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Predictors of transition to heroin use among initially non-opioid dependent illicit pharmaceutical opioid users: A natural history study

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Abstract

Background—Increases in illicit pharmaceutical opioid (PO) use have been associated with risk for transition to heroin use. We identify predictors of transition to heroin use among young, illicit PO users with no history of opioid dependence or heroin use at baseline.

Methods—Respondent-driven sampling recruited 383 participants; 362 returned for at least one biannual structured interview over 36 months. Cox regression was used to test for associations between lagged predictors and hazard of transition to heroin use. Potential predictors were based on those suggested in the literature. We also computed population attributable risk (PAR) and the rate of heroin transition.

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Contributors

R. Carlson, R. Falck, and R. Daniulaityte designed the study and wrote the protocol. R. Carlson wrote the first draft of the methods, results and discussion and made final edits. R. Daniulaityte drafted the Introduction and provided editorial comments on the manuscript. R. Nahhas helped to design the statistical analyses, prepared tables and drafted the statistical methods section. He conducted all statistical analyses and commented on the ms. Silvia Martins helped to design the statistical analyses and provided editorial comments on the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest

Dr. Martins was a consultant for Purdue Pharma between Jan 2013 and December 2015 to assist on secondary data analyses of prescription opioid and alcohol data from the NESARC study, unrelated to the data presented in this manuscript. All other authors declare that there are no conflicts of interest.

Results—Over 36 months, 27 (7.5%) participants initiated heroin use; all were white, and the rate of heroin initiation was 2.8% per year (95% CI=1.9%–4.1%). Mean length of PO at first reported heroin use was 6.2 years (SD=1.9). Lifetime PO dependence (AHR=2.39, 95% CI= 1.07–5.48; PAR=32%, 95% CI=−2%–64%), early age of PO initiation (AHR=3.08, 95%; CI= 1.26–7.47; PAR=30%, 95% CI=2%–59%), using illicit POs to get high but not to self-medicate a health problem (AHR=4.83, 95% CI= 2.11–11.0; PAR=38%, 95% CI=12%–65%), and ever using PO non-orally most often (AHR=6.57, 95% CI=2.81–17.2; PAR=63%, 95% CI=31%–86%) were significant predictors.

Conclusion—This is one of the first prospective studies to test observations from previous cross-sectional and retrospective research on the relationship between illicit PO use and heroin initiation among young, initially non-opioid dependent PO users. The results provide insights into targets for the design of urgently needed prevention interventions.

Keywords

illicit pharmaceutical opioid use; heroin initiation; opioid dependence; time-to-event analysis; natural history study

1. INTRODUCTION

Over the past decade, the non-medical use of pharmaceutical opioids emerged as one of the fastest growing forms of drug abuse in the United States with young adults showing rates higher than other age groups (Johnston et al., 2010; Substance Abuse and Mental Health Services Administration (SAMHSA), 2010). Increases in illicit pharmaceutical opioid (PO) use resulted in escalating accidental overdose death rates (Paulozzi et al., 2006) and increasing prevalence of opioid abuse and dependence disorders (McCabe et al., 2008). Prior research with an Appalachian sample of illicit drug users demonstrated that PO use, in particular illicit use of OxyContin (pre-abuse deterrent formulation), was related to a high risk of transition to injection (Young and Havens 2011).

Growing evidence also suggests that illicit PO use has expanded pathways to heroin initiation and contributed to the heroin epidemic in the United States. Qualitative and cross-sectional quantitative studies conducted in different regions of the country, including Ohio as early as 2002 (Siegal et al., 2003a), Washington (Peavy et al., 2012), California, New York and Pennsylvania (Lankenau et al., 2012; Mars et al., 2014), were among the first to describe a trend of illicit PO users becoming opioid dependent and transitioning to heroin use. Analysis of data from the U.S. National Survey of Drug Use and Health (NSDUH) indicated that between 2002–2004 and 2008–2010, heroin use increased substantially among non-medical users of pharmaceutical opioids but remained unchanged among non-users (Jones, 2013). Martins and colleagues (2015) also found a significant relationship between illicit PO use and heroin use in the years 2008–2011 NSDUH cohort, compared to the 2002–2005 period. Another NSDUH-based study found that the incidence rate of heroin initiation was approximately 19 times greater among prior illicit PO users than among non-users (Muhuri et al., 2013). Data on drug overdose hospitalizations and mortality rates demonstrated significant increases in heroin-related overdoses and reductions in PO-related overdose rates over the past few years (Unick et al., 2013; Dasgupta et al., 2014; Lee et al.,

2014; Rudd et al., 2014). Similar trends were identified in Ohio, with overdose death data showing large increases in heroin-related deaths and leveling off of PO-related deaths in 2012 (Massatti et al., 2014). In Ohio, like other areas of the country, these increases appear to be linked to implementation of stricter pharmaceutical opioid prescription policies and guidelines (Massatti et al., 2014) and the introduction of an abuse-deterrent formulation of extended-release oxycodone (ADF OxyContin; Cicero and Ellis, 2015).

