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Research Paper

Factors associated with 60-day adherence to "safer supply" opioids prescribed under British Columbia's interim clinical guidance for health care providers to support people who use drugs during COVID-19 and the ongoing overdose emergency

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ABSTRACT

Aims: In March 2020, British Columbia issued Risk Mitigation Guidance (RMG) to support prescribing of pharmaceutical alternatives to illicit drugs, in order to reduce risk for COVID-19, overdose, and withdrawal among people who use drugs. This study evaluated factors associated with 60-day adherence to novel opioid alternatives prescribed at an inner-city health centre in Victoria, Canada.

Methods: A chart review was conducted to collect data on sociodemographic information, medical histories, and follow-up services among all clients prescribed novel opioid alternatives from March 2020-August 2020 (n = 286). Bivariable and multivariable regression were used to identify independent and adjusted factors associated with 60-day adherence.

Results: Overall, 77% of 286 clients were still receiving opioids after 60 days of follow-up. Medications included hydromorphone (*n = 274*), sustained-release oral morphine (*n = 2*), and oxycodone (*n = 9*). The adjusted odds of 60-day adherence to novel opioid alternatives were significantly higher for those receiving a mental health medication (*aOR = 3.49, 95%CI = 1.26, 11.00*), a higher maximum daily dosage of RMG prescriptions (*aOR = 1.03 per mg increase, 95%CI = 1.01, 1.04*), and those with continuous receipt of OAT (*aOR = 6.25, 95%CI = 2.67, 15.90*).

Conclusions: Higher dosages and co-prescription of mental health medications and OAT may help support better adherence to this form of prescriber-based "safer supply". Further work is needed to identify optimal prescribing practices and the longer term impacts of differing implementation scenarios.

Introduction

The current toxic illicit drug supply poses an unequivocal risk to people who use drugs (PWUD). In the United States, the mortality rate due to overdoses from illicit synthetic opioids increased by 1040% between 2013 and 2019, with a total of 70,630 overdose deaths in 2019 alone (Mattson et el., 2021). Between January 2016 and June 2021, there were 24,626 apparent opioid toxicity deaths in Canada (Public Health Agency of Canada, 2021). Nearly one third of these deaths have occurred in British Columbia (BC) (BC Coroners Service 2021), a province containing 13% of the Canadian population (Statistics Canada, 2020). In 2016, the BC government declared a public health emergency, now in its sixth year. One of the many impacts of the crisis is a decrease in life expectancy for males in BC (Statistics Canada, 2019). Toxicology analyses confirm that illicit fentanyl (alone and in combination with other drugs) is present in over 80% of provincial drug toxicity deaths (BC Coroners Service 2021).

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The emergence of COVID-19 has further demonstrated the ways in which PWUD, especially those who are precariously housed or homeless, experience health inequities and structural factors that increase their risk of infectious diseases (Vasylyeva et al., 2020; Melamed et al., 2020), complications due to COVID-19 (Spagnolo et al., 2020; Slaunwhite et al., 2020) and overdose (Bonn et al., 2020; Grebely et al., 2020a; Tyndall, 2020). The pandemic has caused disruptions and changes in the illicit drug supply (CCENDU, 2020; Grebely et al., 2020a) and temporarily closed or reduced the scope of addiction treatment, harm reduction, and other support services (Canadian Centre on Substance Use and Addiction, 2020; Lanièce Delaunay et al., 2020; Grebely et al., 2020a). These changes have made it harder for people to find reasonable quality drugs (Wallace et al., 2020), forced people to use drugs alone due to isolation requrements, or exposed people who use drugs to COVID-19 while they are seeking illicit drugs (Tyndall, 2020; Grebely et al., 2020a).

Pharmaceutical alternatives to the toxic drug supply

As part of the response to escalating rates of drug toxicity deaths, governments and non-governmental organisations have scaled up several existing interventions including opioid agonist therapy (OAT), supervised consumption sites (Kerr et al., 2017), take home naloxone programs (Young et al., 2019), and drug checking services (Government of British Columbia, 2017). Some jurisdictions in Canada and elsewhere are introducing options for the prescription of pharmaceutical alternatives to the toxic drug supply. Separate from OAT, these include programs to distribute tablet or injectable hydromorphone and other pharmaceutical opioids to PWUD (Tyndall, 2018; Ivsins et al., 2020a). This is sometimes framed as a prescriber-based model of "safer supply", understanding that safer supply is a much more fulsome concept that refers to a "legal and regulated supply of drugs with mind/body altering properties that traditionally have been accessible only through the illicit drug market" (Canadian Association of People Who Use Drugs, 2019, p. 4,). Prescription-based initiatives (operating within the medical system) build on prior evidence including randomized control trials of injectable hydromorphone and diacetylmorphine, found to be safe, effective, and cost-effective treatments for PWUD (Oviedo-Joekes et al., 2009; Nosyk et al., 2012; Bansback et al., 2018; Oviedo-Joekes et al., 2016). Recent studies of tablet hydromorphone distribution programs have demonstrated reduced street drug use and overdose risk, improvements in health and well-being, management of pain and economic improvements (Ivsins et al., 2020b, Ivsins et al., 2021; Olding et al., 2020).

