

# REGULAR MDMA USE IS ASSOCIATED WITH DECREASED RISK OF DRUG INJECTION AMONG STREET-INVOLVED YOUTH WHO USE ILLICIT DRUGS

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## ABSTRACT

**Objectives:** Childhood trauma is common among street-involved youth, and is associated with injection drug use. Illicit 3,4-Methylenedioxymethamphetamine (MDMA) use is also common among street-involved youth, and data suggests this substance has clinical utility in management of post-traumatic stress disorder (PTSD) and associated harms. Despite this, little is known about co-occurring patterns of MDMA use and injection drug use.

**Methods:** Data were derived from a prospective cohort of street-involved youth using illicit drugs in Vancouver, Canada. Using multivariable generalized estimating equation logistic regression, we examined the association between MDMA use and the use of injection drugs, adjusting for confounders such as polysubstance use and sociodemographic factors.

**Results:** 4941 surveys from 1208 participants between September 2005 and May 2015 were included. Of these, 829 (68.6%) were male, 815 (67.5%) reported white ethnicity, and median age was 21.7 years. Overall, 599 (49.6%) participants reported MDMA use, 544 (45.0%) reported injection drug use, and 244 (20.2%) reported concurrent MDMA and injection drug use at least once during the study period. In multivariable analyses, regular MDMA use was significantly negatively associated with injection drug use (Adjusted Odds Ratio [AOR] = 0.57, 95% CI: 0.46-0.69).

**Discussion:** After accounting for socio-demographic factors and polysubstance use, periods of reported regular MDMA use were negatively associated with reported injection drug use among this cohort. These findings suggest that, unlike the use of most other non-injection drugs, illicit MDMA use does not appear to promote injection drug use, but rather is associated with a reduced likelihood of injection drug use.

**Keywords:** Injection drug use, 3,4-Methylenedioxymethamphetamine (MDMA), Ecstasy, childhood trauma, PTSD

**Word count:** 250

## 1.1 INTRODUCTION

The illicit use of 3,4-Methylenedioxymethamphetamine (MDMA), a component of the drug frequently referred to as “ecstasy” or “molly”, is commonly associated with illicit polysubstance use (Schifano *et al.*, 1998). However, evidence also shows that MDMA has potential therapeutic effects, and is thought to promote behaviours that are useful in a therapeutic setting. These include authenticity, defined as an awareness of and congruence between an individual’s thought process and actions, in addition to prosociality and autobiographical disclosure (Baggott *et al.*, 2016; Carhart-Harris *et al.*, 2014; Wardle *et al.*, 2014). As such, MDMA was used in psychotherapy until it became a scheduled substance in the 1980s (Jerome *et al.*, 2013). Subjective reports from this period in samples of people with psychological difficulties, such as depression and anxiety, attribute MDMA use with improved insight into their condition and increased self-acceptance (Greer and Tolbert, 1986).

More recently, MDMA use in therapeutic settings has been reported to have durable efficacy in combination with psychotherapy for the treatment of post-traumatic stress disorder (PTSD), and this finding has been replicated in clinical trials (Bouso *et al.*, 2008; Mithoefer *et al.*, 2011; Mithoefer *et al.*, 2013; Oehen *et al.*, 2013; Yazar-Klosinski and Mithoefer, 2017). PTSD is a condition defined by re-experiencing, avoidance,

arousal, and negative changes in mood and cognition that follow the experience of a traumatic event (Armour *et al.*, 2016). In the therapeutic setting, MDMA is thought to help allow individuals with PTSD to confront and form a new relationship with their trauma/traumatic memories, and Phase II clinical trials have demonstrated that following MDMA-assisted psychotherapy, 66.7% of participants no longer met the clinical diagnosis for PTSD at 12-month follow-up (Yazar-Klosinski and Mithoefer, 2017).

The experience of trauma, particularly childhood trauma, is known to be associated with the initiation and ongoing use of injection drugs (Debeck *et al.*, 2013; Kerr *et al.*, 2009; Quinn *et al.*, 2016; Taplin *et al.*, 2014). Street-involved youth, defined as being homeless or at risk of homelessness and spending a substantial amount of time on the street or being heavily involved in the street economy, have been shown to experience high levels of childhood maltreatment (Stoltz *et al.*, 2007). This population is also at high risk of problematic substance use, including injection drug use (Debeck *et al.*, 2013; Kerr *et al.*, 2009). Although data suggests that MDMA has therapeutic utility in the treatment of PTSD, little is known about the relationship between illicit use of MDMA, psychological distress, and the use of injection drugs among individuals who have experienced significant trauma. One study that utilized a national monitoring system of people who report MDMA use found that individuals who reported regular use of MDMA also report elevated psychological distress compared with the general

population, with polysubstance use and binge substance use being strong predictors of distress in this population. The use of MDMA itself, however, was not independently associated with levels of distress (George *et al.*, 2010).

