urban	954	(5)	1,645	(7)	3,242	(14)	21,104	(48)	2,112%	<0.001
Urban	17,187	(95)	21,936	(93)	20,500	(86)	22,982	(52)	34%	<0.001
Education										
Less than HS	6,113	(34)	7,182	(31)	6,723	(29)	11,088	(28)	81%	<0.001
HS graduate/Some college	8,036	(45)	10,926	(47)	10,923	(47)	20,362	(52)	153%	<0.001
College grad	3,702	(21)	5,068	(22)	5,555	(24)	7,815	(20)	111%	<0.01
Employment status										
Employed	5,669	(32)	7,869	(34)	6,323	(27)	11,989	(27)	111%	<0.001
Unemployed	5,340	(30)	8,004	(34)	9,779	(42)	15,771	(36)	195%	<0.001
Not in labor force	6,789	(38)	7,433	(32)	7,382	(31)	16,119	(37)	137%	NS
Marital status										
Currently/previously married	5,776	(45)	7,531	(43)	6,392	(40)	9,941	(32)	72%	<0.001
Never married	7,073	(55)	9,910	(57)	9,683	(60)	20,972	(68)	197%	<0.001
Enabling factors										
Health insurance coverage										
Covered	3,934	(48)	4,235	(44)	4,740	(56)	20,428	(88)	419%	<0.001
Not Covered	4,314	(52)	5,365	(56)	3,670	(44)	2,725	(12)	-37%	<0.001
Medicaid expansion										
Yes	16,110	(89)	19,212	(81)	20,856	(88)	41,996	(95)	161%	<0.001
No	2,031	(11)	4,369	(19)	2,886	(12)	2,090	(5)	3%	<0.001
Referral source										
Healthcare	2,798	(15)	3,547	(14)	3,249	(14)	6,682	(15)	139%	<0.001
Criminal justice	755	(4)	667	(3)	654	(3)	1123	(3)	48%	<0.001
Self/other	14,160	(78)	18,980	(80)	19,468	(82)	36,106	(82)	155%	<0.001
Immediate admission										
Yes	3,044	(59)	10,317	(71)	11,866	(70)	28,968	(83)	852%	<0.001
No	2,095	(41)	4,184	(29)	5,133	(30)	5,872	(17)	180%	<0.001

Proportions may not sum to 100% due to rounding; NS = Not significant at p<0.05.

Table 2. Demographic and access to health care characteristics among MAT admissions, and differences by opiate use type—TEDS-A, 2015, N=44,086

Characteristic	PO-only (PO)	Heroin-only (HO)	PO & heroin (CO)	CO vs PO	CO vs HO
	N=11,367 (%)	N=28,173 (%)	N=4,546 (%)	OR (95% CI)	OR (95% CI)
Predisposing characteristics					
Sex[a]					
Male	5162 (45)	16,862 (60)	2,542 (56)	**1.53 (1.42, 1.63)**	**0.85 (0.80, 0.91)**
Female	6204 (55)	11,306 (40)	2,004 (44)	Ref	Ref
Age					
18-25	1316 (12)	3,581 (13)	813 (18)	**2.26 (2.00, 2.55)**	**3.26 (2.93, 3.64)**
26-34	4,829 (42)	9,166 (33)	2,199 (48)	**1.67 (1.51, 1.84)**	**3.45 (3.15, 3.77)**
35-49	2,683 (24)	5,453 (19)	840 (18)	**1.15 (1.02, 1.28)**	**2.21 (1.99, 2.46)**
50+	2,539 (22)	9,973 (35)	694 (15)	Ref	Ref
Race/ethnicity[b]					
NH black	1,106 (10)	6,903 (26)	226 (5)	**0.46 (0.40, 0.54)**	**0.13 (0.12, 0.15)**
NH other	407 (4)	895 (3)	184 (4)	1.03 (0.86, 1.23)	**0.84 (0.72, 0.99)**
Hispanic	916 (8)	4,228 (16)	398 (9)	0.99 (0.87, 1.12)	**0.39 (0.35, 0.43)**
NH white	8,323 (77)	14,994 (55)	3,666 (81)	Ref	Ref
Rurality					
Urban	5,369 (47)	14,710 (52)	2,903 (64)	**1.97 (1.84, 2.12)**	**1.62 (1.52, 1.73)**
Non-urban	5,998 (53)	13,463 (48)	1,643 (36)	Ref	Ref
Education[c]					
Less than HS	2,178 (23)	7,842 (31)	1,068 (24)	1.02 (0.92, 1.13)	**0.51 (0.46, 0.56)**
HS graduate/ Some college	5,039 (52)	13,070 (52)	2,253 (50)	0.93 (0.85, 1.01)	**0.64 (0.59, 0.69)**
College grad	2,388 (25)	4,277 (17)	1,150 (26)	Ref	Ref
Employment status[d]					
Unemployed	3,634 (32)	10,460 (37)	1,677 (37)	**1.19 (1.09, 1.29)**	**0.69 (0.61, 0.75)**
Not in labor force	3,773 (33)	11,017 (39)	1,329 (29)	0.91 (0.83, 0.99)	**0.52 (0.48, 0.56)**
Employed	3,907 (34)	6,561 (23)	1,521 (34)	Ref	Ref
Enabling factors: Access to healthcare					
Health insurance coverage[e]	5,479 (90)	13,771 (89)	1,178 (76)	**0.37 (0.32, 0.43)**	**0.41 (0.36, 0.47)**
Medicaid expansion	10,377 (91)	27,527 (98)	4,092 (90)	**0.86 (0.77, 0.97)**	**0.21 (0.19, 0.24)**
Healthcare referral[f]	2,267 (20)	3,667 (13)	748 (17)	**0.79 (0.72, 0.87)**	**1.31 (1.22, 1.45)**
Criminal justice referral[f]	334 (3)	661 (2)	128 (3)	0.92 (0.75, 1.13)	**1.26 (1.04, 1.53)**
Immediate admission[g]	7,180 (82)	19,826 (85)	1,962 (73)	**0.60 (0.54, 0.67)**	**0.49 (0.44, 0.51)**

[a] Sex missing for 6 (0.02% of) MAT admissions

[b] Race missing for 1,840 (4.17% of) MAT admissions

[c] Education missing for 4,821 (10.94% of) MAT admissions

[d] Employment status missing for 207 (0.47% of) MAT admissions

[e] Health insurance coverage missing for 20,933 (41.62% of) MAT admissions

[f] Referral source missing for 504 (1.14% of) MAT admissions; Reference group is self/other referral source.

[g] Delayed admission missing for 9,246 (20.97% of) MAT admissions

Proportions may not sum to 100% due to rounding.

Bolded values indicate p<0.05.

