Differences in polysubstance use patterns and drug-related outcomes between people who inject drugs receiving and not receiving opioid substitution therapies

Running head: polysubstance use, injecting-related harms and treatment

Abstract word count is 288 words.

Main text word count is 3,499 words.

There are 4 tables and 1 figure.

There is 1 supplementary table and figure.

Dr Kim S. Betts (corresponding author), PhD, MPH, BEd.

Contact details of Kim Betts:

School of Population Health

The University of Queensland

4th floor, Public Health Building

Herston Rd, Herston QLD 4006

Australia

kim.betts@uqconnect.edu.au

phone: +617 33655509

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/add.13339

Dr Gary Chan, PhD, MSc, BSc, BA

Centre for Youth Substance Abuse, University of Queensland, Brisbane, Australia.

c.chan4@uq.edu.au

Dr Fairlie McIlwraith, PhD, MSocSc, BA

QADREC, School of Population Health Building, University of Queensland, Brisbane,

f.mcilwraith@sph.uq.edu.au

Professor Paul Dietze, PhD, BSc(Hons),

MacFarlane Burnet Institute for Medical and Public Health Research, Melbourne, Australia.

pauld@burnet.edu.au

Elizabeth Whittaker BA (Hons), BBusMan,

National Drug and Alcohol Centre, University of New South Wales, NSW 2052, Australia.

e.whittaker@unsw.edu.au

Associate Professor Lucy Burns, PhD, MPH, GradCert(Helath Policy), BA(Hons)

National Drug and Alcohol Centre, University of New South Wales, NSW 2052, Australia.

l.burns@unsw.edu.au

Professor Rosa Alati, PhD, MApplSc(Health Sc), GradDip(Aboriginal Studies), BA(Hons).

School of Public Health and Centre for Youth Substance Abuse Research, University of Queensland, Brisbane, Australia

r.alati@sph.uq.edu.au

Aims: To test if polysubstance use profiles and drug-related outcomes differ between those receiving and not receiving opioid substitution therapies (OST), among people who inject drugs (PWID).

Design: An annual cross-sectional, sentinel sample of PWID across Australia

Setting: Data came from three years (2011-2013) of the Illicit Drug Reporting System (IDRS).

Participants: A total of 2,673 participants who injected drugs from the combined national IDRS samples of 2011 (*n* = 868), 2012 (*n* = 922), and 2013 (*n* = 883)

Measurements: Latent Class Analysis (LCA) was used to summarise participants' self-reported use of 18 types of substances, with the resulting polysubstance use profiles then associated with participant experience of a number of drug-related outcomes.

Findings: Polysubstance use profiles exhibiting a broad-range of substance use were generally at increased risk of negative drug-related outcomes whether participants were receiving OST or not: including thrombosis among OST receivers [odds ratio (OR)=2.13, 95% confidence intervals (CI) = 1.09-4.17], injecting with used needle among OST receivers and non-receivers respectively [OR = 2.78, 95% CI = 1.50-5.13; OR = 2.15, 95% CI = 1.34-3.45], and violent criminal offences among OST receivers and non-receivers respectively [OR = 2.30, 95% CI = 1.16-4.58; OR = 1.87, 95% CI = 1.14-3.07]. An important exception was non-fatal overdose which was specifically related to a class of PWID who were not receiving OST and used morphine frequently [OR = 1.83, 95% CI = 1.06-3.17].

Conclusion: Regardless of opioid substitution therapies usage, people who inject drugs (PWID) who use a broad-range of substances experience greater levels of injecting-related injuries and poorer health outcomes and are more likely to engage in criminal activity than other groups of PWID.

Key words: Drug treatment, polysubstance use, latent class analysis.

Introduction

Polysubstance use in now understood to be the norm among many populations of people who inject drugs (PWID) (1), and increasing effort is being made to understand how an individual's polysubstance use profile (i.e., combinations of illicit, licit and/or prescription substances) impacts on important drug-related outcomes (2, 3). An outcome of considerable interest is response to treatment, with polysubstance use complicating decisions about which substance or substances to target to effectively intervene in an individual's overall substance use (4). The reality among many drug-injecting populations is that individuals are unable to endure the withdrawal symptoms associated with detoxification, leading to high relapse rates, and upon relapsing a greater risk of harms such as overdose due to a decreased tolerance fostered by the detoxification process (5). For PWID who are opioid dependent, opioid substitution therapy (OST) is an effective treatment with strong evidence to support improved health and social outcomes (4, 6), and produces better outcomes than detoxification (7-9).

Although OST is an effective treatment, some individuals receiving OST continue injecting substances, use a number of other substances aside from the substitute, and remain at risk of overdose, potentially even from the substitute itself (4, 10, 11). As one example, a long-term study of heroin users recruited via participation in a methadone maintenance program, found half the sample was deceased after the thirty years of study, while more than 50% of those remaining had used heroin consistently. Many of those who did decrease their use of heroin, increased their use of other substances, most notably shifting to crystal methamphetamine (12). What is more, the existence of maintenance programs has led to the illicit use and injection of opioid substitutes (7, 13).

Treatment is found to be effective in reducing the intensity, frequency and length of relapse, and limit harms to the client (e.g., overdose and injecting-injuries) and to the public (e.g.,

criminal behaviours), but ongoing harmful drug use is a continuing concern and the major sign of treatment failure (4, 10). Despite the fact that the majority of adult PWID are polysubstance users, and some OST clients continue injecting, there is limited research on how OST relates to polysubstance use profiles among PWID and whether these impact on drug-related outcomes (1, 10).

Advances in empirical methods of characterising polysubstance use profiles have led to an increased understanding of how certain drug combinations, rather than individual drugs, can impact important outcomes (2). In this study, we use latent class analysis (LCA) to: (i) test whether or not polysubstance use profiles are invariant between two groups of PWID, those receiving and not receiving OST for at least six months; and then (ii) compare associations among the resulting classes on a range of drug-related outcomes. We add to previous studies investigating the role of OST in reducing drug-related harms and criminal behaviours in individuals who persist to inject drugs (10), by incorporating further differences among these two groups due to polysubstance use profiles. Importantly, we do not aim to assess whether treatment reduces polysubstance use and associated harms, as this is not possible with our cross-sectional data which are drawn from a sample of PWID who inject regularly. Instead, we aim to identify the potential needs of the different types of PWID (summarised by LCA) among those receiving and not receiving OST.

Methods

Sample

The states and territories of Australia have participated in the monitoring of drug trends as part of the national Illicit Drug Reporting System (IDRS) since 2000. The IDRS uses a purposive convenience sampling method, recruiting participants for interview from needle and syringe programs (NSPs), through advertisements, and peer referrals in each capital city. Eligible participants are aged 16 years or older, report injecting an illicit drug at least monthly in the six months prior to interview, and report living in the their recruitment city for 12 months prior to interview. Each jurisdiction obtains ethics approval from relevant ethics committees. More detailed descriptions of methods can be found elsewhere (14). Our analysis was based on a total of 2,673 participants, drawn from the combined national samples of 2011 (n = 868), 2012 (n = 922), and 2013 (n = 883). The choice of the most recent three years was due to the consistency of the survey questions across these three years.

