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Factors Associated with Willingness To Participate in a Pharmacologic Addiction Treatment Clinical Trial Among Illicit Drug Users

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Abstract

Background and Objectives—Although new medications are needed to address the harms of drug addiction, rates of willingness to participate in addictions treatment trials among people who use drugs (PWUD) have not been well characterized.

Methods—One thousand twenty PWUD enrolled in two community-recruited cohorts in Vancouver, Canada, were asked whether they would be willing to participate in an addiction treatment trial. Logistic regression was used to identify factors independently associated with a willingness to participate.

Results—Among the 1,020 illicit drug users surveyed between June 1, 2013 and November 30, 2013, 58.3% indicated a willingness to participate. In multivariate analysis, factors independently associated with a willingness to participate in an addiction treatment trial, included: daily heroin injection (Adjusted Odds Ratio [AOR] = 1.75 [95% Confidence Interval [CI]: 1.13 – 2.72]); daily crack smoking (AOR = 1.81 [95% CI: 1.23 – 2.66]); sex work involvement (AOR = 2.22 [95% CI: 1.21 – 4.06]); HIV seropositivity (AOR = 1.49 [95% CI: 1.15 – 1.94]); and methadone maintenance therapy participation (AOR = 1.77 [95% CI: 1.37 – 2.30]).

Discussion and Conclusions—High rates of willingness to participate in an addiction treatment trial were observed in this setting. Importantly, high-risk drug and sexual activities were positively associated with a willingness to participate, which may suggest a desire for new treatment interventions among illicit drug users engaged in high-risk behaviour.

Scientific Significance—These results highlight the viability of studies seeking to enroll representative samples of illicit drug users engaged in high-risk drug use.

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Declaration of Interest:

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

INTRODUCTION

Addiction medicine is a rapidly expanding area of clinical practice and medical research. The United States National Institutes of Health (NIH) estimated that in 2013, over 4.1 billion dollars were spent on substance abuse research in the U.S.[1] An active area in this field is the development and testing of new medications to treat problematic drug use. In the past few years, methadone, buprenorphine and naltrexone (including extended release formulations) have been extensively examined for the treatment of opioid use disorders and have all emerged as effective treatment options.[2–5] These medications have been shown to decrease illicit opioid use, and to varying degrees decrease several of the health and social harms associated with opioid addiction, such as human immunodeficiency virus (HIV) transmission and risk behaviors, hepatitis C virus transmission, risky sexual practices and arrest and imprisonment.[2,4–12] Unfortunately, current pharmacologic treatment options for stimulant dependence (e.g., cocaine and amphetamine type stimulants) are lacking [13–16], and evidence-based therapies are desperately needed to reduce the health and social harms associated with stimulant use.[17,18]

The National Institute on Drug Abuse (NIDA) has developed the Clinical Trials Network in an attempt to provide rigorous testing of new addiction pharmacotherapies.[19] However, NIDA studies have generally recruited research participants from community treatment programs, suggesting that out-of-treatment drug users may be underrepresented in treatment studies to date. Recruiting out-of-treatment patients for clinical trials may be challenging as they may have little interaction with the health care system, may distrust medical practitioners and researchers and/or research, or may have co-morbid medical or psychiatric conditions that preclude them from research participation.[20–22] There is also the issue of excluding willing research subjects from studies where presumed non-compliance may result in them not being enrolled in clinical trials.[23]

Since little is known regarding willingness to participate or factors associated with willingness to participate in pharmacologic addictions treatment trials among community recruited samples of drug users, the present study was conducted with a cohort of persons who use illicit drugs to assess the prevalence of willingness to participate, and factors associated with willingness to participate in a randomized control trial (RCT) for addiction treatment.

METHODS

Data for this study were derived from the Vancouver Injection Drug Users Study (VIDUS), and AIDS Care Cohort to Evaluate Access to Survival Services (ACCESS), open prospective cohorts of HIV-seronegative individuals (VIDUS) who inject drugs, or HIV-seropositive individuals (ACCESS) who use illicit drugs, in Vancouver, Canada. The design of both studies has previously been described in detail.[17,24] Briefly, participants were eligible for the study if they were 18 years or older, injected or used illicit drugs other than marijuana within the past month, resided in the Greater Vancouver Region, and provided written informed consent. Participants were recruited through extensive street-based outreach methods and snowball sampling beginning in May 1996. At baseline and every six

months thereafter, participants completed an interviewer-administered questionnaire that elicited information regarding socio-demographic characteristics, drug use, HIV risk behaviours and addiction treatment utilization. Participants received $20 CAD remuneration for each visit. Both the VIDUS and ACCESS studies recruitment and follow up procedures are identical, with the exception of questions specific to HIV infection in the ACCESS questionnaire, so as to enable pooled analyses. Both the VIDUS and ACCESS studies were approved by the Research Ethics Board of Providence Health Care/University of British Columbia.