Although there is mounting evidence of the "intertwined" epidemics of illicit PO and heroin use, there is a lack of prospective studies designed to identify the factors associated with heroin initiation among illicit PO users. This study reports the findings of a 36-month natural history study of young adult illicit PO users who, at baseline, were not opioid dependent and had no history of heroin use or illicit injection. We examine associations between selected predictors and time to first heroin use using a time-to-event analysis. Potential predictors were selected mostly based on prior retrospective research findings suggesting associations between heroin initiation and: PO dependence (e.g., Jones, 2013, 2015; Lankenau et al., 2012; Mars et al., 2014); frequency of PO use (Jones, 2013, 2015; Muhuri et al., 2013; Cicero and Ellis, 2015); route of administration (ROA; McCabe et al., 2007a; Kirsh et al., 2012; Young et al., 2010); non-medical use of OxyContin (high abuse liability; Hays, 2004; Ternes and O'Brien, 1990; Siegal et al., 2003a,b; Martins et al., 2009; Cicero and Ellis, 2015; Young and Havens, 2011); and the introduction of ADF OxyContin (Cicero and Ellis, 2015).

2. METHODS

2.1. Sample recruitment

Between April, 2009 and May, 2010, we recruited 383 eligible participants in the Columbus, Ohio, area using respondent-driven sampling (RDS; Heckathorn, 1997, 2002). We limited referrals to three eligible participants and compensated referrers $15 for each person presenting at the project office (Wang et al., 2005, 2007). Daniulaityte and colleagues (2012) provide more details on sample recruitment.

Located in Franklin County, with a population over one million, Columbus is the Ohio state capitol, with a population of 787,033 people, 61% of whom are white, 28% African American, and 11% of other ethnicity (U.S. Census Bureau, 2010). Like much of Ohio, the Columbus area has experienced dramatic increases in the PO/heroin epidemics that began fomenting as early as 2002 when OxyContin was first identified as a potential new risk factor for heroin initiation (Siegal et al, 2003a,b). In Franklin County, unintentional drug overdose deaths increased 41.7% from 139 in 2009 to 197 in 2013 (Ohio Department of Health, 2014). In 2013, heroin was present in 46.6% of overdose deaths and POs in 34.4% (Ohio Department of Health, 2014).

2.2. Eligibility

Eligibility criteria included: 1) age 18–23 years (to recruit those in emerging adulthood when the risk of drug and drug-related behaviors peaks (Arnett, 2000; Bachman et al., 1996); 2) self-reporting non-medical PO use on five or more occasions in the previous 90 days (to recruit active PO users); 3) expressing intentions to use illicit POs again (to capture

active PO users); 4) residence in the Columbus, OH, area; 5) identifying opioids s/he reported having used on a pill card similar to that used in the NSDUH (Caviness et al, 2006), but without drug names listed (to verify reported illicit PO use); 6) no lifetime opioid dependence as ascertained with the DSM-IV Checklist (Forman et al., 2004; Hudziak et al., 1993); 7) no self-reported history of heroin use or history of drug injection as verified by visual inspection of arms for injection track marks; 8) no pending criminal charges (to minimize loss to follow-up); and 9) not involved in formal substance abuse treatment in the past 30 days (to avoid recruiting participants in active recovery who would be different from active users not wishing to stop drug use).

2.3. Data collection

Baseline and follow-up structured questionnaires (conducted every six months for 36 months) were administered by trained interviewers in private offices following completion of an informed consent. Participants were compensated $50 for completing a 1.5–2.5 hour baseline interview. Compensation for follow-up interviews was $40 for briefer semi-annual interviews and $50 for longer, annual follow-up interviews. All protocols were approved by the Wright State University IRB.

The final 36-month follow-up interview was conducted in May 2013, and retention rates were excellent. Of the 383 participants interviewed at baseline, 89.8% returned at 6 months; 88.5% at 12 months; 86.7% at 18 months, 83.3% at 24 months; 78.6% at 30 months; and 73.4% at 36 months.

2.4. Outcome and predictors

The outcome in this time-to-event analysis was time from initiation of illicit PO use to heroin initiation. Age of initiation of illicit PO use was self-reported as a whole number, and initiation of heroin use was self-reported as using heroin for the first time since the most recent follow-up interview. The outcome was computed as the difference between the age at the first interview where heroin use was reported and the age of initiation of illicit PO use.