Substance use

We included 18 categories of drugs, each of which was operationalised as a five-level ordinal variable representing the frequency of use over the past six months (*never/ less than monthly/ monthly/ weekly/ daily*). The drug categories included six illegal substances - heroin, three forms of methamphetamine (speed powder, base, crystal methamphetamine), cocaine and cannabis; three OST drugs – methadone, buprenorphine (Subutex™) and buprenorphine-naloxone (Suboxone™); and eight prescription pharmaceuticals – morphine, oxycodone, other prescription opioids (e.g., fentanyl), quetiapine (an antipsychotic), alprazolam (i.e., Xanax and Kalma), other benzodiazepines (e.g., Valium, Serepax), prescription stimulants (e.g., Ritalin) and over-the-counter opioids. Lastly, alcohol use was included but, due to a high prevalence, tobacco use was excluded (>80% of the sample smoked daily). Information

was collected pertaining to each substance with regards to the mode of administration (i.e., injection, oral administration, or otherwise) and the legality of use (e.g., methadone obtained through valid prescription or from the illicit drug market). However, due to the difficulties in characterising each drug category as illicit/licit and injected/not injected within the proposed statistical framework (i.e., dividing the usage of each of the 18 substances by these characteristics would have led to an unwieldy number of indicator variables and a complex model difficult to interpret), we did not distinguish use by either legality or administration.

Treatment

Treatment was defined as having receiving any form of OST continuously over the past six month period, self-reported by the respondent. OST treatments included methadone, Subutex and Suboxone.

Demographic and injecting-related outcomes

Demographic variables included age (17-35/36-45/46+), gender, currently employed (yes/no), currently in stable housing (yes/no) and having a partner (yes/no). Past month injecting-related and other health and social behaviours and outcomes were all binary (no/yes), self-reported by respondents and separated into four different types; (1) Injuries and harms included having experienced overdose, abscess and thrombosis in the past month, (2) Injecting-related risk behaviours included using a syringe after someone else and not using a filter, (3) Criminal behaviour including having committed an offence in the past month involving property, drug dealing or violence, (4) General health questions including having severe psychological distress and poor physical health. Psychological distress was measured over the past month with the Kessler psychological distress scale (K10) (15), shown to have good validity and reliability (16). We used the established cut-off score of ≥30 out of 50 to represent severe psychological distress (17), resulting in 736 (29% of the sample) identified

as having severe psychological distress. Physical health (past month) was measured using the physical health component of the SF-12 Health Survey, found to be a valid and reliable measure of physical health (18, 19), constructed by summing the six items and defining the top scoring 10% as having poor physical health.

Statistical analysis

We used Latent Class Analysis (LCA) to derive empirical classes of polysubstance use profiles among the full-sample (n=2,673) and test for measurement invariance by OST status, using Mplus version 6 (20) similar to a previous IDRS study (21), and used Full Information Maximum Likelihood (FIML) to account for missing data (22) (for further information see supplementary text 1). Each of the resulting classes was constructed as a dummy variable such that: (i) in analyses where the classes were dependent variables, each class could be predicted by the covariates using all the other classes combined as the reference group; and (ii) in analyses where the classes were independent variables, any number of classes could be excluded from the analyses to form a combined reference group, such that it was possible to identify specific classes which were associated with the outcomes when compared with many or all of the other classes (see table 4).

Results

Among the 2,677 participants across the three years of survey data, 1,009 (37.8%) indicated they had been receiving OST for the past six months, including: 731 individuals receiving methadone/biodone syrup treatment, 80 receiving Subutex treatment and 198 receiving Suboxone treatment. Frequency of substance use varied among different categories, with for example 15.2% and 29.8% of participants reporting daily and weekly heroin use respectively, 24.4% and 10.2% reporting daily and weekly methadone use respectively, and 2.3% and 17.1% reporting daily and weekly crystal methamphetamine use respectively. In the full sample, the BIC suggested that the 4 class solutions provided superior fit, and also had the highest entropy (The BLRT was not informative - supplementary table 1). Next, the chi-square difference test indicated the 4-class solution exhibited measurement non-invariance across the two groups, OST and no OST (chi-square = 2478.068; d.f. = 291; $p < 0.001$ – full results shown in legend of supplementary table 1). Therefore, the 4-class solution was estimated separately in both groups, and subsequent regression analyses were carried out on the resulting eight groups.

Figure 1 shows the 4 classes of polysubstance use in both groups. Among those receiving OST (classes 1-4 in figure 1), there was one class for which buprenorphine (a combination of subutex and suboxone) was the substance used at highest frequency (class 3), while in the other three classes methadone was the most frequently used substance. However, the three methadone classes differed importantly with regards to the frequency of use of other substances, particularly heroin. For example, class 1 and 4 used methadone similarly, but class 1 also used a substantial amount of heroin and used other substances at very low levels, while class 4 used heroin relatively infrequently but did use a number of other substances at more moderate levels (particularly cannabis). Class 2 exhibited a broad-ranging

polysubstance use profile, including relatively frequent heroin and benzodiazepine use. Among those not receiving OST (classes 5-8 in figure 1) the classes were more qualitatively distinct. Class 5 exhibited a broad-ranging polysubstance use profile, while classes 6, 7 and 8 were distinguished by heavy use of heroin, morphine and methamphetamines respectively.

Table 1 shows the bivariate relationships between the demographic variables and the odds of treatment, indicating that being male, not having a partner, employment and housing were all associated with an increased odds for not receiving treatment. Table 2 shows multivariable relationships between the covariates and OST status with the outcomes. Not receiving OST was associated with increased odds for non-fatal overdose, older age was associated with increased odds of thrombosis, unstable housing was associated with increased odds of needle sharing, younger age was associated with more criminal activity and being unemployed and having unstable housing was associated with poorer mental health. Table 3 shows the multivariable associations between the covariates and each class of polysubstance use (using all other classes combined as the reference category). Among those receiving OST the class using methadone (class 1) was associated with older age, while the class using buprenorphine (class 3) was associated with younger age. Among those not receiving OST, the polysubstance use class (class 5) was associated with younger age, while the morphine class (class 7) was associated with older age.

Table 4 shows associations between the classes of polysubstance use with the outcomes adjusted for covariates. The methadone use class (class 7) was associated with increased odds of non-fatal overdose, but decreased odds of committing an offence involving dealing or property when compared with all the other seven classes. The broad-ranging polysubstance use profile classes both among those receiving (class 2), and not receiving (class 5), OST were associated with an increased odds of thrombosis and abscess respectively, when

compared with all the other seven classes combined. These two broad-ranging polysubstance use classes were also associated with increased odds of involvement in violent criminal activity when compared with the rest of the sample, and had the highest odds of involvement in other criminal activities and poorer mental and physical health. Lastly, we re-ran the analyses in a reduced sample excluding respondents who participated in multiple IDRS surveys, finding this sample included virtually the same proportion of individuals receiving OST (36.1%), and resulted in classes which were very similar in both the probability of substance use within classes in addition to class prevalence's (see supplementary figure 1).

