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History of Treatment Access and Drug Use among Participants in a Trial Testing Injectable Opioids under Supervision for Long-Term Heroin Injectors

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Abstract

Background: For opioid-dependent patients not benefitting from conventional treatments (i.e., oral methadone), evidence suggests that supervised injectable medications are effective. The present study aims to describe participants' baseline characteristics in a study comparing injectable diacetylmorphine and hydromorphone and factors independently associated with prior access to methadone at high doses.

Methods: SALOME (Study to Assess Longer-term Opioid Medication Effectiveness) is a phase III, randomized, double blind controlled trial comparing injectable diacetylmorphine and hydromorphone in 202 chronic, opioid-dependent, current injection opioid users in Vancouver who had at least one prior episode of opioid maintenance treatment (OMT). Measures included questionnaires and drug dispensation records. In addition to descriptive statistics, multivariable logistic regression was used to determine characteristics associated with reaching a stable weekly average methadone dose of 100 mgs daily or more during a methadone treatment episode.

Results: Participants had a mean of fifteen years of illicit opioid use, several OMT attempts, medical problems, criminal justice histories, unstable housing, daily use of illicit opioids and regular use of cocaine. Multivariable analysis showed that individual characteristics, such as separation from biological parents, prior prescription of opioids for pain and other medical conditions, and preferred methadone dose were independently associated with prior methadone episodes that reached 100 mgs.

Conclusions: These data emphasize that study participants were in need of alternative treatments at the time of enrolment and fit the profile of patients to whom supervised injectable treatment should be offered. Adding specific dose and duration requirements with respect to prior OMT might exclude individuals who would benefit significantly from injectable treatment.

INTRODUCTION

Agonist maintenance treatment has shown to be an effective approach to treat opioid dependency, which is a chronic relapsing disease [1-3]. Only a relatively small proportion of patients are able to stop using illicit opioids after abstinence oriented treatment [4,5]. Methadone maintenance treatment (MMT) is the most widely studied and available treatment for this condition. However, a diversified opioid maintenance portfolio, including buprenorphine, diacetylmorphine, morphine, and possibly hydromorphone, offered in different program modalities is required to reach and meet the individual needs of all those affected by opioid dependency [6,7].

Randomized controlled trials (RCT) in Europe and Canada have shown supervised injectable diacetylmorphine (the active ingredient in heroin; [DAM]) to be effective for the treatment of long-term opioid dependency [3,8-12]. These RCTs testing injectable DAM recruited long-term opioid (mostly heroin) injectors not benefiting (e.g., continued injection of illicit heroin, poor psychosocial and health outcomes) sufficiently from currently available treatments (primarily methadone) [12,13]. Baseline characteristics across these studies, despite differences between the settings, were quite similar. Overall, participants

in these trials were in their late thirties, had used heroin for fifteen years or more, had two to four prior MMT attempts, and presented with poor physical and psychological health and many psychosocial problems such as unstable housing, illegal activities, repeated incarceration and unemployment [9,14,15].

Although these studies reached very similar target populations, eligibility criteria regarding prior and current methadone treatment differed significantly by setting. For example, currently being on MMT was an inclusion criterion in the trials conducted in the Netherlands and the United Kingdom [8,16], while for the Canadian trial it was an exclusion criterion [12]. For the other trials, it was neither [10,11,15,17]. A previous MMT attempt was an inclusion criterion for the trials in the Netherlands [8], Spain [11], Canada [12] and Belgium [15], and some of them further specified that participants received at least 60 milligrams (mg) of methadone for at least one month.

It has been proposed that treatment with injectable DAM should be offered as a second line option, after the patient has attempted maintenance treatment with oral methadone (or buprenorphine) and if not currently fully benefiting from this or other treatment [13]. Current guidelines state that most MMT patients will achieve stability on daily maintenance doses of 60 mg and above [18], and higher doses have been encouraged when patients cannot reach abstinence or minimal use of illicit opioids [16,19,20]. As this was the case for the target population of the DAM trials (i.e., continuing regular use of illicit opioids), the average MMT dose of the methadone arm in most of these trials was around 100 mg [9-12]. Some have argued that injectable medications such as DAM, should be restricted only to those who have previously experienced extended exposure to methadone doses of 100 mg or higher [21].

