American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol ■, No ■ (■), 2015: pp 1-8
Available online at www.jpain.org and www.sciencedirect.com

Pain Among High-Risk Patients on Methadone Maintenance Treatment

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Abstract: **The complexity of treating concurrent pain and opioid dependence among many methadone-maintained individuals presents a major challenge in many clinical settings. Furthermore, recent expert guidelines have called for increased research on the safety of methadone in the context of chronic pain. This study explores the prevalence and correlates of pain among a prospective cohort of people who use illicit drugs in Vancouver, British Columbia, Canada, who reported enrollment in methadone maintenance treatment (MMT) between 2011 and 2014. Among the 823 participants eligible for this analysis, 338 (40.9%) reported moderate pain and 91 (11.1%) reported extreme pain at the first study visit. In multivariable, generalized, linear mixed model analyses, higher pain severity was positively and independently associated with self-managing pain (adjusted odds ratio [AOR] 2.15, 95% confidence interval [CI] 1.77–2.60), patient perception of methadone dose being too low (AOR 1.82, 95% CI 1.41–2.34), older age (AOR 1.31, 95% CI 1.13–1.51), having a physical disability (AOR 4.59, 95% CI 3.73–5.64), having ever been diagnosed with a mental illness (AOR 1.44, 95% CI 1.13–1.84), white ethnicity (AOR 1.42, 95% CI 1.10–1.83), and marijuana use (AOR 1.25, 95% CI 1.02–1.52). These findings suggest several areas for clinical intervention, particularly related to patient education and alternative analgesic approaches for MMT patients experiencing pain.**

Perspective: ***To better understand the complexity of concurrent pain and opioid dependency among individuals on methadone maintenance treatment, this article describes the prevalence and correlates of higher pain severity among methadone-maintained people who use illicit drugs. Patients on methadone with comorbid pain may benefit from education and alternative analgesic approaches.***

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Key words: *Pain, methadone, substance abuse, self-medication, opioid-induced hyperalgesia.*

Received April 24, 2015; Revised May 28, 2015; Accepted June 6, 2015.
Conference presentation: Part of these data appeared as a poster presentation at the American Pain Society's 34th Annual Scientific Meeting, Palm Springs, CA, May 13–16, 2015.
Disclosures: This study was supported by the U.S. National Institutes of Health (R01DA011591 and R01DA021525). This research was undertaken, in part, thanks to funding from the Canada Research Chairs program through a Tier 1 Canada Research Chair in Inner City Medicine, which supports E.W. J.M. is supported with grants paid to his institution by the British Columbia Ministry of Health and by the U.S. National Institutes of Health (R01DA036307). He has also received limited unrestricted funding, paid to his institution, from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and ViiV Healthcare. P.V. and K.H. are supported by the Canadian Institutes of Health Research. The authors have no other potential competing interests to declare.
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1526-5900/$36.00
© 2015 by the American Pain Society
http://dx.doi.org/10.1016/j.jpain.2015.06.003

Methadone is a long-acting opioid agonist that may be prescribed to treat opioid dependence or chronic pain. When treating opioid-dependent individuals, clinicians are often faced with the complex challenge of treating concurrent chronic pain, which is estimated to be prevalent among 55 to 61% of individuals on methadone maintenance treatment (MMT) compared with 31% of the general adult population.[14]

The physiological mechanisms that may explain the overlap between pain and opioid dependency remain a topic of ongoing debate. One hypothesis that has garnered significant attention is the notion of opioid-induced hyperalgesia, which suggests that consistent exposure to opioids may lead to increased pain sensitivity, decreased pain thresholds, or both. However,

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limited and conflicting evidence has precluded a consensus on this hypothesis.[1,15]

The complexity of concurrent pain and opioid dependence presents substantial challenges for both clinicians and patients. Often, it is difficult to achieve a balance between adequate pain relief and reduced opioid cravings, while at the same time minimizing the risks of deepened dependence, overdose, withdrawal, misuse, or diversion.[23] Furthermore, practitioners' treatment decisions may be influenced by stigma related to people who use illicit substances,[34] interpretations of requests for opioids as drug seeking,[2] or views of MMT as a treatment of either pain or addiction separately.[22] These factors may contribute to inadequate pain management among individuals with high rates of disability and other causes of chronic pain.