Discussion

Our findings provide novel evidence of the patterns of drug use and drug-related outcomes between regular PWID receiving and not receiving OST. Strikingly, in both groups a class emerged exhibiting broad-ranging polysubstance use which was at the greatest risk for most of the negative outcomes. While we must interpret the results from any complex model with caution (in our case there are known difficulties in LCA with regards to deciding upon the 'best' class enumeration), our results reinforce the growing idea of broad-ranging substance use as the polysubstance use profile with particularly negative consequences for the individual and society (2). From a clinical perspective, among individuals who inject drugs and use a broad range of substances, those receiving OST were not found to have better outcomes in our naturalistic and cross-sectional study, suggesting alternative intervention strategies may need to be found. This is in keeping with meta-analytic findings showing those with polysubstance use disorders were among the least responsive to treatment (23), while a recent review suggests further research is needed to conclude as to whether it is more effective to treat multiple substance problems concurrently or sequentially (2).

Further, in considering these two broad-ranging polysubstance use profiles, those receiving OST had the highest odds of participating in all three types of criminal activity, including violent offences. Although reverse causation must be considered (i.e., criminal behaviour resulted in apprehension and enrolment in treatment), this high level of criminal involvement was found despite having received treatment for at least the 6 months prior to interview. Along with the fact that receiving OST in the full sample was not associated with reductions in violent offences and drug dealing, and associated with increased property offences, our findings are inconsistent with an earlier Dutch study which found OST was beneficial in reducing drug-related criminal activity if injecting persisted (10). The reason for this inconsistency is hard to identify, and as the study design is quite similar to ours, is unlikely to be attributed to methodological differences. Instead, we suggest the profile of OST users may differ between Australia and the Netherland, with OST in the former context not related to decreases in crime if injecting persists. When interpreting this result it must be remembered that due to the sample eligibility requirements our findings are not related to individuals who receive OST and stop injecting.

A potential benefit of OST was found in relation to non-fatal overdose. Those not receiving OST had greater odds of experiencing a non-fatal overdose in the previous month, with this increase attributed to morphine users, who were 80% more likely to experience non-fatal overdose when compared with all of the other polysubstance use classes combined. Thus, broad-ranging polysubstance use does not seem to play a role in this outcome. Rather, the heavy use of a single prescription substance (i.e., morphine) was associated with an increased risk of non-fatal overdose, after adjusting for covariates including the advanced age in this class. Even the use of benzodiazepines, known to increase the risk of overdose when combined with opioids (24, 25), was not any greater in this class relative to others. The use of illegitimately acquired prescription opioids, and the use of legitimately acquired opioids

either at higher levels than prescribed, consumed in a manner other than prescribed, or consumed in combination with other substances are well-known causes of overdose (26, 27). However, we are unaware of any previous study that has identified a class of PWID whose habit of frequent morphine use places them at a greater risk of non-fatal overdose than all other PWID. Although further research is needed to determine the source (prescription or black-market) and function (pain relief or recreation) of morphine use in the Australian drug injecting community, our findings suggest stronger regulations of the supply of morphine could have a significant impact on reducing non-fatal overdose among PWID.

After adjustment for demographic confounders, neither group was at an elevated risk of developing thrombosis or abscess. A previous study had found such outcomes occurred more frequently among participants receiving opioid substitution therapy, likely due to the injection of therapeutic drugs designed for oral administration (28). To this we add that thrombosis, one of the more serious injecting-related injuries (29), was strongly associated with PWID receiving OST who exhibited a broad-range of substance use. With regards to the increased odds of criminal offences involving property among those receiving OST, this may have resulted from the 17% of non-OST receiving morphine users who had lower odds of being involved in this type of criminal activity when compared with every other class of polysubstance user. Perhaps an advanced age and/or easier access to morphine for legitimate therapeutic use in some instances may make participation in crime difficult or unnecessary. Lastly, it is important to note the high use of other substances in those PWID receiving OST. In the four classes of PWID receiving OST, individuals were using high levels of heroin and/or moderate levels of a broad-range of other substances. Considering the dangers associated with injecting methadone and buprenorphine, and mixing these substitutes with other substances (4), this is an important public health finding.

Our study includes a number of limitations. Firstly, our data is cross-sectional meaning that differences in polysubstance use and associated outcomes by treatment status must not be understood as resulting from treatment, as such factors may also predict treatment seeking or coercive participation in treatment (eg court diversion). Secondly, some of our outcome variables, including non-fatal overdose and the injection-related injuries and harms were not defined in medical terms by the interviewer, meaning there may have been some variability among participants in how they interpreted questions regarding having an 'abscess' or 'thrombosis'. There currently is no established way to define such concepts (29, 30), affecting the comparison of results across studies. A further limitation of the outcome variables relates to non-fatal overdose and our inability to include individuals who died from an overdose. Future studies are needed which assess the association between empirical polysubstance use profiles with fatal overdose. Thirdly, our group not receiving OST included some participants who had been receiving OST for less than six months (136 participants or roughly 8% of the non-OST sample). Thus, inclusion of these participants may have impacted both the polysubstance use profiles and associated outcomes found among our not receiving OST group. However, as we were primarily interested in how polysubstance use profiles among those who had been receiving OST for the duration of the study period differed with those who did not, and due to the small numbers of participants receiving OST for less than 6 months, we do not expect the interpretation of our findings to have been substantively altered by the inclusion of these participants.

Fourthly, for reasons outlined in the methods, we were unable to characterise substance use by legality or mode of administration, meaning that our findings are applicable only to the general drug injecting population. Had we been able to include these characteristics it is likely we would have identified further polysubstance use profiles, some exhibiting even greater risk of negative outcomes. However, the resulting model would have been very

complex, and questions concerning the role of legality and administration are therefore better dealt with in separate, specific research questions. Lastly, our convenience sample is not representative of all people who regularly injected drugs in Australia during 2011 to 2013 with implications for the generalizability of our findings. However, the purposive convenience sampling method is well established when targeting a sentinel group of people recruited because of their regular injecting drug use and knowledge of illicit drug markets (14). While the use of NSPs as a primary source of recruitment is a potential source of bias, methods of recruitment and interviewing remained the same each year, thereby unlinkley to influence trends over time.

Our study contributes to the literature on polysubstance use and drug-related outcomes by being the first to consider the central role played by OST, as delivered in the Australian context, in the formation of empirical polysubstance use profiles, and comparing associations among these profiles with a number of drug-related outcomes. Firstly, among those receiving and not receiving OST, polysubstance use profiles characterised by broad-ranging substance use exist and are associated with the highest levels of criminal activity and injecting-related injuries. These findings highlight the dangers of broad-range polysubstance use to the individual and society regardless of OST status. Secondly, a class emerged characterised by heavy morphine use and was associated with an increase in non-fatal overdose compared with all other classes combined. This serves to remind us that abuse of a single substance can in some circumstances be more serious than any number of combinations, and morphine users should be targeted by interventions aiming to reduce the occurrence of non-fatal overdose.

Funding and finance

Conflict of interest: All authors declare no conflicts of interest

Funding/Support: R.A. is funded by a NHMRC Career Development Award Level 2 in Population Health (APP1012485).