In March 2020, the British Columbia Centre on Substance Use (BCCSU) issued clinical guidance for healthcare providers to support PWUD during the COVID-19 pandemic and ongoing overdose emergency (British Columbia Centre for Substance Use 2017). This Risk Mitigation Guidance included provisions that empowered physicians to prescribe opioids, stimulants, benzodiazapines, and alternatives for alcohol and tobacco to persons at risk of or with COVID-19 infection, ongoing active substance use and at high risk of withdrawal, overdose, craving or harms related to drug use (British Columbia Centre for Substance Use 2017). The guidance was accompanied by federal and provincial policies that created temporary exemptions from federal drug law (the Controlled Drugs and Substances Act in Canada; Health Canada, 2020), as well as issuing temporary exemptions for OAT prescriptions (College of Pharmacists of British Columbia 2020a; Health Canada, 2020), prescription renewal by pharmacists (previously only allowed by physicians) (College of Pharmacists of British Columbia 2020b), and increased options for telehealth and medication delivery (Doctors of BC, 2020; Bruneau et al., 2020).

The clinical guidance specified tablet hydromorphone (Dilaudid) and sustained-release oral morphine (M-Eslon) as opioid alternatives, alongside additional alternatives for stimulants, benzodiazepine, nicotine, and options for alcohol withdrawal. The prescription of opioid alternatives is distinct from OAT. In Canada, buprenorphine-naloxone (Suboxone) is the current first-line treatment for opioid use disorder (OUD) (Bruneau et al 2020); methadone and slow-release oral morphine (Kadian) are also commonly prescribed. OAT has an established international evidence base supporting its effectiveness (Connery, 2015; Dong et al., 2020; Sordo et al., 2017; Pearce et al., 2020; Uhlmann et al., 2010; Mazhnaya et al., 2018; Grebely et al., 2020b). However, retention in OAT is an issue, with a systematic review estimating 57% retention at 12 months and 38% at three years across 63 observational studies (O'Connor et al., 2020). A recent population-based study in BC found only 33% of people with OUD were presently on OAT and 16% had been maintained on OAT for longer than one year (Piske et al. 2020). Numerous factors, including homelessness, incarceration, lack of income assistance, daily illicit substance use (Lo et al., 2018; Socías et al., 2018; Klimas et al., 2018) and suboptimal OAT dosing (Hser et al., 2014; O'Connor et al., 2020) are associated with discontinuation of OAT treatment and highlight the need for alternatives. Tablet and injectable hydromorphone and other opioid alternatives are a potential option for further promoting service engagement, reducing overdose risk, and supporting health. This is particularly crucial in the context of the current highly toxic drug supply.

Study aims

BC's provincial clinical guidance and the accompanying federal and provincial policy exemptions provided the impetus for scale-up of programs providing pharmaceutical alternatives to the toxic drug supply, following the emergence of COVID-19. Across the province, providers had much leeway to create and implement programs that would work for them. This study offers preliminary insights about a single program operating at a community health centre (CHC) in Victoria, a small urban and capital city of BC. We do not evaluate the impact of this intervention on morbidity or mortality. Rather, the focus of this paper is to examine adherence among enrolled participants. In doing so, we specifically examine adherence to opioid alternatives made available as a result of the Province's risk mitigation guidance. Given what we know about the effectiveness of OAT combined with the barriers PWUD face to adherence, our overall aim was to identify the independent and adjusted factors associated with 60-day adherence to novel opioid alternatives. The 60-day cut-off was determined a priori at the data collection stage of the study and accords with prior work focused on adherence to treatments for OUD (Scott, 2019). While we recognize that this is an arbitrary cut-off, the selection of this timeframe suited our aim of providing early estimates of adherence, given the urgency of understanding these newly emerging interventions.