Table 3. Association of opioid use type and demographics with successful MAT completion—2013 TEDS-D, N=13,883

Characteristic	All discharges N (%)	Completed N (%)	X² p-value	AOR (95% CI)*
All MAT admissions	13,883 (100)	3,164 (22.79)	--	-- --
Need: Problem opioid use type				
PO only	3,934 (29.16)	1,135 (37.83)	**<0.05**	1.19 (0.93, 1.51)
Heroin only	7,641 (56.64)	1,460 (48.67)		**0.70 (0.54, 0.90)**
PO and heroin	1,916 (14.20)	405 (13.50)		Ref
Predisposing characteristics: Demographics				
Sex				
Male	8,318 (59.92)	1,838 (58.09)	**<0.05**	**0.79 (0.65, 0.94)**
Female	5,563 (40.07)	1,324 (41.85)		Ref
Age				
18-25	2,758 (19.91)	690 (21.91)	**<0.05**	0.74 (0.54, 1.01)
26-34	5,183 (37.42)	1,239 (39.35)		0.76 (0.56, 1.00)
35-49	2,572 (18.57)	530 (16.83)		0.90 (0.67, 1.21)
50+	3,337 (24.09)	690 (21.91)		Ref
Race/ethnicity				
NH black	1,773 (12.83)	241 (7.66)	**<0.05**	**0.44 (0.31, 0.62)**
NH other	625 (4.52)	130 (4.13)		0.67 (0.35, 1.29)
Hispanic	2,398 (17.35)	543 (17.25)		1.01 (0.71, 1.43)
NH white	9,025 (65.30)	2,234 (70.97)		Ref
Rurality				
Urban	12,191 (87.81)	379 (11.98)	0.68	**1.31 (1.03, 1.68)**
Non-urban	1,692 (12.19)	2,785 (88.02)		Ref
Education				
Less than HS	4,032 (29.53)	713 (22.97)	**<0.05**	**0.60 (0.46, 0.77)**
HS graduate/ Some college	6,701 (49.08)	1,629 (52.48)		0.84 (0.67, 1.05)
College grad	2,921 (21.39)	762 (24.55))		Ref
Employment status				
Unemployed	3,687 (26.81)	1,027 (32.72)	**<0.05**	**0.81 (0.65, 0.99)**
Not in labor force	5,546 (40.33)	1,186 (37.78)		0.93 (0.72, 1.20)
Employed	4,518 (32.86)	926 (29.50)		Ref

Analyses completed after removing observations missing discharge reason variable (0.9% observations).

Multivariable logistic regression calculated with treatment dropout as reference (Ref) category.
Bolded values indicate $p<0.05$.
*AORs are adjusted for variables significant in bivariate analyses, including enabling factors listed in Table 4.

Table 4. Association between access to healthcare and successful MAT completion, stratified by opioid use type—2013 TEDS-D, N=13,883

Enabling factors: Access to healthcare	All discharges	Completed	X² p-value	All opioids	PO-only	Heroin-only	Co-use
	N (%)	N (%)		AOR (95% CI)*	AOR (95% CI)*	AOR (95% CI)*	AOR (95% CI)*
Health insurance coverage							
Covered	2,173 (54.70)	521 (54.33)	0.80	0.98 (0.81, 1.19)	0.88 (0.70, 1.09)	1.03 (0.80, 1.32)	1.02 (0.76, 1.35)
Not covered	2,624 (45.30)	438 (45.67)		Ref	Ref	Ref	Ref
Medicaid expansion state							
Yes	12,731 (91.91)	2,819 (89.21)	<0.05	0.48 (0.39, 0.59)**	0.90 (0.71, 1.14)	0.53 (0.37, 0.74)	0.90 (0.64, 1.27)
No	1,120 (8.09)	341 (10.79)		Ref	Ref	Ref	Ref
Referral source							
Healthcare	1,729 (12.64)	470 (15.05)	<0.05	2.55 (2.03, 3.22)	2.64 (1.90, 3.67)	2.53 (1.72, 3.73)	3.30 (1.97, 5.53)
Criminal justice	526 (3.85)	218 (6.98)		4.10 (2.93, 5.75)**	2.40 (1.24, 4.64)	2.35 (1.30, 4.23)	5.36 (4.01, 7.16)
Self/other	11,425 (83.52)	2,434 (77.96)		Ref	Ref	Ref	Ref
Immediate admission							
Yes	7,273 (74.31)	1,856 (78.38)	<0.05	0.90 (0.75, 1.08)**	0.76 (0.56, 1.03)	1.33 (1.04, 1.72)	1.24 (0.85, 1.80)
No	2,515 (25.69)	512 (21.62)		Ref	Ref	Ref	Ref

Analyses completed after removing observations missing discharge reason variable (0.9% observations).
Multivariable logistic regression calculated with treatment dropout as reference (Ref) category.
Bolded values indicate p<0.05.
*AORs are adjusted for variables significant in bivariate analyses, including predisposing factors listed in Table 3.
**Moderation significant at p<0.05.

6. References

Agresti, A. (2003). *Categorical data analysis* (Vol. 482): John Wiley & Sons.

Albrecht, J., Lindsay, B., & Terplan, M. (2011). Effect of waiting time on substance abuse treatment completion in pregnant women. *Journal of substance abuse treatment, 41*(1), 71-77.

Alderks, C. E. (2017). Trends in the use of methadone, buprenorphine, and extended-release naltrexone at substance abuse treatment facilities: 2003–2015 (update). In *The CBHSQ report: August 22, 2017*: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Rockville, MD.

Ali, M. M., Teich, J. L., & Mutter, R. (2017). Reasons for Not Seeking Substance Use Disorder Treatment: Variations by Health Insurance Coverage. *The journal of behavioral health services & research, 44*(1), 63-74.

Amato, L., Davoli, M., Perucci, C. A., Ferri, M., Faggiano, F., & Mattick, R. P. (2005). An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *Journal of substance abuse treatment, 28*(4), 321-329.

Andersen, R., & Aday, L. A. (1978). Access to medical care in the US: realized and potential. *Medical care*, 533-546.

Andersen, R., Bozzette, S., Shapiro, M., St Clair, P., Morton, S., Crystal, S., . . . Leibowitz, A. (2000). Access of vulnerable groups to antiretroviral therapy among persons in care for HIV disease in the United States. HCSUS Consortium. HIV Cost and Services Utilization Study. *Health Services Research, 35*(2), 389.

Andersen, R. M. (1995). Revisiting the behavioral model and access to medical care: does it matter? *Journal of health and social behavior*, 1-10.

Arndt, S., Acion, L., & White, K. (2013). How the states stack up: Disparities in substance

    abuse outpatient treatment completion rates for minorities. *Drug and alcohol*

    dependence, 132(3), 547-554.

Bao, Y., Pan, Y., Taylor, A., Radakrishnan, S., Luo, F., Pincus, H. A., & Schackman, B. R. (2016).

    Prescription drug monitoring programs are associated with sustained reductions in

    opioid prescribing by physicians. *Health Affairs, 35*(6), 1045-1051.

