

Prospective Study

e Association Between Socio-Demographic and Health Functioning Variables Among Patients with Opioid Use Disorder Introduced by Prescription: A Prospective Cohort Study

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Disclaimer: This work was funded by the Canadian Institute for Health Research, Peter Boris Centre for Addictions Research and the Chanchlani Research Centre. The funders provided level 6 funding for the large project that the data was obtained from (GENOA) and level 3 funding for this particular study. The funders had no role in the design of the study, analysis of data, or publication of results.

Manuscript received: 12-27-2017
Revised manuscript received:
05-18-2018
Accepted for publication:
06-01-2018

Free full manuscript:
www.painphysicianjournal.com

Background: Prescription opioid misuse in Canada has become a serious public health concern and has contributed to Canada's opioid crisis. There are thousands of Canadians who are currently receiving treatment for opioid use disorder, which is a chronic relapsing disorder with enormous impact on individuals and society.

Objectives: The aim of this study was to compare the clinical and demographic differences between cohorts of patients who were introduced to opioids through a prescription and those introduced to opioids for non-medical purposes.

Study Design: This was an observational, prospective cohort study.

Setting: The study took place in 19 Canadian Addiction Treatment Centres across Ontario.

Methods: We included a total of 976 participants who were diagnosed with Opioid Use Disorder and currently receiving methadone maintenance treatment. We excluded participants who were on any other type of prescription opioid or who were missing their 6-month follow-up urine screens. We measured the participants' initial source of introduction to opioids along with other variables using the Maudsley Addiction Profile. We also measured illicit opioid use using urine screens at baseline and at 6-months follow-up.

Results: Almost half the sample (n = 469) were initiated to opioids via prescription. Women were more likely to be initiated to opioids via a prescription (OR = 1.385, 95% CI 1.027-1.866, *P* = .033). Those initiated via prescription were also more likely to have post-secondary education, older age of onset of opioid use, less likely to have hepatitis C and less likely to have used cannabis. Chronic pain was significantly associated with initiation to opioids through prescription (OR = 2.720, 95% CI 1.998-3.722, *P* < .0001). Analyses by gender revealed that men initiated by prescription were less likely to have liver disease and less likely to use cannabis, while women initiated by prescription had a higher methadone dose.

Limitations: This project was limited by its study design being observational in nature; no causal relationships can be inferred. Also, the data did not allow determination of the role that the prescribed opioids played in developing opioid use disorder.

Conclusions: Our results have revealed that almost half of this methadone maintenance treatment (MMT) population has been introduced to opioids through a prescription. Given that the increasing prescribing rates of opioids has an impact on this at-risk population, alternative treatments for pain should be considered to help decrease this opioid epidemic in Canada.

Key words: Opioid use disorder, chronic pain relief, methadone maintenance treatment, prescriptions, male, female

Pain Physician 2018; 21:E623-E632

In 2015, a report conducted by the United Nations Office on Drugs and Crime reported that approximately 32 to 36 million people worldwide abuse opioids (1). Opioids are the leading cause of drug-related death worldwide and are an even bigger concern for North America (2,3). Recent research has shown that this surge in illicit use is associated with the availability of opioids through medical prescriptions (4). Opioid use disorder (OUD) is a chronic, relapsing disorder that is categorized by serious psychological, social, and physical adversities (5). Negative consequences that may result from OUD include increased risk of infection and death, polysubstance use, psychiatric comorbidity, as well as criminal activity (5–7). OUD also creates an economic toll on the health care system, specifically due to the high costs of managing the disorder (8). In 2015, it was estimated that treatment for OUD in methadone clinics in Ontario alone cost \$156 million (8,9).

Ontario has experienced an unprecedented increase in the number of patients undergoing methadone maintenance treatment (MMT) for OUD in the last 10 years, with over 50,000 individuals reported to be in MMT programs in 2016 (6,8). While MMT may be successful in treating OUD in some patients (10–12), treatment outcomes are highly variable, with other patients exhibiting poor health and social functioning and continuing use of illicit substances (7). The majority of the research conducted in the MMT population has focused on heroin and street users and fails to compare them to

patients who were initiated to opioids via prescription. Differentiating between patients with prescription-influenced OUD and nonmedically influenced OUD is important for establishing a socio-demographic profile and determining unique risk factors for treatment failure in this population. Few studies have looked at the MMT population and dichotomized the study population by source of initiation to opioids. With recent research also finding that there is now an increase in women misusing opioids, with 52% of women and 38% of men seeking treatment having first been exposed to opioids through a prescription (13), an investigation into gender differences is also warranted.