Methods

Study setting

This study was conducted at a community health centre (CHC) located in Victoria, a small urban city and the capital of BC (regional population of 386,000). The Victoria Cool Aid Society's CHC provides low-barrier health services to the local inner-city population that is economically vulnerable, has complex medical needs, and faces multiple barriers to accessing care and other resources needed to support good health. Services are provided free-of-charge to clients, covered by provincial universal insurance programs. The clinical team is multidisciplinary, including primary care physicians, a nurse practitioner, nurses, pharmacists and a range of allied health professionals. The team manages care for approximately 5000 clients annually, many of whom have issues with substance use and mental health. CHC physicians provide OAT to approximately 900 clients annually. In May 2020, the CHC created a distributed model of care to better meet the needs of the population, with clinics and on-call services spread throughout the community including at sheltering sites established in response to COVID-19.

Clinical care standards for the novel prescription program

Immediately after the release of the clinical guidance, the CHC clinical team designed and implemented their clinical care standards for prescribing novel pharmaceutical alternatives, including client inclusion criteria, standards of care, case management strategies, and prescription practices. This process to create the clinical care standards for this program included consultation with addiction medicine specialists and others around the province who were engaged in their own guidance implementation work. Critical within this process was defining the relationship of prescribing RMG to OAT. At the CHC, the clinical care standards specify that those who are currently stable on OAT (defined as taking as prescribed without additional illicit opioid use) are not eligible for the novel prescription program. Co-prescription with OAT is possible for others. Those who are connected with a psychiatrist are likewise ineligible unless consent is obtained from the psychiatrist for program participation. Priority is given to those who are unstably housed (e.g., living in local encampments) and at the sheltering sites.

The provincial clinical guidance specified tablet hydromorphone (Dilaudid) and sustained-release oral morphine (M-Eslon) as opioid alternatives. To this, the CHC clinical team and other local prescribers added oxycodone as options for some clients. All clients are routinely encouraged to start or continue with OAT. Clients pick up their medications daily at community pharmacies; selected pharmacies offer a delivery service to the sheltering sites and other locations to support physical distancing and self-isolation. Unlike OAT, ingestion of the novel pharmaceutical alternatives is not witnessed (for those who are co-prescribed OAT, their use of OAT medications continues to be witnessed). Urine drug screens are done regularly. The CHC serves a limited youth population and so only two clients who participated in the program were under 19 years old.

Data extraction

We conducted a chart review of records held in the CHC's electronic medical record system in combination with prescription dispensations from provincial pharmacy database (BC College of Pharmacists, 2022). Data were extracted for all clients who were prescribed alternative opioid medications (hydromorphone [Dilaudid], oxycodone, or sustained-release oral morphine [M-Eslon]) between March 25, 2020 and August 31, 2020. This time period corresponds to the first 5 months of program delivery. We created a data dictionary and extraction template for the chart review, specifying the nature and form of data fields. The first and final author conceptualized variables for extraction based on available data from clinician notes, diagnostic and laboratory testing, specialist consultations, reports from hospitals, and prescriptions (detailed descriptions of data fields are available in Supplemental Table 1). Four CHC research staff (first author and student interns) extracted the data into an Excel spreadsheet. The first author periodically reviewed the dataset to ensure consistency with specifications. The team met regularly to discuss the process and clarify any questions. For each variable, missing data was recorded as "unknown." It is a limitation of chart review methods that not all data elements will be available. As such, results should be interpreted with due caution.

Data were anonymized at point of extraction. The completed dataset was transferred to a secure server at the University of Victoria via a secure file transfer protocol. Analysis of these anonymized data was approved by University of Victoria's Research Ethics Board (protocol # 20-0370) and conducted according to the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice (ICH/GCP) guidelines.

Variables

Supplemental Table 1 provides detailed descriptions for all extracted variables. The primary outcome variable is 60-day adherence to novel opioid alternatives (listed above), defined as having received a prescription on an average of 4+ days out of 7, during the 60-day follow-up period. This variable was constructed using each clients' dispensation dates. To provide an overall look at retention, we also calculated the number of people receiving RMG prescriptions at the end of the study period, regardless when they started.

Predictor variables include client age, sex, housing status, comorbid diagnoses, and medication history at baseline (at time of first prescription of novel opioid alternatives). These variables were selected on the basis of prior evidence of association with adherence to SUD interventions. In order to include all varieties of opioid RMG within multivariable analysis, an oral morphine equivalent variable was created using ratios from Canadian prescribing guidelines of 1 hydromorphone to 5 morphine, 1 M-Eslon to 1 morphine and 1 oxycodone to 1.5 morphine (Busse et al., 2017). OAT receipt was based on receipt of buprenorphine[/naloxone] (Suboxone, Sublocade), methadone, slow-release oral morphine (Kadian), or sustained-release oral morphine (M-Eslon), and defined for both baseline and follow-up (in the 60 days after the first prescription for novel opioid alternatives). Sustained release (M-Eslon) was prescribed as both an RMG and OAT and defined as an RMG only if client was also receiving another OAT. Baseline OAT receipt was coded as: *yes-ongoing* (referring to receipt on an average of 4+ days out of 7, each week in the past 3 months); *yes-new* (started within one week of the novel opioid alternative); or *no* (including both none or irregular OAT (less than 4 weekly) receipt in past 3 months). Continuous OAT receipt at follow-up was coded as: *yes* (receipt of OAT on an average of 4+ days out of 7, each week during follow-up) or *no* (irregular or no receipt of OAT).