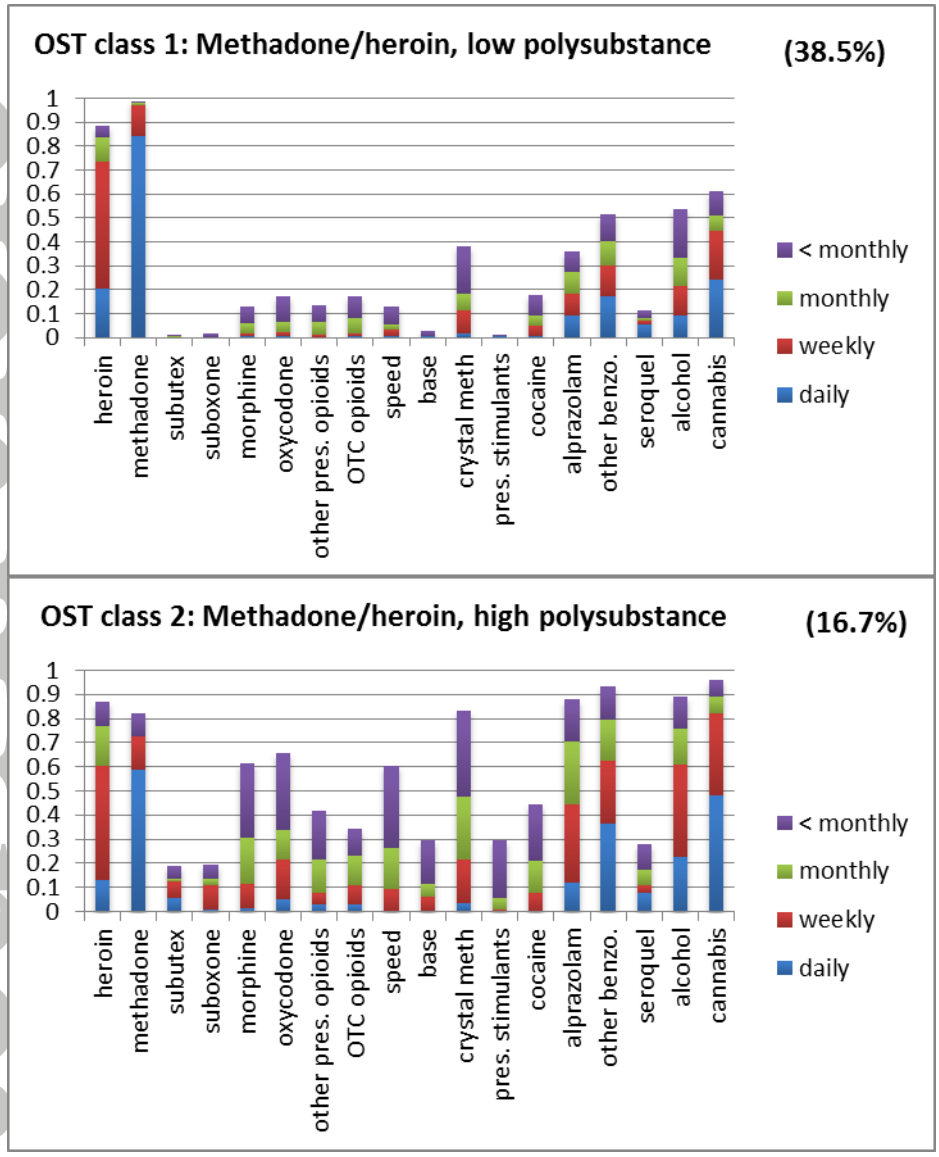
E.W. is funded by a National Drug and Alcohol Research Centre (NDARC, UNSW) PhD Scholarship and Australian Housing and Urban Research Institute (AHURI) Postgraduate Top-up Scholarship.

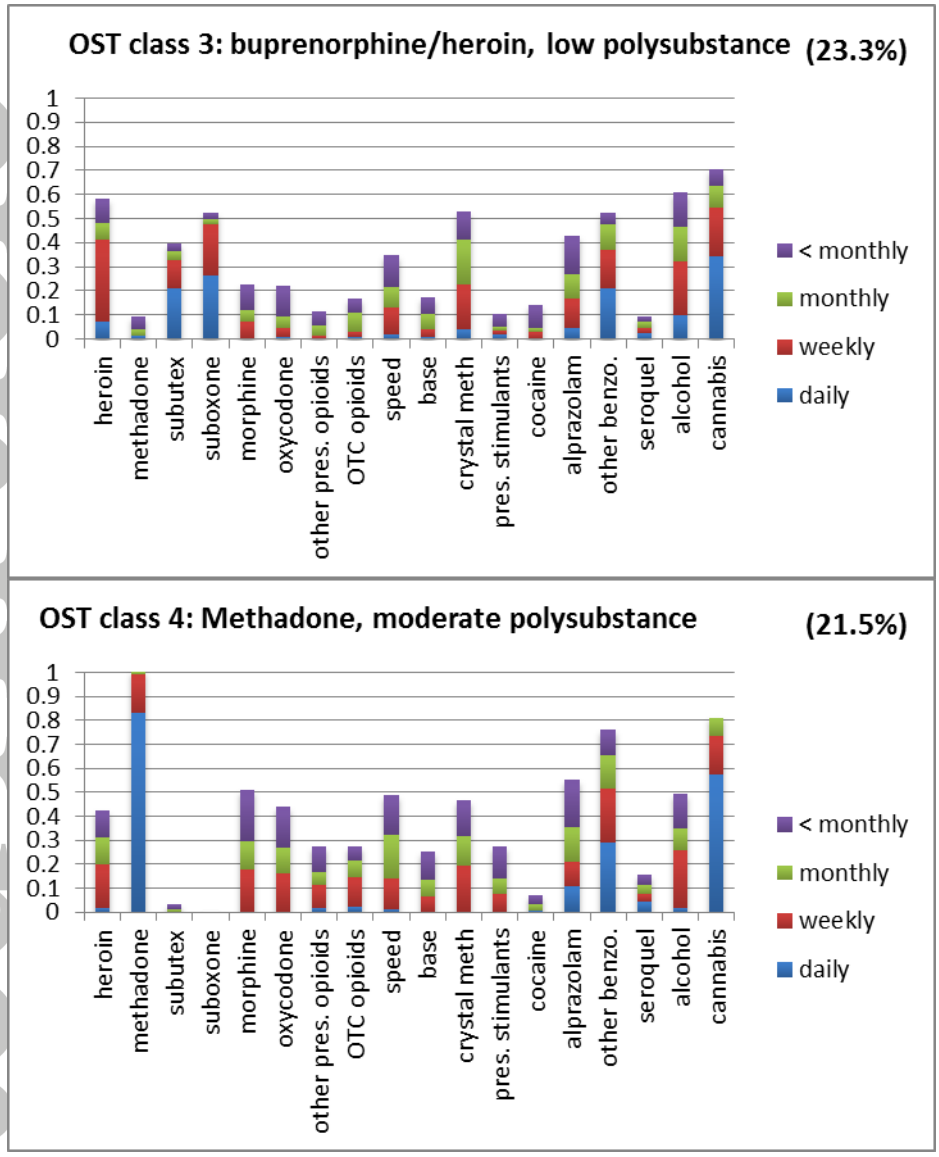
Contributors: KB has been designated principal author and was responsible for the bulk of the literature review, drafting, statistical analysis and discussion. GC played the role of lead statistician and helped develop and interpret the model. FM and RA contributed substantially to the drafting and revision of the manuscript and assisted in the literature review and methodology. PD, EW, LB and helped with numerous revisions of the manuscript.