Barry , C. L., & Huskamp , H. A. (2011). Moving beyond Parity — Mental Health and

    Addiction Care under the ACA. *New England Journal of Medicine, 365*(11), 973-975.

    doi:10.1056/NEJMp1108649

Blum, K., Gold, M., Clark, H. W., Dushaj, K., & Badgaiyan, R. D. (2016). Should the United

    States government repeal restrictions on buprenorphine/naloxone treatment?

    Substance use & misuse, 51(12), 1674-1679.

Brady, T. M., Salvucci, S., Sverdlov, L. S., Male, A., Kyeyune, H., Sikali, E., . . . Yu, P. (2005).

    Methadone dosage and retention: an examination of the 60 mg/day threshold.

    Journal of addictive diseases, 24(3), 23-47.

Buck, J. A. (2011). The looming expansion and transformation of public substance abuse

    treatment under the Affordable Care Act. *Health Affairs, 30*(8), 1402-1410.

Busch, S. H., Meara, E., Huskamp, H. A., & Barry, C. L. (2013). Characteristics of adults with

    substance use disorders expected to be eligible for Medicaid under the ACA.

    Psychiatric Services, 64(6), 520-526.

Cacciola, J. S., Dugosh, K. L., & Camilleri, A. C. (2009). Treatment history: Relationship to

    treatment outcomes. *Substance use & misuse, 44*(3), 305-321.

Carr, C. J. A., Xu, J., Redko, C., Lane, D. T., Rapp, R. C., Goris, J., & Carlson, R. G. (2008).

    Individual and system influences on waiting time for substance abuse treatment.

Journal of substance abuse treatment, 34(2), 192-201.
doi:10.1016/j.jsat.2007.03.005

Clemans-Cope, L., Epstein, M., & Kenney, G. M. (2017). Rapid growth in Medicaid spending
on medications to treat opioid use disorder and overdose. *The Urban Institute*.

Cohen, J., Cohen, P., West, S. G., & Aiken, L. S. (2013). *Applied multiple regression/correlation
analysis for the behavioral sciences*: Routledge.

Compton, W. M., Jones, C. M., & Baldwin, G. T. (2016). Relationship between Nonmedical
Prescription-Opioid Use and Heroin Use. *New England Journal of Medicine, 374*(2),
154-163. doi:doi:10.1056/NEJMra1508490

Connock, M., Juarez-Garcia, A., Jowett, S., Frew, E., Liu, Z., Taylor, R., . . . Roberts, T. (2007).
Methadone and buprenorphine for the management of opioid dependence: a
systematic review and economic evaluation.

D'Onofrio, G., O'Connor, P. G., Pantalon, M. V., Chawarski, M. C., Busch, S. H., Owens, P. H., . . .
Fiellin, D. A. (2015). Emergency department–initiated buprenorphine/naloxone
treatment for opioid dependence: a randomized clinical trial. *JAMA, 313*(16), 1636-
1644.

Deck, D., & Carlson, M. J. (2004). Access to publicly funded methadone maintenance
treatment in two western states. *The journal of behavioral health services & research,
31*(2), 164-177.

Dick, A. W., Pacula, R. L., Gordon, A. J., Sorbero, M., Burns, R. M., Leslie, D. L., & Stein, B. D.
(2015). Increasing Potential Access to Opioid Agonist Treatment in US Treatment
Shortage Areas. *Health affairs (Project Hope), 34*(6), 1028.

Dowell, D., Haegerich, T. M., & Chou, R. (2016). CDC guideline for prescribing opioids for
chronic pain—United States, 2016. *JAMA, 315*(15), 1624-1645.

Feder, K. A., Mojtabai, R., Krawczyk, N., Young, A. S., Kealhofer, M., Tormohlen, K. N., & Crum, R. M. (2017). Trends in insurance coverage and treatment among persons with opioid use disorders following the Affordable Care Act. *Drug and alcohol dependence, 179*, 271-274.

Fischer, B., Patra, J., Cruz, M. F., Gittins, J., & Rehm, J. (2008). Comparing heroin users and prescription opioid users in a Canadian multi-site population of illicit opioid users. *Drug Alcohol Rev, 27*(6), 625-632. doi:10.1080/09595230801956124

Fullerton, C. A., Kim, M., Thomas, C. P., Lyman, D. R., Montejano, L. B., Dougherty, R. H., . . . Delphin-Rittmon, M. E. (2014). Medication-assisted treatment with methadone: assessing the evidence. *Psychiatr Serv, 65*(2), 146-157. doi:10.1176/appi.ps.201300235

Gabay, M. (2015). Prescription Drug Monitoring Programs. *Hospital Pharmacy, 50*(4), 277-278.

Greenland, S. (2000). Principles of multilevel modelling. *International journal of epidemiology, 29*(1), 158-167.

Gryczynski, J., Schwartz, R. P., Salkever, D. S., Mitchell, S. G., & Jaffe, J. H. (2011). Patterns in admission delays to outpatient methadone treatment in the United States. *Journal of substance abuse treatment, 41*(4), 431-439.

Gundel, R., Allen III, N., Osborne, S., & Shwayhat, S. (2017). Risk Factors for Early Discharge from a Residential Addiction Treatment Program. *J Addict Res Ther, 8*(338), 2.

Hall, G., Neighbors, C. J., Iheoma, J., Dauber, S., Adams, M., Culleton, R., . . . Morgenstern, J. (2014). Mobile opioid agonist treatment and public funding expands treatment for disenfranchised opioid-dependent individuals. *Journal of substance abuse treatment, 46*(4), 511-515.

Han, B., Compton, W. M., Jones, C. M., & Cai, R. (2015). Nonmedical prescription opioid use and use disorders among adults aged 18 through 64 years in the United States, 2003-2013. *JAMA, 314*(14), 1468-1478.

Hedegaard, H., Warner, M., & Miniño, A. M. (2018). Drug overdose deaths in the United States, 1999-2016. *NCHS data brief*(273), 1-8.

Jones, C. M. (2013). Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers–United States, 2002–2004 and 2008–2010. *Drug and alcohol dependence, 132*(1), 95-100.

Jones, C. M., Campopiano, M., Baldwin, G., & McCance-Katz, E. (2015). National and state treatment need and capacity for opioid agonist medication-assisted treatment. *Journal Information, 105*(8).

Jones, C. M., Logan, J., Gladden, R., & Bohm, M. K. (2015). Vital signs: demographic and substance use trends among heroin users: United States, 2002–2013. *MMWR Morb Mortal Wkly Rep, 64*(26), 719-725.

