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CANNABIS USE IS ASSOCIATED WITH LOWER RATES OF INITIATION OF INJECTION DRUG USE AMONG STREET-INVOLVED YOUTH: A LONGITUDINAL ANALYSIS

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Abstract

Introduction and Aims—Street-involved youth are known to be at elevated risk of initiating injection drug use. However, the impact of so-called 'gateway' drugs, such as cannabis, on injection initiation is unknown. The objective of this study was to examine the association between cannabis use and initiation of injection drug use among a prospective cohort of street-involved youth in Vancouver, Canada.

Design and Methods—Data for this study were collected from the At-Risk Youth Study. From September 2005 to May 2015, participants aged 14–26 who reported illicit drug use were recruited into this open prospective cohort study. An extended Cox regression model with time-updated covariates was used to identify factors independently associated with injection initiation.

Results—During the study period, 481 street-involved youth were included in this study. Of these, 228 (47.4%) reported at least daily cannabis use, and 103 (21.4%) initiated injection drug use. In a multivariable analysis, >daily cannabis use was associated with slower rates of injection initiation (adjusted relative hazard 0.66, 95% confidence interval 0.45–0.98; P = 0.038). Sub-analyses revealed that cannabis use was negatively associated with initiation of injection stimulants but not initiation of injection opioids.

Discussion and Conclusions—Given the expansion of cannabis legalisation throughout North America, it is encouraging that cannabis use was associated with slower time to initiation of injection drug use in this cohort. This finding challenges the view of cannabis as a gateway substance that precipitates the progression to using harder and more addictive drugs.

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CONFLICT OF INTEREST

None to declare.

INTRODUCTION

Injection drug use is an important risk factor for numerous adverse medical, social and legal outcomes, including HIV and hepatitis C acquisition and transmission, accidental fatal overdose, stigmatisation and criminalization [1–3]. Among illicit drug users, street-involved youth are at elevated risk to initiate injection drug use, which can be partially attributed to increased exposure to drug market activity and the age-linked stress associated with changing economic responsibilities and social roles that occur in this developmental period [4, 5]. Previous studies have found the average age of injection initiation to be between 19 and 23years [6, 7]. Once youth initiate injecting, the majority have been found to quickly progress to regular injecting and experience greater drug-related harm than older and more established people who use injection drugs [8–10]. Specifically, young and recently initiated people who inject drugs are more likely to engage in high-risk drug use practices such as needle sharing and binging [11, 12]. As a result, young people who inject drugs display an increased risk of infectious disease transmission and overdose. Indeed, drug injection is an independent predictor of mortality among this population [9, 13–15]

Risk factors for injection initiation include both structural factors, such as homelessness, unemployment and inability to access addiction treatment, as well as several individual-level exposures [16–19]. For example, experiencing childhood trauma and specific drug use patterns, such as binging and polysubstance use, have been identified as predictors of injection initiation among at-risk youth [17–19]. Additional evidence indicates that the use of specific drugs including crack, powder cocaine, crystal methamphetamine have been linked to greater risks of injection initiation [6, 20, 21]

The so-called gateway hypothesis, or the belief that certain forms of drug use promote progression to using ‘harder’ illicit drugs, has been the subject of much debate [22–25]. Supporters of this theory suggest that substance use escalates from tobacco and alcohol to cannabis, with cannabis use facilitating the transition from licit substances to illicit drugs such as cocaine and heroin [23, 26]. The three specific assertions of the gateway hypothesis are: (i) that few individuals use so-called hard drugs (e.g. heroin and cocaine) without initially experimenting with gateway substances such as cannabis and tobacco; (ii) that drugs earlier in the sequence increase the risk of more serious substance use; and (iii) that the relationship between earlier gateway drugs and subsequent drug use is causal. Several epidemiological studies have supported the gateway sequence, including a 25-year longitudinal study of adolescents, which have reported that cannabis use was significantly associated with the use of other illicit drugs and illicit drug abuse [22, 25]. Despite this evidence, many authors contend that this progression may be attributed to psychosocial, genetic and environmental determinants of drug use rather than causal effects of so-called gateway substances [22, 24, 25]. Detailed examination of proposed gateway substances, particularly cannabis, is needed owing to the liberalisation of cannabis policies in many settings in the Americas. Furthermore, cannabis remains the most-frequently used illicit substance globally and the possible health-related benefits and potential harms, including gateway effects, associated with cannabis use will be important to inform future regulation systems and both clinical and public health practice [45]. Although a wealth of studies have investigated the gateway hypothesis, the impact of so-called gateway drugs on the initiation of high-risk drug use