It is commonly assumed that all non-injection substance use, including but not limited to MDMA, increases risk of injection drug use and related harms (Trenz *et al.*, 2012), but recent data suggests that this may not be universally true. For instance, lower rates of injection drug use initiation have been documented among street-involved youth who frequently use cannabis (Reddon *et al.*, 2018). It has also been established that increasing access to cannabis is associated with lower opioid overdose mortality rates (Bachhuber *et al.*, 2014). It is possible that the clinical utility of cannabis in addressing chronic pain, a frequent root cause of substance use and misuse, might play a role in these findings. Likewise, considering evidence suggesting that MDMA has clinical utility in addressing trauma, and the established relationship between trauma and subsequent problematic substance use, a careful exploration of the relationship between illicit MDMA use and higher risk substance use among populations with elevated levels of childhood trauma is warranted.

Using data from a prospective cohort of street-involved youth who use illicit substances in Vancouver, Canada we examine the association between regular MDMA use and the use of injection drugs. Given the evidence around the therapeutic value of MDMA in the treatment of trauma and associated harms, we hypothesized that MDMA

use may independently be associated with decreased risk of injection drug use in this study population, despite the commonly held assumption that all non-injection illicit drug use is a gateway to more problematic substance use.

## 2.1 MATERIAL AND METHODS

Data for this study were derived from the At-Risk Youth Study (ARYS), an ongoing open prospective cohort. This cohort has been described in detail previously (Wood *et al.*, 2006). Briefly, since 2005, participants have been recruited through self-referral, word-of-mouth and street outreach. Eligibility criteria include residing in the Greater Vancouver region and being at least 14-26 years of age at the time of recruitment. At baseline and semi-annually thereafter, participants complete an interviewer-administered questionnaire. All participants provide written informed consent and are provided with a \$30 CAD stipend at each study visit.

All participants who completed a study visit between September 2005 and May 2015 were included in the present analyses. Use of specific illicit drugs were divided into substance type, route of administration, and frequency of use (no use, less than once per month, 1-3 times per month, once per week, 2 or 3 times per week, once per day). The primary outcome of interest was reported use of any injection drugs in the previous six months (dichotomous, yes vs. no) The primary exposure of interest was

MDMA use in the last six months. Three categories for MDMA use were defined. The reference category was defined as no reported MDMA use in the last six months. The second category was regular MDMA use, defined as reports of using MDMA at least once per month. The third category was infrequent MDMA use defined as reports of using MDMA less than one per month over the last six months. Based on existing literature, we selected other explanatory variables that we hypothesized might be associated with regular use of MDMA and injection drugs. These included the following socio-demographic and behavioural variables: age at baseline (per year older); gender (male vs. female); ethnicity (White vs. Non-White); homelessness (yes vs. no); education ( $\geq$  secondary vs.  $<$  secondary); regular employment (yes vs. no); engagement with substance use treatment (yes vs. no); and residence in the Downtown Eastside neighborhood of Vancouver (yes vs. no). We also considered variables related to other illicit substance use patterns, including: non-injection cocaine use (yes vs. no); non-injection injection heroin use (yes vs. no); non-injection crystal methamphetamine use (yes vs. no); non-injection non-medical pharmaceutical opioid use (yes vs. no); daily cannabis use (yes vs. no); and heavy alcohol use, defined by the National Institute for Alcohol Abuse and Alcoholism (NIAAA) (yes vs. no). Finally, we also included past mental health diagnosis (yes vs. no) and scores from the Childhood Trauma Questionnaire (CTQ), a 28-item survey assessing physical, sexual and emotional abuse in addition to physical and emotional neglect. This survey is valid and reliable when

applied to adolescent and substance-using samples (Bernstein et al., 2003). We compared “moderate and severe” range scores (13-25) against “none and low” range scores (5-12). Aside from age, gender, ethnicity, education, mental health diagnosis, and scores from the CTQ, all variables were treated as time-updated and refer to the six-month period prior to the interview.

## **2.2 Statistical Analyses**

We first examined sample characteristics at baseline, stratified by reported injection drug use, using the Pearson’s Chi-squared test (for binary variables) and Mann-Whitney test (for continuous variables). We then examined these characteristics throughout the study period. Since analyses of factors potentially associated with injection drug use included serial measures for each participant across the study period at six month intervals, we used generalized estimating equations (GEE) with logit link. This method provides standard errors adjusted by multiple observations per person using an exchangeable correlation structure. This methodology considers data from every participant follow-up visit while appropriately accounting for differences in the number of observations for each participant.