Kaiser Family Foundation. (2017). Status of State Action on the Medicaid Expansion Decision. Retrieved from https://www.kff.org/health-reform/state-indicator/state-activity-around-expanding-medicaid-under-the-affordable-care-act/?currentTimeframe=0&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D

Kaiser Family Foundation. (2018). Medicaid Waiver Tracker: Which States Have Approved and Pending Section 1115 Medicaid Waivers? *Medicaid.* Retrieved from https://www.kff.org/medicaid/issue-brief/which-states-have-approved-and-pending-section-1115-medicaid-waivers/?utm_source=web&utm_medium=trending&utm_campaign=waivers

Kaplan, E. H., & Johri, M. (2000). Treatment on demand: an operational model. *Health Care Manag Sci, 3*(3), 171-183.

Keyes, K. M., Cerdá, M., Brady, J. E., Havens, J. R., & Galea, S. (2014). Understanding the rural–urban differences in nonmedical prescription opioid use and abuse in the United States. *American journal of public health, 104*(2), e52-e59.

Kresina, T. F., Litwin, A., Marion, I., Lubran, R., & Clark, H. W. (2009). United States government oversight and regulation of medication assisted treatment for the treatment of opioid dependence. *Journal of Drug Policy Analysis, 2*(1).

Kuehn, B. M. (2014). Driven by prescription drug abuse, heroin use increases among suburban and rural whites. *JAMA, 312*(2), 118-119.

Kwiatkowski, C. F., Booth, R. E., & Lloyd, L. V. (2000). The effects of offering free treatment to street‐recruited opioid injectors. *Addiction, 95*(5), 697-704.

Maclean, J. C., & Saloner, B. (2017). *The Effect of Public Insurance Expansions on Substance Use Disorder Treatment: Evidence from the Affordable Care Act*. Retrieved from

Magura, S., Nwakeze, P. C., & Demsky, S. (1998). Pre‐and in‐treatment predictors of retention in methadone treatment using survival analysis. *Addiction, 93*(1), 51-60.

Maru, D. S.-R., Bruce, R. D., Walton, M., Mezger, J. A., Springer, S. A., Shield, D., & Altice, F. L. (2008). Initiation, adherence, and retention in a randomized controlled trial of directly administered antiretroviral therapy. *AIDS Behav, 12*(2), 284-293.

Mattick, R. P., Breen, C., Kimber, J., & Davoli, M. (2009). Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev, 3*(CD002209).

McCabe, B. E., Santisteban, D. A., Mena, M. P., Duchene, D. M., McLean, C., & Monroe, M. (2013). Engagement, retention, and abstinence for three types of opioid users in Florida. *Substance use & misuse, 48*(8), 623-634.

McLellan, A. T., & Woodworth, A. M. (2014). The affordable care act and treatment for "substance use disorders:" implications of ending segregated behavioral healthcare. *Journal of substance abuse treatment, 46*(5), 541-545.

Mital, S., Windle, M., Cooper, H. L., & Crawford, N. D. (2018). Trends in non-medical prescription opioids and heroin co-use among adults, 2003-2014. *In review*.

Moore, B. A., Fiellin, D. A., Barry, D. T., Sullivan, L. E., Chawarski, M. C., O'Connor, P. G., & Schottenfeld, R. S. (2007). Primary care office-based buprenorphine treatment: comparison of heroin and prescription opioid dependent patients. *Journal of general internal medicine, 22*(4), 527-530.

Neumann, A. M., Blondell, R. D., Azadfard, M., Nathan, G., & Homish, G. G. (2013). Primary care patient characteristics associated with completion of 6-month buprenorphine treatment. *Addictive behaviors, 38*(11), 2724-2728.

Nielsen, S., Hillhouse, M., Mooney, L., Ang, A., & Ling, W. (2013). Buprenorphine pharmacotherapy and behavioral treatment: Comparison of outcomes among prescription opioid users, heroin users and combination users. *Journal of substance abuse treatment, 48*(1), 70-76. doi:10.1016/j.jsat.2014.06.006

Nielsen, S., Larance, B., & Lintzeris, N. (2017). Opioid Agonist Treatment for Patients With Dependence on Prescription Opioids. *JAMA, 317*(9), 967-968. doi:10.1001/jama.2017.0001

Nosyk, B., Anglin, M. D., Brissette, S., Kerr, T., Marsh, D. C., Schackman, B. R., . . . Montaner, J. S. (2013). A call for evidence-based medical treatment of opioid dependence in the United States and Canada. *Health Affairs, 32*(8), 1462-1469.

Paulozzi, L. J., & Xi, Y. (2008). Recent changes in drug poisoning mortality in the United States by urban–rural status and by drug type. *Pharmacoepidemiology and drug safety, 17*(10), 997-1005.

Peterson, J. A., Schwartz, R. P., Mitchell, S. G., Reisinger, H. S., Kelly, S. M., O'Grady, K. E., . . . Agar, M. H. (2010). Why don't out-of-treatment individuals enter methadone treatment programmes? *International Journal of Drug Policy, 21*(1), 36-42.

Potter, J. S., Marino, E. N., Hillhouse, M. P., Nielsen, S., Wiest, K., Canamar, C. P., . . . Saxon, A. J. (2013). Buprenorphine/naloxone and methadone maintenance treatment outcomes for opioid analgesic, heroin, and combined users: findings from starting treatment with agonist replacement therapies (START). *Journal of studies on alcohol and drugs, 74*(4), 605-613.

Pouget, E. R., Fong, C., & Rosenblum, A. (2017). Racial/Ethnic Differences in Prevalence Trends for Heroin use and Non-Medical use of Prescription Opioids Among Entrants to Opioid Treatment Programs, 2005-2016. *Subst Use Misuse*, 1-11. doi:10.1080/10826084.2017.1334070

Ratcliffe, M., Burd, C., Holder, K., & Fields, A. (2016). Defining rural at the US Census Bureau. *United States Census Bureau*.

Rigg, K. K., & Monnat, S. M. (2015). Comparing Characteristics of Prescription Painkiller Misusers and Heroin Users in the United States. *Addictive behaviors, 51*, 106-112. doi:10.1016/j.addbeh.2015.07.013

Saloner, B., & Cook, B. L. (2013). Blacks and Hispanics are less likely than whites to complete addiction treatment, largely due to socioeconomic factors. *Health Affairs, 32*(1), 135-145.

Saloner, B., & Karthikeyan, S. (2015). Changes in substance abuse treatment use among

    individuals with opioid use disorders in the United States, 2004-2013. *JAMA,*

    314(14), 1515-1517.

Sigmon, S. C. (2014). Access to treatment for opioid dependence in rural America:

    challenges and future directions. *JAMA psychiatry, 71*(4), 359-360.

    doi:10.1001/jamapsychiatry.2013.4450

Strang, J., Griffiths, P., Powis, B., Fountain, J., Williamson, S., & Gossop, M. (1999). Which

    drugs cause overdose among opiate misusers? Study of personal and witnessed

    overdoses. *Drug and alcohol review, 18*(3), 253-261.