The objective of this study was to investigate clinical and socio-demographic differences of patients with OUD who were introduced to opioids via prescription compared to those who obtained opioids by other means (i.e., family, friends, street). We also aimed to examine gender differences between the 2 groups, which, to our knowledge, has not been done before.

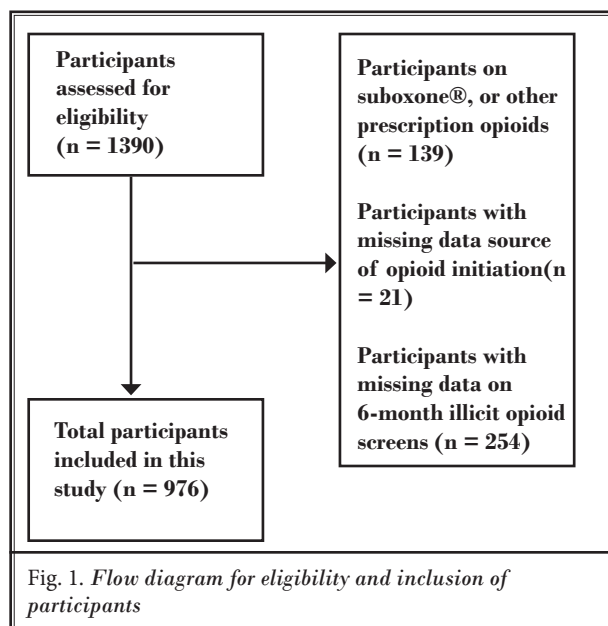
METHODS

Participants and Study Design

The data for this study was obtained from a larger project called the Genetics of Opioid Addiction (GENOA) study program, which is an ongoing multicenter cohort in collaboration with the Populations Genomics Program at McMaster University and Canadian Addiction Treatment Centres (CATC) (14). Patients were recruited from 19 different CATC clinics across Ontario from May 2013 through November 2016. This project was approved by the Hamilton Integrated Research Ethics Board (HIREB; Study ID 11-056).

To be eligible for GENOA, patients had to meet the following inclusion criteria: be over 18 years of age; meet the criteria for opioid dependence using the DSM-IV criteria (modified in DSM-5 to opioid use disorder); receive methadone maintenance treatment; able to provide informed, written consent; and undergo urine drug screens. In addition, patients also had to provide information on source of initiation to opioids. Patients who were receiving an alternate opioid substitution therapy, currently taking prescription opioids, currently on suboxone®, or unable to provide a urine sample were excluded from this study (Fig. 1).

Eligible patients provided informed consent and participated in a structured face-to-face interview at baseline, during which they were asked to provide basic demographic information and answer questions about



their health and social functioning. Specifically, the data collected consisted of information on socio-demographics, family background, psychiatric background, and details on drug use. Details of illicit opioid use were collected through regular urine drug screens at baseline and 6 months.

Measures

All patients in the study were asked about the initial source through which they were introduced to opioids (i.e., physician prescription, family, street) and this information was recorded on case report forms. For this study, this variable was dichotomized into prescribed opioids (initial exposure to opioids through a medical prescription) and illicit opioids (initial exposure to opioids through other means including at home, family member, street, school or friend). Demographic information, including age of onset of opioid use, methadone dose, treatment duration, education, and employment status, was also collected.

The Maudsley Addiction Profile (MAP) was administered to measure health and social functioning (15). Within the MAP, specific details of self-reported drug use were collected, including the number of times the drug was used within the past 30 days, typical dose, and the route(s) of administration. The illicit drugs included heroin, cocaine, illicit methadone, benzodiazepines, amphetamines, and cannabis. Frequency and amount of alcohol use was also collected. The MAP also collected medical history, which asked if the patient had been diagnosed with the following physical health conditions: HIV, hepatitis, chronic pain, liver disease, diabetes, and epilepsy.

Illicit opioid use was measured by regular urine drug screens and reported as the percentage of positive opioid screens (positive opioid screens divided by total urine screens). Illicit opioid use was measured at baseline and at a 6-month follow-up.