behaviours, such as injecting, has not been fully evaluated. Given the high risk of injection-related harm among recently initiated young injectors, as well as intense scrutiny of the possible impacts of cannabis on youth health in general, we sought to examine the impact of frequent cannabis use on rates of injection initiation among a prospective cohort of at-risk youth and young adults in Vancouver, Canada, between September 2005 and May 2015 [9, 13–15, 27]. To build on the existing research in this area, we also conducted sub-analyses to examine the distinct effects of cannabis use on both stimulant and opioid injecting.

METHODS

The data for this investigation were collected from the At-Risk Youth Study (ARYS) in Vancouver, Canada. This ongoing open prospective cohort was established in 2005 and has been described in detail previously [28]. Briefly, recruitment was performed through snowball sampling and extensive street outreach. Participants were eligible for enrolment if they were aged 14–26years at the time of recruitment, had used illicit drugs (other than or in addition to cannabis) in the past 30 days and provided written informed consent. Previous studies of this cohort have reported a high prevalence of non-injection (cocaine: 49%, heroin: 16%, cannabis: 98%) and injection drug use (40%) [20]. Data related to drug use behaviours, including injection drug use, was collected through an interviewer-administered questionnaire at baseline and semi-annually over follow up. At each study visit participants were remunerated $30 CAD to compensate for their time. The University of British Columbia’ s Research Ethics Board has approved the ARYS.

In this study, we included all participants who were injection-naïve at baseline and completed at least one follow-up visit over the study period (September 2005 to May 2015). The primary outcome of interest was the first report of any injection drug use. We defined the date of initiation as the midpoint between the last report of non-injection drug use and the first report of using a needle to inject drugs. The primary explanatory variable of interest was daily cannabis use in the last 6 months. Sociodemographic and drug use variables with the potential to confound the association between cannabis use and injection initiation were also included in the analysis. These variables included gender (non-male vs. male), age (per year older), ethnicity (white vs. other), non-injection cocaine use (yes vs. no), crack smoking (yes vs. no), non-injection crystal methamphetamine use (yes vs. no) and non-injection heroin use (yes vs. no). All drug use variables were treated as time-updated covariates based on semi-annual follow-up visits.

The relationship between cannabis use and injection initiation was first assessed by calculating the incidence density of injection initiation using a Poisson model. The cumulative hazard of injection initiation from the time of study enrolment stratified by cannabis use was calculated using Kaplan–Meier methods. After estimating the unadjusted relative hazards and 95% confidence intervals (CI) for factors associated with injection initiation, an a priori multivariate model building protocol was applied to an extended Cox regression model. As a first step, a full multivariable model including all variables was constructed. The final model was developed by removing one covariate at a time from the full model that produced the smallest relative change in the cannabis use coefficient. This process was repeated in a manual stepwise manner until the minimum change in the

cannabis use coefficient exceeded 5%. The purpose of this strategy is to retain covariates with a greater relative impact on the association between the primary explanatory variable and the outcome [29]. A sub-analysis was also conducted to compare the impact of cannabis use on the initiation of injection opiates and the initiation of injection stimulants. Since the amount of missing data for the predictor variables was very low (0.17%−0.51%), these values were excluded from the analysis. For the outcome of injection initiation, 67.3% of the participants only missed one follow-up visit and since we used time-updated covariates, the values for the missing follow-up visits were imputed using the next most recent follow-up information. All statistical analyses were performed using SAS software version 9.3 (SAS, Cary, NC, USA) and all tests of significance were two-sided.

RESULTS

A total of 1215 street-involved youth enrolled in the ARYS cohort during the study period, of whom 684 (56%) were injection-naïve at the time of recruitment. During the study period, the average yearly loss to follow-up rate among these participants was 2.75%. By the end of study period, a total of 481 youth who were injection-naïve at baseline completed at least one follow-up visit and were therefore eligible for the current analysis. The excluded participants did not differ significantly from the eligible participants in terms of gender (P =0.784), but they were more likely to be Caucasian (P = 0.001) and older in age (P = 0.001). Among the 481 participants included in the current study, the median observation time per participant was 21.9 months (interquartile range, IQR = 12.2–43.2) and participants completed a median of four study visits (IQR = 2–6). The median time between study visits was 6.2 months (IQR= 5.7–8.0).