Strathdee, S. A., & Beyrer, C. (2015). Threading the Needle—How to Stop the HIV Outbreak

    in Rural Indiana. *New England Journal of Medicine, 373*(5), 397-399.

Substance Abuse and Mental Health Administration. (2013). *Treatment Episodes Dataset-*

    Discharges, 2013 Codebook. Retrieved from Rockville, MD:

    http://www.icpsr.umich.edu/icpsrweb/NAHDAP/studies/35509

Substance Abuse and Mental Health Administration. (2014). *National Survey of Substance*

    Abuse Treatment Services (N-SSATS): 2013. Data on Substance Abuse Treatment

    Facilities. Retrieved from Rockville, MD:

Substance Abuse and Mental Health Services Administration. (2014). *The NSDUH Report:*

    Substance Use and Mental Health Estimates from the 2013 National Survey on Drug

    Use and Health: Overview of Findings. Retrieved from Rockville, Maryland:

Unick, G. J., Rosenblum, D., Mars, S., & Ciccarone, D. (2013). Intertwined epidemics: national

    demographic trends in hospitalizations for heroin-and opioid-related overdoses,

    1993–2009. *PloS one, 8*(2), e54496.

Volkow, N. D., Frieden, T. R., Hyde, P. S., & Cha, S. S. (2014). Medication-assisted therapies—

tackling the opioid-overdose epidemic. *New England Journal of Medicine, 370*(22),

2063-2066.

Wen, H., Hockenberry, J. M., Borders, T. F., & Druss, B. G. (2017). Impact of Medicaid

Expansion on Medicaid-covered Utilization of Buprenorphine for Opioid Use

Disorder Treatment. *Medical care, 55*(4), 336-341.

West, B. T. (2016, June 9, 2016). *Fitting weighted multilevel models to complex sample data in

SAS: A case study.* Paper presented at the Michigan SAS Users' Group Conference,

Ann Arbor, MI.

Zarkin, G. A., Dunlap, L. J., Hicks, K. A., & Mamo, D. (2005). Benefits and costs of methadone

treatment: results from a lifetime simulation model. *Health economics, 14*(11), 1133-

1150.

Zhang, Z., Friedmann, P. D., & Gerstein, D. R. (2003). Does retention matter? Treatment

duration and improvement in drug use. *Addiction, 98*(5), 673-684.

Chapter 5: Summary and conclusions

1. Rationale for research

The current opioid epidemic demonstrates that trends in opioid use and related outcomes are dynamic and require continuous monitoring to determine the most appropriate response strategies (Centers for Disease Control and Prevention, 2012; Hedegaard, Warner, & Miniño, 2018). Studies document increased non-medical prescription opioid (NMPO) and heroin use, transition from NMPO-only to heroin use when supply of prescription opioids is limited, and subsequent co-use of both opioids (Maclean & Saloner, 2017; Mars, Bourgois, Karandinos, Montero, & Ciccarone, 2014; Rigg & Monnat, 2015). Transition and co-use are concerning and associated with poorer physical and mental health, less engagement in health services, and a greater risk of overdose (Fischer, Patra, Cruz, Gittins, & Rehm, 2008; Rigg & Monnat, 2015; Strang et al., 1999). While medication-assisted treatment (MAT) is highly effective in treating problem opioid use and reducing risk of overdose and death, the epidemic's response efforts focus on limiting the supply of prescription opioids (POs) and gaps in MAT access persist (Fullerton et al., 2014; Jones, Campopiano, Baldwin, & McCance-Katz, 2015; Mattick, Breen, Kimber, & Davoli, 2009; Volkow, Frieden, Hyde, & Cha, 2014). However, we lacked empirical evidence on the growth in and characteristics of co-use and whether changes in MAT admissions reflect the shifts in populations affected by opioid use. Additionally, gaps in our knowledge of factors related to transition and successful treatment completion hindered the design and targeting of interventions to prevent transition and improve long-term outcomes treatment among opioid users. In response to these gaps, we investigated emerging trends in opioid use, factors related to

transition, corresponding trends in MAT access and correlates of treatment completion. In this chapter, we summarize the aims and findings of this research, present implications for public health practice, and discuss the strengths and limitations of this research along with implications for future studies.

2. Summary of aims and main findings

First, we used the National Surveys on Drug Use and Health (NSDUH) to describe trends in opioid use. Driven by trend theory, we described trends by the type of opioid used. To improve our understanding of the characteristics related to co-use of NMPO and heroin, we also described trends across demographics, non-opioid substance using behaviors, and mental health characteristics. Consistent with recent evidence of transition and our hypothesis, we found that co-use grew 248% from 2003-2014, while prevalence of opioid use overall decreased six percent. In 2014, the number of co-users was more than two times the number of heroin-only users. The prevalence of co-use grew in every demographic, substance use, and mental health subgroup that we examined. By 2014, the highest prevalence of co-use occurred in those who reported no health insurance, unemployment, a major depressive episode (MDE) or psychological distress in the past year, and use or abuse of illicit drugs other than opioids in the past year.

Also using NSDUH, we examined transition from NMPO to heroin and co-use of both opioids in more detail, organized by the socio-ecological model (SEM). To our knowledge, this is the first study to explore transition in a nationally representative sample of adults and include factors beyond the individual level. Given the interconnectedness of increased NMPO and heroin use, we examined whether interpersonal- and individual-level factors related to increased NMPO use are related to transition and co-use. At the interpersonal level, obtaining POs from a provider compared to obtaining them illicitly and perceiving risk of heroin use as less than great compared to great or more were associated with increased

123

odds of transition. Individual-level characteristics associated with transition include being without health insurance coverage and perceiving heroin as easy to obtain. Male sex, non-Hispanic White race/ethnicity and under-employment were demographics associated with transition, along with younger age of NMPO initiation, use of non-opioid illicit drugs and psychological distress.

Lastly, we explored trends in MAT admissions and correlates of treatment completion using data from the Treatment Episodes Datasets (TEDS), which includes admissions and discharge data from publicly-funded and state-certified treatment facilities. Guided by the Behavioral Health Model, we examined demographics as predisposing factors, dimensions of access to healthcare as enabling factors, and opioid use type as an indicator of need. We found that from 2004 to 2015, MAT admissions increased 143% but the proportion of admissions for co-use remained relatively stable over time (between 10-15% of admissions). While admissions for all demographic groups increased, the highest growth was among non-urban admissions (2,112% growth). We observed differences in treatment completion by the type of opioid used where admissions for heroin-only use were less likely to complete treatment, compared to those for co-use. We also found differences in the relationship between healthcare access and treatment completion by opioid use type where referral source was the strongest predictor of treatment completion for co-use, while immediate treatment relative to delayed only predicted treatment completion for heroin-only use.