Even though there is some evidence suggesting that higher methadone doses may be clinically beneficial for people still using illicit opioids, a high dose is not necessarily the appropriate dose [19,22] and flexible individualized doses are recommended for MMT [18]. Roux et al. [23] recently showed that perceived methadone dose inadequacy (too low or too high), and not MMT dose itself, was independently associated with long-term non-adherence. Together with the fact that the DAM trials reached similar populations despite differences in MMT entry criterion suggests that prior detailed MMT requisites might not be enough or adequate as a clinical indicator of treatment with injectables. Moreover, recent evidence showed that DAM was more effective than MMT for those without a prior history of MMT [24]. This opens the possibility that offering injectable maintenance treatment only to individuals who have a history of MMT might further neglect many heroin-dependent individuals who have always remained outside of treatment. Injectable medications are an effective approach to attracting such people into treatment, who may later transition into MMT [25].

SALOME (Study to Assess Longer-term Opioid Medication Effectiveness) is an ongoing randomized double-blind controlled trial testing whether injectable hydromorphone is as effective as diacetylmorphine for the treatment of long-term opioid-dependent individuals who are not benefitting sufficiently from available treatments. The present study aims first, to describe participants' characteristics at study entry; and second, to determine factors independently associated with prior methadone episodes in which participants received high doses. These results could provide clinicians and policy makers with evidence to decide whether high doses of prior MMT should be required to be eligible for treatment with injectable medications.

METHODS

Design, Setting, Participants

SALOME is a two-stage phase III, single site (Vancouver), randomized, double blind non- inferiority controlled trial involving a total of 202 participants. In stage I, half of the 202 participants were randomized to receive injectable DAM, and the other half to receive injectable hydromorphone on a double-blind basis. In stage II, participants still retained in stage I treatment were randomized to continue injection treatment exactly as in stage I or to switch to the oral equivalent of the same medication (DAM or hydromorphone). Double-blinding was maintained in stage II. Study treatments were provided for six months in each stage and were delivered following a similar supervised protocol as in our previous clinical trial [12]. The study received ethical approval from the Providence Health Care/University of British Columbia Research Ethics boards. Prior to administration of research procedures and collection of participant data, participants reviewed the study procedures with research staff and provided informed consent.

The study population was defined as chronic, opioid-dependent, injection drug users who were currently injecting and who had attempted at least one previous episode of opioid maintenance treatment. Eligible participants were aged 19 and older, residing in the greater Vancouver area, had a minimum of five years of illicit opioid dependence (as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition [26], regular injection of illicit opioids in the prior year and at least two prior addiction treatment episodes, one of which must have been in opioid maintenance treatment. Volunteers were excluded if they had severe medical conditions contraindicated for treatment with DAM or hydromorphone (e.g., respiratory problems, stage II or greater hepatic encephalopathy), were pregnant or planning on becoming pregnant, or had an imminent period of extended incarceration. Self-report data, administrative records (e.g., Provincial pharmacy records), urine drug screens and full medical exam were used to confirm inclusion/exclusion criteria. A total of 253 volunteers were screened for the study, which required a minimum of three appointments with the research and clinical care teams and an average of 25.9 (median = 15) days to complete. A full explanation of screening procedures is available elsewhere [27].

Measures

Baseline data were collected during the second screening visit, which occurred prior to randomization and treatment allocation. To evaluate participants lifetime and prior 30 day characteristics at study entry, standardized questionnaires included the following: 1) European Addiction Severity Index (medical status, drug use, legal status) [28], 2) Fagerstrom test for Nicotine dependence (nicotine dependence) [29]; 3) Opioid Treatment Index (physical health) [30]; 4) Symptom Checklist-

90-Revised (mental health) [31]; 5) EuroQol (health related quality of life) [32] and 6) Client satisfaction questionnaire (satisfaction with addiction treatment) [33]). Complementary questionnaires regarding participant's socio-demographic (e.g., ethnicity, housing), health services utilization (e.g., emergency departments, primary care visits) and histories of addiction treatment (e.g., residential treatment, outpatient counseling) were developed to capture comprehensive data that reflected the present study design and context. This questionnaire package was administered by experienced and trained members of the research team [27], who operate independently of the clinical team and in a separate site.

In addition to questionnaire data, laboratory records were collected to determine participant's current medical status, including HIV and hepatitis C virus. Historical administrative records for methadone and Suboxone treatment (licensed in Canada in 2007 [27]) were obtained from the centralized British Columbia (BC) provincial drug dispensation database (PharmaNet). Daily dispensation records were examined from the earliest date available (September 1, 1995) to the date of study treatment allocation. It should be noted this database does not track methadone or Suboxone dispensed in the correctional or acute care systems, or in settings outside of BC.

All research data were held in the confidential research office and then transferred to the data center for entry and storage. Data were accessible only by authorized persons of the research team (Principal Investigator, research coordinators, statisticians, programmers, research assistants) and the clinical team did not have access to any research data.