To account for possible confounding and calculate the best effect estimate, we then fit a multivariable model using an a priori-defined modeling strategy proposed by

Greenland et al (Maldonado and Greenland, 1993). We used a conservative p-value of 0.10 in the bivariate analyses to determine whether a secondary explanatory variable was considered as a potential confounder in the relationship between the primary explanatory variable and the outcome and for inclusion in a full multivariate model. Then, reduced models were constructed in a manual stepwise approach, removing a single secondary explanatory variable each time. Specifically, the value of the coefficient for the primary explanatory variable in the full model and each reduced model was compared, and the secondary explanatory variable corresponding to the smallest relative change was removed. The process was repeated until the smallest relative change in the coefficient for any category of the primary explanatory variable from the full model was greater than 5%.

We also recognized that there might be systematic group differences between participants who regularly engage in MDMA use and those who do not. Further, these same differences may exist between participants who inject drugs and those that do not. In order to minimize these possible systematic group differences, we conducted a sub-analysis which restricted the sample to participants who reported MDMA use at least once during the study period and also reported injection drug use at least once during the study period, and examined bivariable and multivariable associations for this subsample using the same approach outlined above. All *p*-values were two-sided. All statistical analyses were performed using R, version 3.2.4 (Vienna, Austria 2016).

### 3.1 RESULTS

In total, 1208 participants were included in the present study between September 2005 and May 2015. Of these, 829 (68.6%) were male, 815 (67.5%) self-reported white ethnicity and the median age at baseline was 21.7 years (interquartile range [IQR] = 19.8 – 23.5). The median number of study visits per participant was 3 (IQR = 1 – 5). For the 846 participants who had more than one study visit, the median follow-up time per participant was 24.5 months (IQR = 15.5 – 58.4). The baseline prevalence of MDMA use among participants who completed two or less study visits was 35.4% vs. 35.8% among those with greater than two study visits ( $p= 0.894$ ). The baseline prevalence of injection drug use among participants who completed two or less study visits was 34.7% vs. 31.8% among those with greater than two study visits ( $p= 0.304$ ).

Four hundred (33.1%) participants reported injection drug use at baseline and 430 (35.6%) participants reported MDMA use at baseline (although six participants who reported MDMA use did not provide details on the frequency of use). Over the course of the study period, 544 participants (45.0%) reported injection drug use at least once and 599 participants (49.6%) reported use of MDMA at least once. A total of 244 participants (20.2%) reported both the use of MDMA at least once during the study period and also reported injection drug use at least once during study period. Overall,

4941 observations were included in the analysis. A total of 1018 (20.6%) of these observations included reports of any MDMA use in the last six months, with 426 (8.6%) reports of regular use (at least once per month) and 583 (11.8%) reports of infrequent MDMA use (less than once per month).

The baseline characteristics of the sample are reported in Table 1 and the results of the bivariate and multivariable GEE analyses of factors associated with injection drug use are presented in Table 2. In bivariate analysis, regular MDMA use was negatively associated with the use of injection drugs during the previous six month period (Odds Ratio [OR] = 0.60, 95% Confidence Interval [CI] = 0.50-0.72) and infrequent use was not significantly associated with injection drug use (OR = 0.99, 95% CI = 0.86-1.15). In the multivariable model, regular MDMA use remained negatively associated with reported use of injection drugs (Adjusted Odds Ratio [AOR] = 0.57, 95% CI = 0.46-0.69) and infrequent MDMA use was not significantly associated with injection drug use (AOR = 0.95, 95% CI = 0.81-1.11). Non-injection use of non-medical pharmaceutical opioids (AOR = 1.35, 95% CI = 1.11-1.65), homelessness (AOR = 1.21, 95% CI = 1.08-1.36), and physical abuse (AOR = 1.25, 95% CI = 0.98-1.59) were positively associated with injection drug use, while heavy alcohol was negatively associated with the injection drug use (AOR = 0.71, 95% CI = 0.63 – 0.81).

The sub-analysis included 224 participants who reported use of MDMA at least once during the study period and who also reported injection drug use at least once

during study period. In this multivariable model, regular MDMA use remained negatively associated with periods of injection drug use (AOR = 0.41, 95% CI = 0.28-0.61) while infrequent MDMA use was not significantly associated with periods of injection drug use (AOR = 1.11, 95% CI = 0.80-1.53). Non-injection heroin use (AOR = 1.98, 95% CI = 1.37-2.87) and homelessness (AOR = 1.46, 95% CI = 1.11-1.91) were positively associated with periods of injection drug use, and heavy alcohol use remained negatively associated with periods of injection drug use (AOR = 0.53, 95% CI = 0.40 – 0.70). The model was also adjusted for non-injection non-medical pharmaceutical opioid use and emotional neglect (all  $p > 0.05$ ).

## 4.1 DISCUSSION

Our results indicate that periods of reported regular MDMA use are negatively associated with reported injection drug use, even after adjustment for polysubstance use and socio-demographic factors. This observed relationship remained consistent in a sub-analysis restricted to participants with a history of both MDMA and injection drug use. Although preliminary, these findings may be rooted in the acute and enduring prosocial and therapeutic effects that observational, experimental, and clinical studies suggest MDMA may have.