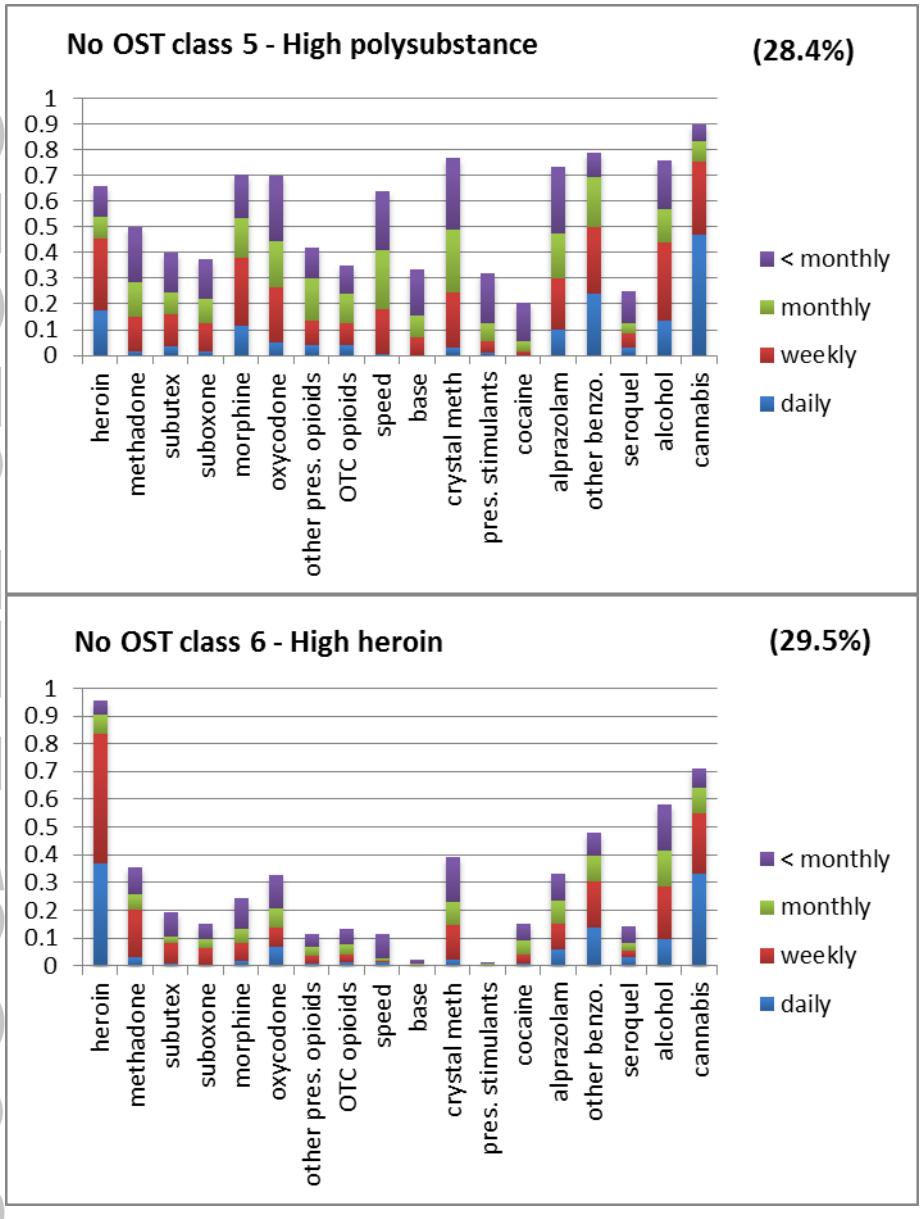
References

1. Calabria B, Degenhardt L, Briegleb C, Vos T, Hall W, Lynskey M, et al. Systematic review of prospective studies investigating "remission" from amphetamine, cannabis, cocaine or opioid dependence. Addict Behav. 2010;35(8):741-9.
2. Connor JP, Gullo MJ, White A, Kelly AB. Polysubstance use: diagnostic challenges, patterns of use and health. Current opinion in psychiatry. 2014;27(4):269-75.
3. Harrell PT, Mancha BE, Petras H, Trenz RC, Latimer WW. Latent classes of heroin and cocaine users predict unique HIV/HCV risk factors. Drug Alcohol Depen. 2012;122(3):220-7.
4. Veilleux JC, Colvin PJ, Anderson J, York C, Heinz AJ. A review of opioid dependence treatment: pharmacological and psychosocial interventions to treat opioid addiction. Clin Psychol Rev. 2010;30(2):155-66.
5. Strang J, McCambridge J, Best D, Beswick T, Bearn J, Rees S, et al. Loss of tolerance and overdose mortality after inpatient opiate detoxification: follow up study. Bmj. 2003;326(7396):959-60.
6. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev. 2009;3.
7. Tiihonen J, Krupitsky E, Verbitskaya E, Blokhina E, Mamontova O, Föhr J, et al. Naltrexone implant for the treatment of polydrug dependence: a randomized controlled trial. American Journal of Psychiatry. 2012;169(5):531-6.
8. Weiss RD, Potter JS, Fiellin DA, Byrne M, Connery HS, Dickinson W, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. Arch Gen Psychiat. 2011;68(12):1238-46.
9. Teesson M, Mills K, Ross J, Darke S, Williamson A, Havard A. The impact of treatment on 3 years' outcome for heroin dependence: findings from the Australian Treatment Outcome Study (ATOS). Addiction. 2008;103(1):80-8.
10. Gjersing L, Bretteville-Jensen AL. Is opioid substitution treatment beneficial if injecting behaviour continues? Drug Alcohol Depen. 2013;133(1):121-6.
11. Amato L, Davoli M, A Perucci C, Ferri M, Faggiano F, P Mattick R. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. Journal of substance abuse treatment. 2005;28(4):321-9.
12. Grella CE, Lovinger K. 30-year trajectories of heroin and other drug use among men and women sampled from methadone treatment in California. Drug Alcohol Depen. 2011;118(2):251-8.
13. Larance B, Degenhardt L, Lintzeris N, Bell J, Winstock A, Dietze P, et al. Post-marketing surveillance of buprenorphine-naloxone in Australia: diversion, injection and adherence with supervised dosing. Drug Alcohol Depen. 2011;118(2):265-73.
14. Hando J, Darke S, O'brien S, Maher L, Hall W. The development of an early warning system to detect trends in illicit drug use in Australia: the Illicit Drug Reporting System. Addiction Research & Theory. 1998;6(2):97-113.
15. Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, Normand S-L, et al. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. Psychological medicine. 2002;32(06):959-76.
16. Andrews G, Slade T. Interpreting scores on the Kessler psychological distress scale (K10). Australian and New Zealand journal of public health. 2001;25(6):494-7.
17. Slade T, Grove R, Burgess P. Kessler psychological distress scale: normative data from the 2007 Australian National Survey of Mental Health and Wellbeing. Australian and New Zealand Journal of Psychiatry. 2011;45(4):308-16.
18. Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. Journal of clinical epidemiology. 1998;51(11):1171-8.
19. Jenkinson C, Layte R. Development and testing of the UK SF-12. Journal of Health Services Research. 1997;2(1):14-8.

