Drug and Alcohol Dependence 205 (2019) 107672

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Willingness to take buprenorphine/naloxone among people who use opioids in Vancouver, Canada

Sarah A. Weicker[a], Kanna Hayashi[a,c], Cameron Grant[a], M.-J. Milloy[a,b], Evan Wood[a,b], Thomas Kerr[a,b,*]

[a] British Columbia Centre on Substance Use, British Columbia Centre for Excellence in HIV/AIDS, St. Paul's Hospital, 608-1081 Burrard Street, Vancouver, BC, V6Z 1Y6, Canada
[b] Department of Medicine, University of British Columbia, St. Paul's Hospital, 608-1081 Burrard Street, Vancouver, BC, V6Z 1Y6, Canada
[c] Faculty of Health Sciences, Simon Fraser University, Blusson Hall, 8888 University Drive, Burnaby, BC, V5A 1S6, Canada

ARTICLE INFO

Keywords:
Opioid agonist therapy
buprenorphine/naloxone
Opioid use disorder

ABSTRACT

Objectives: Opioid agonist therapy is the cornerstone of treatment of opioid use disorder. In Canada, buprenorphine/naloxone has recently been adopted as the first line agonist therapy given its comparable effectiveness to methadone and superior safety profile. This study examines factors associated with willingness to take buprenorphine/naloxone among opioid users.

Methods: Data were derived from two prospective cohorts of high-risk individuals who use drugs in Vancouver, Canada. Multivariable logistic regression analyses were used to determine factors associated with willingness to use buprenorphine/naloxone among people who use opioids and were not currently accessing this treatment option. Participants who were unwilling to use buprenorphine/naloxone were invited to provide reason(s) and their responses were examined in a sub-analysis.

Results: Between December 2014 and May 2018, 1103 participants were interviewed. Overall, 194 (17.6%) respondents indicated that they would be willing to take buprenorphine/naloxone. Variables independently associated with willingness were previous buprenorphine/naloxone treatment (adjusted odds ratio [AOR] = 2.04), having ever used methadone treatment (AOR = 1.87), and age (AOR = 0.98, per year older) (all $p < 0.05$). Satisfaction with current agonist therapy (25.4%), not knowing what buprenorphine/naloxone is (25.1%), and wanting more information about buprenorphine/naloxone (15.1%) were the most commonly cited reasons for unwillingness. A low rate of willingness to use buprenorphine/naloxone (15.1%) was also observed among the sub-set of participants not using methadone.

Conclusions: While an overall low level of willingness to take buprenorphine/naloxone was observed, this appeared to be largely driven by satisfaction with other agonists and a low prevalence of community knowledge about buprenorphine/naloxone.

1. Introduction

Opioid use disorder (OUD) is a chronic relapsing disorder, associated with substantial preventable morbidity and mortality (Schuckit, 2016). In 2017 alone, 4034 apparent opioid-related deaths (equal to 11.1 per 100,000 people) were reported in Canada (PHAC, 2019). The unprecedented opioid crisis has underscored the importance of developing and delivering accessible, evidence-based treatments for substance use disorders.

Opioid agonist therapy (OAT) continues to be the mainstay of treatment for OUD. Engagement of patients in OAT has been associated with reduced rates of opioid-related harms including overdose, all-cause mortality, and HIV and Hepatitis C infection (Grönbladh et al., 1990; MacArthur et al., 2012; Schwartz et al., 2013; Tsui et al., 2014). In Canada, buprenorphine/naloxone (*trade name:* Suboxone) has been recently adopted as the first-line treatment for OUD (Bruneau et al., 2018). Available evidence suggests that buprenorphine/naloxone has comparable effectiveness to methadone when prescribed at appropriate doses, but benefits from a superior safety profile (Luty et al., 2005; Mattick et al., 2014). Specifically, the partial μ-opioid agonist properties of buprenorphine afford it a lower potential for respiratory depression and overdose; indeed, a retrospective study from the UK found

* Corresponding author at: Department of Medicine, University of British Columbia, Senior Scientist, British Columbia Centre on Substance Use, 400-1045 Howe Street, Vancouver, BC, V6Z 2A9, Canada.
E-mail address: bccsu-tk@bccsu.ubc.ca (T. Kerr).

https://doi.org/10.1016/j.drugalcdep.2019.107672
Received 8 May 2019; Received in revised form 25 September 2019; Accepted 27 September 2019
Available online 25 October 2019
0376-8716/

that buprenorphine is six-times safer than methadone with respect to overdose risk (Marteau et al., 2015). In addition, buprenorphine/naloxone has fewer drug-drug interactions and a lower risk of cardiac arrhythmias from QTc prolongation in comparison to methadone (Chou et al., 2014; McCance-Katz et al., 2010).