In addition to these issues, recent guidelines by the American Pain Society call for increased research on the safety of methadone among individuals with chronic pain.[8,45] Therefore, we undertook this study to investigate the prevalence and correlates of pain among opioid-dependent individuals on MMT to inform pain management and risk mitigation strategies among this particularly high-risk population.

Methods

Study Design and Setting

Data for these analyses were derived from 2 ongoing prospective observational cohorts in Vancouver, British Columbia, Canada: the ACCESS (AIDS Care Cohort to Evaluate Exposure to Survival Services) of human immunodeficiency virus (HIV)-seropositive illicit drug users and the VIDUS (Vancouver Injection Drug Users Study) of HIV-seronegative injection drug users. These cohorts have previously been described in detail and have received annual ethics approval from the University of British Columbia and Providence Health Care Research Ethics Board.[39,40] Since 1996, more than 2,000 participants have been recruited into these cohorts through snowball sampling and street outreach methods in Vancouver's Downtown Eastside (DTES). The DTES is a postindustrial neighborhood with an established drug market and widespread illicit drug use, poverty, poor housing conditions, and infectious diseases such as HIV and hepatitis C.[26] The present analyses were restricted to interviews that were conducted between December 1, 2011, and November 30, 2014. These dates coincided with the start of the EuroQol EQ-5D health utility instrument in the study questionnaire and included all subsequent follow-up data available at the time of data analysis.

Participants

Participants are eligible for VIDUS if they are 18 years of age or older and have injected an illicit drug in the month before the baseline interview. Participants are eligible for ACCESS if they are HIV seropositive, are 18 years of age or older, and have used an illicit drug other than cannabinoids within the month before the baseline interview. At baseline and semiannually, participants answer an interviewer-administered questionnaire and provide blood samples for serologic analysis (HIV-negative individuals) or disease monitoring (HIV-positive individuals) and are referred as necessary to medical care and drug and alcohol treatment. All participants provide written informed consent and receive a $30 stipend at the end of each study visit. Participants were eligible for this analysis if they reported being on MMT at the time of their interview.

Variables and Measures

To identify factors associated with pain among individuals enrolled in MMT, our outcome of interest was current pain severity, which was measured using ordinal multinomial categories of participants who reported no pain or discomfort, moderate pain or discomfort, or extreme pain or discomfort at the time of their interview. These data on pain severity were ascertained using the EuroQol EQ-5D health utility instrument, which has been shown to be a valid, responsive, and reliable instrument for individuals with pain and opioid dependence.[18,30,43] In addition, the Brief Pain Inventory (BPI) Short Form was used to elicit information on pain duration and interference. The BPI has been shown to be a valid and reliable self-reported pain instrument, which has been widely used in studies measuring pain among general and substance-using populations.[6,31,35] Because the BPI was introduced later in the study period, data on these additional pain measures are available only for participants who completed the most recent follow-up period from June 1, 2014, to November 30, 2014.

The self-reported demographic, behavioral, social, and structural explanatory characteristics considered in the analyses were age (per 10-year increase), gender (male vs female), ethnicity (white vs other), homelessness (yes vs no), residence in Vancouver's DTES neighborhood (yes vs no), highest education status obtained ($\geq$ high school diploma or equivalent vs < high school diploma), HIV serostatus (positive vs negative), hepatitis C status (positive vs negative), lifetime history of mental illness diagnosis (yes vs no), incarceration (yes vs no), physical disability (yes vs no), self-managed pain (yes vs no), and having been denied pain medication by a health practitioner (yes vs no). The variables related to methadone treatment or drug use included nonfatal overdose (yes vs no), current methadone dose (per 10 mg/d increase), methadone dose perceived to be too low (yes vs no), any illicit methadone injection (yes vs no), any crack cocaine use (yes vs no), any crystal methamphetamine injection (yes vs no), any heroin injection (yes vs no), any cocaine injection (yes vs no), any marijuana use (yes vs no), any heavy alcohol use (yes vs no), any prescription opioid misuse (yes vs no), and any binge injection drug use (yes vs no). As per the National Institute on Alcohol Abuse and Alcoholism, heavy alcohol use was defined as more than 4 drinks per day or more than 14 drinks per week for men or more than 3 drinks per day or more than 7 drinks per week for women.[28] Prescription

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opioid misuse was defined as the injection or noninjection use of prescription opiates not as prescribed or not prescribed to the individual.[37] As per the definition of bingeing in previous studies, binge injection drug use was defined as any period within the previous 6 months from the time of interview during which any drugs were injected more frequently than usual.[16,17] All variables referred to activities or events in the 6 months before the participant's interview, unless otherwise indicated.

