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Methadone maintenance treatment discontinuation among young people use who opioids in Vancouver, Canada

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ABSTRACT

Objective: Retaining adolescents and young adults (AYA) in medications for opioid use disorder (MOUD), like methadone maintenance treatment (MMT), is critical to reducing toxic drug fatalities. This analysis sought to identify factors associated with MMT discontinuation among AYA.

Method: Data were derived from the At-Risk Youth Study, a prospective cohort study of street-involved AYA in Vancouver, Canada, between December 2005 and June 2018. Multivariable extended Cox regression identified factors associated with time to MMT discontinuation among AYA who recently initiated MMT. In sub-analysis, multivariable extended Cox regression analysis identified factors associated with time to 'actionable' MMT discontinuation, which could be addressed through policy changes.

Results: A total of 308 participants reported recent MMT during the study period. Participants were excluded if they reported MMT in the past-six-months at baseline and were retained in MMT (n=94, 30.5%); were missing MMT status data (n=43, 14.0%); or completed an MMT taper (n=11, 3.6%). Of the remaining 160 participants who initiated

MMT over the study period, 102 (63.8%) discontinued MMT accounting for 119 unique discontinuation events. In multivariable extended Cox regression, MMT discontinuation was positively associated with recent weekly crystal methamphetamine use (Adjusted Hazard Ratio (AHR)=1.67, 95% Confidence Interval [CI]: 1.19–2.35), but negatively associated with age of first 'hard' drug use (per year older) (AHR=0.95, 95% CI: 0.90-1.00) and female sex (AHR=0.66, 95% CI: 0.44–0.99). In sub-analysis, recent weekly crystal methamphetamine use (AHR=4.61, 95% CI: 1.78–11.9) and weekly heroin or fentanyl use (AHR=3.37, 95% CI: 1.21–9.38) were positively associated with 'actionable' MMT discontinuation, while older age (AHR=0.87, 95% CI: 0.76–0.99) was negatively associated.

Conclusions: Efforts to revise MMT programming; provide access to a range of MOUD, harm reduction, and treatments; and explore co-prescribing stimulants to AYA with concurrent stimulant use may improve treatment retention` and reduce toxic drug fatalities.

Keywords: Opioid-related Disorders, Heroin Dependence, Fentanyl, Opiate Substitution Treatment, Methadone, Adolescent, Young Adult, Addiction Medicine, Practice Guideline

Introduction:

The toxic drug crisis has led to thousands of preventable deaths across North America.[1] This is particularly true for people with opioid use disorder (OUD), who are at a heightened risk of experiencing a toxic drug poisoning.[2-4] Methadone maintenance treatment (MMT) has proven effective in treating OUD and reducing associated harms.[5; 6] Hence, existing clinical guidelines in North America and in British Columbia (BC), where this study is situated, recommend the prescription of MMT to people who report the regular use of illicit opioids, including adolescents and young adults (AYA).[7; 8]

Existing evidence indicates that being retained in MMT is central to realizing positive treatment outcomes;[9; 10] however, examinations of MMT discontinuation are primarily restricted to adults,[11] while research among AYA primarily focuses on buprenorphine-naloxone retention. For example, one study demonstrated that AYA are less likely to be retained in buprenorphine-naloxone in comparison to adult populations.[12; 13] Additionally, retrospective chart review of AYA at an outpatient pediatric MOUD clinic in the Northeast USA found that female sex, and a negative urine screen for tetrahydrocannabinol and opioid use and positive urine screen for buprenorphine-naloxone after initiating buprenorphine-

naloxone were associated with being retained on buprenorphine-naloxone at follow-up.[10] A randomized controlled trial was also conducted among AYA in the USA, where buprenorphine-naloxone discontinuation was found to be positively associated with baseline cocaine use, not being in an intimate relationship, having children, and having a single parent.[14]

To date, evidence among adult populations suggests people receiving MMT were more likely to be retained in treatment in comparison to other medications for opioid use disorder (MOUD), while alluding to potential factors associated with MMT discontinuation. For example, findings from a 24-week randomized controlled trial among adults found that 74% of participants receiving MMT and 46% of participants receiving buprenorphine-naloxone were retained in the study by the end of the 24-week study period.[15] Similarly, a randomized controlled trial among pregnant people between 6 and 30 weeks of gestation with OUD in the USA, Australia, and Canada that examined MOUD retention at the time of delivery reported higher retention in MMT (82%) when compared to buprenorphine (67%).[16] Additionally, a study examining the association between OUD treatment goals and factors associated with their attainment among AYA in Canada found that those receiving MMT were more likely to decrease their dose 3 months after treatment initiation (Odds Ratio=4.42,