Buprenorphine/naloxone also offers a greater degree of treatment flexibility. Its improved safety profile allows for more routine take-home dosing (Bruneau et al., 2018). In contrast, methadone treatment guidelines generally recommend a period of daily witnessed ingestion at pharmacies for new methadone users (Bruneau et al., 2018). This disruption to patients' daily activities may be required indefinitely for individuals at higher risk of diversion or misuse, such as those with unstable social situations or ongoing illicit opioid use (Bruneau et al., 2018). However, such structural challenges associated with methadone treatment are known to be contributors to low uptake and retention rates (Nosyk et al., 2010; Reisinger et al., 2009). Buprenorphine/naloxone also benefits from greater flexibility in its initiation. In comparison to methadone, buprenorphine/naloxone doses can be more rapidly uptitrated to a therapeutic level (Maremmani and Gerra, 2010). Furthermore, successful inductions have been demonstrated in a variety of settings, including primary care offices, emergency departments, and even patient homes (D'Onofrio et al., 2015; Fatseas and Auriacombe, 2007; Lee et al., 2014). Nonetheless, it should be noted that buprenorphine/naloxone inductions can be challenging and less desirable for some individuals, given that patients are typically required to be in moderate opioid withdrawal prior to induction to prevent precipitated withdrawal (Bruneau et al., 2018). Further, some patients prefer the sedating properties of methadone whereas others view this as an unwelcome side effect of methadone (Bishop et al., 2018).

Although both buprenorphine/naloxone and methadone are mainstays for OAT, methadone still represents the most widely prescribed agonist in British Columbia, Canada; indeed, in 2015/2016, buprenorphine/naloxone was only used by 3445 of 19,057 (18%) patients accessing OAT in the province (Office of the Provincial Health Officer, 2017). To mitigate financial barriers in accessing this treatment, buprenorphine/naloxone was made eligible for coverage under several of the province's Pharmacare plans. Full coverage is provided for those on income assistance, those enrolled in the psychiatric-mediation plan, and those enrolled in the First Nations Health Benefit; for other patients, buprenorphine/naloxone may be partially or fully subsidized through the income-based Fair Pharmacare program (Government of British Columbia, 2019).

The willingness of individuals who use opioids to take buprenorphine/naloxone has not been previously well described. In light of the benefits associated with buprenorphine/naloxone as the first-line treatment and the low levels of usage relative to methadone in the province, we sought to examine the willingness to take buprenorphine/naloxone and associated factors among a cohort of individuals who use opioids in Vancouver, Canada.

2. Methods

2.1. Study participants

We utilized data from two prospective cohorts of people who use drugs in Vancouver, Canada: the Vancouver Injection Drug Users Study (VIDUS) and the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS). These cohorts have been described previously in detail (Wood et al., 2001). Since May 1996, adult participants (18 years of age or greater) have been recruited via street outreach and self-referral. VIDUS is a cohort of HIV-negative adults who report injecting illicit drugs at least once in the month prior to recruitment. The ACCESS cohort includes HIV-positive adults who used illicit drugs (other than or in addition to cannabis, which was illicit during the study period) in the month prior to study enrollment. VIDUS participants who seroconvert are transferred to the ACCESS study. All participants provide informed consent. Individuals who indicated that they were currently not using opioids or were already taking buprenorphine/naloxone were excluded from analysis. Both studies collect data and conduct follow-ups in a harmonized manner to allow for combined analyses. At baseline and follow-up visits every 6 months thereafter, questionnaires are administered by trained interviewers and blood samples are collected by nurses for serologic testing. Study questionnaires ask information about sociodemographic characteristics, drug use behaviours, health-care and treatment engagement, and a range of social-structural exposures. Participants receive a $40 CAD stipend at each interview visit. Both VIDUS and ACCESS were approved by the University of British Columbia/Providence Health Care Research Ethics Board.

2.2. Variables of interest

The primary outcomes of interest in this analysis was self-reported willingness to use buprenorphine/naloxone. Specifically, participants were asked "Would you like to go on Suboxone?" when discussing drug treatment options in a research interview. This question was added to the ACCESS and VIDUS questionnaires in December 2014. Participants' first response during the study period (December 2014 to May 2018) was used in the analysis. Individuals who responded "Yes" were compared to those who answered "No" with regards to a variety of predetermined sociodemographic, drug-use, and treatment variables.

Sociodemographic variables included age, gender identity (female-identified vs. other), ethnicity (white vs. other), HIV serostatus (positive vs. negative), recent homelessness (yes vs. no), recent employment (defined as regular work, temporary work, or self-employment) (yes vs. no), and recent incarceration (yes vs. no). Drug use variables included the following over the last 6 months: daily heroin injection (yes vs. no), daily prescription opioid injection (yes vs. no), daily cocaine injection (yes vs. no), daily non-injection crack use (yes vs. no), daily methamphetamine use (yes vs. no), and non-fatal overdose (yes vs. no). Treatment variables included previous buprenorphine/naloxone treatment (yes vs. no), having ever used methadone agonist treatment (yes vs. no), and recent drug/alcohol treatment other than methadone (such as counselling, peer support groups, residential treatment, and detox) (yes vs. no). For all variables, "recent" was defined as having occurred in the last 6 months.