Statistical Methods

A generalized linear mixed-effects model (GLMM) was chosen because of its abilities to longitudinally analyze individual trajectories of pain over time and capture within-subject correlation and heterogeneity of participants in an attempt to identify individual-level factors.[16,24] The random intercept was used to account for the random variation among participants. Using the GLMM approach, a cumulative ordered logit model was incorporated to investigate the bivariable and multivariable associations between the exposures of interest and the ordinal outcome (categorized as response variables of no pain or discomfort, moderate pain or discomfort, and extreme pain or discomfort). Specifically, the outcome was split into 2 cut points to create 3 ordinal categories of pain: moderate or extreme pain or discomfort versus no pain or discomfort, and extreme pain or discomfort versus no or moderate pain or discomfort. Then, similar to standard logistic regression, we analyzed the proportional odds of individuals belonging to the pain category above each cut point. Thus, the odds ratios (ORs) reported herein represent the odds of an individual being in a higher pain category per unit change in the explanatory variable.[5]

We then analyzed the bivariable and multivariable associations between the explanatory variables of interest and increased pain severity. First, bivariable GLMM analyses were conducted to obtain unadjusted ORs and *P* values for factors associated with higher pain severity. To adjust for potential confounding, all variables that had $P < .10$ in the bivariable analyses were considered in the multivariable GLMM analysis. A standard backward model selection procedure was used to identify the model with the best overall fit as indicated by the lowest Akaike information criterion value. All *P* values were 2 sided, and significant associations were defined as $P < .05$. All statistical analyses were performed using SAS software version 9.3 (SAS Institute Inc, Cary, NC).

Results

Participants in this sample contributed to 3,018 observations during the study period. Table 1 presents the baseline characteristics of the sample at the time of their first visit during this study period. Of the 823 participants eligible for the present analysis, 326 (39.6%) were female and 512 (62.2%) self-reported white ethnicity. The median age at the first study visit was 46 years (interquartile range [IQR] 39–52 years). At the first study visit, 395 (48.0%) participants reported no pain, 337 (40.9%) reported moderate pain, and 91 (11.1%) reported extreme pain. The median methadone doses at the first study visit for individuals reporting no pain, moderate pain, and extreme pain were 80 mg/d (IQR 45–130 mg/d), 85 mg/d (IQR 38–120 mg/d), and 90 mg/d (IQR 60–140 mg/d), respectively.

Of the 256 participants who provided data on pain duration during the final follow-up period included in this analysis, 213 (83.2%) reported chronic pain lasting more than 6 months. The median pain interference score was 5.0 out of 10 (IQR 3.0–6.5) for the total sample who provided data on pain interference during the final follow-up period included in this analysis (n = 211), with median interference scores of 3.8 (IQR 1.7–5.5), 5.2 (IQR 3.5–6.5), and 5.7 (IQR 4.0–7.3) for the no pain, moderate pain, and extreme pain groups, respectively.

Table 2 presents the results of the bivariable and multivariable GLMM analyses. Factors that were significantly associated with higher pain severity in the bivariable analyses only, but were no longer significant in the multivariable analysis, included prescription opioid use ($P < .001$, unadjusted OR 1.65, 95% confidence interval [CI] 1.28–2.13), having been denied prescription analgesia ($P < .001$, OR 1.58, 95% CI 1.24–2.01), higher education status ($P = .006$, OR 1.53, 95% CI 1.13–2.06), and recent nonfatal overdose ($P = .010$, OR 1.79, 95% CI 1.15–2.80). In multivariable GLMM analysis, factors that remained significantly and independently associated with higher pain severity included having a physical disability ($P < .001$, adjusted OR [AOR] 4.59, 95% CI 3.73–5.64), self-managing pain ($P < .001$, AOR 2.15, 95% CI 1.77–2.60), patient perception of methadone dose being too low ($P < .001$, AOR 1.82, 95% CI 1.41–2.34), older age ($P < .001$, AOR 1.31, 95% CI 1.13–1.51), having ever been diagnosed with a mental illness ($P = .004$, AOR 1.44, 95% CI 1.13–1.84), white ethnicity ($P = .007$, AOR 1.42, 95% CI 1.10–1.83), and marijuana use ($P = .033$, AOR 1.25, 95% CI 1.02–1.52).