In experimental settings, MDMA use has been shown to support social outcomes such as increased response to positive emotional stimuli and decreased response to negative emotional stimuli (Bedi *et al.*, 2010; Bedi *et al.*, 2009; Hysek *et al.*, 2014b; Kirkpatrick *et al.*, 2014; Schmid *et al.*, 2014; Wardle and de Wit, 2014). MDMA use has also been demonstrated to improve ability to read socio-emotional information such as facial expressions (Bedi *et al.*, 2010; Hysek *et al.*, 2012; Wardle and de Wit, 2014), improve favorability of social interactions (Wardle *et al.*, 2014), increase empathy (Bedi *et al.*, 2010; Hysek *et al.*, 2014a; Kuypers *et al.*, 2014; Schmid *et al.*, 2014) and altruistic ability and behaviours (Hysek *et al.*, 2014a; Kirkpatrick *et al.*, 2015). These prosocial attributes are thought to underlie the clinical utility of MDMA.

MDMA use has been shown to be beneficial in therapeutic settings for the treatment of PTSD by helping individuals manage the emotionally demanding process of decoupling the re-experience of trauma from actual threat (McLean and Foa, 2013; Steenkamp and Litz, 2014). As some aspects of the usefulness of MDMA in the therapeutic context are thought to be derived from the improved social outcomes observed in experimental settings, these could possibly extend to non-clinical illicit use of the substance and the behaviours that coincide with it. Given that many youth who engage in sustained problematic substance use are also survivors of childhood trauma (Taplin *et al.*, 2014), one possible interpretation for the observed negative association in our sample between MDMA use and injection drug use could be that regular illicit

MDMA use may mediate some negative effects of trauma and discourage harmful substance use behaviours such as drug injecting.

Previous work that also utilizes this cohort of street-involved youth suggests that childhood trauma, in particular physical abuse and emotional neglect, are not only commonly experienced in this sample, but are also predictive of progression to injection drug use (Debeck *et al.*, 2013). Despite data suggesting therapeutic value of MDMA in the treatment of PTSD, and the commonplace illicit use of this substance, little is known about the correlates of MDMA use in populations experiencing high levels of trauma. The results from this sample, although preliminary, suggest that illicit MDMA use, and the constellation of other behaviours that surround it, may play a role in harm reduction. Further, it should be noted that the observed association is largely limited to participants who report using the substance at least monthly, and this frequency of use is congruent with current clinical trials (Mithoefer *et al.*, 2013; Yazar-Klosinski and Mithoefer, 2017). Despite this, it is important to recognize the numerous inherent difficulties in comparing illicit use with the carefully managed containment of the therapeutic setting, which among numerous other benefits is essential to minimize the potential adverse events that can be associated with illicit MDMA use, including extended depressed mood, rhabdomyolysis and serotonin syndrome, among others (Michael White, 2014). It is equally important to note that illicit MDMA use has been shown to be associated with an array of harm reduction behaviours, such as the

avoidance of solitary substance use, and the use of test kits to determine substance identity and purity (Davis and Rosenberg, 2016; Davis and Rosenberg, 2017), and these behaviours may extended to other substance use and may help explain the observed associations in the current study.

Compared to non-injection use of other illicit drugs, such as heroin and methamphetamine, the profile of harms and likelihood of progression to substance use disorder associated with the use of MDMA are known to be less severe (Nutt *et al.*, 2010). Studies that have followed post-experimental and post-clinical use of MDMA by participants/patients have identified few instances of craving or illicit use (Mithoefer *et al.*, 2013). Outside of the experimental/clinical context, it is somewhat difficult to isolate the sequelae of MDMA use from that of poly-substance use (Schifano *et al.*, 1998; Topp *et al.*, 1999), but people that use MDMA have been found to exhibit an increased prevalence of mental health concerns (Parrott *et al.*, 2000). Despite this finding, it seems that these concerns often predate use of MDMA (Lieb *et al.*, 2002; Pedersen and Skrondal, 1999). A longitudinal study found that youth who use MDMA are more likely to use other illicit substances, but are not more likely to engage in sustained use of MDMA (von Sydow *et al.*, 2002). Due to wide illicit availability, a comparatively less harmful risk profile, and possible therapeutic influence, further investigation is warranted to better understand the possible role that illicit MDMA use may play in poly-substance use and related harms.

Our results also indicate that heavy alcohol use was negatively associated with injection drug use. This finding is consistent with existing literature characterizing alcohol use among injection drug users. A study utilizing a national monitoring system of people who regularly use MDMA found that rates of concurrent alcohol use were significantly lower among those who also reported injection drug use (White *et al.*, 2006). It's possible that people who use injection drugs engage in heavy drinking as a replacement behaviour during periods of abstinence from injection drugs. It is also possible that regular MDMA use is strongly associated with regular use of alcohol.