2.3. Statistical methods

Initially, we examined respondent baseline characteristics and used bivariable analyses to identify factors associated with willingness to use buprenorphine/naloxone. The bivariable analysis was performed using maximum likelihood parameter estimates and a Wald chi-square test statistic. Variables which were significant at $p < 0.05$ in the bivariable analyses were included in the initial multivariable analysis. A final multivariable logistic regression model was chosen by performing a backward elimination process. We did this by dropping the variable with the largest type III p-value from the model, one by one, until all variables were dropped. From those models, we then chose the one with the lowest AIC value. All p-values were two-sided. All statistical analyses were performed using SAS software version 9.4 (SAS, Cary, NC).

2.4. Secondary analyses

In a sub-analysis, individuals indicating they were not willing to take buprenorphine/naloxone were invited to provide reason(s) for their unwillingness in response to a follow-up question. Participants could select multiple responses from the following: "Satisfied with Methadose (methadone) program"; "Don't want to go into withdrawal"; "Unable to find a doctor to prescribe Suboxone"; "Would like to, but cost is a barrier"; "Don't know what Suboxone is"; "Need more information about Suboxone"; "Not interested in opioid maintenance program"; and "Other" (other reasons were solicited and recorded in an

Table 1
Baseline characteristics of a sample of people who use opioids, stratified by willingness to take buprenorphine/naloxone (n = 1103).

Characteristic	Willing n = 194 (17.6%)	Not Willing n = 909 (82.4%)	Odds Ratio (95% CI)	p - value
Age				
median (IQR)	42.4 (34–49.8)	46.9 (37.3–53.8)	0.97 (0.95–0.98)	< 0.0001
Gender				
female †	92 (47.4)	354 (38.9)	1.40 (1.03–1.92)	0.0340
other	100 (51.5)	540 (59.4)		
Ethnicity				
white	110 (56.7)	518 (57)	1.00 (0.73–1.37)	0.9981
other	82 (42.3)	386 (42.5)		
Homeless*				
yes	60 (30.9)	204 (22.4)	1.55 (1.10–2.18)	0.0121
no	133 (68.6)	701 (77.1)		
Employment*				
yes	40 (20.6)	224 (24.6)	0.79 (0.54–1.15)	0.2338
no	154 (79.4)	685 (75.4)		
HIV serostatus				
positive	70 (36.1)	338 (37.2)	0.95 (0.69–1.31)	0.7730
negative	124 (63.9)	571 (62.8)		
Incarceration*				
yes	18 (9.3)	68 (7.5)	1.27 (0.72–2.15)	0.3886
no	175 (90.2)	840 (92.4)		
Daily heroin injection*				
yes	80 (41.2)	255 (28.1)	1.80 (1.30–2.48)	0.0003
no	114 (58.8)	654 (71.9)		
Daily prescription opioid injection*				
yes	9 (4.6)	51 (5.6)	0.82 (0.37–1.61)	0.5887
no	185 (95.4)	858 (94.4)		
Daily non-injection crack*				
yes	22 (11.3)	115 (12.7)	0.88 (0.53–1.41)	0.6154
no	172 (88.7)	794 (87.3)		
Daily injection cocaine*				
yes	6 (3.1)	45 (5)	0.61 (0.23–1.35)	0.2678
no	188 (96.9)	864 (95)		
Daily methamphetamine*				
yes	39 (20.1)	125 (13.8)	1.58 (1.05–2.33)	0.0249
no	155 (79.9)	784 (86.2)		
Non-fatal overdose*				
yes	37 (19.1)	116 (12.8)	1.62 (1.07–2.42)	0.0202
no	156 (80.4)	793 (87.2)		
Drug or alcohol treatment*,‡				
yes	15 (7.7)	69 (7.6)	1.02 (0.55–1.78)	0.9463
no	179 (92.3)	840 (92.4)		
Previous buprenorphine/naloxone treatment				
yes	22 (11.3)	41 (4.5)	2.71 (1.55–4.62)	0.0003
no	172 (88.7)	868 (95.5)		
Methadone treatment ever				
yes	178 (91.8)	786 (86.5)	1.73 (1.03–3.09)	0.0499
no	16 (8.2)	122 (13.4)		

* In the last 6 months.
† Includes participants who self-identified as female or as a trans woman.
‡ Excluding methadone treatment.

open-ended fashion).

As our cohort had a high proportion of individuals using methadone, we conducted a sub-analysis to examine willingness to use buprenorphine/naloxone amongst those not on methadone; after excluding participants with self-reported current methadone use, we examined both levels of willingness and reported reasons for unwillingness within this sub-group.

3. Results

Between December 2014 and May 2018, 1568 ACCESS and VIDUS participants responded to the question "Would you like to go on Suboxone?". Of these, 450 (28.7%) responded they were not using opioids and only 15 (1.0%) reported they were already on buprenorphine/naloxone; these individuals were excluded from further analysis. Baseline characteristics of the remaining 1103 participants are displayed in Table 1. Of these participants, 408 were from the ACCESS cohort and 695 were from the VIDUS cohort. Among the study sample, the median age was 46 years (interquartile range [IQR] = 37–53); 446 (40.4%) participants were female-identified and 628 (56.9%) were white. The cohort had a high prevalence of previous methadone use, with 964 (87.4%) respondents indicating that they had used methadone at least once before. Overall, 711 (64.5%) were taking methadone at the time of the interview.