Statistical analysis

Descriptive statistics (means and frequencies) were used to analyze the baseline characteristics of study participants. For convenience, we define "MMT-100" as the subgroup who, in the prior five years, had a least one continuous period of MMT treatment where there was no interruption in doses of more than 30 days [34], and within the treatment period, they reached a stable weekly average dose of 100 mgs daily or more in at least 30 out of a 40 day treatment episode. This dose was selected as it represented the high end of the stated range for stabilization [18] as well as the average methadone dose in the MMT arm of prior studies testing heroin assisted treatment [9-12].Chi-square and t-tests were performed for categorical and continuous variables respectively for bivariable analyses of participant characteristics and the defined 100 mg MMT episode.

A multivariable logistic regression model was built to test the independent association between participant characteristics and experiencing MMT-100 in the prior five years. Covariates from the bivariable analyses were selected to enter the model using an entry criterion of p-value≤0.20. We also explored interaction terms for age and gender, age and education and Aboriginal ancestry and separation from biological parents using the same model selection criteria. At each stage, covariates for age, gender and Aboriginal ancestry were forced into the model. The backward selection approach was used and the final model was selected based on the smaller Akaike information criterion. Data presented from the model are the adjusted odds ratios (OR) and 95% confidence interval (95% CI); for the interaction between age and gender, OR and 95% CI were estimated holding the coefficients for age and other parameters constant at their mean level. All analyses were performed in SAS version 9.4 [35] and R [36].

RESULTS

A total of 202 participants met eligibility criteria, provided informed consent and were randomized to SALOME. The mean age of participants was 44.3 years (standard deviation [SD] =9.6) and 69.3% were men. Women were significantly younger (Mean=40.7; SD=9.3) than men (Mean = 46; SD=9.3). A total of 74 participants were originally from BC. Among those not originally from BC, only 14 (14/128 = 10.9%) had moved to BC in the two years prior to study start (data not shown). Aboriginal ancestry, including Metis, First Nations or Inuit was identified by 30.7% of participants. A history of separation from biological mother, father or both was reported by 60.9%, and more likely by those with Aboriginal ancestry (57.1% versus 71.7%; Chi-square statistic =3.74; p-value 0.053). Participants were involved in illegal activities for profit (i.e., other than illicit drug use) for an average of 14.1 (SD=13.7) days in the month prior the baseline evaluation. Regarding health status, 55.4% of participants had a chronic medical problem that interfered with their life, and lab results showed that 86.1% and 14.9% were positive with hepatitis C and HIV antibodies, respectively (Table 1).

Table 2 outlines participants' lifetime and prior month illicit drug use at study enrolment. Participants reported an average of 15.4 (SD= 9.4) years of heroin injection. Ninety-two participants also reported regularly injecting illicit morphine or hydromorphone for an average of 8.7 (SD=9.3) and 8.1 (SD=8.8) years, respectively. In the prior month, participants used illicit opioids an average of 28 (SD=4.2) days, of which heroin injection had the highest average days of use (Mean = 25.4; SD=8.1). In addition to injecting illicit heroin, participants reported smoking crack cocaine an average of 10.3 days (SD=12.7).

Treatment and health services use are described in Table 3. Based on BC PharmaNet records, participants had an average of 5.1 (SD=3.4; range 1 to 21) methadone episodes since 1995 with an average dose of 110 mgs and in the prior five years had an average of 2.8 (SD=2.1) methadone episodes. A total of 92 (45.5%) participants stated they did not want methadone when asked about their preferred MMT dose. Among those who indicated a dose preference, their average preferred dose was 93.7 (SD= 65.4) mgs. In the month prior study enrolment, participants received an average of 16.1 (SD= 13.6) days of methadone treatment. In addition to opioid agonist treatment, participants also reported attempting outpatient withdrawal an average of 5.6 (SD=7.7) times in their life and 63% of participants had accessed outpatient counseling. Other health services used in the month before enrolment were emergency department visits and health care providers (e.g., addiction physician, nurse), which were accessed by 9.4% and 79.7% of the participants, respectively.

Few baseline characteristics differed significantly by MMT-100 group in the bivariable analyses (Table 1,2,3). Of note is that there were a significantly higher proportion of participants

Table 1: Socio-demographic and health profile of SALOME participants at baseline.