Discussion

In this study, a high proportion of participants on MMT reported moderate or extreme pain. Factors that were positively and independently associated with higher pain severity included physical disability, self-managing pain, patient perception of methadone dose being too low, older age, lifetime history of mental health diagnosis, white ethnicity, and marijuana use.

The high prevalence of moderate to severe pain at the first study visit in our study (52.0%) is consistent with previous studies that found high rates of pain among individuals on MMT. Specifically, other studies have found that 55 to 61% of patients on MMT report having a current chronic pain condition, with rates of moderate to severe pain among MMT patients ranging from 24 to 39%.[3,20,32,33,35,41] Considering that the prevalence of chronic pain among the general adult population is estimated to be 31% in the United States and between 15 and 29% in Canada, the comparatively higher prevalence of pain among individuals on MMT is not

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Table 1. Baseline Characteristics of Methadone-Maintained People Who Use Illicit Drugs in Vancouver, BC, Canada, Stratified by Pain Severity (N = 823)

Variable	Value	Total 823 (100%) n (%)	No Pain 395 (48.0%) n (%)	Moderate Pain 337 (40.9%) n (%)	Extreme Pain 91 (11.1%) n (%)
Age	Total	823 (100.0)	395 (100.0)	337 (100.0)	91 (100.0)
	Median, y (IQR)	46 (39–52)	44 (38–50)	47 (42–53)	48 (43–53)
Gender	Male	497 (60.4)	238 (60.3)	201 (59.6)	58 (63.7)
	Female	326 (39.6)	157 (39.7)	136 (40.4)	33 (36.3)
Ethnicity	White	512 (62.2)	228 (57.7)	216 (64.1)	68 (74.7)
	Other	311 (37.8)	167 (42.3)	121 (35.9)	23 (25.3)
Homelessness*‡	Yes	106 (12.9)	54 (13.7)	42 (12.5)	10 (11.0)
	No	715 (86.9)	340 (86.1)	294 (87.2)	81 (89.0)
DTES residence*	Yes	510 (62.0)	244 (61.8)	207 (61.4)	59 (64.8)
	No	313 (38.0)	151 (38.2)	130 (38.6)	32 (35.2)
Highest education level obtained‡	≥ High school diploma	396 (48.1)	173 (43.8)	180 (53.4)	43 (47.3)
	< High school diploma	407 (49.5)	214 (54.2)	149 (44.2)	44 (48.4)
HIV serostatus*	Positive	348 (42.3)	168 (42.5)	143 (42.4)	37 (40.7)
	Negative	475 (57.7)	227 (57.5)	194 (57.6)	54 (59.3)
Hepatitis C status*	Positive	758 (92.1)	362 (91.6)	316 (93.8)	80 (87.9)
	Negative	65 (7.9)	33 (8.4)	21 (6.2)	11 (12.1)
Mental illness diagnosis†	Yes	505 (61.4)	220 (55.7)	222 (65.9)	63 (69.2)
	No	318 (38.6)	175 (44.3)	115 (34.1)	28 (30.8)
Incarceration*‡	Yes	55 (6.7)	26 (6.6)	24 (7.1)	5 (5.5)
	No	765 (93.0)	368 (93.2)	311 (92.3)	86 (94.5)
Physical disability*	Yes	376 (45.7)	102 (25.8)	204 (60.5)	70 (76.9)
	No	447 (54.3)	293 (74.2)	133 (39.5)	21 (23.1)
Self-managed pain*‡	Yes	446 (54.2)	178 (45.1)	206 (61.1)	62 (68.1)
	No	370 (45.0)	215 (54.4)	128 (38.0)	27 (29.7)
Denied pain medication*‡	Yes	104 (12.6)	32 (8.1)	50 (14.8)	22 (24.2)
	No	714 (86.8)	361 (91.4)	284 (84.3)	69 (75.8)
Nonfatal overdose*‡	Yes	35 (4.3)	12 (3.0)	18 (5.3)	5 (5.5)
	No	786 (95.5)	382 (96.7)	319 (94.7)	85 (93.4)
Current methadone dose‡	Total	808 (98.2)	391 (99.0)	327 (97.0)	90 (98.9)
	Median, mg/d (IQR)	85 (50–130)	80 (45–130)	85 (38–120)	90 (60–140)
Methadone dose perceived to be too low*‡	Yes	133 (16.2)	53 (13.4)	58 (17.2)	22 (24.2)
	No	679 (82.5)	335 (84.8)	275 (81.6)	69 (75.8)
Illicit methadone injection*	Yes	4 (.5)	2 (.5)	2 (.6)	0 (.0)
	No	819 (99.5)	393 (99.5)	335 (99.4)	91 (100.0)
Crack cocaine use*	Yes	483 (58.7)	230 (58.2)	201 (59.6)	52 (57.1)
	No	340 (41.3)	165 (41.8)	136 (40.4)	39 (42.9)
Crystal meth injection*	Yes	139 (16.9)	68 (17.2)	62 (18.4)	9 (9.9)
	No	684 (83.1)	327 (82.8)	275 (81.6)	82 (90.1)
Heroin injection*‡	Yes	355 (43.1)	175 (44.3)	147 (43.6)	33 (36.3)
	No	467 (56.7)	220 (55.7)	189 (56.1)	58 (63.7)
Cocaine injection*‡	Yes	217 (26.4)	95 (24.1)	98 (29.1)	24 (26.4)
	No	605 (73.5)	299 (75.7)	239 (70.9)	67 (73.6)
Marijuana use*‡	Yes	331 (40.2)	153 (38.7)	140 (41.5)	38 (41.8)
	No	490 (59.5)	241 (61.0)	196 (58.2)	53 (58.2)
Heavy alcohol use*‡	Yes	99 (12.0)	47 (11.9)	42 (12.5)	10 (11.0)
	No	722 (87.7)	348 (88.1)	293 (86.9)	81 (89.0)
Prescription opioid use*‡	Yes	124 (15.1)	47 (11.9)	55 (16.3)	22 (24.2)
	No	697 (84.7)	347 (87.9)	281 (83.4)	69 (75.8)
Binge injection drug use*‡	Yes	195 (23.7)	84 (21.3)	91 (27.0)	20 (22.0)
	No	625 (75.9)	309 (78.2)	245 (72.7)	71 (78.0)