Frequency of illicit PO use was ascertained through an author-generated item previously employed (Carlson et al., 2005; Falck et al., 2005; Siegal et al., 1998): “During the past six months, how often did you use non-prescribed pain pills (e.g., Vicodin, Percocet)?” Seven response options ranged from “never/none” to “daily” and were collapsed to ≤ 1, about 2, and ≥ 3 days per week. The predictor, “frequency of pain pill use,” represents the maximum reported value since the baseline interview.

At baseline and follow-up interviews, lifetime use (yes/no) of other drugs (alcohol, marijuana, sedatives (“non-prescribed tranquilizers like Xanax, Ativan, Valium”), cocaine, non-prescribed stimulants (‘like Ritalin, Adderall, Concerta”), MDMA, and LSD were ascertained using the questions “Have you ever used [drug]?” and “Since your last interview, have you used [drug]?” Use of immediate-release oxycodone was ascertained via the question: “Have you ever (since your last interview) used Percocet, Percodan, Tylox, or other drugs containing immediate-release oxycodone?” Use of OxyContin was assessed by asking a similar question. Use of ADF OxyContin was added as a distinct question in

November, 2010, roughly coinciding with the availability of the reformulation in December, 2010 (Cicero and Ellis, 2015).

Lifetime opioid dependence was assessed using the DSM-IV checklist (Forman et al., 2004; Hudziak et al., 1993). The computerized version of the Diagnostic Interview Schedule (CDIS) was used to ascertain lifetime dependence on other drugs, and lifetime psychiatric comorbidity (ASPD, depression, GAD, mania, or PTSD; Robins et al., 1999). The only drugs with greater than minimal prevalence of dependence for both those who did and did not transition to heroin were alcohol and marijuana. Thus, other drug dependence variables (sedatives, cocaine, stimulants, MDMA, LSD) were excluded as predictors.

Route of non-medical pharmaceutical opioid administration (ROA) was assessed with the question, “In the past 6 months, how did you most often use non-prescribed pain pills (e.g., Vicodin, Percocet)?” Responses included: “smoke,” “orally,” “sniff/snort,” “inject,” “other,” and “do not know/Refused.” Non-oral routes of administration were grouped together because only one participant reported an ROA other than “oral” or “sniff/snort.” The predictor used was “PO ever administered non-orally most often” (yes/no).

Other predictors were sex, employment (unemployed vs. part-time vs. full-time), post high-school education (yes/no), age of PO initiation (considered both as a continuous version and dichotomized as age of initiation ≤ 15 years old), and reasons for illicit PO use (ever used “pain pills illicitly to get high”; and, ever used “pain pills illicitly to self-medicate a health problem”).

2.5. Statistical analysis of time to initiation of heroin use

Rate of transition to heroin use was computed as the number of participants who initiated heroin use before the end of our study divided by the number of person-years these participants were observed prior to heroin use, and then expressed as an annual percentage (rate per 100 persons per year). A 95% CI for the rate was computed using the OpenEpi free calculator (0penEpi, 2010).

Time to heroin initiation was analyzed using Cox regression (Cox, 1972), accounting for left truncation and right censoring. The hazard of transition to heroin use was modeled as a function of each predictor individually, and collectively using a multivariate model. Predictor effect sizes were quantified as hazard ratios (HR) and, in the multivariate model, adjusted hazard ratios (AHR). A predictor with HR or AHR > 1 is associated with shorter time to initiation. The non-proportional hazards assumption was checked (and met) for time-invariant predictors (age of illicit PO initiation, early initiation of PO, and sex). The model was fit via SAS PROC PHREG (SAS Institute, 2010). All tests were two-sided and conducted at the $\alpha = 0.05$ level.

To prevent biased HR estimates due to reverse causation (in which a predictor changes because of initiation of heroin use rather than vice versa), the predictor value associated with heroin initiation was the value at the previous interview. Almost everyone used alcohol and marijuana; therefore, they were excluded as predictors. Lifetime use of immediate-release oxycodone, use of OxyContin, and non-medical use of POs to get high were universal

among heroin initiates and were excluded from the analyses (due to non-convergence of the algorithm). Multicollinearity among predictors was checked by computing variance inflation factors, all of which were low. Stepwise variable selection was employed to determine the final multivariate model; predictors with $p < 0.05$ were included in the final model, and adjusted hazard ratios (AHR) were estimated for each. Finally, for predictors in the final model, we computed the population attributable risk (PAR) = prevalence of risk factor among those who initiated heroin × (AHR-1)/AHR, which is an estimate of the reduction in heroin initiation that would occur if a particular risk factor was eliminated (Natarajan et al., 2007).