95% Confidence Interval: 1.40-14.0) in comparison to those receiving buprenorphine.[17] This finding is supported by evidence of a higher preference for MMT among AYA who are interested in initiating OAT, which may be explained by perceptions that it is more effective at addressing mental illness and physical pain.[18]

Within the study setting, Vancouver, BC, research among adults found self-reported Indigenous identity, recent incarceration, sex work, and injection heroin use were negatively associated with MMT use, while female sex, HIV-positive status, and crack cocaine smoking were positively associated.[19] Additionally, one study examined the impacts of regulatory changes to the MMT formulation on substance use and other health outcomes among HIV-positive people, finding that a switch to a more concentrated Methadose™ formulation in January 2014 was associated with significant increases in heroin injection.[20] One study from Vietnam found that HIV-positivity, higher education, challenges managing life skills, and disclosing one's health conditions to their partner were negatively associated with methadone adherence, while older age, living with pain, and mental illness were positively associated with MMT retention.[21] Lastly, one qualitative study examining how AYA navigate MOUD treatment in Vancouver, Canada identified health policy barriers to MMT retention, which included burdensome, required daily witnessed dispensation; stringent missed dose and re-

initiation policies; limited or inaccessible take-home dosing; and recommended dosage levels that were insufficient in the context of the potent illicit drug supply.[22]

Of the evidence examining MMT among AYA, there has been one retrospective chart review of AYA accessing MOUD in Sydney, Australia. This study found that participants who received MMT were retained for an average of 354 days versus 58 days in buprenorphine-naloxone,[23] suggesting that some AYA are better retained in MMT compared to buprenorphine-naloxone. In the context of the toxic drug crisis,[24] this knowledge gap highlights the need for additional research into ways to prevent MMT discontinuation among AYA.

Given existing guidelines support the use of MMT for AYA in the study setting[7] our research sought to understand ways to improve MMT retention among AYA. This involved identifying reasons for and factors associated with time to MMT discontinuation among AYA who reported initiating MMT over the study period. Additionally, this study sought to examine factors associated with potentially 'actionable' MMT discontinuation, which are reasons for MMT discontinuation that can be addressed through policy or guideline changes.

Materials & Methods:

Data Source & Study Sample

Our study drew on data from the At-Risk Youth Study (ARYS), an open prospective cohort study of 'street-involved' AYA between ages 14 and 26 who were homeless or accessing services intended for homeless AYA at the time of recruitment, which has been described previously.[25] The study commenced in October 2005, and street-based outreach and snowball sampling approaches were used by ARYS staff to recruit AYA from street-based settings and youth-serving agencies, and through peer networks. To be eligible individuals, are required to report illicit drug use in the past 30 days (other than or in addition to cannabis use) and provide informed consent to participate. Upon recruitment, participants complete an interviewer-administered questionnaire and a follow-up interview at six-month intervals. Participants also see a study nurse and complete a nurse-administered questionnaire, and have access to wound care, infectious disease testing, and nursing support. All participants provided written informed consent were reimbursed $40 CAD for each study visit. This study received ethical approval from the University of British Columbia/Providence Health Care Research Ethics Board.

For our study, the analysis was restricted to the period between December 2005 and June 2018, which is the period of which data was available, and the sample was restricted to participants who reported any weekly or daily illicit opioid use in the last six months at any point over the study period. Existing clinical guidelines recommend the use of MOUD, including MMT, for all AYA who use opioids regularly given the increased presence of toxic, synthetic opioids within the illicit drug supply.[7] Participants who responded affirmatively to the question "in the last 6 months, have you been in any kind of alcohol or drug treatment (including methadone/Methadose™ or Suboxone®)?" and subsequently reported accessing MMT were eligible for inclusion in the analytic sample. Participants who, at their baseline interview, reported MMT enrolment in the last six months were excluded from the analysis due to the inability to deduce when these participants commenced MMT; however, participants were re-included in the sample if they re-initiated MMT at any point over the study period. Additionally, participants were right-censored if they reported a MMT discontinuation event, but they were re-included in the analysis if they subsequently re-initiated MMT and they could therefore contribute more than one initiation event. Participants were also right-censored if they were lost to follow-up or if they reported recent MMT at the end of the study period, hence we expected high censoring rates in this study.

More specifically, we observed an 83.4% censoring rate in the primary analysis, which was positively associated with female sex but negatively associated with older age, and a 93.6% censoring rate in the sub-analysis, though the sample size was small, and no statistically significant differences were observed. Given the intentional use of censoring and that we do not suspect the study conditions to impact participants' decisions to initiate MMT, we assessed that censoring is likely to be non-informative.