20. Muthén LK, & Muthén, B.O. Mplus user's guide. Los Angeles: Muthén & Muthén; 1998-2010.
21. McIlwraith F, Betts KS, Jenkinson R, Hickey S, Burns L, Alati R. Is low BMI associated with specific drug use among injecting drug users? Substance use & misuse. 2014;49(4):374-82.
22. Byrne BM. Structural equation modeling with Mplus : basic concepts, applications, and programming. New York: Routledge Academic; 2012. xvii, 412 p. p.
23. Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW. A meta-analytic review of psychosocial interventions for substance use disorders. The American journal of psychiatry. 2008;165(2):179-87.
24. Jones JD, Mogali S, Comer SD. Polydrug abuse: a review of opioid and benzodiazepine combination use. Drug Alcohol Depen. 2012;125(1):8-18.
25. Dietze P, Jolley D, Fry C, Bammer G. Transient changes in behaviour lead to heroin overdose: results from a case-crossover study of non-fatal overdose. Addiction. 2005;100(5):636-42.
26. Bonar EE, Ilgen MA, Walton M, Bohnert AS. Associations among Pain, Non-Medical Prescription Opioid Use, and Drug Overdose History. The American Journal on Addictions. 2014;23(1):41-7.
27. Carlson RG, Nahhas RW, Daniulaityte R, Martins SS, Li L, Falck R. Latent class analysis of non-opioid dependent illegal pharmaceutical opioid users in Ohio. Drug Alcohol Depen. 2014;134:259-66.
28. Dwyer R, Topp L, Maher L, Power R, Hellard M, Walsh N, et al. Prevalences and correlates of non-viral injecting-related injuries and diseases in a convenience sample of Australian injecting drug users. Drug Alcohol Depen. 2009;100(1):9-16.
29. Topp L, Iversen J, Conroy A, Salmon AM, Maher L. Prevalence and predictors of injecting-related injury and disease among clients of Australia's needle and syringe programs. Australian and New Zealand journal of public health. 2008;32(1):34-7.
30. Britton PC, Wines Jr JD, Conner KR. Non-fatal overdose in the 12 months following treatment for substance use disorders. Drug Alcohol Depen. 2010;107(1):51-5.







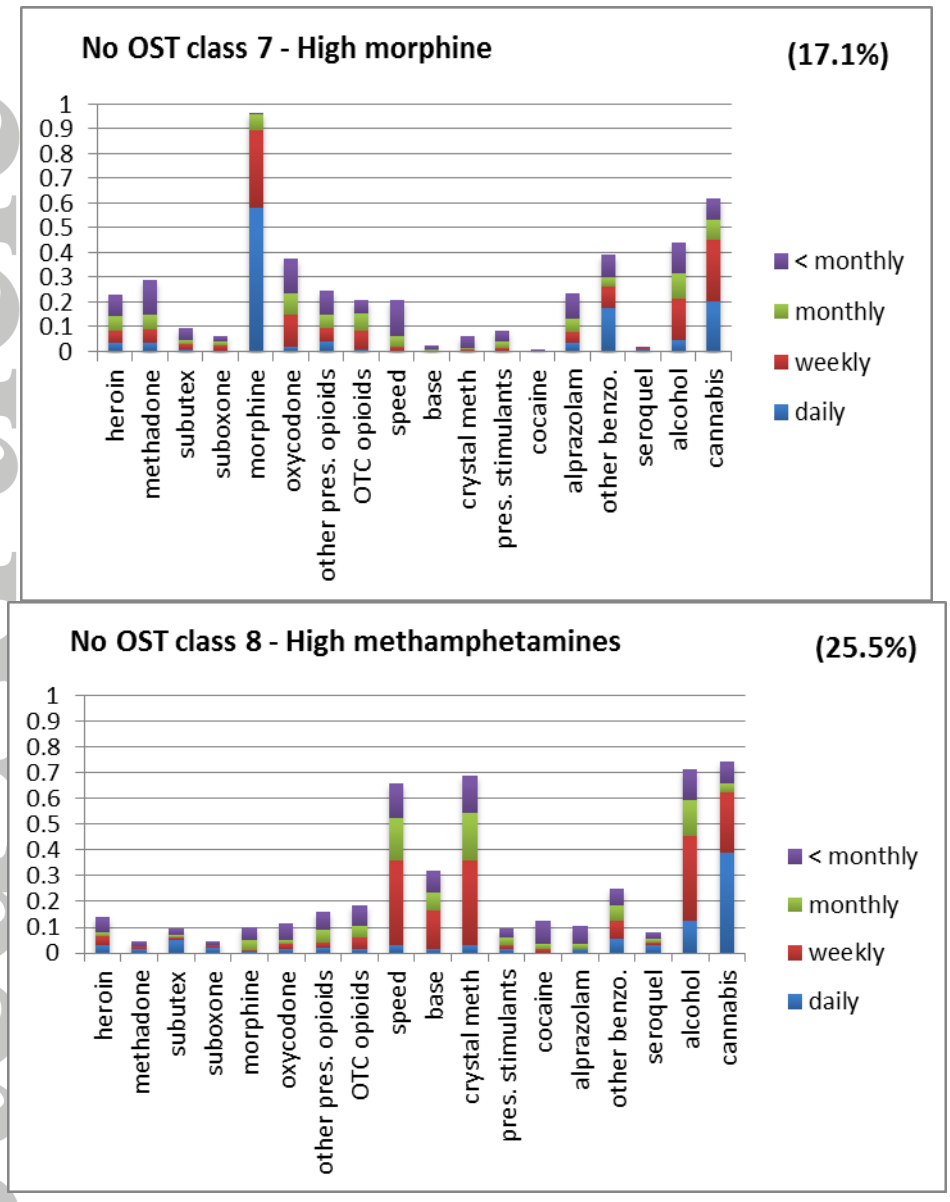


Figure 1: The Y-axis represents the probability of indicator endorsement for each class. 4 class LCA solution showing the probability of using each of the 18 substances at the frequency indicated separately among the two groups (i) OST and (ii) no OST (four classes in each group). OST, opioid substitution therapy; pres, prescription; benzo, benzodiazepines. Note: the prevalence estimates of each class are group specific, prevalence's of each class with respect to the entire sample are: class 1 (14.9%); class 2(6.1%); class 3 (8.9%); class 4 (7.9%); class 5 (17.7%); class 6 (18.3%); class 7 (10.7%); class 8 (15.6%).

Table 1: Univariable associations between demographic variables and <u>not</u> receiving opioid substitution therapy [expressed as odds ratios with 95% Confidence Intervals (95% CI)]

Predictor *(ref)*	**Prevalence % (*n*)**	**No treatment**
Gender *(male)*	(*n* = 2,658)	
female	34.2% (909)	**0.69 (0.57, 0.81)**
Age *(ref = 17-35)*	(*n* = 2,668)	
36-45	38.4% (1,025)	0.99 (0.81, 1.21)
46-71	25.7% (686)	0.93 (0.76, 1.36)
Partner *(yes)*	(*n* = 2,699)	
no	61.3% (1,636)	**1.45 (1.24, 1.70)**
Employed *(yes)*	(*n* = 2,671)	
no	88.3% (2,359)	**1.40 (1.11, 1.78)**
Housing *(stable)*	(*n* = 2,098)	
unstable	21.4% (570)	**1.45 (1.20, 1.77)**
Education *(tertiary)*	(*n* = 2,664)	
no tertiary	48.8% (1,300)	1.07 (0.92, 1.25)

Note: Analyses were logistic regression (adjusted only for survey year).