Our study has several limitations. Most importantly, this is an observational study and we cannot infer causation from the observed associations. This sample is not random, as it is drawn from street-involved youth using street outreach methods and snowball sampling. Therefore, our findings may not generalize beyond this population. Further, our study includes data across ten years, during which time the composition of illicit MDMA and the culture surrounding its use in this cohort may have shifted, each potentially contributing to associated behaviors. Other limitations inherent in our study design include self-report of MDMA and injection drug use and frequency, and also unknown identity, composition and purity of reported drugs consumed. Poly-substance use is prevalent in our sample, and despite our best attempts to adjust for relevant confounders, we cannot ascertain the exact role of individual substances in the complicated constellation of poly-substance use observed among many of our

participants. For instance, MDMA use may simply coincide with a reduced likelihood of injection drug use without directly contributing to it. Although our observations are consistent with prior research demonstrating that MDMA use in therapeutic settings can help treat PTSD, which is known to be associated with injection drug use, further study is needed. An important focus of further study should be ongoing monitoring of indicators related to psychological trauma and well-being during the illicit use of MDMA and other substances, which is a significant limitation of this study.

## 4.2 Conclusions

In summary, we found that periods of regular MDMA use were independently associated with a reduced likelihood of reporting injection drugs in a prospective observational cohort of street-involved youth who use illicit drugs, and have experienced significant childhood trauma. While the experience of trauma is a known risk factor for injection drug use, and evidence indicates that MDMA in therapeutic settings has clinical utility in the treatment of PTSD, little is known about the correlates of illicit MDMA use in individuals who have experienced significant trauma. Although preliminary, our findings suggest that after accounting for the complex constellation of poly-substance use in this population and other predictive factors, the illicit use of MDMA does not appear to promote injection drug use, but rather is associated with a reduced likelihood of injection drug use. Further research in this area is warranted.

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## 5.1 REFERENCES

- Armour, C., Mullerova, J., Elhai, J.D., 2016. A systematic literature review of PTSD's latent structure in the Diagnostic and Statistical Manual of Mental Disorders: DSM-IV to DSM-5. *Clinical psychology review* 44, 60-74.
- Bachhuber, M.A., Saloner, B., Cunningham, C.O., Barry, C.L., 2014. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA internal medicine* 174(10), 1668-1673.
- Baggott, M.J., Coyle, J.R., Siegrist, J.D., Garrison, K.J., Galloway, G.P., Mendelson, J.E., 2016. Effects of 3,4-methylenedioxymethamphetamine on socioemotional feelings, authenticity, and autobiographical disclosure in healthy volunteers in a controlled setting. *Journal of psychopharmacology* 30(4), 378-387.
- Bedi, G., Hyman, D., de Wit, H., 2010. Is ecstasy an "empathogen"? Effects of +/-3,4-methylenedioxymethamphetamine on prosocial feelings and identification of emotional states in others. *Biological psychiatry* 68(12), 1134-1140.
- Bedi, G., Phan, K.L., Angstadt, M., de Wit, H., 2009. Effects of MDMA on sociability and neural response to social threat and social reward. *Psychopharmacology* 207(1), 73-83.
- Bernstein, D.P., Stein, J.A., Newcomb, M.D., Walker, E., Pogge, D., Ahluvalia, T., Stokes, J., Handelsman, L., Medrano, M., Desmond, D., Zule, W., 2003. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child abuse & neglect* 27(2), 169-190.
- Bouso, J.C., Doblin, R., Farre, M., Alcazar, M.A., Gomez-Jarabo, G., 2008. MDMA-assisted psychotherapy using low doses in a small sample of women with chronic posttraumatic stress disorder. *Journal of psychoactive drugs* 40(3), 225-236.
- Carhart-Harris, R.L., Wall, M.B., Erritzoe, D., Kaelen, M., Ferguson, B., De Meer, I., Tanner, M., Bloomfield, M., Williams, T.M., Bolstridge, M., Stewart, L., Morgan, C.J., Newbould, R.D., Feilding, A., Curran, H.V., Nutt, D.J., 2014. The effect of acutely administered MDMA on subjective and BOLD-fMRI responses to favourite and worst autobiographical memories. *The international journal of neuropsychopharmacology* 17(4), 527-540.
- Davis, A.K., Rosenberg, H., 2016. Using the Theory of Planned Behavior to predict implementation of harm reduction strategies among MDMA/ecstasy users. *Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors* 30(4), 500-508.
- Davis, A.K., Rosenberg, H., 2017. Specific harm reduction strategies employed by 3,4-methylenedioxymethamphetamine/ ecstasy users in the United States and the United Kingdom. *Drug Science, Policy and Law* 3, 2050324517711069.
- Debeck, K., Kerr, T., Marshall, B.D., Simo, A., Montaner, J., Wood, E., 2013. Risk factors for progression to regular injection drug use among street-involved youth in a Canadian setting. *Drug and alcohol dependence* 133(2), 468-472.