Participants who provided an affirmative response to receiving MMT in the past six months at some point over the study follow-up period were asked the follow-up question of "are you currently on MMT?". Participants who responded affirmatively were considered retained, while participants who responded negatively were deemed to have discontinued MMT. Participants who reported that they were not currently on MMT were then asked to provide one or more reasons for ceasing MMT from a list or could provide an open-ended response; however, participants who discontinued MMT between study periods were not asked for their reasons for MMT discontinuation and therefore did not have the opportunity to provide a reason. Participants who reported that they had discontinued MMT due to treatment completion (e.g. physician-initiated tapering, switching to another MOUD) were excluded from the analysis, and the remaining reasons for MMT discontinuation were tabulated.

Study Variables

The primary outcome of interest was time to any MMT discontinuation while the secondary outcome was time to MMT discontinuation that could possibly be addressed through policy or guideline changes, which included: missing a dose or being taken off by a healthcare provider; having difficulty accessing a pharmacy; and experiencing cost or affordability barriers. Dependent variable selection was guided by the Risk Environment[26] and Patient-Centered Accessibility[27] conceptual frameworks, and also drew from prior literature examining MMT discontinuation among AYA and adult populations. A number of variables hypothesized to be associated with the outcomes of interest were considered, and include: age (per year older); age of first 'hard' drug use (per year older); sex (male vs. female); self-reported Indigenous identity, defined as First Nations,[28] Inuit,[29] or Métis peoples[30] (Indigenous vs. white), which may act as a proxy for the impacts of anti-Indigenous racism, socioeconomic status, and intergenerational trauma; Other self-reported racialized or ethnic identities, defined as an affirmative response to being Black, South Asian, Chinese, Other Asian, Latinx, Middle Eastern, or other (Other vs. white); moderate to severe depression (yes vs. no), measured using the Centre for Epidemiological Studies Depression scale;[31] child

welfare involvement (yes vs. no); and moderate to severe levels of the following five categories of childhood adverse events – sexual abuse (yes vs. no), physical abuse (yes vs. no), emotional abuse (yes vs. no), physical neglect (yes vs. no), and emotional neglect (yes vs. no) – measured using the Childhood Trauma Questionnaire.[32] Other variables include: MMT initiation period, defined as having initiated MMT before or after the introduction of Methadose™ in the study setting (≥2014 vs. ≤2013);[33] recently living in the Downtown Eastside (DTES) (in the last six months) (yes vs. no), which is an inner-city neighborhood of Vancouver with high levels of poverty and illicit drug use; any injection drug use (yes vs. no); any and recent injection drug use (yes vs. no); non-fatal overdose, defined as an overdose or acute reaction following drug use (yes vs. no) in the last six months;[34] recent daily illicit opioid use (yes vs. no), a combined variable that includes daily injection and non-injection heroin, fentanyl, or non-medical prescription opioid use (NMPOU); recent weekly heroin or fentanyl use (yes vs. no); recent weekly NMPOU (yes vs. no); recent weekly cocaine use (yes vs. no); recent weekly crack cocaine use (yes vs. no); and recent weekly crystal methamphetamine use (yes vs. no). Additional factors included: recent employment (yes vs. no), defined as legal self-employment, regular or temporary work; recent homelessness, defined as sleeping on the street, having no fixed address, staying with friends or staying in a shelter or hostel (yes vs. no); recent incarceration, defined as being in detention, prison or

jail overnight or longer in the past six months (yes vs. no); recent non-pharmacological addiction treatment access, defined as accessing a treatment centre, recovery house, counselor, Narcotics Anonymous, Cocaine Anonymous, Alcoholics Anonymous, Self-Management and Recovery Training, or any other non-pharmacological treatments (yes vs. no); recent difficulty accessing addiction treatment services (yes vs. no); and, recent difficulty accessing health and social services (yes vs. no).

Statistical Analyses

A baseline analysis comparing participants who were retained in MMT to those who discontinued MMT was conducted. Pearson's χ^2 test was employed to compare binary variables and the Mann-Whitney U-test was used to make comparisons for continuous variables. A multivariable extended Cox regression model with time-dependent variables was used among participants who reported initiating MMT at any point over the study period. Given that participants could report multiple MMT initiation and re-initiation events, an extended Cox model allows the analysis to proceed without requiring that the proportional hazard assumption be met.[35]

An initial examination of the bivariate associations between the explanatory variables and our outcome of interest was conducted, and then a full model was built that consisted of all variables that were significant at $p<0.10$. A backwards model selection approach was used whereby explanatory variables with the largest p-values were removed until a reduced model with the lowest Akaike Information Criterion (AIC) was identified. The variance inflation factor was calculated to determine collinearity between variables, which was not present. Previous ARYS studies have described and utilized this approach.[36-38]

A multivariable extended Cox regression sub-analysis was also conducted to identify factors associated with time to potentially 'actionable' MMT discontinuation events. This was defined as MMT discontinuation that could be addressed through policy or clinical guideline changes, and the sub-analysis was restricted to participants who reported discontinuing MMT due to missing a dose or being taken off by a healthcare provider, having difficulty accessing a pharmacy, or experiencing cost or affordability barriers. The same model-building approach was employed as previously described and involved a backwards model selection approach until a reduced model with the lowest AIC was identified. all significance tests were two-sided at a significance level of $p<0.05$, and statistical analyses were conducted using SAS software version 9.4 (SAS, Cary, NC). Study data is not publicly available;

however, and study data can be made available by the corresponding author upon reasonable request.