Weighted estimates are often used in studies using RDS to sample from hard-to-reach populations of interest, particularly in cross-sectional surveillance studies where there is significant interest in external validity and making inferences to the population (Johnston and Sabin, 2010). We considered using weighted estimates in our analyses, but chose not to because our focus was on ensuring the internal validity of the study. In addition, a number of issues also made using weighted estimates impractical. Since our longitudinal cohort is a subset of the original RDS sample, referral chains are broken so that RDS weights cannot be properly created when using the RDS analysis tool RDSAT. Accurate network size information is also critical to the validity of RDS weighting in producing population estimates (Johnston, 2008; Johnston et al, 2008). However, the eligibility criteria for our study were comparatively restrictive to improve internal reliability and not completely revealed to participants to prevent individuals from lying to obtain study admission. As a result, our self-reported network sizes are likely not reflective of the target population. In addition, despite lengthy recruitment chains, our sample did not reach equilibrium for racial/ethnic composition (Daniulaityte et al., 2012:26). Lack of equilibrium undermines the validity of applying RDS weights to race/ethnicity (Johnston, 2008; Johnston et al., 2008). The absence of equilibrium in terms of ethnic composition is most likely due to high homophily levels observed among Whites (.79) and African Americans (.80) (Daniulaityte et al., 2012), indicating that the two groups recruited almost exclusively from their own group, producing a “bottleneck” in the network and impacting the quality of RDS estimates (Goel and Salganik, 2009; Gile and Handcock, 2010). Finally, the ability of RDS weights to produce population estimates for parameters in complex analyses (for example, the adjusted hazard ratios we estimate) is questionable (Li, 2012), particularly for longitudinal analyses (Yan 2012). Despite these limitations, using RDS provided a practical and efficient means to recruit the sample.

3. RESULTS

About 50% of the sample were White (including Hispanic); among the 180 non-Whites, 92.8% were African American, 2.2% were Asian or Pacific Islander, and 5% biracial. On average, Whites and non-Whites had been using POs non-medically for about four years at baseline, with a mean age of PO initiation of 16.6 years for Whites and 17.3 years for non-Whites (Table 1). For further details regarding the baseline sample, see Carlson and colleagues (2014).

3.1. Characteristics of individuals who initiated heroin use

Over 36 months, 27 (7.5%) participants initiated heroin use, and the rate was 2.8% per year (95% CI=1.9%–4.1%). All participants who transitioned to heroin use were white (including one Hispanic). About 56% of heroin initiates were male, and more than half had some post-secondary education. Four (14.8%) heroin initiates reported that their most frequent route of heroin administration (during the first 6-month period they reported heroin initiation) was smoking, 11 (40.7%) reported sniff/snort, and 12 (44.4%) reported injection (data not shown).

Table 2 provides characteristics of heroin users and non-users at the most recent lagged follow-up interview. The mean number of years from first illicit PO use to heroin initiation was 6.2. All heroin initiates reported lifetime use of OxyContin, compared to only 46.3% of those who did not transition to heroin. The two groups did not differ in terms of immediate-release oxycodone use. Only three (11%) heroin users reported ADF OxyContin use before heroin initiation. Non-oral route of PO administration was more commonly reported among those who transitioned to heroin use (74.1% versus 21.5%). Over 55% of heroin initiates became opioid dependent prior to using heroin, compared to 43.3% of non-heroin initiates. All the heroin users and about 93% of non-users had used pharmaceutical opioids non-medically to “get high.” In contrast, use of POs to self-medicate a health problem was more commonly reported among non-heroin users than heroin initiates (89.0% vs. 51.9%). The two groups also differed in terms of frequency of PO; 63% of heroin initiates reported using PO ≥ 3 days per week, compared to 46% of non-heroin users.

3.2. Time-to-event analysis: unadjusted heart ratios (HRs)

Unadjusted HRs and 95% confidence intervals (CI) for all candidate predictors are shown in Table 3. Significant predictors of heroin initiation included three predictors related to PO use: developing lifetime opioid dependence (HR=2.74; 95% CI=1.27–6.08); having a higher lifetime maximum number of opioid dependence criteria (HR=1.37; 95% CI=1.11–1.68); and a higher maximum frequency of PO use (3–7 days per week vs. 1 day per week, HR=2.58; 95% CI=1.06–7.19; 3–7 days per week vs. 2 days per week, HR=2.87; 95% CI=1.06–9.98). Two age-related predictors were significant: age of initiation ≤ 15 years (HR=3.12; 95% CI=1.30–7.45); and younger age of initiation (as a continuous variable) (HR=0.69, 95% CI=0.54–0.89). Using POs to self-medicate a health problem (HR=0.18, 95% CI=0.08–0.40) was significantly (negatively) related to heroin initiation. Ever reporting non-oral use of POs (HR=10.1; 95% CI=4.46–25.9); alcohol dependence (HR=2.16, 95% CI=1.01–4.76); and each of ever having used sedatives (HR=2.91, 95% CI=1.17–8.80), cocaine (HR=6.34, 95% CI=2.67–17.5), stimulants (HR=2.34, 95% CI=1.09–5.13), MDMA (HR=2.53, 95% CI=1.10–6.54), and LSD (HR=3.89, 95% CI=1.75–9.53) were also significant predictors.