- George, J., Kinner, S.A., Bruno, R., Degenhardt, L., Dunn, M., 2010. Contextualising psychological distress among regular ecstasy users: the importance of sociodemographic factors and patterns of drug use. *Drug and alcohol review* 29(3), 243-249.
- Greer, G., Tolbert, R., 1986. Subjective reports of the effects of MDMA in a clinical setting. *Journal of psychoactive drugs* 18(4), 319-327.
- Hysek, C.M., Domes, G., Liechti, M.E., 2012. MDMA enhances "mind reading" of positive emotions and impairs "mind reading" of negative emotions. *Psychopharmacology* 222(2), 293-302.
- Hysek, C.M., Schmid, Y., Simmler, L.D., Domes, G., Heinrichs, M., Eisenegger, C., Preller, K.H., Quednow, B.B., Liechti, M.E., 2014a. MDMA enhances emotional empathy and prosocial behavior. *Social cognitive and affective neuroscience* 9(11), 1645-1652.
- Hysek, C.M., Simmler, L.D., Schillinger, N., Meyer, N., Schmid, Y., Donzelli, M., Grouzmann, E., Liechti, M.E., 2014b. Pharmacokinetic and pharmacodynamic effects of methylphenidate and MDMA administered alone or in combination. *The international journal of neuropsychopharmacology* 17(3), 371-381.
- Jerome, L., Schuster, S., Yazar-Klosinski, B.B., 2013. Can MDMA play a role in the treatment of substance abuse? *Current drug abuse reviews* 6(1), 54-62.
- Kerr, T., Stoltz, J.A., Marshall, B.D., Lai, C., Strathdee, S.A., Wood, E., 2009. Childhood trauma and injection drug use among high-risk youth. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine* 45(3), 300-302.
- Kirkpatrick, M., Delton, A.W., Robertson, T.E., de Wit, H., 2015. Prosocial effects of MDMA: A measure of generosity. *Journal of psychopharmacology* 29(6), 661-668.
- Kirkpatrick, M.G., Lee, R., Wardle, M.C., Jacob, S., de Wit, H., 2014. Effects of MDMA and Intranasal oxytocin on social and emotional processing. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 39(7), 1654-1663.
- Kuypers, K.P., de la Torre, R., Farre, M., Yubero-Lahoz, S., Dziobek, I., Van den Bos, W., Ramaekers, J.G., 2014. No evidence that MDMA-induced enhancement of emotional empathy is related to peripheral oxytocin levels or 5-HT1a receptor activation. *PLoS one* 9(6), e100719.
- Lieb, R., Schuetz, C.G., Pfister, H., von Sydow, K., Wittchen, H., 2002. Mental disorders in ecstasy users: a prospective-longitudinal investigation. *Drug and alcohol dependence* 68(2), 195-207.
- Maldonado, G., Greenland, S., 1993. Simulation study of confounder-selection strategies. *American journal of epidemiology* 138(11), 923-936.
- McLean, C.P., Foa, E.B., 2013. Dissemination and implementation of prolonged exposure therapy for posttraumatic stress disorder. *Journal of anxiety disorders* 27(8), 788-792.
- Michael White, C., 2014. How MDMA's pharmacology and pharmacokinetics drive desired effects and harms. *Journal of clinical pharmacology* 54(3), 245-252.

- Mithoefer, M.C., Wagner, M.T., Mithoefer, A.T., Jerome, L., Doblin, R., 2011. The safety and efficacy of {+/-}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *Journal of psychopharmacology* 25(4), 439-452.
- Mithoefer, M.C., Wagner, M.T., Mithoefer, A.T., Jerome, L., Martin, S.F., Yazar-Klosinski, B., Michel, Y., Brewerton, T.D., Doblin, R., 2013. Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study. *Journal of psychopharmacology* 27(1), 28-39.
- Nutt, D.J., King, L.A., Phillips, L.D., Independent Scientific Committee on, D., 2010. Drug harms in the UK: a multicriteria decision analysis. *Lancet* 376(9752), 1558-1565.
- Oehen, P., Traber, R., Widmer, V., Schnyder, U., 2013. A randomized, controlled pilot study of MDMA (+/- 3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). *Journal of psychopharmacology* 27(1), 40-52.
- Parrott, A.C., Sisk, E., Turner, J.J., 2000. Psychobiological problems in heavy 'ecstasy' (MDMA) polydrug users. *Drug and alcohol dependence* 60(1), 105-110.
- Pedersen, W., Skrondal, A., 1999. Ecstasy and new patterns of drug use: a normal population study. *Addiction* 94(11), 1695-1706.
- Quinn, K., Boone, L., Scheidell, J.D., Mateu-Gelabert, P., McGorray, S.P., Beharie, N., Cottler, L.B., Khan, M.R., 2016. The relationships of childhood trauma and adulthood prescription pain reliever misuse and injection drug use. *Drug and alcohol dependence* 169, 190-198.
- Reddon, H., DeBeck, K., Socias, M.E., Dong, H., Wood, E., Montaner, J., Kerr, T., Milloy, M.J., 2018. Cannabis use is associated with lower rates of initiation of injection drug use among street-involved youth: A longitudinal analysis. *Drug and alcohol review*.
- Schifano, F., Di Furia, L., Forza, G., Minicuci, N., Bricolo, R., 1998. MDMA ('ecstasy') consumption in the context of polydrug abuse: a report on 150 patients. *Drug and alcohol dependence* 52(1), 85-90.
- Schmid, Y., Hysek, C.M., Simmler, L.D., Crockett, M.J., Quednow, B.B., Liechti, M.E., 2014. Differential effects of MDMA and methylphenidate on social cognition. *Journal of psychopharmacology* 28(9), 847-856.
- Steenkamp, M.M., Litz, B.T., 2014. Prolonged exposure therapy in veterans affairs: the full picture. *JAMA psychiatry* 71(2), 211.
- Stoltz, J.A., Shannon, K., Kerr, T., Zhang, R., Montaner, J.S., Wood, E., 2007. Associations between childhood maltreatment and sex work in a cohort of drug-using youth. *Social science & medicine* 65(6), 1214-1221.
- Taplin, C., Saddichha, S., Li, K., Krausz, M.R., 2014. Family history of alcohol and drug abuse, childhood trauma, and age of first drug injection. *Substance use & misuse* 49(10), 1311-1316.