Analysis

The analysis includes all CHC clients who were prescribed alternative opioid medications between March 25, 2020 and August 31, 2020. Exploratory descriptive, bivariable, and multivariable statistics were calculated in R Studio. Binary logistic regression was used to identify the unadjusted (bivariable) and independent and adjusted (multivariable) predictors associated with 60-day adherence to alternative opioid medications. A multivariable logistic regression model was constructed by including variables of theoretical interest identified by our study team, listed above.

Results

Sample description at baseline

During the reporting period, 286 clients were prescribed one or more of the novel opioid alternatives (Table 1). Most (54.5%, n = 156/286) were previously under the care of CHC clinicians, while 84 clients (29.4%, n = 84/286) were new to the CHC or had rarely or not been seen for years (12.9%, n = 37/286). A few clients (3.1%, 9/286) were started by non CHC prescribers or accessing prescribers for OAT at other OAT Clinics. The majority were aged 30-49 (60.5%, n = 173/286) and were identified as male 63.6% (n = 182/286). Over 83% (n = 239/286) of clients were homeless at baseline. Two-thirds (62.6%, n = 179/286) seen were offered temporary accommodations in sheltering sites. Two thirds of the sample used methamphetamine (65.7%, n = 188/286) in the past six months. Approximately one-quarter (24.8%, n = 71/286) had a recorded overdose in the past six months. Many clients were living with chronic conditions that are exacerbated by homelessness and substance use, including respiratory issues (i.e., asthma, COPD, or chronic bronchitis; 17.1%, n = 49/286) and soft tissue abscesses and cellulitis (44.1%, n = 126/286). Many clients experience chronic pain (37.1%, n = 106/286), as well as acute dental pain or infections (13.3%, n = 38/286). A total of 54 (18.9%) had impaired cognition resulting from traumatic brain injuries, including those resulting from

Table 1
Sample description by 60-day adherence to novel opioid alternatives.