In total, 194 (17.6%) individuals indicated they would be willing to use buprenorphine/naloxone for treatment of OUD. As shown in Table 1, in bivariable analyses willingness to use buprenorphine/naloxone was associated with younger age (Odds Ratio [OR] 0.97 per year older, 95% Confidence Interval [CI] 0.95–0.98), female gender identity (OR 1.40, 95% CI 1.03–1.92), recent homelessness (OR 1.55, 95% CI 1.10–2.18), daily heroin injection (OR 1.80, 95% CI 1.30–2.48), daily methamphetamine use (OR 1.58, 95% CI 1.05–2.33), recent non-fatal overdose (OR 1.62, 95% CI 1.07–2.42), previous buprenorphine/naloxone treatment (OR 2.71, 95% CI 1.55–4.62), and having ever used methadone treatment (OR 1.73, 95% CI 1.03–3.09).

In a multivariable logistic regression analysis (Table 2), willingness to use buprenorphine/naloxone remained significantly associated with previous buprenorphine/naloxone treatment (Adjusted Odds Ratio [AOR] 2.04, 95% CI 1.15–3.63), having ever used methadone treatment (AOR 1.87, 95% CI 1.06–3.30), and younger age (AOR 0.98 per year older, 95% CI 0.96–0.999).

Among the 909 (82.4%) individuals who indicated they were not willing to take buprenorphine/naloxone, 920 reasons were provided (Fig. 1). The most common responses included the following: 231 (25.1%) stated that they did not know what buprenorphine/naloxone (Suboxone) was; 234 (25.4%) were satisfied with methadone or other agonist therapy; 139 (15.1%) said they needed more information about buprenorphine/naloxone; 66 (7.2%) didn't want to go into withdrawal; 69 (7.5%) were not interested in opioid agonist treatment; 34 (3.7%) reported previous negative experiences with buprenorphine/naloxone; and 19 (2.1%) felt that buprenorphine/naloxone would be not be sufficient in addressing their pain or that other opioid medications were needed for pain. There were 128 other responses which included the following themes: perceiving buprenorphine/naloxone as an ineffective treatment; not wanting to stop using opioids or take anything that would block their effects; expressing concern about potential side effects; not using opioids frequently enough to warrant treatment; and wanting to start a different agonist treatment. No participants indicated that they were unable to find a doctor to prescribe it, and only one

Table 2
Multivariable analysis of factors associated with willingness to take buprenorphine/naloxone (n = 1103).

Variable	Adjusted Odds Ratio (AOR)	95% Confidence Interval (CI)	p - value
Age (per one year older)	0.98	(0.96–0.999)	0.0385
Gender (female-identified† vs. other)	1.22	(0.88–1.70)	0.2412
Homeless* (yes vs. no)	1.16	(0.79–1.72)	0.4476
Daily heroin injection* (yes vs. no)	1.41	(0.99–2.00)	0.0561
Overdose* (yes vs. no)	1.27	(0.81–2.00)	0.2887
Previous buprenorphine/naloxone treatment (yes vs. no)	2.04	(1.15–3.63)	0.0150
Methadone treatment ever (yes vs. no)	1.87	(1.06–3.30)	0.0301

* In the last 6 months.
† includes participants who self-identified as female or as a trans woman.

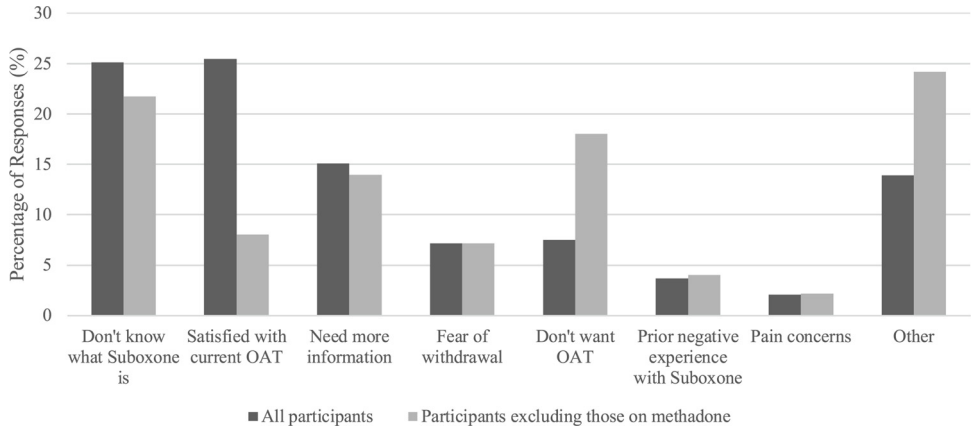

Fig. 1. Reasons provided by respondents who indicated that they were unwilling to use buprenorphine/naloxone (Suboxone).

person reported that cost was a barrier.