3.3. Time-to-event analysis: Adjusted hazard ratios

In the final multivariate model (Table 4), predictors of heroin initiation included: lifetime PO dependence (AHR=2.39, 95% CI= 1.07–5.48); early age of PO initiation (age ≤ 15 years) (AHR=3.08, 95%; CI= 1.26–7.47); never reporting PO use to self-medicate a health problem (AHR=4.83, 95% CI= 2.11–11.0); and ever reporting administering POs non-orally

most often (AHR=6.57, 95% CI=2.81–17.2). Maximum frequency of PO use, lifetime maximum number of PO dependence criteria, and lifetime PO dependence (yes/no) were almost interchangeable in the final model in terms of estimated AHRs for the other predictors and model fit, with greater frequency and more criteria each associated with shorter time to heroin initiation. Since frequency of PO use is related to the development of opioid disorder, this is not surprising. Of these three equivalent final models, we chose lifetime PO dependence because it was the predictor in which we were most interested.

The PARs were 63% (95% CI=31%–86%) for non-oral PO administration, 38% (95% CI=12%–65%) for never self-medicating (i.e., using only to get high), 32% (95% CI=−2%–64%) for PO dependence, and 30% (95% CI=2%–59%) for early illicit PO initiation.

4. DISCUSSION

To our knowledge, this is the first prospective study to use a community-based sample to examine the relationship between illicit PO use and heroin initiation among young adults in the U.S. who, at baseline, were not opioid dependent and had no history of heroin use or any illicit drug injection. In addition, it is the first community-based study to provide an estimate of the rate of heroin initiation among young PO users as well as PAR estimates associated with significant predictors.

Over 36 months, among our sample of 362, 18–23 year olds, 27 (7.5%) participants initiated heroin use. Our findings suggest that the rate of transition to heroin initiation among initially non-opioid dependent PO users is 2.8% per year in a Midwest U.S. metropolitan area in the heart of the opioid epidemics.

Muhuri and colleagues (2013) reported rates of heroin initiation based on a 2009–2011 cohort of lifetime illicit PO users and heroin use based on NSDUH data. However, these estimates are not truly comparable with our estimate. For instance, the NSDUH national sampling method and resulting sample characteristics differ substantially from ours. Nevertheless, in their study, the age group with the highest annual average rate (0.26%) is 18–25 year olds, and the racial/ethnic group with the highest annual average rate (0.14%) is non-Hispanic Whites. Thus, our higher rate estimate (2.8%) reflects the age and race/ethnic group arguably at highest risk.

All of the 27 heroin initiates were White (including one Hispanic). Identifying the reasons for the racial/ethnic variation in the relationship between PO use and heroin initiation is important and challenging, particularly given that 47.2% of non-Whites became opioid dependent, yet none initiated heroin use (data not shown). We offer preliminary observations regarding why non-Whites did not transition to heroin use. Our RDS study (Daniulaityte et al, 2012) indicated high levels of in-group recruitment, indicating greater social distance between Whites and non-Whites; subcultural views on drug use practices may vary Whites and non-Whites. Among 180 non-Whites, only 14 (7.8%) used POs non-orally most often prior to their last visit (data not shown), which was the most significant predictor among Whites who transitioned to heroin. Low levels of non-oral PO use among non-Whites may be related to a subcultural values regarding non-oral administration routes. When asked why there are comparatively lower levels of heroin use among non-Whites, a

treatment provider in Columbus, OH, (personal communication December 4, 2015) suggested that a long history of heroin use in African-American communities may have engendered negative views about heroin use among younger generations. Mars and colleagues (2014) identified similar racial/ethnic differences in terms of heroin initiation in ethnographic studies in Philadelphia and San Francisco. We agree with their call for further research to examine the effects of ethnicity, segregation, socio-economic status, and geography on heroin initiation risk. We also suggest that the potential impact of stigmatization of heroin use among non-Whites should be examined.

Among significant AHR predictors, ever administering PO non-orally (sniffing/snorting) most often before heroin initiation had the highest PAR estimate (63%). This finding is consistent with previous research indicating the significance of ROA in increasing the rate of drug absorption and speed of onset, and, thereby, its association with transition to dependence, regardless of drug (e.g., Gossop et al., 1994; Strang et al., 1992, 1998; Samaha and Robinson, 2005). The finding supports previous research that crossing the bridge from illicit oral PO administration to crushing POs and sniffing/snorting (or smoking, injecting) them indicates an intensifying relationship with the drug and "high" as well as the potential for drug-related problems (Kirsh et al., 2012; McCabe et al., 2007a; Young et al., 2010). As such, ROA is an important target for intervention among non-opioid dependent illicit PO users.