Socio-demographic Characteristics	Total		No MMT-100a		At least one MMT-	
	(n=202)		(n=93)		100b	
					(n=109)	
	Mean [sd] / N (%)		Mean [sd] / N (%)		Mean [sd] / N (%)	
Age	44.3 [9.6]		45.7 [9.7]		43.2 [9.4]	
Women c	62	(30.7)	25	(26.9)	37	(33.9)
Currently has an intimate partner	74	(36.7)	33	(35.5)	41	(37.6)
Aboriginal ancestry	62	(30.7)	22	(23.7)	40 (36.7)*	
High school certificate or higher	108	(53.5)	56	(60.2)	52	(47.7)
Ever separated from biological parents d	123	(60.9)	48	(51.6)	75 (68.8)*	
Placed into foster care e	48	(23.8)	19	(20.4)	29	(26.6)
Years spent in foster care f	3.2 [3.3]			2.7 [3]	3.5 [3.4]	
Any non-stable housing in prior 3 years g	141	(69.8)	62	(66.7)	79	(72.5)
Any street housing in prior 3 years	45	(22.3)	16	(17.2)	29	(26.6)
Any non-stable housing in prior 30 days	119	(58.9)	54	(58.1)	65	(59.6)
Income from current non-illicit work h	0 [0, 0]		0 [0, 175]		0 [0, 0]	
Ever paid in exchange for sex	82	(40.6)	33	(35.5)	49 (45)	
Paid in exchange for sex in the prior month i	19 (9.4)			8 (8.6)	11	(10.1)
Months ever incarcerated	37.06 [65]		37.9	[71.2]	36.96	[59.8]
Days of illegal activities for profit in prior month	14.1	[13.7]	13.3	[13.5]	14.9	[13.9]
Money spent on drugs in prior month j	1500 [1000, 3000]		1500 [950, 3000]		1625 [1000, 3000]	
Health						
Ever attempted suicide	52	(25.7)	22	(23.7)	30	(27.5)
Ever had unintentional overdoses	136	(67.3)	60	(64.5)	76	(69.7)
Has chronic medical problem(s) k	112	(55.4)	50	(45.9)	62	(56.9)
Hepatitis C Positive	174	(86.1)	77	(82.8)	97 (89)	
HIV Positive	30	(14.9)	10	(10.8)	20 (18.4)*	
OTI - Physical health l	22.5	[11.9]	21.2	[11.1]	23.7	[12.5]
SCL-90 GSI - Psychological health m	0.9 [0.7]		0.8 [0.7]			1 [0.8]
EQ5D - Health related quality of life n	0.8 [0.2]		0.8 [0.2]		0.8 [0.2]	

Statistics are p-values for t-test or chi-square test: * $p < 0.05$.

Table Notes:

a. Participants who attempted methadone in the prior five years but did not reach a stable dose of 100 mg or more in a 30 out of 40 day period.

b. Participants who in the prior five years had a least one continuous period of MMT treatment where there was no interruption in doses of more than 30 days, and within the treatment period, they reached a stable weekly average dose of 100 mgs or more in at least 30 out of a 40 day treatment episode.

c. Includes 3 participants who identified as transgendered-female.

d. Based on n= 200, 2 missing.

e. Question is only applicable to participants who were separated from both biological parents simultaneously.

f. Among those who were ever in foster care (n=46; n missing = 2).

g. Non-stable housing is single resident occupancy hotel rooms with restrictions or couch surfing. Street housing is defined as outdoor, vehicles or in public places.

h. Median [interquartile range] Canadian dollar value of money/goods/services earned from legal employment activities, including employment and alternative employment, such as returns on recycling.

i. Among those who ever did sex work and reported at least 1 day of sex work in the prior month (total n=19; n= 8 in the 'NoMMT-100' group; n=11 in the' MMT-100' group).

j. Median [interquartile range] Canadian dollars.

k. European Addiction Severity Index- self-reported chronic medical problems that interfered with life.

l. Opioid Treatment Index total health scores range from 0 to 51, higher score is indicative of higher physical conditions.

m. Symptom Checklist - 90 Global severity index scores range from 0 to 1, higher score is indicative of higher psychological symptoms.

n. Euroquol with Canadian weights scores range from 0 to 1; higher scores are indicative of better health status.

Table 2: Substance use history of SALOME participants at baseline.