Statistical Analysis

To summarize the demographic data of the study population, descriptive statistics were used. The continuous variables are presented as means and standard deviations, while dichotomous variables are depicted as percentages.

The primary analysis used multivariable logistic regression to examine the relationship between socio-demographic factors, health functioning, and illicit drug use in relation to source of initial opioid use. Covariates included age, gender, methadone dose, and treatment

duration. The variables of ethnicity, marital status, education, and drug use (heroin, cocaine, illicit methadone, alcohol, benzodiazepines, and amphetamines) were transformed into dichotomous variables. Ethnicity was categorized as Caucasian and other. Education was categorized as high school or less and post-secondary education (trade school/college/university/postgraduate). Marital status was grouped into currently with a partner (currently married/common-law) or no current partner (never married/separated/divorced/widowed). Drug use was categorized as any drug use within the past 30 days or no drug use. A secondary analysis that looked at gender differences was conducted using the same model, variables, and covariates.

The data analysis was conducted using SPSS Version 23.0 (16). The results reported a 95% confidence interval, adjusted odds ratio, and the alpha level of significance set to $\alpha = .05$ for the primary analysis. For the secondary analysis looking at differences between men and women, $\alpha = .025$ was set. Collinearity was considered by looking at the variance inflation factor (VIF); none of the variables had a VIF of 10 or greater. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (17).

Sample size was calculated by using the logistic regression rule of having at least 10 events per predictor variable (18). This rule was satisfied, as we included 976 participants in the primary regression with 23 predictors. In the secondary analysis, we included 441 women and 535 men with 22 predictors each.

RESULTS

A total of 1390 patients were potentially eligible for this study. A total of 82 patients were excluded, as they were on suboxone®, and 57 patients were excluded, as they were taking additional prescribed opioids. Additionally, 21 patients were excluded for missing data on initial opioid exposure and 254 patients were missing data on their 6-month urine screens. A total of 976 patients were included in the analysis (Fig. 1).

Demographics

Our sample included comparable numbers of prescription-initiated opioid users ($n = 469$) and illicit opioid users ($n = 507$). Approximately half of all patients in the prescription-initiated opioids group were women (51.0%), which was considerably higher in comparison to the illicit opioids group (39.8%). The prescribed opioids group's average age of onset of opioid use was 27.4 years ($SD = 8.87$), which was higher than the illicit opi-

oids group's mean age of onset, 23.1 (SD = 8.04). The average daily methadone dose for prescribed opioid-users was 78.2 mg (SD = 41.8), which was marginally greater than the average dose of 74.1 mg (SD = 46.0) for the illicit opioids group. The prescribed opioids group also had approximately twice as many patients experiencing chronic pain (51.8%) in comparison to the illicit opioids group (25.6%). We had a total of 0.9% of patients with HIV in the prescription-initiated and 0.2% of patients in the illicit opioids group. With these numbers being very small, we had to remove these patients from the primary and secondary analyses. A complete summary of demographic and clinical characteristics comparing prescribed opioid-users and illicit opioid-users is reported in Table 1.

Primary Analysis

The results of the multivariable logistic regression for the association between source of opioid initiation and other socio-demographic and health functioning variables are provided in Table 2. There was a significant association between being female and being initiated to opioids via prescription, after adjusting for current age, methadone dose, and treatment duration (OR = 1.385, 95% CI 1.027-1.866, $P = .033$). Education was found to be significantly associated with being initially prescribed opioids, suggesting that patients in the prescribed group were more likely to have post-secondary education in comparison to the illicit opioids group (OR = 1.76, 95% CI 1.78-2.44, $P = 0.001$). Patients who were initiated to opioids via prescription were almost 3 times as likely to have been diagnosed with chronic pain (OR = 2.72, 95% CI 1.97-3.75, $P < .001$). Age of onset of opioid use was significantly higher in those introduced to opioids through a prescription (OR = 1.05, 95% CI 1.03-1.08, $P < .001$). Patients who had been introduced to opioids through nonmedical means had significantly higher rates of hepatitis (OR = 0.64, 95% CI 0.44-0.94, $P = .022$) and were more likely to have used cannabis in the past 30 days (OR = 0.66, 95% CI 0.49-0.90, $P = .008$).