		Overall	Adherence at 60 days		p-value
			Yes	No	
		N = 286	**N = 221**	**N = 65**	
Demographics					
Age (mean (SD))		39.02 (10.63)	39.93 (10.82)	35.94 (9.39)	0.008
Sex (%)	F	104 (36.4)	77 (34.8)	27 (41.5)	0.401
	M	182 (63.6)	144 (65.2)	38 (58.5)	
Client (%)	New client	84 (29.4)	59 (26.7)	25 (38.5)	0.02
	Outreach only	9 (3.1)	5 (2.3)	4 (6.2)	
	Existing client	156 (54.5)	131 (59.3)	25 (38.5)	
	Client limited Interaction	37 (12.9)	26 (11.8)	11 (16.9)	
Comorbidities					
HCV Diagnosis (%)	No	129 (45.1)	96 (43.4)	33 (50.8)	<0.001
	Yes	120 (42.0)	104 (47.1)	16 (24.6)	Yes
	Unknown	37 (12.9)	21 (9.5)	16 (24.6)	
HIV Diagnosis (%)	No	225 (78.7)	179 (81.0)	46 (70.8)	0.065
	Yes	13 (4.5)	11 (5.0)	2 (3.1)	
	Unknown	48 (16.8)	31 (14.0)	17 (26.2)	
Asthma, COPD, or Chronic Bronchitis Diagnosis (%)	No	200 (69.9)	158 (71.5)	42 (64.6)	0.004
	Yes	49 (17.1)	42 (19.0)	7 (10.8)	
	Unknown	37 (12.9)	21 (9.5)	16 (24.6)	
Head injury or Stroke Diagnosis (%)	No	192 (67.1)	148 (67.0)	44 (67.7)	<0.001
	Yes	54 (18.9)	50 (22.6)	4 (6.2)	
	Unknown	40 (14.0)	23 (10.4)	17 (26.2)	
Chronic Pain Diagnosis (%)	No	142 (49.7)	107 (48.4)	35 (53.8)	0.005
	Yes	106 (37.1)	91 (41.2)	15 (23.1)	
	Unknown	38 (13.3)	23 (10.4)	15 (23.1)	
Dental Pain Diagnosis (%)	No	199 (69.6)	160 (72.4)	39 (60.0)	0.077
	Yes	38 (13.3)	29 (13.1)	9 (13.8)	
	Unknown	49 (17.1)	32 (14.5)	17 (26.2)	
Skin or Tissue Damage (%)	No	130 (45.5)	101 (45.7)	29 (44.6)	0.003
	Yes	126 (44.1)	104 (47.1)	22 (33.8)	
	Unknown	30 (10.5)	16 (7.2)	14 (21.5)	
Injection Drug Use (Ever; %)	No	12 (4.2)	12 (5.4)	0 (0.0)	0.067
	Yes	214 (74.8)	167 (75.6)	47 (72.3)	
	Unknown	60 (21.0)	42 (19.0)	18 (27.7)	
Mental Disorder (%)	No	21 (7.3)	18 (8.1)	3 (4.6)	0.03
	Yes	198 (69.2)	159 (71.9)	39 (60.0)	
	Unknown	67 (23.4)	44 (19.9)	23 (35.4)	
ADHD Diagnosis (%)	No	163 (57.0)	134 (60.6)	29 (44.6)	0.021
	Yes	39 (13.6)	31 (14.0)	8 (12.3)	
	Unknown	84 (29.4)	56 (25.3)	28 (43.1)	
Anxiety Diagnosis (%)	No	113 (39.5)	94 (42.5)	19 (29.2)	0.018
	Yes	93 (32.5)	74 (33.5)	19 (29.2)	
	Unknown	80 (28.0)	53 (24.0)	27 (41.5)	
Depression Diagnosis (%)	No	112 (39.2)	91 (41.2)	21 (32.3)	0.027
	Yes	89 (31.1)	73 (33.0)	16 (24.6)	
	Unknown	85 (29.7)	57 (25.8)	28 (43.1)	
Bipolar Disorder Diagnosis (%)	No	191 (66.8)	156 (70.6)	35 (53.8)	0.022
	Yes	11 (3.8)	9 (4.1)	2 (3.1)	
	Unknown	84 (29.4)	56 (25.3)	28 (43.1)	
PTSD Diagnosis (%)	No	128 (44.8)	106 (48.0)	22 (33.8)	0.011
	Yes	69 (24.1)	56 (25.3)	13 (20.0)	
	Unknown	89 (31.1)	59 (26.7)	30 (46.2)	
Complex or Conduct Disorder Diagnosis (%)	No	135 (47.2)	106 (48.0)	29 (44.6)	0.001
	Yes	74 (25.9)	66 (29.9)	8 (12.3)	
	Unknown	77 (26.9)	49 (22.2)	28 (43.1)	
Received Mental Health Medications (%)	No	191 (66.8)	139 (62.9)	52 (80.0)	0.001
	Yes	77 (26.9)	71 (32.1)	6 (9.2)	
	Unknown	18 (6.3)	11 (5.0)	7 (10.8)	
Substance Use History					
Recent Overdose in Past Six Months (%)	No	121 (42.3)	97 (43.9)	24 (36.9)	0.533
	Yes	71 (24.8)	52 (23.5)	19 (29.2)	
	Unknown	94 (32.9)	72 (32.6)	22 (33.8)	
Recent Crystal Meth Use (%)	No	86 (30.1)	68 (30.8)	18 (27.7)	0.754
	Yes	188 (65.7)	143 (64.7)	45 (69.2)	
	Unknown	12 (4.2)	10 (4.5)	2 (3.1)	
Recent Injection Drug Use (%)	No	78 (27.3)	62 (28.1)	16 (24.6)	0.173
	Yes	181 (63.3)	142 (64.3)	39 (60.0)	
	Unknown	27 (9.4)	17 (7.7)	10 (15.4)	
Recent Smoking Drug Use (%)	No	33 (11.5)	27 (12.2)	6 (9.2)	0.278
	Yes	205 (71.7)	161 (72.9)	44 (67.7)	
	Unknown	48 (16.8)	33 (14.9)	15 (23.1)	
Housing Conditions					
Was Homeless	No	46 (16.1)	37 (16.7)	9 (13.8)	0.732
	Yes	239 (83.6)	183 (82.8)	56 (86.2)	
	Unknown	1 (0.3)	1 (0.5)	0 (0.0)	
Initiated Prescription While in Homeless Camp (%)	No	199 (69.6)	154 (69.7)	45 (69.2)	0.986
	Yes	73 (25.5)	56 (25.3)	17 (26.2)	
	Unknown	14 (4.9)	11 (5.0)	3 (4.6)	
Participant Admitted to Temporary Sheltering Site during Follow-up (%)	No	104 (36.4)	75 (33.9)	29 (44.6)	0.247
	Yes	179 (62.6)	144 (65.2)	35 (53.8)	
	Unknown	3 (1.0)	2 (0.9)	1 (1.5)	

Table 2
Prescription patterns by 60-day adherence to novel opioid alternatives.