Given the high prevalence of individuals on methadone within our cohort and the large number of participants indicating that they were satisfied with their current agonist therapy, we sought to examine willingness to take buprenorphine/naloxone among participants not on methadone. In a sub-analysis, we excluded 711 individuals taking methadone. Of the remaining 392 participants, 59 (15.1%) reported willingness to use buprenorphine/naloxone. There were 322 reasons provided for unwillingness within this sub-group (Fig. 1). The most common responses included the following: 70 (21.7%) did not what buprenorphine/naloxone was; 58 (18.0%) were not interested in OAT; 45 (14.0%) wanted more information about buprenorphine/naloxone; 26 (8.1%) were satisfied with other agonist therapies (including sustained-release oral morphine and injectable hydromorphone); and 23 (7.1%) did not want to go into withdrawal.

4. Discussion

In this study, a low level of willingness (17.6%) to take buprenorphine/naloxone was observed among a cohort of people who use opioids in Vancouver, Canada. We found that previous buprenorphine/naloxone treatment and having ever used methadone treatment were positively associated with willingness, while age was negatively associated. The most commonly reported reasons for unwillingness included satisfaction with other OAT regimens and a lack of knowledge about buprenorphine/naloxone. To our knowledge, this is the first study to specifically examine the willingness of individuals with OUD to take buprenorphine/naloxone in a Canadian setting. Prior studies have examined factors influencing provider willingness to prescribe buprenorphine (Huhn and Dunn, 2017; Netherland et al., 2009), and patient-focused analyses have explored willingness to take OAT among opioid users in Ukraine (Makarenko et al., 2016), willingness to use IV buprenorphine in individuals refractory to oral treatment in France (Roux et al., 2017), and OUD treatment preferences among people who engage in non-medical prescription opioid use in the U.S. (Huhn et al., 2017).

In our multivariable analysis, having ever used methadone was associated with willingness to use buprenorphine/naloxone. We hypothesize that this association may be attributable to two reasons. Firstly, we expect that opioid users who have previously used agonist therapy may be more comfortable engaging with the healthcare system and accepting pharmacologic treatment. Secondly, participants who have previously used methadone may be seeking treatment alternatives which afford them more flexibility in their daily activities (i.e. without the requirement of witnessed ingestion) (McNeil et al., 2015; Reisinger et al., 2009). Of note, at the time of data collection, Canadian physicians were required to have a federal exemption to prescribe methadone. As this created barriers for many patients, the need for the exemption was removed in 2018, and methadone treatment was increasingly made available via various low-threshold (i.e. primary care-based) venues (Ahamad et al., 2015). Following this policy change, the impacts on physician willingness to prescribe methadone and, consequently, ease of accessing methadone treatment are not fully known.

Previous treatment with buprenorphine/naloxone was the characteristic most strongly associated with willingness to use buprenorphine/naloxone in multivariable analysis. While there are likely unmeasured confounding variables at play, this finding may also be reflective of individuals who previously had success in treating their OUD with this management option. Additionally, prior exposure to buprenorphine/naloxone would likely afford these participants a greater degree of familiarity with this treatment option relative to other respondents.

Interestingly, in our sub-analysis, we found that lack of education and knowledge about buprenorphine/naloxone are important contributors to unwillingness; common reasons provided for unwillingness to use buprenorphine/naloxone included “Don’t know what Suboxone is” and “Need more information” (together accounting for 40.2% of responses). These findings suggest a need for targeted interventions to increase awareness and knowledge of buprenorphine/naloxone. Benefits of educational interventions have previously been demonstrated in studies examining willingness to accept treatment for Hepatitis C; indeed, patients who had received educational interventions were more likely to report willingness to access treatment (Gupta et al., 2007; Zeremski et al., 2014). Furthermore, given the well-described impacts of peer-based educational programming, future interventions focused on increasing knowledge regarding buprenorphine/naloxone should likely involve peer educators (Callon et al., 2013; Sherman et al., 2009). Interest in using this treatment option could be fostered through explanations about the safety profile of buprenorphine/naloxone as well as the potential for greater treatment flexibility and take-home dosing.

Although less prevalent than anticipated, the desire to avoid opioid withdrawal was another reason cited for unwillingness to use buprenorphine/naloxone (accounting for 7.2% of responses). Most buprenorphine/naloxone induction protocols require patients to be in moderate withdrawal, as determined by a clinical opioid withdrawal score (COWS) of greater than 12 (BC Centre on Substance Use (BCCSU, 2017). This is done to minimize the risk of precipitated withdrawal – a more severe, rapid onset opioid withdrawal caused displacement of weaker binding opioids (such as heroin) by the partial agonist buprenorphine. Given that our cohort reported low levels of knowledge about buprenorphine/naloxone, fear of withdrawal may become a more prevalent concern as individuals gain familiarity with the buprenorphine/naloxone induction process. Recently, alternative inductions protocols such as micro-dosing and the use of fentanyl bridges have been employed to address this patient concern (Azar et al., 2018; Hammig et al.,

2016; Klaire et al., 2019). While not widely used now, these protocols represent promising methods of mitigating withdrawal symptoms and may be more broadly applied in the future. Other reasons for unwillingness expressed by our participants, such as prior negative experiences with buprenorphine/naloxone and fear of untreated pain, were consistent with those previously described; a qualitative study from the United States similarly identified that prior experiences with agonist therapy (positive or negative), fear of withdrawal, and desire for pain control were key factors in influencing patient treatment preference (Yarborough et al., 2016).