Results:

Among 696 participants who reported any weekly opioid use within the past six months, 308 (44.3%) participants reported recent MMT during the study period. Participants who had initiated MMT prior to their baseline interview (n=94, 30.5%), were missing data on their MMT status (n=43, 14.0%), or who discontinued MMT due to treatment completion (i.e. tapering) (n= 11, 3.6%) were excluded from the analysis. Of the remaining 160 participants who initiated MMT at some point over the study period, 102 (63.8%) reported discontinuing MMT and contributed 119 unique MMT discontinuation events. The baseline descriptive statistics comparing participants who were retained in MMT to participants who discontinued MMT are provided in Table 1.

Of the MMT discontinuation events, a total of n=33 (27.7%) included an assessment of the reason for discontinuation, while n=86 (72.3%) events occurred between study follow-up periods and participants' reasons for MMT discontinuation were not captured. The primary

reasons for MMT discontinuation were missing doses or being taken off by healthcare provider (n=9), not wanting to take it anymore (n=8) and having difficulty accessing the pharmacy (n=5), with additional reasons listed in Table 2.

Multivariable extended Cox regression was then employed among participants who reported initiating MMT at some point over the study period and who conducted a subsequent follow-up interview (n=137). As demonstrated in Table 3, results demonstrate that time to MMT discontinuation was positively associated with recent weekly crystal methamphetamine use (Adjusted Hazard Ratio (AHR): 1.67, 95% Confidence Interval [CI]: 1.19–2.35). Conversely, older age of first 'hard' drug use (AHR: 0.95, 95% CI: 0.90-1.00) and female sex (AHR=0.66, 95% CI: 1.01–2.28) were negatively associated with MMT discontinuation, after adjusting for age (per year older) (AHR: 0.95, 95% CI: 0.90–1.00), MMT initiation period (≥2014 vs. ≤2013) (AHR=1.10, 95% CI: 0.74–1.64), self-reported Indigenous identity (Indigenous vs. white) (AHR=1.29, 95% CI: 0.88–1.89).

Results from the sub-analysis of factors associated with time to 'actionable' MMT discontinuation are presented in Table 4. Findings indicate that time to 'actionable' MMT discontinuation was positively associated with recent regular crystal methamphetamine use

(AHR: 3.79, 95% CI: 1.46–9.81) and recent regular heroin or fentanyl use (AHR=3.37, 95% CI: 1.21–9.38). However, older age (AHR=0.87, 95% CI: 0.76–0.99) was negatively associated with time to 'actionable' MMT discontinuation, after adjusting for MMT initiation period (≥2014 vs. ≤2013) (AHR=1.84, 95% CI: 0.63–5.35), non-pharmacological treatment access (AHR=1.81, 95% CI: 0.72–4.56), self-reported racialized or ethnic identity (other vs. white) (AHR=1.77, 95% CI: 0.54–5.72), self-reported Indigenous identity (Indigenous vs. white) (AHR=0.93, 95% CI: 0.31–2.76), and ever any injection drug use (AHR=0.39, 95% CI: 0.11–1.38).

Discussion:

Our findings demonstrate that over two-thirds of AYA in the study sample who initiated MMT subsequently discontinued treatment. Given evidence that AYA are retained in MMT for longer durations than other MOUD,[23; 39] the low levels of MMT retention observed in the study setting are concerning. This may be explained by AYAs' views on OAT as a short-term intervention to support their immediate transition off of illicit opioids, as reported in recent qualitative research in the study setting.[18]

Although a majority of participants were not asked for their reason for discontinuing MMT, the reasons for MMT discontinuation described by a sub-sample of participants provide some insight into ways that treatment services may be improved to better meet the needs of AYA. For example, the most common reasons for MMT discontinuation – such as missing doses, being taken off by a care provider, or having difficulty accessing a pharmacy – highlight potential policy and clinical changes that have potential to prevent discontinuation. In the study setting, clinical guidelines stipulate that missing three consecutive doses of MMT that requires patients to re-initiate MMT at a lower dose.[40] Although this is appropriate for individuals who have been abstaining or reducing their overall consumption of opioids, for AYA who missed MMT doses because they were consuming illicit street opioids – which are characterized in the study setting by highly potent, synthetic opioids – re-initiating MMT at a lower dose is likely insufficient to meet their physical dependence and may contribute to MMT discontinuation.