		Overall	Adherence at 60 days		p-value
			Yes	No	
		N = 286	**N = 221**	**N = 65**	
Mode of Delivery (%)	Delivery	121 (42.3)	103 (46.6)	18 (27.7)	0.025
	Pick up	109 (38.1)	78 (35.3)	31 (47.7)	
	Unknown	56 (19.6)	40 (18.1)	16 (24.6)	
Dispensed without Interruption (%)	No	159 (55.6)	116 (52.5)	43 (66.2)	0.070
	Yes	127 (44.4)	105 (47.5)	22 (33.8)	
Type of opioid (%)	Hydromorphone	274 (95.8)	211 (95.5)	63 (96.9)	0.196
	Hydromorphone and Fentanyl Patch	1 (0.3)	0 (0.0)	1 (1.5)	
	M-Eslon	2 (0.7)	2 (0.9)	0 (0.0)	
	oxycodone	9 (3.1)	8 (3.6)	1 (1.5)	
Days on Opioid Prescription (mean (SD))		108.43 (62.32)	133.28 (45.35)	23.94 (29.03)	<0.001
Days on Opioid Prescription (%)	60 days or more	220 (76.9)	218 (98.6)	2 (3.1)	<0.001
	Less than 60 days	66 (23.1)	3 (1.4)	63 (96.9)	
Maximum Daily Dose Opioid – Morphine Equivalent (mean (SD))		346.59 (192.76)	371.43 (199.55)	262.15 (138.60)	<0.001
Co-prescribed OAT at baseline (%)	No	26 (9.1)	19 (8.6)	7 (10.8)	0.07
	Started	123 (43.0)	88 (39.8)	35 (53.8)	
	Yes	137 (47.9)	114 (51.6)	23 (35.4)	
Active OAT Prescription at 60-days (%)	No	124 (43.4)	77 (34.8)	47 (72.3)	<0.001
	Not prescribed OAT	26 (9.1)	19 (8.6)	7 (10.8)	
	Yes	136 (47.6)	125 (56.6)	11 (16.9)	

hypoxia related to overdose. Over 69% (n = 198/286) had mental disorder, most commonly anxiety (32.5%, n = 93/286)), depression (31.1%, n = 89/286), bipolar (3.8%, n = 11/286)), PTSD (24.1%, n = 69/286), and ADHD (13.6%, n = 39/286). Over a quarter (25.9%, n = 74/286) had diagnoses or encounters related to complex mental health including psychosis (including drug-induced), Borderline Personality Disorder, delusional and conduct disorder. More than 26% (n = 77/286) were currently prescribed medications related to their mental health.

Clients received tablet hydromorphone (95.8%, n = 274/286), oxycodone (3.1%, n = 9/286), and sustained-release oral morphine (0.7%, n = 2/286). 90.9% (n = 260/286 were co-prescribed OAT as baseline: 47.9% (n = 137) were already regularly dispensed an OAT, 43.0% (n = 123/286) started within a week of RMG and 9.1% (n = 26/286) were not prescribed an OAT. Sixty (21.0%) clients were co-prescribed RMG stimulants at baseline, either dexedrine (75.0%, n = 45/60) or methylphenidate (25.0%, n = 15/60).

Prescription patterns over follow-up

As of October 2020, 77.3% of clients (n = 221/286) met the criteria for 60 day adherence (on average dispensed at least 4 doses per week (Table 2). Over the follow-up period, 47.6% (n = 136/286) were still dispensed OAT at least 4 doses per week, and 43.4% (n = 124/286) were not. The maximum daily opioid equivalent mean was 346.59. As noted earlier, the vast majority were prescribed hydromorphone. Maximum daily doses for hydromorphone ranged from ≤32mg/day (19.3%, n = 53/274), 33-48mg/day (26.6%, n = 73/274), 49-64mg/day (16.4%, n = 45/274), 65-96mg/day (19.7%, n = 54/274), to 97-128mg/day (15.6%, n = 43/274). Only 9 (3.3%) were prescribed over 128mg/day (see Supplemental Table 2).