Table 2: Multivariable associations between the outcomes with treatment status and potential covariates

	Injecting-related harms and injuries			**Injecting-related risks**	
	overdose	thrombosis	abscess	used needle	no filter used
OST treatment *(yes)*					
no	**1.58 (1.01, 2.48)**	0.72 (0.50, 1.05)	0.97 (0.71, 1.33)	0.98 (0.73, 1.31)	1.19 (0.82, 1.72)
Gender *(male)*					
female	1.06 (0.69, 1.63)	1.27 (0.86, 1.87)	**1.47 (1.07, 2.02)**	0.95 (0.70, 1.28)	0.83 (0.57, 1.22)
Age *(ref = 17-35)*					
36-45	0.81 (0.49, 1.32)	**0.53 (0.32, 0.89)**	0.66 (0.44, 0.98)	1.33 (0.89, 1.99)	1.24 (0.80, 1.93)
46-71	0.73 (0.44, 1.20)	1.01 (0.65, 1.56)	0.84 (0.58, 1.22)	**1.53 (1.04, 2.25)**	0.88 (0.56, 1.39)
Partner *(yes)*					
no	1.36 (0.87, 2.13)	0.93 (0.63, 1.37)	1.03 (0.75, 1.42)	**0.59 (0.44, 0.79)**	1.10 (0.76, 1.59)
Employed *(yes)*					
no	1.30 (0.64, 2.64)	**2.43 (1.11, 5.32)**	1.16 (0.71, 1.89)	1.57 (0.93, 2.63)	1.78 (0.91, 3.45)
Housing *(stable)*					
unstable	0.96 (0.59, 1.58)	0.80 (0.49, 1.31)	1.39 (0.97, 1.99)	**1.43 (1.03, 1.98)**	0.83 (0.53, 1.29)
Education *(tertiary)*					
no tertiary	1.06 (0.71, 1.58)	0.86 (0.59, 1.25)	0.74 (0.55, 1.01)	1.26 (0.95, 1.67)	0.97 (0.68, 1.37)
	Criminality			**General health**	
	violent	property	dealing	physical health	poor mental health
OST treatment *(yes)*					
no	1.23 (0.81, 1.86)	**0.81 (0.66, 0.99)**	0.88 (0.73, 1.06)	0.99 (0.75, 1.31)	0.94 (0.78, 1.12)
Gender *(male)*					
female	**0.46 (0.28, 0.74)**	1.01 (0.81, 1.25)	**0.71 (0.58, 0.87)**	**2.23 (1.69, 2.94)**	**1.74 (1.44, 2.09)**
Age *(ref = 17-35)*					
36-45	**3.10 (1.63, 5.91)**	**3.06(2.28, 4.12)**	**1.64 (1.28, 2.10)**	**0.55 (0.38, 0.79)**	**1.54 (1.22, 1.96)**
46-71	**2.45 (1.28, 4.69)**	**2.03 (1.50, 2.74)**	**1.43 (1.12, 1.82)**	0.84 (0.61, 1.16)	**1.38 (1.09, 1.74)**
Partner *(yes)*					
no	**0.59 (0.40, 0.89)**	0**.81 (0.66, 0.99)**	**0.73 (0.60, 0.88)**	1.17 (0.87, 1.56)	1.01 (0.84, 1.22)
Employed *(yes)*					
no	2.00 (0.91, 4.41)	**1.73 (1.21, 2.47)**	1.36 (1.00, 1.84)	**3.55 (1.79, 7.06)**	**1.80 (1.32, 2.47)**
Housing *(stable)*					
unstable	**1.65 (1.08, 2.51)**	**1.27 (1.01, 1.62)**	0.92 (0.73, 1.15)	1.14 (0.82, 1.58)	**1.41 (1.14, 1.74)**
Education *(tertiary)*					
no tertiary	1.29 (0.87, 1.91)	0.99 (0.81, 1.22)	0.90 (0.75, 1.08)	1.14 (0.87, 1.49)	1.09 (0.91, 1.30)

Note: All analyses were multivariable logistic regression (i.e., estimates show the multivariable relationship between each of the outcomes with treatment status and the covariates). Estimates are also adjusted for year of survey.

Table 3: Multivariable associations between demographic variables and polysubstance use [expressed as odds ratios with 95% Confidence Intervals (95% CI)]

Predictor *(ref)*	**Group receiving OST**			
	class 1 methadone/ heroin, low poly.	**class 2** methadone/ heroin, high poly.	**class 3** buprenorphine low poly.	**class 4** methadone moderate poly.
Gender *(male)*				
female	**1.65 (1.29, 2.10)**	0.82 (0.55, 1.21)	0.83 (0.61, 1.13)	**1.40 (1.02, 1.92)**
Age *(ref = 17-35)*				
36-45	**0.52 (0.38, 0.71)**	1.17 (0.73, 1.88)	**1.57 (1.06, 2.33)**	1.17 (0.76, 1.79)
46-71	**0.72 (0.54, 0.96)**	1.18 (0.74, 1.89)	**1.49 (1.02, 2.19)**	1.28 (0.85, 1.93)
Partner *(yes)*				
no	**0.65 (0.50, 0.83)**	0.69 (0.48, 1.00)	**1.44 (1.06, 1.96)**	0.79 (0.57, 1.09)
Employed *(yes)*				
no	**0.66 (0.47, 0.92)**	0.66 (0.40, 1.08)	0.77 (0.51, 1.16)	1.38 (0.80, 2.35)
Housing *(stable)*				
unstable	**0.69 (0.50, 0.96)**	1.35 (0.89, 2.04)	0.69 (0.48, 1.01)	**0.64 (0.41, 0.99)**
Education *(tertiary)*				
no tertiary	1.12 (0.88, 1.42)	1.09 (0.76, 1.56)	0.88 (0.66, 1.18)	0.87 (0.63, 1.19)
Predictor *(ref)*	**Group not receiving OST**			
	class 5 polysubstance	**class 6** heroin	**class 7** morphine	**class 8** methamphetamine
Gender *(male)*				
female	**0.73 (0.57, 0.94)**	0.89 (0.70, 1.14)	1.00 (0.75, 1.35)	0.96 (0.75, 1.23)
Age *(ref = 17-35)*				
36-45	**1.66 (1.23, 2.24)**	0.93 (0.70, 1.23)	**0.44 (0.31, 0.62)**	**1.48 (1.09, 2.01)**
46-71	**1.40 (1.04, 1.89)**	0.80 (0.60, 1.05)	**0.59 (0.43, 0.81)**	1.34 (0.99, 1.82)
Partner *(yes)*				
no	0.82 (0.65, 1.03)	1.16 (0.92, 1.46)	**1.58 (1.16, 2.15)**	**1.30 (1.02, 1.65)**
Employed *(yes)*				
no	1.32 (0.90, 1.92)	1.25 (0.86, 1.82)	1.12 (0.70, 1.80)	1.05 (0.72, 1.54)
Housing *(stable)*				
unstable	**1.57 (1.22, 2.03)**	**1.32 (1.02, 1.72)**	0.66 (0.46, 0.96)	0.96 (0.72, 1.27)
Education *(tertiary)*				
no tertiary	0.82 (0.65, 1.03)	0.85 (0.68, 1.06)	**1.41 (1.07, 1.86)**	1.19 (0.94, 1.49)

Note: Analyses were eight separate multivariable logistic regressions, in which each class was compared to all other classes combined on a number of demographic and social factors (i.e., the estimates represent the increase in the dependent variables in the specified class compared with the reference which is composed of all individuals not in the specified class). Estimates are also adjusted for year of survey.