	Total		No MMT-100a		At least one MMT-100b	
	(n=202)		(n=93)		(n=109)	
	Mean [sd] / N (%)		Mean [sd] / N (%)		Mean [sd] / N (%)	
Age of first injection	22.1	[7.4]	23.1	[7.8]	21.3 [7]	
Heroin was the first opioid used illicitly	146	(72.3)	74 (79.6)		72 (66.1)*	
Lifetime regular use						
Injected heroin, *years*	15.4	[9.4]	15	[9.7]	15.9	[9.1]
Ever used heroin non-injection	76	(37.6)	33 (35.5)		43 (39.5)	
Injected hydromorphone or morphine	92	(45.5)	34 (36.6)		58 (53.2)*	
Years of hydromorphone injection	8.1	[8.8]	7.7	[8.7]	8.3	[8.9]
Years of morphine use injection	8.7	[9.3]	12	[8.6]	7.1 [9.3]*	
Used cocaine powder or crack cocaine	170	(84.2)	72 (77.4)		98 (89.9)*	
Years of cocaine powder injection	11.8	[9.3]	11.8	[9.5]	11.8	[9.2]
Years of crack cocaine non-injection	11.2	[7.9]	12.1	[8.3]	10.5	[7.7]
Prior month use in days						
Any illicit opioids	28	[4.2]	28.8	[3.3]	27.3 [4.7]*	
Heroin, injection	25.4	[8.1]	25.7	[8.5]	25.1	[7.7]
Times of heroin use on a typical day	3.4	[2.5]	3.3	[2.2]	3.5	[2.9]
Hydromorphone, injection	2.5	[6.4]	3.2	[7.6]	1.8	[5.1]
Morphine, injection	3	[7.1]	3.4 [8]		2.6	[6.3]
Speedball, injection	3.4	[7.5]	2.5	[6.6]	4.2	[8.1]
Cocaine powder, injection	4.8	[9.1]	3.9	[8.5]	5.6	[9.6]
Amphetamine, injection	3.2	[7.1]	2.1	[5.7]	4.1 [8.1]*	
Crack cocaine, smoked	10.3	[12.7]	8.5 [12.1]		11.9 [13.1]	
Times of crack cocaine use on a typical day	4.4	[8.7]	3.6	[7.8]	5	[9.4]
Sedatives, oral	0.9	[3.7]	1	[3.9]	0.7	[3.5]
Cannabis, oral or smoked	6.3	[10.7]	5.2	[9.6]	7.3 [11.5]	
Alcohol over threshold c	0.4	[2.5]	0.5	[3.3]	0.3	[1.4]
Fagerstrom - Nictotine Dependence d	4.4	[2.4]	4.3	[2.6]	4.4	[2.4]

Statistics are p-values for t-test or chi-square test: * $p < 0.05$.

Table Notes:

a. Participants who attempted methadone in the prior five years but did not reach a stable dose of 100 mg or more in a 30 out of 40 day period.

b. Participants who in the prior five years had a least one continuous period of MMT treatment where there was no interruption in doses of more than 30 days, and within the treatment period, they reached a stable weekly average dose of 100 mgs or more in at least 30 out of a 40 day treatment episode.

c. European Addiction Severity Index – Alcohol over threshold refers to number of days where five or more alcoholic drinks per day are taken or alcohol taken to the point of intoxication.

d. Fagerstrom Test for Nicotine Dependence, scores range from 0 to 10, higher scores indicative of higher nicotine dependence.

with Aboriginal ancestry, history of separation from biological parents, lifetime regular hydromorphone and morphine use, lifetime cocaine use and HIV among the MMT-100 group. In addition, there were opioid treatment related characteristics that differed by MMT-100 group; specifically, age of regular opioid maintenance prescription, years of regular opioid maintenance treatment, ideal and preferred doses, ever prescribed opioids for pain or other medical conditions and days of MMT in the prior month.

Table 4 shows the results of the multivariable model for characteristics independently associated with at least one MMT episode in the prior five years as previously defined. Socio-demographic characteristics independently associated with the defined 100 mg MMT episode were age, gender, the interaction between age and gender, and being separated from biological parents (OR = 2.18; 95% CI = 1.05-4.54). The interaction between

Table 3: History and prior 30 day addiction treatment and health services use of SALOME participants at baseline.