The high levels of treatment discontinuation also point to the need for research into ways to improve MMT retention, including through improvements to existing clinical guidelines. Our finding that missing a dose or being removed by a healthcare provider was the most commonly reported reasons for MMT discontinuation reinforces previous findings that AYA

view the required daily witnessed dispensation of MMT as overburdening and constraining.[18] To address this, there have been suggestions that take-home dosing be expanded for AYA when able to be done safely;[18] however, existing clinical guidelines limit take-home dosing. Given that existing guidelines around missed doses and re-induction were designed at a time when highly potent synthetic opioids were not widespread within the illicit drug supply, it is important that these guidelines are reviewed in the current context – and in light of interim Risk Mitigation Guidelines that improved access to take-home dosing and daily OAT delivery services to promote social distancing in the study setting[41; 42] – to improve MMT retention among AYA.

In addition to the reasons for MMT discontinuation provided, the analyses of factors associated with MMT discontinuation highlight additional ways to improve retention among AYA. Firstly, our finding that female AYA were less likely to discontinue MMT in comparison to male AYA suggests sex- and gender-based differences in treatment retention. This is complemented by evidence that adult women, and especially pregnant people,[43] are retained in MMT for longer durations than men.[44] Given trauma-informed perinatal programming, which prescribes MMT, is accessible within the study setting,[45-48] the negative association between female sex and MMT discontinuation may reflect the availability of

these supports. Alternatively, evidence has found that peer networks significantly influence male AYAs' substance use treatment decision-making compared to female AYA,[49] reiterating the importance of engaging with peer networks to identify ways to improve MMT retention.[50-53] Nevertheless, an AYA-specific gender-based analysis on MMT retention may highlight ways to address gender-based gaps in MMT retention among AYA.

Another important finding was the association between recent crystal methamphetamine use and time to 'actionable' MMT discontinuation. This finding may be due to the increased use of stimulants in order to counteract the negative side effects of MMT (i.e., lethargy, tiredeness, etc.), due to participants' seeking pleasure, or because of the high levels of polysubstance use reported among AYA in comparison to adult populations.[54] Study findings support exploration of novel treatment approaches to address simultaneous opioid and stimulant use among AYA. A potential intervention that has demonstrated some promising results among adults who report polysubstance use is the dual prescription of MOUD alongside prescription stimulants. To date, preliminary research has found that when adequately dosed, the provision of stimulants alongside MOUD reduces both illicit opioid and stimulant use.[55-58] Given the potential benefits of prescribing both prescription opioids

and stimulants to AYA, future research investigating the use of both types of medications and their impact on the health of AYA may be beneficial.

The positive association between recent weekly fentanyl or heroin use and MMT discontinuation also provides some insight into ways to potentially improve the retention of AYAs' in treatment. Firstly, this may be due to AYA receiving an insufficient MMT dose and so increasing their dosage may support reductions in illicit opioid use. Alternatively, AYA who continue to use illicit opioids alongside MMT may benefit from being offered alternative types of OAT, such as slow-release oral morphine or injectable OAT, to reduce their reliance on the illicit drug supply. This is an important step to effectively address physical dependency and reduce overdose risk,[59-61] especially in the context of an increasingly toxic drug supply.

Lastly, the non-statistically significant, positive association between non-pharmacological treatment access and 'actionable' MMT discontinuation is notable and raises concerns that some AYA may be discouraged from continuing MMT when accessing other treatment services. Adding to this, our findings suggest that younger participants are more likely to report 'actionable' MMT discontinuation. This similarly raises concerns of a specific bias or

stigma against prescribing MOUD to adolescents versus young adults, which is reinforced by evidence that adolescent-tailored treatment facilities are significantly less likely to provide MOUD to AYA in comparison to adult facilities.[62-64] Study results signal the importance of further research into stigma towards MMT and other MOUD within non-pharmacological treatment settings, and especially among adolescent populations. Additionally, there may be benefits to implementing protections to ensure access to MOUD for all AYA to address stigma-related barriers to treatment access and continuation.

There are several limitations with the ARYS cohort that have been described previously, including generalizability, unmeasured confounding, and social desirability bias.[65-67] This analysis is additionally limited by the study questionnaire, which did not capture participants' reasons for MMT discontinuation if they discontinued MMT between study follow-up periods. Hence, certain reasons for MMT discontinuation, such as being imprisoned, are expected to be underrepresented in the reasons provided and in the statistical analyses. Conversely, participants could have discontinued MMT between study follow-up periods due to treatment completion (i.e., tapered off of MMT), which could have led to the inclusion of 'treatment completers' within the analytic sample and minimized or conflated the observed associations, or they could have discontinued and re-initiated MMT in the previous six-

months but still have been considered retained in MMT as the questionnaire did not discern this. Another limitation is that some participants may have received both methadone and Methadose™ due to changes MMT provision during the study period and we were therefore unable to account for dosage in this analysis. The sub-analysis is also limited by the small sample size and findings should be interpreted with caution, but this analysis meets sample size requirements[68-70] and provides preliminary insight into ways to address 'actionable' MMT discontinuation. Lastly, the study period for these analyses was restricted to the period before the adoption of clinical guidelines for the treatment of OUD among AYA in the study setting, and so future research investigating the impacts of those clinical guidelines on MMT retention would be valuable.