For the primary analysis, a new question was added to the questionnaire in June 2013, and responses to the question were gathered from June 1, 2013 to November 30, 2013. The question assessed whether participants were willing to participate in an RCT for drug treatment by asking, “If a new medication was being developed that might help you cut down on your drug use, would you be interested in enrolling in a clinical trial to test it? You would be regularly assessed by an addiction doctor and would provide urine samples for drug testing.” The definition of an RCT was provided, if needed to ensure understanding, and participants could answer “yes” or “no” and a follow up question for those responding “no” provided several response options inquiring about the reasons for their negative response. Participants who answered, “yes” were compared to those who answered “no” on *a priori* selected demographic, behavioural and drug use variables, hypothesized to be associated with a willingness to participate based on previous research.[25,26] These variables included: age (per year older); female gender (yes vs. no); ethnicity (Caucasian vs. other); daily heroin injection (yes vs. no); daily cocaine injection (yes vs. no); daily crack smoking (yes vs. no); homelessness (yes vs. no); involvement in sex work, defined as exchanging sex for money, gifts, food, shelter, clothes, drugs or other (yes vs. no); HIV seropositivity (yes vs. no); participation in methadone maintenance therapy (MMT) (yes vs. no); or participation in drug treatment, defined as alcohol and/or drug treatment other than MMT (yes vs. no). All behavioural and drug risk characteristics refer to the six-month period prior to the interview. All variable definitions were identical to those used extensively in prior analyses.[27,28]

We used bivariate and multivariate logistic regression analyses to determine factors associated with the willingness to participate in an RCT. To adjust for potential confounding and identify the independent correlates of willingness to participate in an RCT, only variables that had a p-value < 0.10 in the bivariate analyses were considered in the full multivariate model. Using the backwards model selection procedure, we constructed the final multivariate model with the best fit, as indicated by the lowest AIC value.[29] All statistical analyses were performed using the SAS software version 9.3 (SAS, Cary, NC, USA). All p-values are two sided.

RESULTS

Between June 1, 2013 and November 30, 2013, observations from 1,020 VIDUS and ACCESS participants were included in the present analysis. Among these individuals, median age was 48 years (Inter-quartile range [IQR]: 42 – 54), 345 (33.8%) were female and 576 (56.5%) were Caucasian. Of the 1,020 participants recruited into VIDUS and ACCESS,

595 (58.3%) indicated a willingness to participate in an RCT. As shown in Table 1, the following behavioural and drug risk characteristics were significantly associated with a willingness to participate: daily heroin injection (Odds Ratio [OR] = 1.97 [95% Confidence Interval [CI]: 1.30 – 3.00]); daily crack smoking (OR = 2.20 [95% CI: 1.51 – 3.20]); homelessness (OR = 1.53 [95% CI: 1.03 – 2.26]); sex work (OR = 2.84 [95% CI: 1.58 – 5.09]); HIV seropositivity (OR = 1.34 [95% CI: 1.04 – 1.73]); and MMT participation (OR = 1.74 [95% CI: 1.35 – 2.24]) (all *p-value* < 0.05).

The results of the multivariate analysis are presented in Table 2. The following factors were significantly and independently associated with a willingness to participate in an RCT: daily heroin injection (Adjusted Odds Ratio [AOR] = 1.75 [95% CI: 1.13 – 2.72]); daily crack smoking (AOR = 1.81 [95% CI: 1.23 – 2.66]); sex work involvement (AOR = 2.22 [95% CI: 1.21 – 4.06]); HIV seropositivity (AOR = 1.49 [95% CI: 1.15 – 1.94]); and MMT participation (AOR = 1.77 [95% CI: 1.37 – 2.30]).

DISCUSSION

In the present study, we found high rates of willingness to participate in a pharmacologic addiction treatment RCT among a community-recruited cohort of illicit drug users. We also found that willingness to participate was significantly associated with daily heroin injection, daily crack smoking, sex work involvement, HIV seropositivity and MMT participation. To our knowledge, this is the first study to examine willingness to participate in a pharmacologic addictions treatment RCT among a community-recruited sample of illicit drug users.