Given that satisfaction with current agonist therapy was a frequently cited reason for unwillingness (accounting for 25.4% of responses), we sought to examine willingness to take buprenorphine/naloxone among participants not currently taking methadone. Interestingly, a low rate of willingness to use buprenorphine/naloxone was also observed among this sub-set of participants. Overall, 15.1% of individuals not using methadone reported willingness, which was comparable to the levels within the entire cohort (17.6%). Again, low levels of knowledge seemed to be a major contributor to unwillingness, with "Don't know what Suboxone is" and "Need more information" together accounting for 35.7% of reasons provided. While fewer responses indicated satisfaction with current agonist therapy, this was accompanied by a concomitant increase in the number of individuals indicating they were uninterested in OAT. This cohort sub-set likely represents a heterogeneous mixture of participants, including individuals not yet engaged in OAT, people with more complex or refractory OUD using third- and fourth-line treatments (such as sustained-release oral morphine and injectable agonists), as well as individuals with low levels of opioid use. Future research should seek to determine how willingness to use buprenorphine/naloxone may differ between individuals newly starting or re-initiating OAT versus those switching from one agonist treatment to another.

Our research has limitations. Our study sample was not random and was derived from two cohorts of high-risk individuals; thus, our sample cannot be presumed to be representative of the entire population of individuals with opioid use disorder within Vancouver. The data used in this study were self-reported by participants (with the exception of serologic data) and are subject to response bias. Lastly, the respondent data were collected over a period of 3.5 years; as a consequence, participant attitudes and knowledge of buprenorphine/naloxone may have evolved since the start of the study and impact current-day levels of willingness.

In summary, we identified low rates of willingness to use buprenorphine/naloxone among a cohort of opioid users in Vancouver, Canada. Previous treatment with buprenorphine/naloxone and having ever used methadone were positively associated with willingness, whereas age was negatively associated. The most common reasons for unwillingness were satisfaction with other agonists and insufficient knowledge about buprenorphine/naloxone. Fear of withdrawal was also identified as a barrier, although less frequently than anticipated. Additional research is needed to further identify and address the barriers to buprenorphine/naloxone treatment, in particular exploring the impact of educational interventions on patient willingness.

Role of Funding Source

The study was supported by the US National Institutes of Health (U01DA0251525, U01DA038886). 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 Dr. Evan Wood. Dr. M-J Milloy is supported by the United States National Institutes of Health (U01-DA0251525), a New Investigator award from the Canadian Institutes of Health Research, and a Scholar Award from the Michael Smith Foundation for Health Research. He is the Canopy Growth professor of cannabis science at the University of British Columbia, a position established by arms' length gifts to the university from Canopy Growth, a licensed producer of cannabis, and the Government of British Columbia's Ministry of Mental Health and Addictions. Dr. Kanna Hayashi is supported by a Canadian Institutes of Health Research (CIHR) New Investigator Award (MSH-141971), a Michael Smith Foundation for Health Research (MSFHR) Scholar Award, and the St. Paul's Foundation.

Contributors

SAW and TK designed the study and drafted the manuscript. CG undertook the statistical analysis. KH, MJM, and EW critically reviewed the draft and suggested improvements. All authors contributed to and approved the final manuscript.

Declaration of Competing Interest

No conflict declared.

Acknowledgements

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

References

Ahamad, K., Hayashi, K., Nguyen, P., Dobrer, S., Kerr, T., Schütz, C.G., Montaner, J.S., Wood, E., 2015. Effect of low-threshold methadone maintenance therapy for people who inject drugs on HIV incidence in Vancouver, BC, Canada: an observational cohort study. Lancet HIV 2, e445–e450. https://doi.org/10.1016/S2352-3018(15)00129-0.

Azar, P., Nikoo, M., Miles, I., 2018. Methadone to buprenorphine/naloxone induction without withdrawal utilizing transdermal fentanyl bridge in an inpatient setting—Azar method. Am. J. Addict. 27, 601–604. https://doi.org/10.1111/ajad.12809.

BC Centre on Substance Use (BCCSU), 2017. Guideline for the Clinical Management of Opioid Use Disorder. BC Ministry of Health. Retrieved from: http://www.bccsu.ca/wp-content/uploads/2017/06/BC-OUD-Guidelines_June2017.pdf (Accessed April 2019).

Bishop, B., Gilmour, J., Deering, D., 2018. Readiness and recovery: transferring between methadone and buprenorphine/naloxone for the treatment of opioid use disorder. Int. J. Mental Health Nurs. 28, 226–236. https://doi.org/10.1111/inm.12523.

Bruneau, J., Ahamad, K., Goyer, M.È., Poulin, G., Selby, P., Fischer, B., Wild, T.C., Wood, E., 2018. Management of opioid use disorders: a national clinical practice guideline. Cmaj 190, e247–e257. https://doi.org/10.1503/cmaj.170958.