Conclusion

Consistent with previous research among adults and AYA, this study demonstrated high levels of MMT discontinuation among the study sample, suggesting MMT may be a limited response in the context of a toxic drug crisis. While study findings point to potential opportunities to optimize MMT programming through measures such as providing access to a broader range of MOUD and treatment services and exploring the potential benefits of

providing prescription stimulants to AYA who report polysubstance use, a key implication is that MMT is not sufficient for many AYA. Innovative interventions and ones that center harm reduction remain critical to protecting the health of AYA.

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TABLE 1. Baseline descriptive statistics of adolescents and young adults (AYA) who reported initiating methadone or Methadose maintenance treatment (MMT) stratified by ever reporting MMT discontinuation between December 2005 and June 2018 (n=160).

Characteristic	Total (%) (*n* = 160)	Discontinued MMT		*p* - value
		Yes (%) (*n* = 102)	No (%) (*n* = 58)	
Age (med, Q_1–Q_3)	24 (22 – 27)	24 (22 – 26)	25 (22 – 27)	0.448[i]
Age first drug use (med, IQR)	14 (12 – 15)	13 (12 – 15)	14 (12 – 15)	0.208[i]
MMT Initiation Period (≥2014 vs. ≤2013)	67 (41.9)	33 (32.4)	34 (58.6)	0.001
Sex (female vs. male)	58 (36.3)	32 (31.4)	26 (44.8)	0.089
Indigenous identity (vs. white)	38 (23.8)	26 (25.5)	12 (20.7)	0.410
Other race/ethnicity (vs. white)[a]	11 (6.9)	8 (7.8)	3 (5.2)	0.596[j]
Highschool education (vs. <highschool education)	55 (34.4)	29 (28.4)	26 (44.8)	0.036
Depression[b] (yes vs. no)	65 (40.6)	37 (36.3)	28 (48.3)	0.137
Child welfare involvement (yes vs. no)	84 (52.5)	60 (58.8)	24 (41.4)	0.034
Sexual abuse[c] (yes vs. no)	33 (20.6)	21 (20.6)	12 (20.7)	0.914
Physical abuse[c] (yes vs. no)	47 (29.4)	33 (32.4)	14 (24.1)	0.337
Emotional abuse[c] (yes vs. no)	74 (46.3)	51 (50.0)	23 (39.7)	0.239
Physical neglect[c] (yes vs. no)	51 (31.9)	34 (33.3)	17 (29.3)	0.772
Emotional neglect[c] (yes vs. no)	79 (49.4)	50 (49.0)	29 (50.0)	0.765
Living in the DTES[d, e] (yes vs. no)	76 (47.5)	54 (52.9)	22 (37.9)	0.068
Injection drug use (yes vs. no)	142 (88.8)	88 (86.3)	54 (93.1)	0.297[j]
Injection drug use[d] (yes vs. no)	120 (75.0)	80 (78.4)	40 (69.0)	0.184
Non-fatal overdose[d] (yes vs. no)	22 (13.8)	13 (12.7)	9 (15.5)	0.624
Daily illicit opioid use[d] (yes vs. no)	92 (57.5)	62 (60.8)	30 (51.7)	0.265
Weekly heroin or fentanyl use[d] (yes vs. no)	100 (62.5)	63 (61.8)	37 (63.8)	0.799
Weekly NMPO use[d, f] (yes vs. no)	20 (12.5)	14 (13.7)	6 (10.3)	0.534
Weekly cocaine use[d] (yes vs. no)	16 (10.0)	13 (12.7)	3 (5.2)	0.172[j]
Weekly crack use[d] (yes vs. no)	40 (25.0)	29 (28.4)	11 (19.0)	0.184
Weekly CM use[d, g] (yes vs. no)	58 (36.3)	41 (40.2)	17 (29.3)	0.169
Employment[d] (yes vs. no)	44 (27.5)	22 (21.6)	22 (37.9)	0.026
Homelessness[d] (yes vs. no)	74 (46.3)	48 (47.1)	26 (44.8)	0.786
Incarceration[d] (yes vs. no)	29 (18.1)	19 (18.6)	10 (17.2)	0.827
Non-pharmacological treatment[d, h] (yes vs. no)	55 (34.4)	36 (35.3)	19 (32.8)	0.745
Difficulty accessing treatment[d, h] (yes vs. no)	16 (10.0)	13 (12.7)	3 (5.2)	0.174[j]
Difficulty accessing services[d, i] (yes vs. no)	34 (21.3)	22 (21.6)	12 (20.7)	0.959