*Denotes activities/events in the previous 6 months.
†Denotes activities/events within the participant's lifetime.
‡Indicates missing responses as follows: homelessness (2 missing responses), highest education level obtained (20 missing responses), incarceration (3 missing responses), self-managed pain (7 missing responses), denied pain medication (5 missing responses), nonfatal overdose (2 missing responses), current methadone dose (15 missing responses), methadone dose perceived to be too low (11 missing responses), heroin injection (1 missing response), cocaine injection (1 missing response), marijuana use (2 missing responses), heavy alcohol use (2 missing responses), prescription opioid use (2 missing responses), binge injection drug use (3 missing responses).

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Table 2. Bivariable and Multivariable GLMM Analyses of Factors Associated With Higher Pain Severity Among Methadone-Maintained People Who Use Illicit Drugs in Vancouver, BC, Canada (N = 823 Contributing to a Total of 3,018 Observations)

	Unadjusted		Adjusted	
Variable	OR (95% CI)	P Value	OR (95% CI)	P Value
Age (per 10-year increase)	1.64 (1.38–1.95)	<.001	1.31 (1.13–1.51)	<.001
Gender (male vs female)	1.01 (.74–1.36)	.970		
Ethnicity (white vs other)	1.88 (1.38–2.56)	<.001	1.42 (1.10–1.83)	.007
Homelessness* (yes vs no)	.99 (.72–1.36)	.941		
DTES residence* (yes vs no)	1.21 (.94–1.55)	.134		
Highest education level obtained (≥ high school diploma vs < high school diploma)	1.53 (1.13–2.06)	.006	1.21 (.95–1.53)	.120
HIV serostatus* (positive vs negative)	.94 (.70–1.28)	.702		
Hepatitis C status* (positive vs negative)	.89 (.50–1.58)	.695		
Mental illness diagnosis† (yes vs no)	1.78 (1.31–2.41)	<.001	1.44 (1.13–1.84)	.004
Incarceration* (yes vs no)	1.25 (.80–1.94)	.323		
Physical disability* (yes vs no)	5.28 (4.32–6.45)	<.001	4.59 (3.73–5.64)	<.001
Self-managed pain* (yes vs no)	2.80 (2.31–3.39)	<.001	2.15 (1.77–2.60)	<.001
Denied pain medication* (yes vs no)	1.58 (1.24–2.01)	<.001	1.20 (.94–1.52)	.146
Nonfatal overdose* (yes vs no)	1.79 (1.15–2.80)	.010	1.40 (.90–2.18)	.137
Current methadone dose (per 10 mL/d increase)	1.01 (.99–1.03)	.451		
Methadone dose perceived to be too low (yes vs no)	1.85 (1.43–2.41)	<.001	1.82 (1.41–2.34)	<.001
Illicit methadone injection* (yes vs no)	.59 (.11–3.09)	.528		
Crack cocaine use* (yes vs no)	1.08 (.86–1.36)	.523		
Crystal meth injection* (yes vs no)	1.05 (.79–1.41)	.735		
Heroin injection* (yes vs no)	1.17 (.94–1.45)	.163		
Cocaine injection* (yes vs no)	1.19 (.94–1.51)	.158		
Marijuana use* (yes vs no)	1.32 (1.07–1.63)	.009	1.25 (1.02–1.52)	.033
Heavy alcohol use* (yes vs no)	1.31 (.94–1.81)	.106		
Prescription opioid use* (yes vs no)	1.65 (1.28–2.13)	<.001	1.23 (.95–1.58)	.112
Binge injection drug use* (yes vs no)	1.06 (.84–1.34)	.604		

*Denotes activities/events in the previous 6 months.
†Denotes activities/events within the participant's lifetime.

surprising, given the known higher rates of injury and disability among this population, and warrants increased attention to pain management strategies for this population.[4,21,27,42]