Predictors of 60-day adherence

Tables 1 and 2 show the factors associated with 60-day adherence to the novel opioid alternatives (on an average of 4+ days out of 7, each week). Bivariable tests showed that 60-day adherence was more likely given older age (p = 0.008), for existing CHC clients (p = 0.02), and for those with a history of HCV (p < 0.001), chronic pain (p = 0.005), or complex mental disorders (p = 0.001). It was also higher for those receiving mental health medications (p = 0.001), higher daily maximum doses of the opioid alternatives (p < 0.001), and whose prescriptions were delivered (p = 0.025). Finally, adherence was more likely for those who were already receiving OAT in the 3 months prior to their first prescription for novel opioid alternatives but was less likely among those who newly started OAT at this time. Over the follow-up period, continuous receipt of OAT (on an average of 4+ out of 7 days, each week) was strongly associated with higher 60-day adherence (p < 0.001). Among those who were active on OAT 125/136 (92%) remained on RMG at 60 days; compared to only 19/26 (73%) of those not prescribed OAT and 77/124 (62%) of those not active on OAT.

In multivariable models, associations persisted for receipt of mental health medications, maximum doses of opioid alternatives, and continuous OAT receipt (Table 3). The adjusted odds of 60-day adherence to novel opioid alternatives were significantly higher for those receiving a mental health medication (*aOR = 3.49, 95%CI = 1.26, 11.00*), a higher

Table 3
Multivariable Results for Factors Associated with RMG Adherence at 60-days.

	aOR	95% CI	
Age	1.02	0.98	1.06
Client Status			
New Client	1.00		
Outreach only	1.44	0.23	9.76
Existing Client	1.99	0.84	4.78
Client limited interaction	1.23	0.43	3.64
History of Chronic Pain			
No	1.00		
Yes	1.19	0.50	2.88
Unknown	0.42	0.15	1.11
Active OAT Prescription at 60 Days			
No	1.00		
Not Prescribed OAT	1.25	0.42	4.01
Yes	**6.09**	**2.67**	**15.07**
Received Mental Health Medications			
No	1.00		
Yes	4.01	**1.53**	**12.15**
Unknown	0.56	0.16	1.99
Max Daily Dose of Oral Morphine Equivalent RMG	**1.00**	**1.01**	**1.01**
Mode of Delivery			
Delivered	1.00		
Picked-up	0.50	0.20	1.22
Unknown	1.07	0.39	3.01
RMG Dispensed without Interruption	0.60	0.27	1.30
Admission to Temporary Shelter Site			
No	1.00		
Yes	2.07	0.89	4.90
Unknown	0.42	0.01	27.74

maximum daily dosage of RMG prescriptions (*aOR = 1.03 per oral morphine mg equivalent increase, 95%CI = 1.01, 1.04*), and those with continuous receipt of OAT (*aOR = 6.25, 95%CI = 2.67, 15.90*).

Discussion

In this study we sought to identify the factors associated with continued short-term adherence to prescriptions for novel opioid alternatives, issued to PWUD under British Columbia's Risk Mitigation Guidance. Clients were prescribed these medications under the clinical care standards developed by the clinical team at an inner-city CHC, located in Victoria (a small urban city in BC). Among the earliest published study reporting empirical data on programs to emerge from the clinical guidance, our findings contribute to an important dialogue in Canada and elsewhere about the role of pharmaceutical alternatives to the toxic drug supply, alongside OAT and other treatment and harm reduction services.

Overall, we found good adherence in the short-term, with over two-thirds of clients receiving continuous dispensation of novel opioid alternatives (primarily hydromorphone) for 60 days. This is roughly similar to the retention rate in the previous clinical trials investigating injectable diacetylmorphine and hydromorphone prescribing (Nosyk et al., 2012; Oviedo-Joekes et al., 2016; Strang et al., 2015). In multivariable models, higher dosages of the opioid alternatives and co-prescription of mental health medications and OAT emerged as independent predictors of adherence.

Although this study considered a short period of follow-up, the initial weeks of a therapeutic episode are critical periods for engagement, and high rates of drop-out are a challenge during this period (Kurz et al., 2021; Timko et al., 2016). These findings suggest that appropriate dosages and mental health medications may help to support engagement in these novel prescription programs. They echo other research highlighting the need for attention to individualized dosing for OAT and mental health medications (Trafton et al., 2006; Bao et al., 2009). The finding on dosing is not surprising; suboptimal OAT dosing has previously been linked with treatment drop out (Hser et al., 2014; O'Connor et al., 2020). A holistic approach to providing care to PWUD that works to identify barriers and provide suitable and appropriate medication therapies may help to ensure that clients are experiencing the full benefits.