Secondary Analysis

Our secondary analyses by gender looked at the relationship between source of opioid and a variety of variables (Tables 3 & 4). Similar to the primary analyses, chronic pain, education, and age of onset of opioid use were associated with initiation to opioids via prescription for both men and women. Among men, liver disease was associated with illicit opioid use (OR = 0.278, 95% CI = 0.104-0.742, $P = 0.011$). There was no signifi-

cant association in the subgroup analyses by gender for continued illicit opioid use at 6 months.

Interpretation

This prospective cohort study compared individuals in MMT who were initiated to opioids via medical prescription versus those introduced through illicit means with respect to social-demographic characteristics, health functioning, and continued illicit substance use. Almost half of the sample was introduced through a medical prescription ($n = 469$); these patients were more likely to have older age of onset of opioid use, have post-secondary education, be female, and less likely to use cannabis. We also found that the prescription-initiated group was less likely to have hepatitis C and more likely to have chronic pain. When we explored these differences by gender, we found that among men, the prescription-initiated group had a lower prevalence of liver disease and cannabis use. Among women, those in the prescription-initiated group were less likely to have hepatitis and more likely to have a higher methadone dose.

Our findings highlight important distinguishing characteristics for the prescription-initiated group, consistent with the literature. The literature has suggested that with increased physician-prescribing of opioids, there has been a rise in older-age patients misusing opioids (19–21). Opioids are most commonly prescribed for chronic, non-cancer pain conditions (19,21) typically prevalent among older adults, such as low back pain, arthritis, and fibromyalgia (22,23). Some studies have suggested that up to 60% of chronic pain patients are at high risk for prescription misuse (24). The prescription-initiated group was more likely to have post-secondary education. There may be many factors influencing this, but a significant one may be that the recreationally-initiated group was younger at age of onset of opioid use; their early start to recreational drug use may have influenced further education. Research has found that youth who begin to use heroin at a young age have significantly higher high school dropout rates in comparison to the prescription-using group (25). Additionally, women are more susceptible to chronic pain for a variety of factors, including greater amounts of estrogen in comparison to men. Estrogen has been shown to increase pain sensitivity and the risk of developing inflammation-related diseases (23,26,27). Recent research shows that women are more likely to be prescribed painkillers such as Percocet®, OxyContin,

Socio-Demographic and Health Functioning Variables Among Patients with Opioid Use Disorder

Table 1. Demographic characteristics of study sample

Variables (n = 976)	Prescribed Opioids	Illicit Opioids
Total number of patients	469	507
Age (SD)	40.8 (10.4)	36.9 (11.2)
Gender, % women	51.0	39.8
Currently employed, n (%)	158 (33.7)	183 (36.1)
Marital Status		
Never married (%)	177 (37.7)	270 (53.3)
Currently married/Common-law (%)	150 (32.0)	156 (30.8)
Separated/Divorced/Widowed(%)	142 (30.2)	81 (16)
Ethnicity		
Caucasian (%)	418 (89.1)	438 (86.4)
Native North American (%)	28 (6.0)	34 (6.7)
Other (%)	23 (4.9)	35 (6.6)
Level of Education		
None/Elementary School (%)	96 (20.5)	115 (22.7)
High school (%)	208 (44.3)	278 (54.8)
Trade school (%)	21 (4.5)	11 (2.2)
College/university (%)	140 (29.9)	98 (19.3)
Postgraduate (%)	2 (0.4)	2 (0.4)
Details of Opioid Use		
Age of onset of opioid use in yrs (SD)	27.4(8.87)	23.1(8.04)
Methadone treatment duration in mos (SD)	51.3(49.2)	48.1(48.7)
Methadone dose in mg/day (SD)	78.2(41.8)	74.1(46.0)
Baseline illicit opioid use, % positive screens	17.0	18.8
Medical History, %		
HIV	0.9	0.2
Hepatitis	21.7	28.8
Diabetes	6.2	4.9
Liver disease	4.1	6.1
Chronic pain	51.8	25.6
Epilepsy	2.1	2.0
Other medical conditions*	52.9	40.2
Self-reported Drug Use At Least Once in Past 30 Days, %		
Heroin	5.8	12.8
Illicit methadone	1.3	1.2
Illicit benzodiazepine	7.3	8.0
Cocaine	12.4	17.5
Cannabis	44.7	55.8
Amphetamine	3.0	3.1
Alcohol	36.4	44.4

*The "other medical conditions" category consists of any other responses, the most common being hypertension, acid reflux, asthma, cancer, celiac disease, Crohn's disease, migraines, colitis, degenerative disc disease, hyperthyroidism, hypothyroidism, gout, heart murmur, and ulcers.