Our finding that MMT patients with higher pain severity in this study were more likely to self-manage their pain is concerning, given our previous research on self-managed pain,[44] which found that participants who reported self-managing pain often did so using high-risk methods, which most commonly included injecting heroin or obtaining diverted prescription analgesia (most commonly opioid based) off the street or from another person. In this study, we found that 61.1% of participants with moderate pain reported self-managing pain, compared with a slightly higher proportion of participants with extreme pain who reported self-managing pain (68.1%) at their first study visit. The strong association between self-managed pain and higher pain severity in this study further suggests that pain may be poorly managed among this sample of individuals on MMT. In this regard, clinicians have a key role to play in addressing patients' pain concerns and self-management behaviors to prevent high-risk self-medication in ways that pose high risk for morbidity and mortality.

In this study, individuals on MMT with higher pain severity were more likely to perceive that their methadone dose was too low. Although we did not find current methadone dose to be significantly associated with higher pain severity in our statistical analysis, we found that the median methadone doses in our sample appeared to trend upward with increasing pain severity (80 mg/d, 85 mg/d, and 90 mg/d for no pain, moderate pain, and extreme pain, respectively), consistent with other studies that have found higher doses of methadone among patients with higher pain severity.[20,32] Although the responses to this question in our survey did not specify whether participants believed their doses were insufficient with regard to reducing pain, opioid cravings, or both, this finding presents several potential implications in the context of pain management. First, if we assume that our participants believed their doses were insufficient with regard to reducing pain, this finding is consistent with other studies suggesting that pain may be undertreated among MMT patients.[20,35,38] Conversely, in the context of the theory of opioid-induced hyperalgesia, consistent exposure to opioids may paradoxically exacerbate rather than relieve pain-related symptoms, which may lead patients to believe that they require a higher opioid dose to

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relieve their heightened pain.[14] This finding illustrates the need for patient and practitioner education related to methadone dosing for individuals with concurrent pain; the need for conclusive evidence related to opioid-induced hyperalgesia and how best to counteract its potential effects; and the need for effective and evidence-based treatment regimens for MMT patients with pain, whether via alternative methadone dosing or timing strategies, alternative opioid therapies with less potential for hyperalgesia, or other adverse effects such as buprenorphine, or nonopioid analgesic alternatives.[23]

Our finding that MMT patients with physical disabilities were more likely to report higher pain severity is consistent with other studies investigating pain among MMT patients.[33,35] Previous literature suggests that individuals with physical disabilities are more likely to experience chronic problematic pain that affects their lifestyle choices and that these individuals may be hesitant to discuss pain management with health care providers.[10,13] Therefore, clinicians may consider proactively discussing pain management approaches and behaviors among MMT patients with physical disabilities. Furthermore, greater pain catastrophizing has been found to be associated with increased pain-related disability and greater pain intensity among MMT patients.[17] Additional research on pain-related disability among MMT patients is necessary given the limited amount of literature on this topic.