Our final model indicates that developing PO dependence is a significant predictor of heroin initiation (PAR=32%). The finding is consistent with previous cross-sectional retrospective research (Cicero et al., 2014; Lankenau et al., 2012; Mars et al. 2014; Peavy et al., 2012; Pollini et al., 2011; Siegal et al. 2003a,b). As some studies (e.g., Siegal et al., 2003a) propose, transition to PO dependence becomes increasingly costly over time, access to POs becomes more problematic, and heroin is a less-expensive, easily accessible alternative that largely markets itself. The field lacks an understanding of changes in social networks as non-dependent PO users transition to opioid dependence and engage with heroin using networks.

Illicit PO users who used the drug more frequently were also more likely to transition to heroin use. This finding is consistent with the fact that frequency of PO use is likely to be related to transition to opioid dependence. As such, reducing frequency of PO use is an important target for intervention to prevent transition to opioid dependence and potential risk for heroin initiation.

The PAR estimate (38%) for never having used illicit POs to "self-medicate a health problem" (i.e., in our study, only ever using "to get high") was very similar to the PAR for opioid dependence (32%). This finding is consistent with McCabe and colleague's (2009, 2013) hypothesis that use of POs for "self-treatment of pain" would be associated with fewer substance abuse problems, while use for recreational motives ("to get high" in our study) would result in greater negative effects. In our LCA of the baseline sample (Carlson et al., 2014), we reported that the classes with the greatest proportion of individuals who used POs only to self-medicate had the fewest negative characteristics associated with PO

use. The findings further support McCabe and colleagues‘ (2007a; 2009) point that motive for illicit PO use is an important variable that could inform intervention approaches.

The final significant predictor in the multivariate analysis was early age of PO initiation (≤ 15 years) with the lowest PAR of 30%. Numerous studies have identified age of onset of drug use as a predictor of progression to problematic drug use (e.g., Kandel and Yamaguchi, 1993 Hingson et al., 2006). Findings are consistent with McCabe and colleague‘s (2007b) study indicating that early age of illicit PO onset is associated with developing opioid dependence (placing users at higher risk of heroin initiation). Based on a NSDUH sample of U.S. adolescents, Cerdá and colleagues (2015) found that those initiating illicit PO use at ages 10–12 (followed by 13–15 year-olds) had the highest risk of heroin initiation, thus supporting our findings and confirming the importance of preventing early onset of illicit PO use.

All heroin initiates had used OxyContin, compared to just over 46% of those who did not initiate heroin use. This predictor could not be included in the analysis because when one group has no variation, the HR is not estimable. Nevertheless, our findings are consistent with previous studies indicating a relationship between OxyContin use and heroin use (Martins et al., 2009). We were among the first to report an emerging relationship between OxyContin use and heroin initiation in 2002 (Siegal et al., 2003a,b; Daniulaityte et al., 2006). Importantly, Young and Havens (2011) reported that OxyContin use was associated with faster transition to injection among rural Appalachians in Kentucky.

The introduction of ADF OxyContin has been associated with increases in transition to heroin use (Cicero and Ellis, 2015). Use of ADF OxyContin was not a significant predictor of heroin initiation, although the unadjusted HR was fairly large in magnitude (HR=2.60). To examine the potential influence of the introduction of the abuse-deterrent formulation of OxyContin on heroin transition further, we calculated incidence rates before and after the availability of ADF OxyContin, using December 1, 2010 (Cicero and Ellis, 2015) as an approximate date for availability. In the pooled sample with all participants, the incidence rate was 2.8% (27 transitions in 950 person-years). From the start of the study through November 30, 2010, the incidence rate was 4.7% (13 transitions in 276 person-years). From December 1, 2010 to the end of the study, the incidence rate was 2.1% (14 transitions in 658 person-years). Thus, the rate did change after the approximate date of availability of ADF OxyContin (December 2010), but not in the direction that would be expected.

4.1. Limitations

Our study was limited to 18–23 year-olds; results may be different for older or younger non-dependent PO users. Our study was limited to a metropolitan area in the U.S.; however, Columbus, Ohio, is located in one of the “hot spots” of the opioid epidemics, and has been for over a decade (Siegal et al. 2003a). Predictors of heroin initiation among similar community-based samples may vary. In addition, the design excluded individuals who were pharmaceutical opioid dependent at baseline, thereby limiting the scope of our study. To make the sample as representative as possible, we used RDS. However, the sample may be biased by income level, education, employment, and other factors. In addition, the inability to adjust for RDS weighting is a limitation to the study. The recruited sample was young,

with some participants still financially dependent on their families, making assessment of socioeconomic status challenging. Additionally, since no non-white participants transitioned to heroin, it was not possible to adjust for race/ethnicity in the analysis. Thus, HRs and AHRs for predictors that differed greatly between racial/ethnic groups, in particular, non-oral route of administration, may be biased. Finally, the findings are based on self-report, but there is substantial support for the validity and reliability of self-report data (Adair et al., 1995; Darke, 1998; Passik et al., 2006).