Although there is a paucity of research regarding willingness to participate in pharmacologic addictions treatment trials, a body of literature exists regarding drug users willingness to participate in HIV and hepatitis C trials.[24,30–34] In a cohort of injection drug users, 56% were willing to participate in an HIV vaccine trial.[34] Among young injection drug users surveyed to participate in a hepatitis C vaccine study, 67% and 43% were willing to participate in a 1 and 4-year study, respectively.[31] Taken together, these numbers are comparable to the rates observed in our study (58.3%). Fry et al showed that motivations for research involvement among drug users was multi-dimensional, and included economic gain, altruism, activism and information seeking, among others.[32]

Our study found that daily injection heroin use and non-injection crack cocaine use were associated with willingness to participate in a pharmacologic addiction treatment RCT. This is similar to a study by Miller et al, which found that frequent heroin injection among injection drug users was associated with a willingness to participate in a heroin prescription program.[26] This may reflect that active daily users have failed other pharmacologic treatment options and are interested in exploring new therapies. Although several pharmacologic options already exist for the treatment of opioid addiction, including methadone, buprenorphine, and extended release naltrexone,[2,4,5,7,8,35] these options do not sustain abstinence in all users,[36] necessitating continued research into new medications and different formulations of existing ones. No approved pharmacologic treatment options presently exist for stimulant use disorders[14–16] and it is therefore unsurprising that

individuals engaged in frequent crack-cocaine use would be eager to participate in drug treatment trials. Developing new medical treatments for stimulant addiction, including crack-cocaine, is a major public health priority given the health and social harms associated with crack-cocaine use.[37–40] It is therefore encouraging that these individuals are willing to participate in new trials.

In our study, HIV seropositivity was associated with a willingness to participate. Increasing enrollment of HIV positive persons from vulnerable populations into clinical trials is a current priority of HIV research.[41,42] This focus may increase the likelihood that HIV positive persons are willing to participate in other types of clinical trials. It is also possible that their frequent contact with the health care system, or enrollment in previous HIV medicine trials, makes them amenable to participating in addiction treatment RCTs. Doab *et al.* showed that illicit drug users who were trial experienced had better understanding of clinical trial concepts and were more likely to find those concepts acceptable.[33] Whether previous participation in an RCT makes individuals more, or less willing to participate in subsequent trials is an area of potential future research.

While we have identified subgroups of illicit drug users that may be more likely to participate in RCTs, developing specific recruitment strategies is beyond the scope of the current analysis. This will be an important area of research as pharmacologic addictions treatment RCTs move forward. As well, developing effective treatments for illicit drug users at varying levels of drug use intensity remains an important priority. Future RCTs could prioritize recruiting participants across varying levels of use, and different strategies may be needed for each group. Illicit drug users remain a heterogeneous group and having a diverse sample to participate in RCTs would increase the generalizability of new pharmacotherapies found to be effective.

This study has limitations. As our study sample was generated through street-based recruitment methods, generalizing our findings to other populations of illicit drug users requires caution. However, it is noteworthy that the cohort demographics are similar to other local and international studies of injection drug users [43–46]. Secondly, as our outcome of interest was willingness to participate in a hypothesized trial it is possible that recruitment into an actual clinical trial may result, as in previous research, in lower levels of willingness to participate [47]. However, a recent study among participants in the VIDUS cohort found that reported willingness measures predicted subsequent use of a safe injecting facility, and that measures of willingness measures in this population were a valid tool [25]. The development of several new addiction treatment RCTs in the study area will allow us to determine whether a difference exists between hypothesized and actual recruitment. Thirdly, socially desirable responding is a concern in studies of marginalized populations [48]. Although interviewers were trained to build trust and rapport with participants, and confidentiality is assured, it is possible we overestimated the percentage of individuals willing to participate. Also, previous studies have reported that individuals are less willing to participate in an RCT when more details, such as randomization, are provided [49,50]. Although more details were provided to participants if necessary, it is possible that a detailed description of RCT methodology would result in less willingness to participate. Finally, it is possible that the motivation to enroll in an RCT is for financial compensation

and not to seek new drug treatments. This factor was not assessed in our study but is an important area of future research.

Importantly, participant's motivation to change and participant's perceived drug use severity were not assessed in this study. It is possible that participants with the highest perceived drug use severity are more motivated to change drug use practices. It is also possible that participants who are more motivated to change are more likely to participate in pharmacologic RCTs. Future analyses in this, and other populations of illicit drug users, could assess whether perceived severity of drug use translates into motivation to change, and whether motivation to change predicts subsequent enrollment in pharmacologic RCTs.