The observed significant associations between higher pain severity and older age and lifetime diagnosis with mental illness are consistent with other studies investigating pain among MMT patients.[14,35] As noted by Eyler,[14] an increasing demand for effective pain management is likely to coincide with the aging population of MMT patients, which necessitates increased attention to pain research and care for these individuals. Furthermore, MMT patients with pain would benefit greatly from improved integration of pain, addiction, and psychiatric care, rather than having clinicians from these specialties providing fragmented care.[23]

Our finding that higher pain severity was significantly associated with white ethnicity differs from existing literature on ethnicity and pain, much of which has focused on general populations in the Unites States and has found that whites tend to have lower pain severity compared with Hispanics or African Americans.[9,12] There have been few comparisons of pain among ethnic populations outside the United States and, in particular, among individuals with a history of substance use, opioid dependence, or both. Therefore, this is an area that would benefit from further research.

This study found a significant association between marijuana use and higher pain severity among individuals on MMT, which is consistent with other studies that have found marijuana to be commonly used among MMT patients with significant or chronic pain, particularly compared with the less frequent use of marijuana among MMT patients without significant or chronic pain.[19,25,35] Taking into consideration that patients in these studies reported using marijuana specifically for treating pain[35] and that MMT was found to be effective in reducing illicit opioid use at comparable rates between patients with and without pain independent of marijuana use,[19] these findings warrant further investigation into the effectiveness of medicinal marijuana as a potential adjunct treatment of MMT patients with significant or chronic pain.

This study has several limitations. First, our study relied on self-reported data, which are susceptible to socially desirable reporting and recall bias. Second, our analysis did not adjust for potential false-positive results; however, as previously described, the prevalence of pain in our study is comparable with other studies among similar populations. In addition, the EuroQol EQ-5D has been previously demonstrated to be a valid, responsive, and reliable survey instrument among individuals with pain and substance users.[18,30,43] Furthermore, we expect that potential misclassification of pain severity in our study would be nondifferential, which would likely mean that our observed estimates are more conservative (ie, biased toward the null) than they would be if there were no false-positive results in our study.[36] Third, the EuroQol EQ-5D captures participants' self-reports of pain or discomfort, and although discomfort is certainly related to pain, caution should be taken when interpreting the results pertaining to pain severity in this study, as it is possible that factors other than physical pain (eg, discomfort related to opioid withdrawal) may have contributed to participants' responses. Fourth, our analysis used assessments of pain at the time of participants' interviews, compared with other variables that were assessed with a reference period of 6 months before participants' interviews. This approach has been widely adopted in the literature and found to be valid.[7,11,29,35] Fifth, because the study sample was not randomly selected, these results may not be generalizable to other populations. As in all observational studies of this kind, we are unable to disentangle the temporal ordering of the observed associations, particularly when ascertaining whether certain factors preceded or followed one another within each given 6-month follow-up period.

A high proportion of individuals on MMT reported higher pain severity in our study. We found that patients on MMT with higher pain severity were more likely to have a physical disability, believe their methadone dose was insufficient, self-manage pain, have a lifetime history of mental illness, and have a higher education status. These findings suggest several areas for future research, clinical intervention, and patient education, particularly regarding the risks of self-managing pain, the potential for opioid-induced hyperalgesia, and the potential for alternative analgesic approaches for MMT patients experiencing pain.

Acknowledgments

The authors thank the VIDUS and ACCESS study participants for their contribution to the research, as well as current and past researchers and staff. We would

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specifically like to thank Sabina Dobrer, Tricia Collingham, Carmen Rock, Deborah Graham, Peter Vann, Jennifer Matthews, Steve Kain, and Lianping Ti for their assistance with this research.

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