At baseline, the median age of the participants was 21.5 (IQR= 19.5–23.2) years, 333 (69.2%) were male, and 228 (47.4%) participants reported at least daily cannabis use (Table 1). During the study period, 103 (21.4%) participants reported initiating injection drug use, resulting in an incidence density of 8.3 events per 100 person-years (95% confidence interval, CI 6.8–10.1). From study enrolment, the median time to injection initiation was 13.0 months (IQR = 4.0–27.7). The cumulative incidence rate was not significantly different among those who reported daily cannabis use at baseline compared to those who did not (log-rank P = 0.521). The proportion of baseline daily cannabis users who initiated injection drug use over follow up was 48.5% compared to 49.5% among those who did not report daily cannabis use at baseline.

The unadjusted and adjusted relative hazards (ARH) of injection initiation are presented in Table 2. At least daily cannabis use (ARH 0.66, 95% CI 0.45–0.98; P = 0.038) was protective against injection initiation in the adjusted analysis. Other drug use variables associated with injection initiation included crack smoking (ARH 2.53, 95% CI 1.69–3.77; P < 0.001) and crystal methamphetamine use (ARH 3.66, 95% CI 2.46–5.46; P < 0.001). A sub-analysis revealed that at least daily cannabis use was protective against the initiation of stimulant injecting (relative hazards 0.55, 95% CI 0.33–0.92; P = 0.021), but the association was not significant for initiation of opioid injecting (relative hazards 0.71, 95% CI 0.44–1.15; P = 0.166) (Table 3).

DISCUSSION

In the present study, we observed a high rate of injection initiation among at-risk street-involved youth. Our results indicate that periods of frequent cannabis use were associated with slower rates of initiation: daily cannabis use was associated with a 34% decrease in the hazard rate of injection initiation. Sub-analyses revealed that this association was mainly driven by protecting against initiation of stimulant injection. No association between frequent cannabis use and opioid injection initiation was found. The decreased rate of injection initiation among frequent cannabis users challenges the claim of the gateway hypothesis that there is a causal link between cannabis use and initiation of subsequent so-called hard drug use.

To our knowledge, only two studies have previously analysed how cannabis use influences injection initiation among youth and young adults and these have reported conflicting results [6, 30]. The first study was conducted in Baltimore, Maryland and found that cannabis use in the previous 2 years was positively associated with injection initiation [6]. Conversely, the second study found that among youth in Vancouver, Canada, cannabis use was associated with a decreased risk of injection initiation [30]. To explain this association, the authors speculate that cannabis users may represent a distinct subpopulation of young drug users who are uninterested in injection drug use based on the risk associated with injecting [30]. Qualitative evidence from street youth living in Montreal also indicate that certain groups avoid the use of ‘hard’ drugs, including cocaine and heroin, due to concerns about addiction, dependence and the risk of these drugs interfering with life goals [31]. It is possible that a portion of the cannabis users in the ARYS cohort may reflect this characterisation and seek out ‘softer’ drugs that are assumed to carry less risk of dependence [30]. It is also important to acknowledge that cannabis use was defined as at least daily use in this study and less frequent cannabis use may not have the same impact on injection initiation.

Although previous studies suggest that cannabis use is a high-risk behaviour that increases the risk of using other illicit drugs, it is encouraging that cannabis use did not increase the risk of injection initiation in this study. There is evidence to suggest that the impact of cannabis use on subsequent drug use behaviours may be moderated by additional exposures including environmental, psychosocial and genetic risk factors [24, 32, 33]. An analysis of nationally representative data from 17 countries (N > 85 000) demonstrated that the association between cannabis use and subsequent illicit drug use was weaker in countries with higher rates of cannabis use, suggesting that drug use progressions may be moderated by drug prevalence and social acceptability of certain substances [33, 34]. This pattern is believed to reflect differences in social norms, whereby use of less accessible drugs reflects a marker of ‘deviance’ more so than highly prevalent substances [34]. These studies suggest that drug prevalence may moderate the association between use of a specific substance, such as cannabis, and more extreme subsequent drug use patterns such as injecting [34]. In line with this theory, data from Statistics Canada revealed that the prevalence of past year cannabis use among a household population aged 15 years and older in Vancouver (14.3%) is second only to Nova Scotia (15.7%) within Canada. Therefore, cannabis use in this setting may be less likely to be regarded as a deviant behaviour, and in turn this may reduce the risk of progressing to more severe drug use [35]. In the Netherlands, where cannabis use is highly