4.2. Conclusion

Many areas of the U.S. have experienced over a decade of the evolution of the pharmaceutical opioid and heroin epidemics. The synergism between these epidemics is unmistakable and ever-changing. It is, in part, motivated by marketing of pharmaceutical opioids, changes in prescribing practices, and the availability of heroin that fills the gap when illicit pharmaceutical opioids are difficult to obtain as tolerance to opioids increases, all in the context of apparent growing demand for central nervous system depressants (Unick et al., 2013). The opioid epidemics are escalating public health crises that require a public health response proportionate in scale. Our results suggest that preventing transition to non-oral pharmaceutical opioid use, preventing transition to opioid dependence (by reducing/maintaining (or eliminating) frequency of PO use), and educating PO users about the risks involved in reasons for use among those non-opioid dependent are important intervention targets. Finally, prevention of early age of illicit PO initiation is also vital (Cerdá et al., 2015).

Our prospective findings from a community-based sample provide insights into key dimensions for the design and testing of urgently needed interventions that require additional investment of resources. A harm-reduction intervention approach might include testing of office-based, or peer leader-based, interventions to prevent transition to opioid dependence among non-opioid dependent PO users as well as interventions for opioid dependent users who have not initiated heroin use. Such interventions could also include overdose prevention and prevention of blood-borne disease transmission.

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Highlights

- Identify heroin initiation predictors among pharmaceutical opioid (PO) users
- Over 36 months, 7.5% (27) of 362 participants initiated heroin use
- Predictors: PO dependence; early age PO use; using PO to get high; non-oral PO use

Table 1

Baseline descriptive statistics by ethnicity.

Variable	Level	White (n=182)		Non-White (n=180)	
		Mean or N	SD or %	Mean or N	SD or %
Length of PO use (years)		4.3	2.0	3.8	2.1
Age (years)		20.9	1.6	21.1	1.7
Age of initiation of use of POs (years)		16.6	1.9	17.3	2.0
Early initiation (age of initiation ≤ 15 years)		46	25.3	28	15.6
Sex	Male	111	61.0	86	47.8
Employment	Unemployed	43	23.6	80	44.4
	Part-time	86	47.3	45	25.0
	Fulltime	53	29.1	55	30.6
Post-high school education		87	47.8	58	32.2
Frequency of pain pill use (past 6 months)	≤ 1 day/week	104	57.1	59	32.8
	About 2 days/week	38	20.9	74	41.1
	3–7 days/week	40	22.0	47	26.1
Immediate-release oxycodone (lifetime)		179	98.4	171	95.0
OxyContin (lifetime)		100	54.9	54	30.0
ADF OxyContin (lifetime)		0	0.0	0	0.0
Used POs to get high (past 6 months)		154	84.6	147	81.7
Used POs to self-medicate a health problem (past 6 months)		122	67.0	128	71.1
POs administered non-orally most often (past 6 months)		48	26.4	6	3.3
Alcohol dependence (lifetime)		60	33.0	43	23.9

Variable	Level	White (n=182)		Non-White (n=180)	
		Mean or N	SD or %	Mean or N	SD or %
Marijuana dependence (lifetime)		50	27.5	56	31.1
Sedative use (lifetime)		115	63.2	48	26.7
Cocaine use (lifetime)		83	45.6	17	9.4
Stimulant use (lifetime)		91	50.0	16	8.9
MDMA/Ecstasy use (lifetime)		91	50.0	66	36.7
LSD use (lifetime)		100	54.9	16	8.9
Psychiatric comorbidity (lifetime)		88	48.4	114	63.3

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Table 2

Length of PO use and age at event time (first interview where heroin use was reported or, for non-users, last interview), and lagged predictors at event time (predictor values at interview prior to event time).