Table 2. Multivariable logistic regression analysis on factors associated with source of opioid initiation (n = 976)

	OR	95% CI	P Value
Age	1.008	0.988-1.027	.443
Gender	1.385	1.027-1.866	.033*
Currently Working	0.847	0.612-1.172	.316
Methadone Dose (mg/day)	1.000	0.997-1.004	.802
Treatment Duration	1.000	0.996-1.003	.842
Currently Married/Common-law	1.108	0.746-1.389	.909
Ethnicity	0.810	0.522-1.255	.345
Education	1.765	1.278-2.437	.001*
Age of Opioid Use Onset	1.049	1.028-1.072	<.001*
Epilepsy	1.252	0.471-3.326	.653
Hepatitis	0.616	0.424-0.893	.011*
Liver Disease	0.480	0.232-0.994	.048
Chronic Pain	2.720	1.998-3.722	<.001*
Diabetes	0.872	0.455-1.672	.680
Other medical condition	1.213	0.902-1.632	.201
Heroin	0.605	0.343-1.066	.082
Illicit Methadone	1.251	0.483-3.242	.605
Alcohol	0.838	0.622-1.128	.244
Cannabis	0.671	0.501-0.900	.008*
Benzodiazepine	1.106	0.671-1.821	.694
Amphetamine	1.112	0.553-2.236	.766
Cocaine	0.865	0.587-1.295	.481
Illicit Opioid Use at 6 Mos (% Positive Screens)	1.112	0.510-2.427	.789

Heroin, illicit methadone, alcohol, cannabis, benzodiazepines, amphetamine, cocaine interpreted as categorical variables consisting of 2 levels: no days drug used and used drug at least once in 30 days.

Ethnicity interpreted as a categorical variable: Caucasian and other.

Marital status interpreted as a categorical variable: currently with a partner and currently not with a partner.

*Significant at $P < .05$

Abbreviations: OR, odds ratio; CI, confidence interval.

and Vicodin, with higher dosages in emergency settings (28). We found that women initiated by prescription were likely to have a higher methadone dose, which has been shown to help with chronic pain, as methadone is a synthetic opioid (29). There is stereotyping towards men which assumes that men are more likely to misuse substances (30); however, this may not hold true in the OUD population. This study suggests that women diagnosed with OUD are more likely to have been prescribed an opioid and to be older, more educated, and have a history of chronic pain.

We found that those initiated to opioids through a prescription were less likely to have hepatitis C and less likely to use cannabis (31,32). In our analysis by gender,

we also found that men initiated to opioids through a prescription were less likely to have liver disease. Injection drug use increases the likelihood of contracting hepatitis through the sharing of needles; hepatitis has a significant impact on the liver, as does use of multiple substances (33–35).

Men introduced to opioids through a legitimate prescription were also less likely to use cannabis. Though we cannot infer any causal relationship from our results due to the cross-sectional nature of the study, this finding suggests that those who began opioid use through illicit means may require additional care to manage ongoing use of cannabis. Previous research has shown that it is important to manage cannabis use, as it is as-

Table 3. *Multivariable logistic regression analysis on factors associated with source of opioid initiation in women (n = 441)*

	OR	95% CI	P value
Age	1.015	0.984-1.047	.357
Currently Working	0.901	0.536-1.514	.694
Age of Opioid Use Onset	1.065	1.029-1.102	<.0001
Methadone Dose (mg/day)	1.006	1.001-1.012	.031
Treatment Duration	0.998	0.993-1.003	.417
Epilepsy	1.545	0.408-5.855	.533
Hepatitis	0.551	0.308-0.986	.045
Liver Disease	1.149	0.346-3.817	.821
Chronic Pain	2.267	1.381-3.719	.001
Diabetes	0.477	0.184-1.236	.128
Other medical conditions	1.259	0.794-1.995	.328
Ethnicity	0.959	0.508-1.809	.897
Marital Status	1.035	0.641-1.673	.888
Education	1.683	1.044-2.712	.033
Alcohol	0.810	0.504-1.301	.383
Heroin	0.401	0.135-1.187	.099
Illicit Methadone	1.216	0.267-5.536	.801
Benzodiazepine	1.271	0.561-2.879	.565
Cocaine	0.677	0.364-1.259	.218
Amphetamine	1.614	0.432-6.030	.477
Cannabis	0.677	0.430-1.064	.091
Illicit Opioid Use at 6 Mos (% Positive Screens)	0.375	0.099-1.416	.148