We acknowledge it is possible that unmeasured client characteristics (particularly around goals, motivations, and relationships with providers) may have contributed to adherence or discontinuation of novel opioid prescriptions. Underscoring this reality, our findings demonstrate that adherence to RMG was highest among those who were actively on OAT (i.e., 92%) – as anticipated. However, those who were not prescribed OAT (i.e., 73%) actually had higher adherence than those who received a prescription but did not continue using OAT (i.e., 62%). The relatively lower levels of adherence among those who were prescribed but not receiving active OAT at follow-up highlights the realities that external factors likely play in shaping medication adherence – not just to RMG, but also to OAT. Nonetheless, our findings suggest that co-prescription with OAT – and likely other adherence supports – may act to reduce barriers to care in support of these populations. This issue warrants further study, as care providers in BC and elsewhere continue to work on creating clinical care standards in their jurisdictions. There is prior evidence showing that concurrent treatment for mental health and OAT is associated with improved clinical outcomes and reduced mortality among people with substance use disorder (Torrens et al., 2012; Konstenius et al., 2014; Levin et al., 2015; Morin et al., 2020). More specifically, integrated ADHD treatment (including high-dose central acting stimulants) and OAT is linked to improved outcomes and retention among those with co-occurring OUD and ADHD (Torrens et al., 2012; Konstenius et al., 2014; Levin et al., 2015). For PWUD with ADHD, combined psychosocial treatments, ADHD medication and OAT is associated with the highest change of treatment adherence, in the absence of other illicit drugs (Levin et al., 2006; Carpentier & Levin, 2017). These studies, in combination with our findings, support a movement towards hybridizing mental health and substance use programs in a holistic approach to care.

As BC and other jurisdictions options for policy and clinical practice, further work is needed to identify optimal prescribing practices for opioid alternatives, including medication options (e.g., fentanyl patches, sufentanyl, diacetylmorphine, injectable hydromorphone), dosages, and co-prescriptions (including for people who are not amenable to OAT). Additional work is needed to evaluate other aspects of implementation, including settings, witnessed ingestion, and urine drug screens. Witnessed or individualized on demand dispensing in overdose prevention sites or other innovations may help alleviate clinician hesitancy in prescribing these new options for their clients. A larger population-based, controlled mixed methods study of BC's clinical guidance is underway (Nosyk et al., 2021).

Finally, it is important that policy makers work with communities to find non-medicalized, non-prescription based pathways for an acceptable and effective safer illicit drug supply. This is a necessary ongoing policy development process that will require the committed engagement of clients, front-line service providers, professional organizations, and policy makers at multiple levels of government. Feedback from people with lived and living experience of drug use is urgently needed to inform best practices.

Strengths and limitations

Limitations of this study include the relatively short follow-up period of 60 days, the lack of a control group, and reliance on chart review methods. These limitations can result in misclassification and selection biases. In particular, chart review methods have known limits to sensitivity and are prone to missing data. We acknowledge that missingness poses a considerable challenge for this analysis. Our choice to include an "unknown" category for variables in the analysis likely biases estimates downward and inflates our standard errors. Nevertheless, we assume that the missingness arises predominately from charting practices rather than systematic features of prescribing practices or client adherence. Further, the alternative option of removing missing observations would reduce our statistical power. Given the study methods, we were also limited to variables that could be ascertained through client charts and did not have access to potentially relevant factors, such as how patients used the supplied medications, or a broader assessment of patient-reported outcomes (e.g., satisfaction, quality of life). Given the lack of an equivalent control group, we cannot rule out unmeasured confounders of the associations with 60-day adherence. We also recognize that some measures are time-varying (e.g., dosing and adherence), but our chart review did not extract data in such a way as to capture this detail. Additionally, we recognize that a family-wise p-value correction was not used for this analysis, despite a large number of variables collected through our chart review. Finally, as an evaluation of the clinical care standards implemented at one CHC in a small urban setting, our findings may not generalize to all settings and populations of PWUD. We further note that our study is not intended to be an evaluation of the Risk Mitigation Guidance, but rather aims to provide practical insight into what factors might contribute to improved retention in programs such as the one implemented at our CHC. Given the methods of this study, all results should be interpreted with caution and warrant replication through further study.

Conclusion

This study contributes to an important dialogue in Canada and elsewhere about the role of pharmaceutical alternatives to the toxic drug supply, as governments strive to respond to high rates of overdoses in the population. We have identified several features of prescribing that support continued adherence to opioid medications (e.g., provisions for

mental health medications and OAT). With consideration of other findings which demonstrate that safer supply models can be beneficial in preventing overdose deaths (Ivsins et al., 2021; Preuss et al., 2021), our study highlights the need for careful thought regarding the development and implementation of programs to reach key populations. In doing so, we recognize that implementation of safe supply programs will vary from location to location and that continued evaluation of the implementation and nature of various prescribing models is needed to arrive at best practice guidelines that can be broadly utilized to inform local public health programming.

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Ethics approval

Ethics for was approved through the University of Victoria Protocol # 20-0370

Declarations of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2022.103709.

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