Variable	Level	Used (n=27)		Never Used (n=335)	
		Mean or N	SD or %	Mean or N	SD or %
Length of PO use (years)		6.2	1.9	6.7	2.1
Age (years)		22.0	1.8	23.8	1.7
Age of initiation of use of POs (years)		15.8	1.6	17.1	2.0
Early initiation (age of initiation ≤ 15 years)		12	44.4	62	18.5
Sex	Male	15	55.6	182	54.3
Ethnicity	White	27	100.0	155	46.3
Employment	Unemployed	6	22.2	105	31.4
	Part-time	15	55.6	116	34.7
	Fulltime	6	22.2	113	33.8
Post-high school education		15	55.6	159	47.6
PO dependence (lifetime)		15	55.6	145	43.3
Number of PO dependence criteria (lifetime max)		3.2	1.9	2.6	1.7
Frequency of pain pill use (max since 6 months before baseline)	≤ 1 day/week	6	22.2	107	31.9
	About 2 days/week	4	14.8	73	21.8
	3–7 days/week	17	63.0	155	46.3
Immediate-release oxycodone use (lifetime)		27	100.0	329	98.2
OxyContin (lifetime)		27	100.0	155	46.3
ADF OxyContin (lifetime)		3	11.1	25	7.5
Used POs to get high (since 6 months before baseline)		27	100.0	310	92.5

Variable	Level	Used (n=27)		Never Used (n=335)	
		Mean or N	SD or %	Mean or N	SD or %
Used POs to self-medicate a health problem (since 6 months before baseline)		14	51.9	298	89.0
POs ever administered non-orally most often (since 6 months before baseline)		20	74.1	72	21.5
Alcohol dependence (lifetime)		15	55.6	122	36.4
Marijuana dependence (lifetime)		9	33.3	141	42.1
Sedative use (lifetime)		22	81.5	206	61.5
Cocaine use (lifetime)		21	77.8	116	34.6
Stimulant use (lifetime)		15	55.6	110	32.8
MDMA/Ecstasy use (lifetime)		20	74.1	181	54.0
LSD use (lifetime)		19	70.4	115	34.3
Psychiatric comorbidity (lifetime)		17	63.0	189	56.4

Table 3

Unadjusted associations between lagged predictors and hazard of transition to heroin

	Unadjusted		
Predictor	**HR**	**95% CI**	**p-value**
PO dependence (lifetime)	2.74	(1.27, 6.08)	0.0109
PO dependence criteria (lifetime max)	1.37	(1.11, 1.68)	0.0037
Frequency of pain pill use (maximum since 6 months before baseline)	--	--	0.0409
3–7 days/week vs. ≤ 1 day/week	2.58	(1.06, 7.19)	0.0362
About 2 days/week vs. ≤ 1 day/week	0.90	(0.23, 3.16)	0.8696
3–7 days/week vs. 2 days/week	2.87	(1.06, 9.98)	0.0377
Early initiation (age of initiation ≤ 15 years)	3.12	(1.30, 7.45)	0.0111
Age of initiation of use of POs (years)	0.69	(0.54, 0.89)	0.0043
Sex (male vs. female)	1.06	(0.49, 2.32)	0.8805
Employment	--	--	0.0751
Fulltime vs. unemployed	1.03	(0.32, 3.30)	0.9617
Part-time vs. unemployed	2.46	(0.99, 6.93)	0.0519
Fulltime vs. Part-time	0.42	(0.15, 1.03)	0.0587
Some college (vs. ≤ HS/GED)	1.42	(0.66, 3.09)	0.3703
ADF OxyContin (lifetime)	2.60	(0.61, 7.60)	0.1712
Used POs to self-medicate a health problem (since 6 months before baseline)	0.18	(0.08, 0.40)	<0.0001
POs ever administered non-orally most often (since 6 months before baseline)	10. 1	(4.46, 25.9)	<0.0001
Alcohol dependence (lifetime)	2.16	(1.01, 4.76)	0.0482
Marijuana dependence (lifetime)	0.74	(0.32, 1.63)	0.4628
Sedative use (lifetime)	2.91	(1.17, 8.80)	0.0201
Cocaine use (lifetime)	6.34	(2.67, 17.5)	<0.0001
Stimulant use (lifetime)	2.34	(1.09, 5.13)	0.0289
MDMA/Ecstasy use (lifetime)	2.53	(1.10, 6.54)	0.0277
LSD use (lifetime)	3.89	(1.75, 9.53)	0.0007
Psychiatric comorbidity (lifetime)	1.22	(0.57, 2.77)	0.6204

Table 4

Multivariate adjusted associations between lagged predictors and hazard of transition to heroin

Predictor	AHR	95% CI	p-value	PAR	95% CI
PO dependence (lifetime)	2.39	(1.07, 5.48)	0.0345	32%	(−2%, 64%)
Early initiation (age of initiation ≤ 15 years)	3.08	(1.26, 7.47)	0.0139	30%	(2%, 59%)
Has never used POs to self-medicate (only to get high) (lifetime)	4.83	(2.11, 11.0)	0.0003	38%	(12%, 65%)
POs ever administered non-orally most often (since 6 months before baseline)	6.57	(2.81, 17.2)	<0.0001	63%	(31%, 86%)

[a] This 0/1 variable is expressed as 1 – "Used PO to self-medicate a health problem (since 6 months before baseline)" so that all AHRs are > 1, facilitating comparison of their relative sizes.