Callon, C., Charles, G., Alexander, R., Small, W., Kerr, T., 2013. "On the same level": facilitators' experiences running a drug user-led safer injecting education campaign. Harm Reduct. J. 10, 1–10. https://doi.org/10.1186/1477-7517-10-4.

Chou, R., Weimer, M.B., Dana, T., 2014. Methadone overdose and cardiac arrhythmia potential: findings from a review of the evidence for an american pain society and college on problems of drug dependence clinical practice guideline. J. Pain 15, 338–365. https://doi.org/10.1016/j.jpain.2014.01.495.

D'Onofrio, G., O'Connor, P.G., Pantalon, M.V., Chawarski, M.C., Busch, S.H., Owens, P.H., Bernstein, S.L., Fiellin, D.A., 2015. Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial. JAMA - J. Am. Med. Assoc. 313, 1636–1644. https://doi.org/10.1001/jama.2015.3474.

Fatseas, M., Auriacombe, M., 2007. Why buprenorphine is so successful in treating opiate addiction in France. Curr. Psychiatry Rep. 9, 358–364.

Government of British Columbia, 2019. Coverage of Drugs for the Treatment of Opioid Use Disorder. Retrieved from: https://www2.gov.bc.ca/gov/content/health/health-drug-coverage/pharmacare-for-bc-residents/what-we-cover/drug-coverage/coverage-of-drugs-for-opioid-use-disorder (Accessed July 2019). .

Grönbladh, L., Öhlund, L.S., Gunne, L.M., 1990. Mortality in heroin addiction: impact of methadone treatment. Acta Psychiatr. Scand. 82, 223–227. https://doi.org/10.1111/j.1600-0447.1990.tb03057.x.

Gupta, K., Romney, D., Briggs, M., Benker, K., 2007. Effects of a brief educational program on knowledge and willingness to accept treatment among patients with hepatitis C at inner-city hospitals. J. Commun. Health 32, 221–230. https://doi.org/10.1007/s10900-007-9046-8.

Hammig, R., Kemter, A., Strasser, J., von Bardeleben, U., Gugger, B., Walter, M., Dursteler, K., Vogel, M., 2016. Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. Subst. Abuse Rehabil. 99–105. https://doi.org/10.2147/SAR.S109919.

Huhn, A.S., Dunn, K.E., 2017. Why aren't physicians prescribing more buprenorphine? J. Subst. Abuse Treat. 78, 1–7. https://doi.org/10.1016/j.jsat.2017.04.005.

Huhn, A.S., Tompkins, D.A., Dunn, K.E., 2017. The relationship between treatment accessibility and preference amongst out-of-treatment individuals who engage in non-medical prescription opioid use? Drug Alcohol Depend. 180, 279–285. https://doi.org/10.1016/j.drugalcdep.2017.08.019.

Klaire, S., Zivanovic, R., Barbic, S.P., Sandhu, R., Mathew, N., Azar, P., 2019. Rapid micro-induction of buprenorphine/naloxone for opioid use disorder in an inpatient setting: a case series. Am. J. Addict. https://doi.org/10.1111/ajad.12869.

Lee, J.D., Vocci, F., Fiellin, D.A., 2014. Unobserved "home" induction onto buprenorphine. J. Addict. Med. 8, 299–308. https://doi.org/10.1097/ADM.0000000000000059.

Luty, J., O'Gara, C., Sessay, M., 2005. Is methadone too dangerous for opiate addiction? BMJ 331, 1352–1353.

MacArthur, G.J., Minozzi, S., Martin, N., Vickerman, P., Deren, S., Bruneau, J., Degenhardt, L., Hickman, M., 2012. Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis. BMJ 345, 1–16. https://doi.org/10.1136/bmj.e5945.

Makarenko, I., Mazhnaya, A., Polonsky, M., Marcus, R., Bojko, M.J., Filippovych, S., Springer, S., Dvoriak, S., Altice, F.L., 2016. Determinants of willingness to enroll in opioid agonist treatment among opioid dependent people who inject drugs in Ukraine. Drug Alcohol Depend. 165, 213–220. https://doi.org/10.1016/j.drugalcdep.2016.06.011.

Maremmani, I., Gerra, G., 2010. Buprenorphine-based regimens and methadone for the medical management of opioid dependence: selecting the appropriate drug for treatment. Am. J. Addict. 19, 557–568. https://doi.org/10.1111/j.1521-0391.2010.00086.x.

Marteau, D., McDonald, R., Patel, K., 2015. The relative risk of fatal poisoning by methadone or buprenorphine within the wider population of England and Wales. BMJ Open 5, e007629. https://doi.org/10.1136/bmjopen-2015-007629.

Mattick, R., Breen, C., Kimber, J., Davoli, M., 2014. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst. Rev., CD002207. https://doi.org/10.1002/14651858.CD002207.pub4.www.cochranelibrary.com.

McCance-Katz, E.F., Sullivan, L.E., Nallani, S., 2010. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. Am. J. Addict. 19, 4–16. https://doi.org/10.1111/j.1521-0391.2009.00005.x.