prevalent, cannabis users are far less likely to initiate use of other illicit substances compared to the United States where cannabis use is less common [33]. Twin and adoption studies have also indicated that drug use behaviours across substances may have common genetic influences that increase disinhibited drug use behaviours [32, 36, 37]. These findings have led some authors to contend that the gateway sequence is a 'progression of convenience' that reflects drug accessibility, drug prevalence, individual predisposition and social acceptability of cannabis use, rather than a causal relationship between cannabis use and successive drug use [32, 36, 38]. Cannabis may precede 'harder' drug use since it is more socially accepted, more common and represents a less extreme deviant behaviour compared to using other substances such as those that are commonly injected [36, 38]

There is some biological plausibility for our finding that cannabis was associated with slower rates of initiation of injection stimulants. The two primary cannabinoids in cannabis, Δ9 tetrahydrocannabinol and cannabidiol (CBD), have been shown to reduce measures of cocaine-induced cravings in rat models [39]. These findings suggest that cannabis use may have beneficial effects by reducing intensity of stimulant use or reducing drug cravings associated with stimulant use. However, caution should be exercised when applying findings from rodent models to humans, and this was the first study to report this association. It should also be noted that the concentration of CBD in confiscated cannabis has remained low, although the concentration does vary based on region, season, quality and type of cannabis product [40, 41]. Our findings, along with the absence of any pharmacotherapies for the treatment of stimulant use disorders, lends further support to recent calls for experimental trials in humans to investigate the therapeutic potential of cannabinoids for crack-cocaine use [42]. While we did not observe a significant association between at least daily cannabis use and initiation of opioid injecting, there is evidence supporting cannabis use to reduce drug craving among heroin users [43, 44]. Two pilot trials in humans demonstrated that single doses of 400 or 800 mg of CBD over three consecutive days effectively decreased cue-induced craving, general craving and anxiety among heroin-dependent users that persisted for up to 7 days [43, 44]. Based on this preliminary evidence, the potential role of cannabinoids for the treatment of stimulant and opioid use disorder warrants further investigation.

Strengths of this study include the prospective repeated-measures design. This approach permitted the analysis of multiple independent risk factors for injection initiation that were time-updated during a 9 year and 8 month study period. This study also has limitations. Since ARYS represents a high-risk population of street-involved youth and is not a random sample, these findings may not be generalisable to non-marginalised young people who use drugs from the general population. Although the reliability and validity of self-reported drug use measures has been demonstrated previously, socially desirable reporting of stigmatised and criminalised behaviours, and recall error remain concerns. We were also unable to assess the age of initiation for cannabis use and other illicit substances, which may have an important influence on the associations we identified. Although the amount of missing data in this analysis was low, we acknowledge that the imputation for missing values may have influenced the results. The observational study design also creates the potential for residual confounding to influence the association between cannabis use and injection initiation.

In summary, we prospectively analysed injection initiation among 481 participants in a longitudinal cohort of street-involved youth in Vancouver, Canada and found that frequent cannabis use was negatively associated with injection initiation. Sub-analyses revealed that this effect was restricted to the initiation of stimulant injecting and there was no significant effect of cannabis use on the initiation of opioid injecting. Given the disproportionate harm experienced by youth who inject drugs, it is encouraging that cannabis use did not increase the risk of injection initiation in a setting with a high prevalence of cannabis use [35]. With the legalisation of cannabis use continuing to expand throughout North America and intense debates over the possible impacts of cannabis on youth health, future studies analysing the impact of cannabis use on high-risk drug behaviours are needed to address other potential concerns surrounding these policies.

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Table 1.