This was the first in-depth examination into NMPO and heroin co-use with a focus on responding to the opioid epidemic by improving our understanding of MAT access. Overall, we found that trends in and characteristics of opioid use and MAT treatment utilization differ by opioid use type. This underscores the need for

independent investigation into each category of opioid use, instead of grouping NMPO and heroin use together or studying them separately, as many studies do. By distilling opioid use by type, we uncovered substantial growth in co-use, despite a slight decrease in opioid use overall. We also revealed an unchanged proportion of MAT admissions for co-use while MAT use overall increased drastically. These nuances have important implications for public health practice.

3. Practical implications

Our findings inform targeted interventions and policies to reduce opioid use. One such intervention is improving screening practices that identify patients before the onset of problem use, which includes transition, abuse, and dependence. Aligning with previous studies, we found that transition and co-use are associated with co-morbidity, compared to NMPO- and heroin-only use (Fischer et al., 2008; Rigg & Monnat, 2015). Therefore, routine screening at service delivery points including mental health services, primary care and emergency departments is important. Expanding on current prescribing guidelines, screening practices should assess for poly-drug use, including use of more than one type of opioid, and prioritize referrals to treatment for those reporting use of multiple substances (Dowell, Haegerich, & Chou, 2016). For those prescribed opioids, frequent interaction with healthcare providers can lead to primary and secondary prevention of more problematic opioid use. Healthcare providers can also deliver messaging on the risks and benefits associated with opioid use. Pharmacists may be a good source of these messages, as they interact with patients just prior to PO use. Screening for initiation of NMPO use is particularly important for adolescents. The relationship between initiating NMPO use before adulthood and risk of transition calls for adolescent-focused interventions, prior to NMPO initiation, as these may prevent NMPO use, problem use, and related outcomes (Cerda, Santaella, Marshall, Kim, & Martins, 2015; Lankenau et al., 2012).

Evidence of transition to heroin among NMPO-only users, the growth in co-use, the high prevalence of other illicit drug use among co-users suggests vulnerability and that people with problem opioid use seem to use whatever they have access to (Al-Tayyib, Koester, & Riggs, 2017; Cicero, Ellis, & Harney, 2015). Our findings align with previous studies arguing that supply-side interventions drive transition and heroin use (Cicero, Ellis, & Surratt, 2012; Unick, Rosenblum, Mars, & Ciccarone, 2013). In response, interventions should focus on demand reduction by promoting and expanding access to MAT. They should target subgroups at higher risk of transition and those with disproportionately low rates of MAT use. Communications campaigns can facilitate access to harm reduction interventions by tempering perceptions of drug availability and related harms with messages that improve social norms around MAT and educating the public on its accessibility (Schuchat, Houry, & Guy, 2017).

Our most promising finding, the substantial growth of MAT admissions for non-urban residing opioid users, speaks to some progress in addressing the current opioid epidemic through expanded access to demand reduction interventions (Dick et al., 2015; Keyes, Cerdá, Brady, Havens, & Galea, 2014; Kuehn, 2014). We must learn from and build on these successes to redress current disparities in MAT access. However, we also highlight severe gaps in MAT service delivery where the trends in MAT admissions for several subgroups do not reflect improvement in the prevalence of opioid use. We see this most clearly for co-use, where prevalence of use grew substantially, but the proportion of MAT admissions for co-use remained stable. In terms of race/ethnicity, growth in MAT admissions was highest for non-Hispanic Whites while co-use increased much more for other race/ethnicities than it did for non-Hispanic Whites, consistent with findings from previous studies (Han,

Compton, Jones, & Cai, 2015; Martins, Santaella-Tenorio, Marshall, Maldonado, & Cerdá,

2015). This is also consistent with evidence of poor treatment engagement among poly-

drug users and racial and ethnic minority groups, who may have higher rates of co-

occurring health disorders (Elwy, Ranganathan, & Eisen, 2008). Receipt of MAT in primary

care settings rather than specialty mental health and substance use clinics may address

barriers to treatment success and may already be occurring among these populations, and

future studies should assess this (Alderks, 2017; Baxter, Clark, Samnaliev, Leung, &

Hashemi, 2011; Bonhomme, Shim, Gooden, Tyus, & Rust, 2012).

We found that MAT discharge due to treatment completion was relatively low as it

made up only 23% of discharges among first-time admissions. This means that the majority

of MAT enrollees drop out at some point, do not fully benefit from MAT, likely resume risky

drug-using behaviors, and are at risk of associated harms including overdose (Fullerton et

al., 2014; Zhang, Friedmann, & Gerstein, 2003). This, and the fact that opioid use often

occurs in groups, make current and previous MAT patients prime recipients for overdose

education and prevention interventions (Strang, Best, Man, Noble, & Gossop, 2000; Tai &

Volkow, 2013). As not to undermine treatment goals, MAT program staff can deliver them

as bystander interventions, training patients to avoid overdose, identify signs of overdose,

and respond to another person's overdose event through timely administration of naloxone.

MAT programs could prioritize delivery of these interventions among those at higher risk of

dropout, including heroin and co-users, males, and those with a non-urban residence. Since

poly-drug use is a risk factor for overdose, increased co-use along with a flat trend in MAT

admissions for co-use may explain the tripling of heroin-related overdose deaths from

2010-2015 (Centers for Disease Control and Prevention, 2017; Strang et al., 1999). In

general, implementation of Good Samaritan policies and allowing over-the-counter

pharmacy naloxone dispensing can increase uptake of overdose prevention interventions

and interaction between opioid users and healthcare providers, leading to reduced

overdose deaths (Compton, Boyle, & Wargo, 2015; Franklin et al., 2015).

Finally, these findings call for policies that improve access to healthcare,

including expanded health insurance coverage. We found that lack of health

insurance coverage was associated with transition and decreased frequency of MAT

admissions, highlighting vulnerability among those not covered by health insurance

(Feder et al., 2017). Access to healthcare allows for monitoring of PO use and

intervening before problem opioid use begins. It can also serve as a bridge to MAT,

and health insurance can eliminate cost as a barrier to accessing these services.

Policies like Medicaid expansion under the Affordable Care Act that aim to increase

access to health services by giving coverage to individuals who previously did not

qualify, many of whom have co-morbidities like substance use issues, are critical

(Buck, 2011; Compton, Jones, & Baldwin, 2016). Apart from health insurance

coverage, other systems-level initiatives to make MAT available at low or no cast are

needed to expand access (D'Onofrio et al., 2015).

4. **Strengths, limitations and implications for future research**

This dissertation research has many strengths and its limitations have

implications for future research. First, use of NSDUH and TEDS produced

generalizable findings and allowed for investigation of theoretically-relevant

constructs related to NMPO and heroin transition, co-use, and treatment. However,

our reliance on the variables available in NSDUH and TEDS presented limitations

with respect to examining additional constructs. While factors at higher levels of

SEM are associated with opioid and MAT use, such as opioid availability, policies

related to drug use, and health service offerings, they are not included in NSDUH

and TEDS. While NSDUH collects state codes, the data portal that makes them

publicly available has not been functional for several years, preventing our ability to examine state-level variables. Researchers with access to the restricted data must complete these analyses, and SAMHSA should prioritize resuming the functionality of the portal to enable critical opioid-related research.