	Total		No MMT-100a		At least one MMT-	
	(n=202)		(n=93)		100b	
					(n=109)	
	Mean [sd] / N (%)		Mean [sd] / N (%)		Mean [sd] / N (%)	
Opioid Maintenance Treatment History						
Age of regular prescribed opioids for addiction	33.6	[9.3]	35.1	[9.1]	32.4 [9.2]*	
Years of regular prescribed opioids for addiction	5.5	[5.3]	4.4	[4.5]	6.5 [5.8]**	
Times ever attempted MMT since 1995 c	5.1	[3.4]	4.7	[3.1]	5.4 [3.7]	
Times attempted MMT in prior 5 years c	2.8	[2.1]	2.8	[2.1]	2.8 [2.1]	
Highest daily dose of methadone in milligrams c d	110 [85, 155]		80 [60, 100]		140 [120, 175]***	
Ideal dose in milligrams e	93.7	[65.4]	58.5	[39.2]	121.4 [68.7]***	
Methadone dose preferences: f						
Ideal dose is < 80 milligrams	38	(18.8)	29	(31.1)	9 (8.3) ***	
Ideal dose is ≥ 80 milligrams	55	(27.2)	12	(12.9)	43	(39.5)
Does not want methadone	92	(45.5)	39	(41.9)	53	(48.6)
Unsure	15	(7.4)	12	(12.9)		3 (2.8)
Ever attempted suboxone c	30	(14.9)	18	(19.4)	12 (11)	
Days suboxone ever dispensed c	122.2 [251.9]		65.5	[79.1]	207.2 [380.1]	
Maximum suboxone dose in milligrams c	15.2	[17.6]	15.4	[20.9]	14.8	[11.7]
More than 6 months ago since last OMT access c	41	(20.3)	23	(56.1)	18	(43.9)
Days of MMT in prior month c	16.1	[13.6]	13.2	[13.4]	18.6 [13.3]**	
CSQ- Satisfaction with last addiction treatment g	20.1 [6.9]		20 [6.8]		20.1 [6.9]	
Other Health Services Use						
Times attempted outpatient withdrawal	5.6 [7.7]		5.7 [7.5]		5.5 [7.8]	
Ever accessed outpatient counselling	127	(62.9)	57	(61.3)	70	(64.2)
Regular lifetime use of safe injection site	87	(43.1)	44	(47.3)	43	(39.5)
Regular prescribed opioids for pain or medical						
conditions	93 (46)		33 (35.5)		60 (55)**	
Ever prescribed sedatives	103 (51)		48	(51.6)	55	(50.5)
Ever prescribed stimulants	41	(20.3)	17	(18.3)	24 (22)	
Days received outpatient counseling in prior month	0.3 [1.6]		0.4 [3.2]		0.1 [0.4]	
Days accessed the safe injection site in prior month	9.9	[11.3]	11	[11.7]	8.8	[10.9]
Visited the emergency department in prior month	19 (9.4)		10	(10.8)		9 (8.3)
Accessed health care provider in prior month	161	(79.7)	71	(76.3)	90	(82.6)

Statistics are p-values for t-test or chi-square test: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
MMT = methadone maintenance treatment; OMT = Opioid Maintenance Treatment

Table Notes:

a. Participants who attempted methadone in the prior five years but did not reach a stable dose of 100 mg or more in a 30 out of 40 day period.

b. Participants who in the prior five years had a least one continuous period of MMT treatment where there was no interruption in doses of more than 30 days, and within the treatment period, they reached a stable weekly average dose of 100 mgs or more in at least 30 out of a 40 day treatment episode.

c. Based on current Pharma Net records since 1995, all participants had at least one methadone attempt since 1995.

d. Median [interquartile range]

e. Response to question "if you could choose your ideal methadone dose, how many milligrams would you like", data presented for n=93 who reported an ideal dose greater than 0 milligrams.

f. Response to question "if you could choose your ideal methadone dose, how many milligrams would you like", responses greater than 0 milligrams (n=93) were categorized to less than or greater than or equal to 80 milligrams. Participants responded 0 milligrams when they did not want this treatment or selected unsure (n missing = 2).

g. Client Satisfaction Questionnaire, scores range from 8-32, higher scores are indicative of higher satisfaction. N=200; 185 of participants completed this questionnaire in reference to methadone treatment, 14 in reference to suboxone and one in reference to a prior abstinence oriented treatment.

Table 4: Logistic regression model adjusting for age, gender and ethnicity for variables associated with MMT-100.

Variable	Coefficient (SE)	OR	95% CI
Constant	1.743 (1.63)	-	-
Age	-0.12 (0.04) ***	-	-
Gender	Ref		
Man			
Woman	-3.92 (1.87) *	-	-
Age * Gender a			
Man	Ref		
Woman	0.1 (0.04) *	-	-
Separated from biological parents			
No	Ref	Ref	
Yes	0.78 (0.37) *	2.18	1.05 - 4.54
Regular injection of illicit HDM or morphine			
No	Ref	Ref	
Yes	0.74 (0.36) *	2.10	1.03 - 4.25
Regularly prescribed opioids for pain or other			
medical conditions	Ref	Ref	
No			
Yes	0.92 (0.38) **	2.51	1.18 - 5.31
Preferred methadone dose b	Ref	Ref	
Less than 80 mgs			
Does not want methadone c	1.54 (0.51) **	4.69	1.71 - 12.87
More than 80 mgs	2.54 (0.60) ***	12.67	3.93 - 40.82