Baseline characteristics stratified by injection initiation during follow-up among street-involved youth (*n* = 481)

	Injection initiation			
	Yes (*n* = 103), *n* (%)	**No (*n* = 378), *n* (%)**	**Odds ratio, HR (95% CI)**	***P*-value**
Daily cannabis use[a,b]				
Yes	50 (48.5)	178 (47.1)	1.10 (0.71–1.70)	0.682
No	51 (49.5)	199 (52.6)		
Age (HR per additional year)				
Median	21.4	21.5		0.762
IQR	(19.7–22.7)	(19.5–23.4)		
Caucasian ethnicity				
Yes	70 (68.0)	229 (60.6)	1.38 (0.87–2.19)	0.171
No	33 (32.0)	149 (39.4)		
Female gender				
Yes	30 (29.1)	118 (31.2)	0.91 (0.56–1.46)	0.684
No	73 (70.9)	260 (68.8)		
Heroin use[a,b,c]				
Yes	26 (25.2)	56 (14.8)	1.98 (1.17–3.37)	**0.010**
No	74 (71.8)	316 (83.6)		
Cocaine use[a,b,c]				
Yes	47 (45.6)	183 (48.4)	0.91 (0.59–1.42)	0.686
No	54 (52.4)	192 (50.8)		
Crack smoking[a,b]				
Yes	72 (69.9)	199 (52.6)	2.18 (1.36–3.52)	**0.001**
No	29 (28.2)	175 (46.3)		
Crystal methamphetamine use[a,b,c]				
Yes	53 (51.5)	132 (34.9)	2.06 (1.32–3.22)	**0.001**
No	47 (45.6)	241 (63.8)		

[a]Activities in the 6 months prior to follow-up interview.

[b]Refers to the activities lagged to the pervious available study follow up.

[c]Non-injection use.

P-values based on Wald test. Not all cells add up to 462 as participants may choose not to answer sensitive questions.

CI, confidence interval; HR, hazard ratio; IQR, interquartile range, bold text refers to *P*-values <0.05.

Table 2.

Extended Cox analysis of factors associated with injection initiation among street-involved youth (n = 481)

Characteristic	Unadjusted and adjusted Cox regression analysis			
	Unadjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
Daily cannabis use[a]				
Yes	0.75 (0.51–1.11)	0.148	0.66 (0.45–0.98)	**0.038**
No				
Age (HR per additional year)				
Median	0.98 (0.92–1.05)	0.613		
IQR				
Caucasian ethnicity				
Yes	1.36 (0.90–2.05)	0.140		
No				
Female gender				
Yes	0.99 (0.64–1.51)	0.953		
No				
Heroin use[a,b]				
Yes	3.35 (2.14–5.26)	**<0.001**		
No				
Cocaine use[a,b]				
Yes	1.08 (0.71–1.65)	0.728		
No				
Crack smoking[a]				
Yes	2.61 (1.75–3.91)	**<0.001**	2.53 (1.69–3.77)	**<0.001**
No				
Crystal methamphetamine use[a,b]				
Yes	3.70 (2.48–5.51)	**<0.001**	3.66 (2.46–5.46)	**<0.001**
No				

[a] Activities in the 6 months prior to follow-up interview.

[b] Denotes non-injection use.

CI, confidence interval; HR, hazard ratio; IQR, interquartile range, bold text refers to *P*-values <0.05.

Table 3.

Sub-analysis of factors associated with injection initiation split by opioid injection initiations vs. stimulant injection initiations

Characteristic	Stimulant injection initiations (*n* = 64)		Opiate injection initiations (*n* = 66)	
	Adjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
Daily cannabis use[a]				
Yes	0.55 (0.33–0.92)	**0.021**	0.71 (0.44–1.15)	0.166
No				
Age (HR per additional year)				
Median				
IQR				
Caucasian ethnicity				
Yes				
No				
Female gender				
Yes				
No				
Heroin use[a,b]				
Yes				
No				
Cocaine use[a,b]				
Yes				
No				
Crack smoking[b]				
Yes	2.31 (1.41–3.77)	**<0.001**	2.52 (1.53–4.15)	**<0.001**
No				
Crystal methamphetamine use[a,b]				
Yes	7.73 (4.33–13.77)	**<0.001**	2.22 (2.46–5.46)	**0.001**
No				

[a]Activities in the 6 months prior to follow-up interview.

[b]Non-injection use.

CI, confidence interval; HR, hazard ratio; IQR, interquartile range, bold text refers to *P*-Values <0.05.