Much of the previous research on transition is adolescent-focused so our examination of adults nationally serves as another strength of this research. While co-use increased among young adults aged 18-25, the most substantial increase was among those aged 26-34. Similarly, MAT admissions grew the most in the 26-34 year-old age group while young adults performed best in terms of complete treatment. This warrants continued examination of changing patterns in opioid and MAT use outside of adolescents and young adults, as older age groups may be disproportionately affected by more severe forms of opioid use and treatment dropout.

While NSDUH is a nationally-representative survey and TEDS is a national census of publicly-funded treatment facilities, some groups are nonetheless excluded from these data. NSDUH does not capture people who are incarcerated, homeless, or hospitalized which may underestimate use as these populations often have a higher likelihood of engaging in substance use (49). Studies enrolling cohorts or surveillance systems that capture these cohorts must fill this data gap. Only substance abuse treatment facilities receiving public funds are required to submit data to TEDS. Therefore, findings do not include all MAT use. The inability to determine if our findings are consistent with admissions to private treatment facilities and provision of MAT (buprenorphine) in physicians' offices is a significant limitation to generalizability (Alderks, 2017). Future research should explore the relevancy of our findings to clients who access MAT outside of publicly-funded facilities.

Use of serial, cross-sectional data prevents us from making conclusions about individual trends or within-person patterns over time. It also prevented direct assessment

of changes in opioid use and MAT use, and specifically transition. As a strength of this research, we used the best measure available to examine transition and co-use at a national level since the literature indicates that the vast majority of recent heroin initiation follows NMPO use (Jones, 2013; Muhuri, Gfroerer, & Davies, 2013). We also may have erroneously defined intermittent NMPO and heroin use as transition or co-use. In the future, prospective cohort studies that recruit participants who report transition or follow NMPO users longitudinally to assess transition, and describe corresponding MAT access will improve investigation of this phenomenon.

In our study of factors related to transition and co-use, prevalence of the outcome was small—less than 5%. This is consistent with other studies, which use varying methodologies to produce transition rates ranging from 3.6% to 7.5% (Carlson, Nahhas, Martins, & Daniulaityte, 2016; Compton et al., 2016). However, the small prevalence of the outcome makes statistical analysis of transition difficult and in our case, it prevented moderation analyses (Center for Behavioral Health Statistics and Quality, 2016). Examining correlates of transition and MAT completion stratified by sex, race, and rurality will expand our knowledge of these relationships and help in the development of response strategies. Exploring these differences requires qualitative methods with comparative analyses and sufficiently powered quantitative studies.

5. **Overall contributions of the research**

In response to shifts in NMPO and heroin use, we answered multiple calls to examine trajectories of opioid use, factors related to transition and co-use, and corresponding shifts in MAT use. Specifically, this research makes five significant contributions to the literature. First, it provides evidence that a cohort of NMPO and

heroin co-users emerged and grew substantially. Second, it shows that those who transition from NMPO to heroin and co-use both opioids are distinct from NMPO- and heroin-only users, with greater prevalence of use of non-opioid drugs and mental health issues. Next, in exploring the risk of transition and other trends in opioid use, it underscores the importance of assessing factors beyond the individual level, which can explain and address the root causes of this phenomenon. Fourth, it documents that treatment admissions are not keeping pace with the growth in co-use and growing rates of opioid use and related outcomes in other groups. Finally, it indicates disparities in treatment completion among heroin and co-users relative to NMPO users but shows that provider referrals and treatment on demand can improve this outcome. This research also adds to the extant literature by going beyond qualitative and cohort-specific, cross-sectional research to provide nationally-representative findings. Findings inform efforts to identify and reach those at risk of transition and co-use, and those who do not benefit from MAT. In turn, this research makes substantial contributions to the evidence base, and hopefully, to tackling the current opioid epidemic.

6. References

Al-Tayyib, A. A., Koester, S., & Riggs, P. (2017). Prescription opioids prior to injection drug use: Comparisons and public health implications. *Addictive behaviors, 65*, 224-228.

Alderks, C. E. (2017). Trends in the use of methadone, buprenorphine, and extended-release naltrexone at substance abuse treatment facilities: 2003–2015 (update). In *The CBHSQ report: August 22, 2017*: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Rockville, MD.

Baxter, J. D., Clark, R. E., Samnaliev, M., Leung, G. Y., & Hashemi, L. (2011). Factors associated with Medicaid patients' access to buprenorphine treatment. *Journal of substance abuse treatment, 41*(1), 88-96.

Bonhomme, J., Shim, R. S., Gooden, R., Tyus, D., & Rust, G. (2012). Opioid Addiction and

Abuse in Primary Care Practice: A Comparison of Methadone and Buprenorphine as

Treatment Options. *Journal of the National Medical Association, 104*(0), 342-350.

Buck, J. A. (2011). The looming expansion and transformation of public substance abuse

treatment under the Affordable Care Act. *Health Affairs, 30*(8), 1402-1410.

Carlson, R. G., Nahhas, R. W., Martins, S. S., & Daniulaityte, R. (2016). Predictors of transition

to heroin use among initially non-opioid dependent illicit pharmaceutical opioid

users: A natural history study. *Drug and alcohol dependence, 160*, 127-134.

Center for Behavioral Health Statistics and Quality. (2016). *2015 National Survey on Drug

Use and Health: Methodological summary and definitions*. Retrieved from Rockville,

MD:

Centers for Disease Control and Prevention. (2012). CDC grand rounds: prescription drug

overdoses-a US epidemic. *MMWR Morb Mortal Wkly Rep, 61*(1), 10.

Centers for Disease Control and Prevention. (2017). QuickStats: Rates of Drug Overdose

Deaths Involving Heroin,* by Selected Age Groups - United States, 2006-2015.

MMWR Morb Mortal Wkly Rep, 65(52), 1497. doi:10.15585/mmwr.mm6552a12

Cerda, M., Santaella, J., Marshall, B. D., Kim, J. H., & Martins, S. S. (2015). Nonmedical

Prescription Opioid Use in Childhood and Early Adolescence Predicts Transitions to

Heroin Use in Young Adulthood: A National Study. *J Pediatr, 167*(3), 605-612 e602.

doi:10.1016/j.jpeds.2015.04.071

Cicero, T. J., Ellis, M. S., & Harney, J. (2015). Shifting patterns of prescription opioid and

heroin abuse in the United States. *New England Journal of Medicine, 373*(18), 1789-

1790.

Cicero, T. J., Ellis, M. S., & Surratt, H. L. (2012). Effect of abuse-deterrent formulation of

OxyContin. *New England Journal of Medicine, 367*(2), 187-189.