* p<0.05; ** p<0.01; ***p<0.001

Table definitions: SE= standard error; OR= odds ratio; 95% CI = 95% confidence interval; HDM= hydromorphone; mgs= milligrams.
Notes: Model was built with 194 observations (8 observations were removed: 4 participants responded about preferred dose in reference to suboxone; 2 participants stated 'prefer not to answer' to the question about being separated from biological parents; 2 participants had a missing response to the question about ideal dose). Aboriginal ancestry, age and gender were forced in. Additional variables that entered the model but were not significant and not shown here are: aboriginal ancestry (coefficient (SE) = 0.34 (0.43)), education (coefficient (SE) = -3.11 (1.74)), an interaction between age and education (coefficient (SE) = 0.07 (0.04)) and hepatitis C infection (coefficient (SE) = 1.06 (0.56)).
a. Interaction between age and gender: The interaction between age and gender suggests that the odds of having the defined 100mg MMT episode in the prior five years depended on participants' ages. For example, compared to a 40 year old man, the odds that a woman at age 40 had the defined 100 mg MMT episode was 0.94 (95% CI=0.42-10.10) and at age 45 was 1.53 (95% CI=0.67-16.57).
b. n=15 participants reported that they were unsure what their preferred methadone dose would be. This category was entered into the final model and is not displayed. The odds of having an MMT episode with 100 milligrams in the prior five years for those with an unsure dose is 0.98 (95% Confidence Interval =0.19, 5.07) times the odds of those with an ideal dose of less than 80 milligrams.
c. Participants responded 0 milligrams when they did not want this treatment or selected unsure

age and gender suggests that the odds of having an MMT-100 episode in the prior five years depended on participants' ages. For example, the odds ratio that a woman at age 40 had an MMT-100 episode was 0.94 (95% CI=0.42-10.10) and at age 45 was 1.53 (95% CI=0.67-16.57), compared to men at the same ages.

In this model, the odds ratio of having the defined 100 mg MMT episode was higher for participants with a history of regular prescription of opioids for pain or other medical conditions (OR = 2.51; 95% CI = 1.18-5.31) and regular injection of illicit hydromorphone or morphine (OR=2.10; 95% CI = 1.03-4.25). In addition, compared to participants who indicated an ideal dose of less than 80 milligrams, participants who preferred no methadone (i.e., reported 0 milligrams to the question about preferred dose) or more than 80 mgs of methadone had 4.69 (95% CI= 1.71-12.87) and 12.67 (95% CI= 3.93-40.82) times the respective adjusted odds of having an MMT-100 episode in the prior five years.

DISCUSSION

SALOME participants presented at baseline with a profile similar to prior clinical trials with injectable diacetylmorphine, including the preceding Canadian trial [8-11,15,37]. Participants had been injecting heroin for more than fifteen years, had

several attempts at MMT, and had medical problems, histories with the correctional system and current involvement in illicit activities, unstable housing, daily use of illicit opioids, mostly heroin, and regular use of cocaine and crack cocaine. As in the prior Canadian study, Aboriginal people were overrepresented in SALOME compared to the provincial population (30.7% versus approximately 5%).

Treatment with supervised injectable DAM is aimed at reaching long-term illicit opioid users with major physical and social complications and for whom oral, long-acting opioid maintenance currently is not effective [13]. The profile of the SALOME participants shows profound disadvantages in social and health conditions. For instance, there was an appallingly high prevalence of separation from biological parents with a slightly higher prevalence among those with Aboriginal ancestry. More than half of the participants expressed they had a chronic medical condition that interfered with their lives and approximately nine out of ten participants were hepatitis C and/or HIV positive. This is also an older cohort (average age was 44) despite the inclusion criterion was a minimum age of nineteen). As in other studies with similar populations, women were younger [38,39] than men; this difference could be explained by other findings showing that women progressed to opioid dependence more quickly than men and engaged in treatment sooner [38,40-42]. In addition, participants had attempted oral methadone treatment an average of five times since 1995, reaching an average dose of 110 mg, and the majority continued attempting MMT six months prior to enrolling in SALOME. Therefore, it is clear that the SALOME participants belong to the drug using population that could benefit from an intensive and alternative treatment, as those offered in the trial.