- Topp, L., Hando, J., Dillon, P., Roche, A., Solowij, N., 1999. Ecstasy use in Australia: patterns of use and associated harm. *Drug and alcohol dependence* 55(1-2), 105-115.
- Trenz, R.C., Scherer, M., Harrell, P., Zur, J., Sinha, A., Latimer, W., 2012. Early onset of drug and polysubstance use as predictors of injection drug use among adult drug users. *Addictive behaviors* 37(4), 367-372.
- von Sydow, K., Lieb, R., Pfister, H., Hofler, M., Wittchen, H.U., 2002. Use, abuse and dependence of ecstasy and related drugs in adolescents and young adults-a transient phenomenon? Results from a longitudinal community study. *Drug and alcohol dependence* 66(2), 147-159.
- Wardle, M.C., de Wit, H., 2014. MDMA alters emotional processing and facilitates positive social interaction. *Psychopharmacology* 231(21), 4219-4229.
- Wardle, M.C., Kirkpatrick, M.G., de Wit, H., 2014. 'Ecstasy' as a social drug: MDMA preferentially affects responses to emotional stimuli with social content. *Social cognitive and affective neuroscience* 9(8), 1076-1081.
- White, B., Day, C., Degenhardt, L., Kinner, S., Fry, C., Bruno, R., Johnston, J., 2006. Prevalence of injecting drug use and associated risk behavior among regular ecstasy users in Australia. *Drug and alcohol dependence* 83(3), 210-217.
- Wood, E., Stoltz, J.A., Montaner, J.S., Kerr, T., 2006. Evaluating methamphetamine use and risks of injection initiation among street youth: the ARYS study. *Harm reduction journal* 3, 18.
- Yazar-Klosinski, B.B., Mithoefer, M.C., 2017. Potential Psychiatric Uses for MDMA. *Clinical pharmacology and therapeutics* 101(2), 194-196.