a. Other self-reported racialized or ethnic identities include Black, Latinx, and Middle Eastern
b. Refers to moderate or severe depression as measured by the Centre for Epidemiological Studies Depression Scale
c. Refers to child welfare involvement, moderate or severe childhood sexual abuse, physical abuse or neglect, and emotional abuse or neglect as measured by the subscales of the Childhood Trauma Questionnaire
d. Refers to activities in the last six months
e. Denotes the Downtown Eastside
f. Denotes non-medical prescription opioids
g. Denotes crystal methamphetamine
h. Refers to treatments for substance use disorders
i. Refers to health and social services
j. P-value is generated using Mann-Whitney U-test
k. P-value is generated using Fisher's Exact Test because of small cell count

TABLE 2. Reasons for MMT discontinuation among a prospective cohort of street-involved AYA who initiated and discontinued MMT at some point between December 2005 and June 2018 in Vancouver, Canada (n=102, 119 unique discontinuation events).

Reasons for MMT discontinuation (n=119)[a]	Total (n)
Missed doses or taken off by healthcare provider	9
Did not want to take it anymore	8
Difficulty accessing pharmacy	5
Side effects	5
Was not effective or could not find preferred dose	4
Too restrictive	1
Cost or affordability	1

a. A total of n=86 unique MMT discontinuation events occurred between study follow-up visits where participants were not asked to provide a reason for MMT discontinuation.

TABLE 3. Extended bivariate and multivariable Cox proportional hazard model of factors associated with time to MMT discontinuation among street-involved AYA who report initiating MMT between December 2005 and June 2018 (n=137).

	Unadjusted		Adjusted	
Characteristic	**Odds Ratio (95% CI)**	***p* value**	**Odds Ratio (95% CI)**	***p* value**
Age (per year older)	0.96 (0.91 – 1.01)	0.095	0.95 (0.90 – 1.00)	0.057
Age first drug use (per year older)	0.94 (0.90 – 0.99)	0.015	0.95 (0.90 – 1.00)	0.044
MMT Initiation Period (≥2014 vs. ≤2013)	1.13 (0.77 – 1.67)	0.095	1.10 (0.74 – 1.64)	0.626
Sex (female)	0.72 (0.60 – 1.06)	0.095	0.66 (0.44 – 0.99)	0.047
Indigenous identity (vs. white)	1.33 (0.92 – 1.93)	0.135	1.29 (0.88 – 1.89)	0.199
Other race/ethnicity (vs. white)[a]	1.88 (1.04 – 3.39)	0.036	1.80 (1.00 – 3.24)	0.051
Highschool education	0.70 (0.48 – 1.04)	0.075		
Depression[b]	0.67 (0.48 – 0.94)	0.021		
Child welfare involvement	1.27 (0.91 – 1.77)	0.158		
Sexual abuse[c]	1.04 (0.65 – 1.65)	0.883		
Physical abuse[c]	1.28 (0.90 – 1.82)	0.168		
Emotional abuse[c]	0.90 (0.64 – 1.27)	0.539		
Physical neglect[c]	1.40 (0.96 – 2.05)	0.078		
Emotional neglect[c]	0.89 (0.63 – 1.26)	0.511		
Living in the DTES[d, e, f]	1.18 (0.83 – 1.69)	0.348		
Injection drug use	0.79 (0.56 – 1.10)	0.162		
Injection drug use[d, e]	1.01 (0.73 – 1.40)	0.939		
Non-fatal overdose[d, e]	1.17 (0.71 – 1.93)	0.545		
Daily illicit opioid use[d, e]	1.08 (0.76 – 1.55)	0.665		
Weekly heroin or fentanyl use[d, e]	1.19 (0.83 – 1.69)	0.342		
Weekly NMPO use[d, e, g]	0.67 (0.34 – 1.34)	0.259		
Weekly cocaine use[d, e]	0.99 (0.61 – 1.59)	0.958		
Weekly crack use[d, e]	0.82 (0.54 – 1.25)	0.355		
Weekly CM use[d, e, h]	1.47 (1.04 – 2.07)	0.031	1.67 (1.19 – 2.35)	0.003
Employment[d, e]	0.99 (0.63 – 1.54)	0.959		
Homelessness[d, e]	0.83 (0.57 – 1.21)	0.324		
Incarceration[d, e]	1.26 (0.78 – 2.03)	0.341		
Non-pharmacological treatment[d, e, i]	1.03 (0.71 – 1.50)	0.872		
Difficulty accessing treatment[d, e, i]	1.02 (0.52 – 2.00)	0.946		
Difficulty accessing services[d, e, j]	1.04 (0.67 – 1.60)	0.871		