McNeil, R., Kerr, T., Anderson, S., Maher, L., Keewatin, C., Milloy, M.J., Small, W., 2015. Negotiating structural vulnerability following regulatory changes to a provincial methadone program in Vancouver, Canada: a qualitative study. Soc. Sci. Med. 133, 168–176. https://doi.org/10.1016/j.socscimed.2015.04.008.

Netherland, J., Botsko, M., Egan, J.E., Saxon, A.J., Cunningham, C.O., Finkelstein, R., Gourevitch, M.N., Renner, J.A., Sohler, N., Sullivan, L.E., Weiss, L., Fiellin, D.A., 2009. Factors affecting willingness to provide buprenorphine treatment. J. Subst. Abuse Treat. 36, 244–251. https://doi.org/10.1016/j.jsat.2008.06.006.

Nosyk, B., Marsh, D.C., Sun, H., Schechter, M.T., Anis, A.H., 2010. Trends in methadone maintenance treatment participation, retention, and compliance to dosing guidelines in British Columbia, Canada: 1996–2006. J. Subst. Abuse Treat. 39, 22–31. https://doi.org/10.1016/j.jsat.2010.03.008.

Office of the Provincial Health Officer, 2017. BC Opioid Substitution Treatment System, Performance Measures 2014/2015-2015/2016. British Columbia Ministry of Health. Retrieved from: https://www2.gov.bc.ca/assets/gov/health/about-bc-s-health-care-system/office-of-the-provincial-health-officer/reports-publications/special-reports/bc-ost-system-measures-14-15-and-15-16.pdf (Accessed July 2019).

Public Health Agency of Canada (PHAC), Special Advisory Committee on the Epidemic of Opioid Overdoses, 2019. National Report: Apparent Opioid-Related Deaths in Canada (January 2016 to September 2018). Retrieved from: https://infobase.phac-aspc.gc.ca/datalab/national-surveillance-opioid-mortality.html (Accessed April 2019). .

Reisinger, H.S., Schwartz, R.P., Mitchell, S.G., Peterson, J.A., Kelly, S.M., O'Grady, K.E., Marrari, E.A., Brown, B.S., Agar, M.H., 2009. Premature discharge from methadone treatment: patient perspectives. J. Psychoactive Drugs 41, 285–296. https://doi.org/10.1080/02791072.2009.10400539.

Roux, P., Rojas Castro, D., Ndiaye, K., Briand Madrid, L., Laporte, V., Mora, M., Maradan, G., Morel, S., Spire, B., Carrieri, P., 2017. Willingness to receive intravenous buprenorphine treatment in opioid-dependent people refractory to oral opioid maintenance treatment: results from a community-based survey in France. Subst. Abus. Treat. Prev. Policy 12, 1–11. https://doi.org/10.1186/s13011-017-0131-4.

Schuckit, M.A., 2016. Treatment of opioid-use disorders. N. Engl. J. Med. 375, 357–368. https://doi.org/10.1056/NEJMra1604339.

Schwartz, R.P., Gryczynski, J., O'Grady, K.E., Sharfstein, J.M., Warren, G., Olsen, Y., Mitchell, S.G., Jaffe, J.H., 2013. Opioid agonist treatments and heroin overdose deaths in Baltimore, Maryland, 1995-2009. Am. J. Public Health 103, 917–922. https://doi.org/10.2105/AJPH.2012.301049.

Sherman, S.G., Sutcliffe, C., Srirojn, B., Latkin, C.A., Aramratanna, A., Celentano, D.D., 2009. Evaluation of a peer network intervention trial among young methamphetamine users in Chiang Mai, Thailand. Soc. Sci. Med. 68, 69–79. https://doi.org/10.1016/j.socscimed.2008.09.061.

Tsui, J.I., Evans, J.L., Lum, P.J., Hahn, J.A., Page, K., 2014. Association of opioid agonist therapy with lower incidence of hepatitis c virus infection in young adult injection drug users. JAMA Intern. Med. 174, 1974–1981. https://doi.org/10.1001/jamainternmed.2014.5416.

Wood, E., Tyndall, M.W., Spittal, P.M., Li, K., Kerr, T., Hogg, R.S., Montaner, J.S., O'Shaughnessy, M.V., Schechter, M.T., 2001. Unsafe injection practices in a cohort of injection drug. C. Can. Med. Assoc. J. 165, 405–410.

Yarborough, B.J.H., Stumbo, S.P., McCarty, D., Mertens, J., Weisner, C., Green, C.A., 2016. Methadone, buprenorphine and preferences for opioid agonist treatment: a qualitative analysis. Drug Alcohol Depend. 160, 112–118. https://doi.org/10.1016/j.drugalcdep.2015.12.031.

Zeremski, M., Dimova, R.B., Zavala, R., Kritz, S., Lin, M., Smith, B.D., Zibbell, J.E., Talal, A.H., 2014. Hepatitis C virus-related knowledge and willingness to receive treatment among patients on methadone maintenance. J. Addict. Med. 8, 249–257. https://doi.org/10.1097/ADM.0000000000000041.