Although some odds ratios are modest, they nevertheless represent statistically significant findings. Given the lack of research in this area, it is unclear whether these results represent clinically meaningful effect sizes. Examinations of enrollment patterns as pharmacologic addiction treatment RCTs begin enrolling participants in the current and other study sites will provide the means to assess whether there is actual increased enrollment by the out-of-treatment populations identified in our study.

In summary, the present study found high rates of willingness to participate in an pharmacologic addiction treatment RCT among community-recruited illicit drug users and that willingness was associated with daily heroin injection and daily crack smoking, sex work involvement, HIV seropositivity and MMT participation. These findings appear to highlight both the desire for new drug treatment strategies among high-risk drug users and the feasibility of studies seeking to enroll participants from populations of high-risk drug users. The levels of willingness in the current study underscore the importance of focusing addiction pharmacotherapy trials on a broad range of drug using populations, including out-of-treatment and high-risk drug users.

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Table 1

Factors associated with willingness to participate in a randomized clinical trial (n = 1,020)

		Willing to participate			
Characteristic	**Total (%), *N* = 1020**	**No (%), *N* = 425**	**Yes (%), *N* = 595**	**Odds ratio, (95% CI)**	***p*-value**
Age [Median, (IQR)]	48 (42 – 54)	49 (42 – 55)	48 (42 – 53)	0.99 (0.97 – 1.00)	0.077
Gender					
Male	675 (66.2)	293 (68.9)	382 (64.2)		
Female	345 (33.8)	132 (31.1)	213 (35.8)	1.24 (0.95 – 1.61)	0.115
Caucasian					
No	444 (43.5)	181 (42.6)	263 (44.2)		
Yes	576 (56.5)	244 (57.4)	332 (55.8)	0.94 (0.73 – 1.20)	0.609
Daily heroin injection*					
No	898 (88.0)	391 (92.0)	507 (85.2)		
Yes	121 (11.9)	34 (8.0)	87 (14.6)	1.97 (1.30 – 3.00)	0.001
Daily cocaine injection*					
No	957 (93.8)	404 (95.1)	553 (92.9)		
Yes	63 (6.2)	21 (4.9)	42 (7.1)	1.46 (0.85 – 2.51)	0.168
Daily crack smoking*					
No	859 (84.2)	382 (89.9)	477 (80.2)		
Yes	161 (15.8)	43 (10.1)	118 (19.8)	2.20 (1.51 – 3.20)	<0.001
Homelessness*					
No	889 (87.2)	382 (89.9)	507 (85.2)		
Yes	127 (12.5)	42 (9.9)	85 (14.3)	1.53 (1.03 – 2.26)	0.035
Sex work*					
No	949 (93.0)	410 (96.5)	539 (90.6)		
Yes	71 (7.0)	15 (3.5)	56 (9.4)	2.84 (1.58 – 5.09)	<0.001
HIV seropositivity					
No	564 (55.3)	253 (59.5)	311 (52.3)		
Yes	456 (44.7)	172 (40.5)	284 (47.7)	1.34 (1.04 – 1.73)	0.022
Methadone maintenance therapy*					

Characteristic	Total (%), *N* = 1020	Willing to participate		Odds ratio, (95% CI)	*p*-value
		No (%), *N* = 425	Yes (%), *N* = 595		
No	484 (47.5)	236 (55.5)	248 (41.7)		
Yes	529 (51.9)	187 (44.0)	342 (57.5)	1.74 (1.35 – 2.24)	<0.001
Participation in drug treatment**					
No	828 (81.2)	348 (81.9)	480 (80.7)		
Yes	184 (18.0)	75 (17.7)	109 (18.3)	1.05 (0.76 – 1.46)	0.753

Percentages do not necessarily sum to 100% due to missing data or rounding error.

* In last 6 months.

** Defined as drug and/or alcohol treatment other than a methadone program.

Table 2

Multivariate analysis of factors associated with willingness to participate in a randomized clinical trial

Characteristic	Adjusted odds ratio (95% CI)	*p*-value
Daily heroin injection*		
Yes vs No	1.75 (1.13 – 2.72)	0.013
Daily crack smoking*		
Yes vs No	1.81 (1.23 – 2.66)	0.003
Homelessness*		
Yes vs No	1.43 (0.95 – 2.15)	0.089
Sex work*		
Yes vs No	2.22 (1.21 – 4.06)	0.010
HIV seropositivity		
Yes vs No	1.49 (1.15 – 1.94)	0.003
Methadone maintenance therapy*		
Yes vs No	1.77 (1.37 – 2.30)	<0.001

* In last 6 months.