While it has been proposed that treatment with injectable DAM should be offered after attempting maintenance treatment with oral methadone (or buprenorphine) [13], it remains unclear if high doses and longer time engaged in prior MMT should be required to offer this treatment. This study tested variables independently associated with having received MMT with 100 mg or more for at least 30 days (in a 40 days period) in the prior five years. Age, gender, separation from biological parents, history of regular illicit morphine or hydromorphone injection, having been regularly prescribed opioids for pain or other medical conditions and preferred MMT dose were independently associated with the defined 100 mg MMT episode in the last five years. None of the factors related to treatment conditions such as treatment retention (e.g., years on MMT), access to treatment (e.g., number of times attempted MMT), satisfaction with treatment or access to counseling was independently associated with higher doses. Thus, these findings suggest that having reached high doses of MMT in the past might be an inadequate indicator of the type of treatment participants need at present.

The findings also indicate that being prescribed opioids regularly for pain management or other medical conditions was independently associated with reaching higher doses of methadone in the last five years. An important number of patients receiving MMT have reported chronic pain [43-45]; however, this population faces specific challenges to receive adequate pain management. For example, prescription of other opioids while receiving MMT might be avoided for safety reasons (e.g., drug interactions) or concern about diversion [44,46]. Results regarding the relationship between the use of MMT to manage both pain and opioid dependence are mixed. Some studies have found that among MMT patients, those in need of pain treatment had higher methadone doses compared to those who did not [44,45], while others have shown that there were no differences in methadone doses between opioid dependent patients with and without pain [47,48]. Despite differences in study findings, lack of adequate doses due to concerns over safety or diversion, may be one explanation for participants' continued illicit opioid use and combinations of illicit opioids used [22]. In the present study, history of regular hydromorphone or morphine injection was also associated with higher methadone doses. When the relationship of pain and regular use of non-prescribed opioids with higher methadone doses is considered together, the findings suggest that these participants may benefit from coordinated treatment for pain and addiction.

This study also provides additional support for the importance of integrating patient preferences in the provision of treatment. Participants' dose preferences were strongly and independently related to participant's prior five-year MMT episodes with 100 mgs. While higher doses may be clinically beneficial to reduce the use of illicit opioids [49], perceived dose inadequacy has been associated with poor outcomes [23], and dose-adjustment should be made from an individual clinical perspective [19,22,50]. Incorporating patient perspectives [51] and improving patient-provider relationships [52] are necessary for optimal patient outcomes with maintenance treatment.

Maintenance treatment with injectable medications is an intensive treatment beneficial for patients not attracted to and not benefitting from oral maintenance treatment. A considerable body of evidence in the chronic disease literature shows that patients' illness state and treatment regimen are closely related [53]; for example, as patients experience acute symptom episodes, more comprehensive treatments are necessarily prescribed. Thus, in patients with fifteen years or more of heroin addiction, with its attendant social and medical problems, who continue to use illicit opioids despite the availability of effective treatments, it is conceivable that one treatment regimen may not be effective throughout such a patient's lifespan. Therefore, diversified opioid maintenance treatments, offered in different program modalities, are likely required to meet every individual's needs over time [6,7,25].

The centralized drug dispensation database in British Columbia allowed us to determine characteristics of prior methadone (or Suboxone) treatment attempts by participants enrolled in the study. However, administrative databases have limited capacity to explore the potential relationship between episode characteristics with the care delivered, due to the nature of the data collected. For example, the records do not include information about the prescribing physician's approach, whether the clinic was low-threshold or if other ancillary services were offered. Although our baseline questionnaires included extensive questions on addiction treatment and health services received, we cannot match them to the drug dispensation dataset. The aim of this study was not to determine the effectiveness of prior MMT episodes at an individual basis, but such evidence would

justify requiring specific days and milligrams prior to accessing a program offering more intensive injectable treatments.

Most of the participants in this study had accessed and received stable and high doses of MMT and were currently injecting street opioids regularly. Thus, we must consider alternative treatments to reduce the harms associated with illicit opioid use for this particular group. Our data demonstrate that these participants were in need of alternative treatments at the time of enrolment and fit the profile of those whom may benefit from supervised injectable treatment. The findings further support the importance of individualized treatment planning [54]. Specific doses and days in prior MMT may not provide health authorities with enough and adequate information regarding which patients should have access to injectable treatment in the context of diversified opioid maintenance programs.

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Contributors

EOJ, MTS, MK, SB and AHA are investigators in the SALOME study. EOJ, KM, KL and SM made substantial contributions to the collection of baseline data. DG analysed the data. EOJ, KM and MTS wrote the first draft of the manuscript. EOJ, SB, SM, MTS, DG and KMs contributed to the interpretation of the data. All authors gave approval to the final version of the paper and are accountable for the integrity of the work.

CONFLICT OF INTEREST

The authors declare they have conflict of interests.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.'

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