a. Other self-reported racialized or ethnic identities include Black, Latinx, and Middle Eastern
b. Refers to moderate or severe depression as measure by the Centre for Epidemiological Studies Depression Scale
c. Refers to child welfare involvement, moderate or severe childhood sexual abuse, physical abuse or neglect, and emotional abuse or neglect as measured by the subscales of the Childhood Trauma Questionnaire
d. Refers to activities in the last six months
e. Refers to variables that were lagged to the previous study visit
f. Denotes the Downtown Eastside
g. Denotes non-medical prescription opioids
h. Denotes crystal methamphetamine
i. Refers to treatments for substance use disorders
j. Refers to health and social services

TABLE 4. Bivariate and multivariable extended Cox proportional hazard model of factors associated with time to MMT discontinuation that could be addressed through policy change among street-involved AYA who initiated MMT between December 2005 and June 2018 (n=62).

	Unadjusted		Adjusted	
Characteristic	**Odds Ratio (95% CI)**	***p* value**	**Odds Ratio (95% CI)**	***p* value**
Age (per year older)	0.89 (0.80 – 0.99)	0.038	0.87 (0.76 – 0.99)	0.031
Age first drug use (per year older)	0.82 (0.71 – 0.95)	0.010		
MMT Initiation Period (≥2014 vs. ≤2013)	2.31 (0.88 – 6.09)	0.090	1.84 (0.63 – 5.35)	0.262
Sex (female)	0.73 (0.30 – 1.79)	0.490	0.57 (0.22 – 1.59)	0.241
Indigenous identity (vs. white)	1.30 (0.56 – 3.32)	0.548	0.93 (0.31 – 2.76)	0.897
Other race/ethnicity (vs. white)[a]	2.21 (0.76 – 6.40)	0.145	1.77 (0.54 – 5.72)	0.343
Highschool education	0.78 (0.33 – 1.82)	0.567		
Depression[b]	0.86 (0.38 – 1.97)	0.721		
Child welfare involvement	1.65 (0.74 – 3.67)	0.219		
Sexual abuse[c]	0.67 (0.21 – 2.11)	0.494		
Physical abuse[c]	1.87 (0.87 – 4.02)	0.109		
Emotional abuse[c]	0.94 (0.39 – 2.27)	0.898		
Physical neglect[c]	2.57 (1.15 – 5.77)	0.022*		
Emotional neglect[c]	1.33 (0.58 – 3.08)	0.499		
Living in the DTES[d, e, f]	0.83 (0.38 – 1.82)	0.636		
Injection drug use	0.37 (0.15 – 0.91)	0.031	0.39 (0.11 – 1.38)	0.145
Injection drug use[d, e]	1.86 (0.69 – 5.04)	0.220		
Non-fatal overdose[d, e]	1.80 (0.68 – 4.72)	0.234		
Daily illicit opioid use[d, e]	2.11 (0.87 – 5.11)	0.097		
Weekly heroin or fentanyl use[d, e]	4.14 (1.56 – 11.0)	0.004	3.37 (1.21 – 9.38)	0.020
Weekly NMPO use[d, e, g]	1.80 (0.49 – 6.57)	0.376		
Weekly cocaine use[d, e]	0.52 (0.07 – 3.84)	0.522		
Weekly crack use[d, e]	0.21 (0.03 – 1.48)	0.117		
Weekly CM use[d, e, h]	3.47 (1.50 – 8.05)	0.004	4.61 (1.78 – 11.9)	0.002
Employment[d]	0.93 (0.37 – 2.32)	0.871		
Homelessness[d]	1.89 (0.87 – 4.14)	0.110		
Incarceration[d]	2.15 (0.76 – 6.06)	0.148		
Non-pharmacological treatment[d, i]	1.99 (0.91 – 4.36)	0.085	1.81 (0.72 – 4.56)	0.205
Difficulty accessing treatment[d, i]	0.71 (0.09 – 5.76)	0.752		
Difficulty accessing services[a, j]	0.87 (0.32 – 2.38)	0.781		

a. Other self-reported racialized or ethnic groups include Black, Latinx, and Middle Eastern
b. Refers to moderate or severe depression as measure by the Centre for Epidemiological Studies Depression Scale
c. Refers to child welfare involvement, moderate or severe childhood sexual abuse, physical abuse or neglect, and emotional abuse or neglect as measured by the subscales of the Childhood Trauma Questionnaire
d. Refers to activities in the last six months
e. Refers to variables that were lagged to the previous study visit
f. Denotes the Downtown Eastside
g. Denotes non-medical prescription opioids
h. Denotes crystal methamphetamine
i. Refers to treatments for substance use disorders
j. Refers to health and social services