Heroin, illicit methadone, alcohol, cannabis, benzodiazepines, amphetamine, cocaine interpreted as a categorical variables consisting of 2 levels: no days drug used and used drug at least once in 30 days.

Ethnicity interpreted as a categorical variable: Caucasian and other.

Marital status interpreted as a categorical variable: currently with a partner and currently not with a partner.

*Significant at $P < .025$

Abbreviations: OR, odds ratio; CI confidence interval.

sociated with ongoing opioid use during MMT among a subset of the population (36).

Limitations

This study is limited by its observational design, such that we cannot make any causal inferences about the association between the source of opioid use and health functioning. We also could not determine the extent to which prescription opioids contribute to the development of opioid use disorder from our collected data. However, the concept of identifying the initial source of introduction to opioids is novel, and, to our knowledge, no other study looking at a large MMT population has examined this. The information collected on illicit drug use was mainly reliant on self-report, and therefore susceptible to social desirability bias. In an

attempt to reduce this bias, all research assistants were trained to build rapport with the study participants and administer the questionnaire in a standardized manner.

CONCLUSION

Few studies have compared functioning and treatment outcomes for MMT patients who were exposed to opioids by medical prescription versus recreational use. Our study shows that important differences exist between these groups of patients, including significantly greater comorbid chronic pain in the prescription opioid group, which has implications for developing specific treatment plans for these groups of patients. Given that approximately half of the MMT sample was initiated to opioids by a physician prescription, it is important to note the differences between this group

Table 4. Multivariable logistic regression analysis on factors associated with source of opioid initiation in men (n = 535)

	OR	95% CI	P value
Age	1.003	0.977-1.030	.829
Currently Working	0.751	0.505-1.208	.267
Age of Opioid Use Onset	1.045	1.016-1.074	.002
Methadone Dose (mg/day)	0.997	0.992-1.002	.197
Treatment Duration	1.002	0.997-1.006	.463
Epilepsy	0.934	0.208-4.318	.930
Hepatitis	0.721	0.431-1.206	.212
Liver Disease	0.278	0.104-0.742	.011
Chronic Pain	3.146	2.062-4.798	<.0001
Diabetes	1.251	0.500-3.130	.633
Other medical conditions	1.196	0.798-1.796	.386
Ethnicity	0.596	0.310-1.144	.120
Marital Status	1.024	0.667-1.571	.915
Education	1.941	1.221-3.085	<.0001
Alcohol	0.875	0.586-1.305	.512
Heroin	0.732	0.359-1.494	.392
Illicit Methadone	1.097	0.280-4.298	.894
Benzodiazepine	1.012	0.521-1.965	.973
Cocaine	0.999	0.569-1.754	.998
Amphetamine	0.817	0.344-1.943	.648
Cannabis	0.646	0.428-0.974	.037
Illicit Opioid Use at 6 Mos (% Positive Screens)	2.292	0.825-6.370	.112

Heroin, illicit methadone, alcohol, cannabis, benzodiazepines, amphetamine, cocaine interpreted as categorical variables consisting of 2 levels: no days drug used and used drug at least once in 30 days.

Ethnicity interpreted as a categorical variable: Caucasian and other.

Marital status interpreted as a categorical variable: currently with a partner and currently not with a partner.

*Significant at $P < .025$

Abbreviations: OR, odds ratio; CI, confidence interval.

of patients and those who obtained opioids by other means. Differences in education level, comorbid medical issues, and concurrent substance use may be important to consider when developing treatment programs as well as specific goals of care for MMT patients. Many recent investigations, including our study, have shown the heterogeneity among the MMT patient popula-

tion indicating a need for personalized care for these patients. The source of initial opioid use may be useful in clinical practice to promote discussion about specific concerns, such as hepatitis C treatment, concurrent substance use, and chronic pain; and to recommend appropriate harm reduction strategies to patients.

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