**Table 1: Factors associated with injection drug use at baseline among 1208 at-risk youth in Vancouver, Canada**

Characteristic	Yes n (%) n = 400	No n (%) n = 808	Odds Ratio (95% CI)	p - value
<b>MDMA+</b>				
<b>Regular use</b> (at least monthly use vs no use)	28 (7.0)	176 (21.8)	0.24 (0.15 - 0.37)	<0.001
<b>Infrequent use</b> (less than monthly use vs. no use)	61 (15.3)	159 (19.7)	0.58 (0.41 - 0.82)	<0.001
<b>No use reported*</b>	311 (77.8)	473 (58.7)		
<b>Age Median (IQR)</b>	22.4 (21-24)	21.5 (20-23)		<0.001
<b>Male gender</b>	254 (63.5)	575 (71.2)	0.70 (0.55 - 0.91)	0.008
<b>White ethnicity</b>	299 (74.8)	516 (63.9)	1.68 (1.28 - 2.19)	<0.001
<b>Education (≥ secondary)</b>	138 (34.5)	296 (36.6)	0.90 (0.70 - 1.16)	0.445
<b>Regular employment†</b>	176 (44.0)	482 (59.7)	0.53 (0.42 - 0.68)	<0.001
<b>Homelessness†</b>	311 (77.8)	588 (72.8)	1.32 (0.99 - 1.75)	0.057
<b>DTES residence†</b>	158 (39.5)	192 (23.8)	2.09 (1.62 - 2.71)	<0.001
<b>Drug treatment†</b>	173 (43.3)	197 (24.4)	2.35 (1.82 - 3.04)	<0.001
<b>Non-injection prescription opioids†</b>	76 (19.0)	93 (11.5)	1.78 (1.28 - 2.47)	0.001
<b>Non-injection crack cocaine†</b>	283 (70.8)	589 (72.9)	0.87 (0.67 - 1.14)	0.337
<b>Non-injection methamphetaminet</b>	215 (53.8)	323 (40.0)	1.72 (1.35 - 2.19)	<0.001
<b>Non-injection heroin†</b>	143 (35.8)	145 (17.9)	2.53 (1.92 - 3.32)	<0.001
<b>Daily cannabis†</b>	137 (34.3)	390 (48.3)	0.55 (0.43 - 0.71)	<0.001
<b>Heavy alcohol †</b>	83 (20.8)	345 (42.7)	0.35 (0.26 - 0.46)	<0.001
<b>Mental illness diagnosis</b>	633 (52.4)	575 (47.6)	1.47 (1.14 - 1.88)	0.002
<b>Emotional abuse</b>	563 (46.6)	549 (45.4)	1.20 (0.93 - 1.56)	0.158
<b>Emotional neglect</b>	532 (44.0)	574 (47.5)	1.45 (1.11 - 1.88)	0.004
<b>Physical Abuse</b>	321 (26.6)	791 (65.5)	1.14 (0.85 - 1.51)	0.357
<b>Physical neglect</b>	333 (27.6)	778 (64.4)	1.06 (0.80 - 1.40)	0.725
<b>Sexual abuse</b>	187 (15.5)	912 (75.5)	1.32 (0.93 - 1.85)	0.102

† Denotes activities in the previous six months

\*six participants reported MDMA use at baseline did not report frequency of use, and were excluded  
IQR= Interquartile range

**Table 2. Bivariable and multivariable generalized estimating equations (GEE) analyses of factors associated with use of injection drugs among 1208 at-risk youth in Vancouver, Canada.**

Characteristic	Unadjusted		Adjusted	
	Odds Ratio (95% CI)	<i>p</i> - value	Odds Ratio (95% CI)	<i>p</i> - value
<b>MDMA†</b>				
<b>Regular Use</b> (at least monthly use vs no use)	0.60 (0.50-0.72)	<0.001	0.57 (0.46-0.69)	<0.001
<b>Infrequent Use</b> (less than monthly use vs. no use)	0.99 (0.86-1.15)	0.912	0.95 (0.81-1.11)	0.514
<b>Age at baseline</b> (per year older)	1.1 (1.05-1.14)	<0.001		
<b>Gender</b> (men vs. women)	0.78 (0.62-0.97)	0.027		
<b>Ethnicity</b> (White vs. non-White)	1.43 (1.14-1.80)	0.002		
<b>Education</b> (≥ secondary vs. < secondary)	0.89 (0.71-1.12)	0.315		
<b>Employment†</b> (yes vs. no)	0.77 (0.69-0.86)	<0.001		
<b>Homelessness†</b> (yes vs. no)	1.17 (1.04-1.31)	0.008	1.21 (1.08-1.36)	0.002
<b>DTES residence†</b> (yes vs no)	1.39 (1.24-1.57)	<0.001		
<b>Drug treatment†</b> (yes vs no)	1.21 (1.08-1.37)	0.002		
<b>Non-injection prescription opioids†</b> (yes vs. no)	1.29 (1.08-1.55)	0.006	1.35 (1.11-1.65)	0.002
<b>Non-injection crack cocaine†</b> (yes vs. no)	1.03 (0.92-1.17)	0.579		
<b>Non-injection methamphetamine†</b> (yes vs. no)	1.38 (1.22-1.56)	<0.001		
<b>Non-injection heroin†</b> (yes vs. no)	1.58 (1.34-1.87)	<0.001		
<b>Daily Cannabis†</b> (yes vs. no)	0.81 (0.72-0.91)	0.001		
<b>Heavy alcohol †</b> (yes vs. no)	0.69 (0.61-0.78)	<0.001	0.71 (0.63-0.81)	<0.001
<b>Mental illness diagnosis</b> (yes vs. no)	1.42 (1.18 -1.72)	<0.001		
<b>Emotional abuse</b> (moderate/severe vs, none/low)	1.27 (1.02 -1.58)	0.035		

<b>Emotional neglect</b>				
(moderate/severe vs, none/low)	1.50 (1.20 -1.88)	<0.001		
<b>Physical Abuse</b>				
(moderate/severe vs, none/low)	1.28 (1.01 -1.64)	0.043	1.25 (0.98-1.59)	0.075
<b>Physical neglect</b>				
(moderate/severe vs, none/low)	1.18 (0.92 -1.50)	0.187		
<b>Sexual abuse</b>				
(moderate/severe vs, none/low)	1.26 (0.94 -1.67)	0.116		

<sup>†</sup> Denotes activities in the previous six months.