Compton, W. M., Boyle, M., & Wargo, E. (2015). Prescription opioid abuse: problems and responses. *Preventive medicine, 80*, 5-9.

Compton, W. M., Jones, C. M., & Baldwin, G. T. (2016). Relationship between Nonmedical Prescription-Opioid Use and Heroin Use. *New England Journal of Medicine, 374*(2), 154-163. doi:doi:10.1056/NEJMra1508490

D'Onofrio, G., O'Connor, P. G., Pantalon, M. V., Chawarski, M. C., Busch, S. H., Owens, P. H., . . . Fiellin, D. A. (2015). Emergency department–initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial. *JAMA, 313*(16), 1636-1644.

Dick, A. W., Pacula, R. L., Gordon, A. J., Sorbero, M., Burns, R. M., Leslie, D. L., & Stein, B. D. (2015). Increasing Potential Access to Opioid Agonist Treatment in US Treatment Shortage Areas. *Health affairs (Project Hope), 34*(6), 1028.

Dowell, D., Haegerich, T. M., & Chou, R. (2016). CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA, 315*(15), 1624-1645.

Elwy, A. R., Ranganathan, G., & Eisen, S. V. (2008). Race-ethnicity and diagnosis as predictors of outpatient service use among treatment initiators. *Psychiatr Serv, 59*(11), 1285-1291. doi:10.1176/appi.ps.59.11.1285

10.1176/ps.2008.59.11.1285

Feder, K. A., Mojtabai, R., Krawczyk, N., Young, A. S., Kealhofer, M., Tormohlen, K. N., & Crum, R. M. (2017). Trends in insurance coverage and treatment among persons with opioid use disorders following the Affordable Care Act. *Drug and alcohol dependence, 179*, 271-274.

Fischer, B., Patra, J., Cruz, M. F., Gittins, J., & Rehm, J. (2008). Comparing heroin users and prescription opioid users in a Canadian multi-site population of illicit opioid users. *Drug Alcohol Rev, 27*(6), 625-632. doi:10.1080/09595230801956124

Franklin, G., Sabel, J., Jones, C. M., Mai, J., Baumgartner, C., Banta-Green, C. J., . . . Tauben, D. J. (2015). A comprehensive approach to address the prescription opioid epidemic in Washington State: milestones and lessons learned. *American journal of public health, 105*(3), 463-469.

Fullerton, C. A., Kim, M., Thomas, C. P., Lyman, D. R., Montejano, L. B., Dougherty, R. H., . . . Delphin-Rittmon, M. E. (2014). Medication-assisted treatment with methadone: assessing the evidence. *Psychiatr Serv, 65*(2), 146-157. doi:10.1176/appi.ps.201300235

Han, B., Compton, W. M., Jones, C. M., & Cai, R. (2015). Nonmedical prescription opioid use and use disorders among adults aged 18 through 64 years in the United States, 2003-2013. *JAMA, 314*(14), 1468-1478.

Hedegaard, H., Warner, M., & Miniño, A. M. (2018). Drug overdose deaths in the United States, 1999-2016. *NCHS data brief*(273), 1-8.

Jones, C. M. (2013). Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers–United States, 2002–2004 and 2008–2010. *Drug and alcohol dependence, 132*(1), 95-100.

Jones, C. M., Campopiano, M., Baldwin, G., & McCance-Katz, E. (2015). National and state treatment need and capacity for opioid agonist medication-assisted treatment. *Journal Information, 105*(8).

Keyes, K. M., Cerdá, M., Brady, J. E., Havens, J. R., & Galea, S. (2014). Understanding the rural–urban differences in nonmedical prescription opioid use and abuse in the United States. *American journal of public health, 104*(2), e52-e59.

Kuehn, B. M. (2014). Driven by prescription drug abuse, heroin use increases among suburban and rural whites. *JAMA, 312*(2), 118-119.

Lankenau, S. E., Teti, M., Silva, K., Bloom, J. J., Harocopos, A., & Treese, M. (2012). Initiation into prescription opioid misuse amongst young injection drug users. *International Journal of Drug Policy, 23*(1), 37-44.

Maclean, J. C., & Saloner, B. (2017). *The Effect of Public Insurance Expansions on Substance Use Disorder Treatment: Evidence from the Affordable Care Act.* Retrieved from

Mars, S. G., Bourgois, P., Karandinos, G., Montero, F., & Ciccarone, D. (2014). "Every 'never' I ever said came true": transitions from opioid pills to heroin injecting. *International Journal of Drug Policy, 25*(2), 257-266.

Martins, S. S., Santaella-Tenorio, J., Marshall, B. D., Maldonado, A., & Cerdá, M. (2015). Racial/ethnic differences in trends in heroin use and heroin-related risk behaviors among nonmedical prescription opioid users. *Drug and alcohol dependence, 151*, 278-283.

Mattick, R. P., Breen, C., Kimber, J., & Davoli, M. (2009). Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev, 3*(CD002209).

Muhuri, P. K., Gfroerer, J. C., & Davies, M. C. (2013). Associations of nonmedical pain reliever use and initiation of heroin use in the United States. *The CBHSQ Data Review*.

Rigg, K. K., & Monnat, S. M. (2015). Comparing Characteristics of Prescription Painkiller Misusers and Heroin Users in the United States. *Addictive behaviors, 51*, 106-112. doi:10.1016/j.addbeh.2015.07.013

Schuchat, A., Houry, D., & Guy, G. P. (2017). New data on opioid use and prescribing in the United States. *JAMA, 318*(5), 425-426.

Strang, J., Best, D., Man, L., Noble, A., & Gossop, M. (2000). Peer-initiated overdose resuscitation: fellow drug users could be mobilised to implement resuscitation. *Int J Drug Policy, 11*(6), 437-445.

Strang, J., Griffiths, P., Powis, B., Fountain, J., Williamson, S., & Gossop, M. (1999). Which

      drugs cause overdose among opiate misusers? Study of personal and witnessed

      overdoses. *Drug and alcohol review, 18*(3), 253-261.

Tai, B., & Volkow, N. D. (2013). Treatment for substance use disorder: opportunities and

      challenges under the Affordable Care Act. *Social work in public health, 28*(3-4), 165-

      174.

Unick, G. J., Rosenblum, D., Mars, S., & Ciccarone, D. (2013). Intertwined epidemics: national

      demographic trends in hospitalizations for heroin-and opioid-related overdoses,

      1993–2009. *PloS one, 8*(2), e54496.

Volkow, N. D., Frieden, T. R., Hyde, P. S., & Cha, S. S. (2014). Medication-assisted therapies—

      tackling the opioid-overdose epidemic. *New England Journal of Medicine, 370*(22),

      2063-2066.

Zhang, Z., Friedmann, P. D., & Gerstein, D. R. (2003). Does retention matter? Treatment

      duration and improvement in drug use. *Addiction, 98*(5), 673-684.