Table 4: Multivariable associations between the outcomes with the 8 polysubstance use classes [expressed as odds ratios with 95% Confidence Intervals (95% CI)]

	Injecting-related harms and injuries						**Injecting-related risks**			
	overdose		thrombosis		abscess		used needle		no filter used	
	Ref: lowest	Ref: combined	Ref: lowest	Ref: combined	Ref: lowest	Ref: combined	Ref: lowest	Ref: combined	Ref: lowest	Ref: combined
Class 1	1.15 (0.26, 5.01)	*ref*	2.28 (0.89, 5.82)	*ref*	1.48 (0.63, 3.48)	*ref*	**2.70 (1.08, 6.74)**	1.44 (0.85, 2.44)	*ref*	*ref*
Class 2	3.70 (0.91, 15.05)	*ref*	**4.03 (1.47, 11.07)**	**2.13 (1.09, 4.17)**	2.42 (0.98, 5.94)	*ref*	**5.23 (1.95, 14.01)**	**2.78 (1.50, 5.13)**	**6.16 (1.55, 24.52)**	**4.48 (1.96, 10.25)**
Class 3	1.41 (0.32, 6.24)	*ref*	2.45 (0.88, 6.84)	*ref*	1.71 (0.71, 4.13)	*ref*	**3.02 (1.14, 7.98)**	1.61 (0.87, 2.97)	1.85 (0.41, 8.43)	*ref*
Class 4	*ref*	*ref*	1.50 (0.45, 4.99)	*ref*	*ref*	*ref*	2.08 (0.74, 5.85)	*ref*	**11.49 (3.01, 43.78)**	**8.36 (4.26, 16.40)**
Class 5	2.84 (0.81, 9.95)	*ref*	2.37 (0.91, 6.16)	*ref*	**2.26 (1.04, 4.89)**	**1.61 (1.08, 2.39)**	4.04 (1.63, 10.00)	**2.15 (1.34, 3.45)**	**8.90 (2.55, 31.06)**	**6.46 (3.59, 11.62)**
Class 6	2.64 (0.75, 9.27)	*ref*	1.77 (0.67, 4.69)	*ref*	1.15 (0.50, 2.61)	*ref*	**3.70 (1.51, 9.10)**	**1.97 (1.23, 3.16)**	1.66 (0.41, 6.80)	*ref*
Class 7	**3.67 (1.03, 13.06)**	**1.83 (1.06, 3.17)**	*ref*	*ref*	1.58 (0.68, 3.67)	*ref*	*ref*	*ref*	**11.18 (3.16, 39.56)**	**8.13 (4.37, 15.13)**
Class 8	1.39 (0.36, 5.41)	*ref*	1.62 (0.60, 4.39)	*ref*	1.16 (0.50, 2.67)	*ref*	2.33 (0.91, 5.98)	*ref*	1.02 (0.21, 4.93)	*ref*
	Criminality						**General health**			
	violent		property		dealing		physical health		mental health	
	Ref: lowest	Ref: combined	Ref: lowest	Ref: combined	Ref: lowest	Ref: combined	Ref: lowest	Ref: combined	Ref: lowest	Ref: combined
Class 1	1.78 (0.39, 8.08)	*ref*	**2.14 (1.19, 3.85)**	-	1.56 (0.97, 2.52)	*ref*	1.92 (0.99, 3.71)	*ref*	**1.45 (1.01, 2.09)**	1.33 (0.98, 1.80)
Class 2	**5.57 (1.28, 24.19)**	**2.30 (1.16, 4.58)**	**5.27 (2.85, 9.74)**	-	**4.30 (2.53, 7.29)**	**3.26 (2.14, 4.96)**	**3.88 (1.85, 8.11)**	**2.74 (1.53, 4.89)**	**3.11 (1.98, 4.88)**	**2.84 (1.89, 4.27)**
Class 3	*ref*	*ref*	**2.96 (1.62, 5.42)**	-	**2.13 (1.28, 3.53)**	**1.62 (1.10, 2.39)**	1.28 (0.55, 2.95)	*ref*	1.25 (0.82, 1.90)	*ref*
Class 4	3.50 (0.81, 15.09)	*ref*	**3.24 (1.75, 5.99)**	-	**2.60 (1.54, 4.37)**	**1.97 (1.31, 2.95)**	**2.97 (1.47, 5.98)**	**2.09 (1.22, 3.58)**	**1.58 (1.03, 2.42)**	1.45 (0.99, 2.11)
Class 5	**4.53 (1.18, 17.47)**	**1.87 (1.14, 3.07)**	**4.04 (2.30, 7.10)**	-	**3.53 (2.24, 5.56)**	**2.68 (1.96, 3.65)**	**3.57 (1.86, 6.85)**	**2.53 (1.64, 3.91)**	**2.34 (1.64, 3.32)**	**2.14 (1.60, 2.85)**
Class 6	3.71 (0.95, 14.56)	*ref*	**2.28 (1.29, 4.04)**	-	**1.75 (1.08, 2.82)**	1.33 (0.94, 1.87)	**2.12 (1.10, 4.08)**	1.50 (0.95, 2.37)	**1.68 (1.19, 2.37)**	**1.53 (1.15, 2.04)**
Class 7	1.27 (0.23, 7.13)	*ref*	*ref*	-	*ref*	*ref*	**2.60 (1.34, 5.08)**	**1.84 (1.13, 3.00)**	1.11 (0.73, 1.70)	*ref*
Class 8	2.33 (0.56, 9.60)	*ref*	**2.04 (1.14, 3.66)**	-	**1.65 (1.02, 2.66)**	1.25 (0.88, 1.77)	*ref*	*ref*	*ref*	*ref*

Note: Class 1, OST-methadone/heroin, low polysubstance; Class 2, OST-methadone/heroin high polysubstance; Class 3, OST-buprenorphine, low polysubstance; Class 4, OST-methadone, moderate polysubstance; Class 5, No OST-polysubstance; Class 6, No OST-heroin; Class 7, No OST-morphine; Class 8, No OST-methamphetamines. Estimates adjusted for confounders included in table 3. As detailed in the methods section, the first column for each outcome uses the polysubstance use class with the lowest odds as the reference group, while the second column uses a combination of all classes which did not differ significantly from the class with the lowest odds as the reference.