Association between poly-substance use and substance use disorder treatment non-completion admitted to multiple treatments between 2010-2019 in Chile

Andrés González-Santa Cruz [a,b,c]; José Ruiz-Tagle Maturana[b,d]; Mariel Mateo Pinones [b,f]; Álvaro Castillo-Carniglia [b,c,g];

[a] Doctoral Program in Public Health, Institute of Population Health, Faculty of Medicine, Universidad de Chile, Chile[b] Millennium Nucleus for the Evaluation and Analysis of Drug Policies (nDP), Chile.
[c] Associate Professor, Department of Public Health, Facultad de Medicina y Ciencia, Universidad San Sebastian, Chile.
[d] Fundación Instituto Profesional DUOC UC, Santiago, Chile.
[f] School of Criminology and Criminal Justice, Griffith University, Australia
[g] Millennium Nucleus on Sociomedicine (SocioMed), Chile.

**Correspondence to:*

Disclosure: The authors report no relevant conflicts of interest.

ABSTRACT

Background: Evidence regarding the implications of reporting polysubstance use (PSU) at admission on substance use treatment (SUT) outcomes is limited. Moreover, most studies come from the Global North and have focused on individual substances in isolation, with one SUT episode. They also have considered PSU as an exclusion criterion for studies on treatment effectiveness, raising concerns about its translatability to real health contexts. Therefore, it is crucial to determine the role of reporting PSU in treatment non-completion (i.e., treatment dropouts, spelled by misconduct) to improve treatment for these groups, especially outside the Global North.

Methods: This comprehensive retrospective cohort study was based on adult treatment records from the Chilean National Substance Use Agency from 2010 to 2019. A total of 13,317 individuals were analyzed, with 30,988 treatment episodes. SUT completion status was categorized as completed or non-completed. The primary outcome was treatment non-completion. We used Poisson general estimating equations, controlling for several covariates of each patient (i.e., sociodemographic information, mental health and substance use patterns), to estimate the relative risk (RR) and 95% confidence intervals (95%CI) of non-completion by reporting PSU. Sensitivity analyses were conducted through marginal structural models using weights accounting for the inverse intensity of treatments, and by separating patients with and without alcohol as their secondary substance of concern.

Results: The risk of non-completion was higher in intensive ambulatory settings for the general population (RR= 1.04 95%CI 1.01-1.07) and in women-only residential settings (RR= 1.14 95%CI 1.06-1.23). However, this association was inconsistent across all treatment settings (Cochran's Q = 14.49, p = 0.0059). Sensitivity analyses were consistent with the

main results regarding direction, although attenuated associations between PSU and treatment non-completion.

Conclusions: Reporting PSU at admission was modestly associated with a higher risk of non-completion. The analysis, adjusted for various covariates and accounting for irregular observation times, highlighted the association between PSU reporting and treatment outcomes in specific settings. This study is one of the few from outside the Global North and could have significant implications for substance use treatment worldwide. Findings underscore the necessity for personalized interventions tailored to patients reporting PSU in different treatment settings.

Keywords: Polysubstance use; Substance use; Treatment non-completion; Administrative data; Chile.

Abstract words: 350/350

Manuscript words: 3913

Abstracts should be 350 words or fewer, structured into sections describing the Introduction, Methods, Results, and Conclusions. Do not include in-text citations in the abstract.

- All figures (include relevant captions) in separate files
- All tables (including titles, description, footnotes) in separate files

1. INTRODUCTION

People with substance use disorder (SUD) tend to use more than one substance unintentionally, unconsciously (e.g., due to unregulated and contaminated supplies), or intentionally (Bunting et al., 2023; Quek et al., 2013) during active use in their lifetime (Connor et al., 2014). Some reasons for intentional polysubstance use (PSU) include additive or synergistic reward, compensation for undesired effects or negative internal states, predisposition, or being related to supply (e.g., due to shortages of the main substance) (Karamouzian et al., 2024). Importantly, people with PSU are a high-risk population because they are related to a higher mortality rate (Gjersing & Bretteville-Jensen, 2018), a higher risk of relapse (Chen et al., 2019; Hassan & Le Foll, 2019), less responsiveness to substance use treatment (Bonfiglio et al., 2022), and other detrimental features such as risky sexual behavior (Daskalopoulou et al., 2014; Sewell et al., 2017), violence (Choi et al., 2022; Steele & Peralta, 2020), and psychiatric comorbidities (Mefodeva et al., 2022). Over the last three decades, evidence has shown that the number of people with PSU has significantly increased in high-income countries from North America, Europe, and Australia (Bonfiglio et al., 2022), highlighting the relevance of studying this topic.

Despite the association between completing SUD treatment and long-term benefits, such as a lower risk of readmission to treatment (Ruiz-Tagle Maturana et al., 2023), lower risk of relapse (Andersson et al., 2019), abstinence (McPherson et al., 2017), and better quality of life (Choi & DiNitto, 2020) is well known, evidence regarding the long-term consequences of reporting PSU on treatment outcomes is limited and mixed. The lack of research on PSU is partly explained because most studies have focused on individual substances in isolation and have considered multiple substance use history as an exclusion

criterion for clinical studies on treatment effectiveness, which raises the problem of its translatability to real-world health contexts (Bonfiglio et al., 2022). Regarding treatment outcomes, some studies have reported a lower likelihood of treatment completion among people with PSU (Andersson et al., 2021; Levola et al., 2021), while others have found no association (Andersson et al., 2018) or higher completion rates (Basu et al., 2017). It is crucial to determine the role of reporting PSU in treatment completion to improve treatment effectiveness and research translatability (Crummy et al., 2020). However, this role must be understood in patients who experience multiple recursive treatments (Bórquez et al., 2024). People with persistent SUD show different characteristics from those who no longer have a disorder after a single treatment or without any treatment (Beaulieu et al., 2022).

Given that SUD is understood as a chronic condition (Fleury et al., 2016), the association between reporting PSU and treatment completion on the first SUD treatment alone requires accounting for some patients to be readmitted to treatment throughout the follow-up period. Thus, checking for biases and adjusting for confounders is warranted (Griffin et al., 2014; Hansen et al., 2020). Additionally, these treatments are irregularly spaced but not random, as the time between treatments might be related to biopsychosocial and treatment-related factors. Hence, patients with worse outcomes in previous treatments might have a more or less intense frequency of treatments in the future, which may also explain treatment outcomes, such as completion or dropout (Hansen et al., 2020; Vázquez-Real et al., 2022).

More importantly, the relationship between people reporting PSU and treatment completion can be affected by various factors such as heterogeneous PSU patterns (Bhondoekhan et al., 2023; Price et al., 2023), treatment goals, patient characteristics,

resource availability, and SUD severity profiles. These characteristics are highly dependent on treatment settings (Fiestas & Ponce, 2012; Reif et al., 2021; Tiet et al., 2007). In Chile, treatments for adults with SUD are delivered in residential, intensive ambulatory, and basic ambulatory settings. Residential settings have a planned duration of one year, and are offered from five to seven days a week with at least five weekly interventions, while intensive ambulatory have a duration of six to eight months, with weekly sessions that have a duration of six hours and up to four interventions. These also are divided into treatments for the general population and women-specific treatments (i.e., with tailored needs often directed to pregnant women or having children), but basic ambulatory settings are only available within general population programs. Olivari et al. found that women-specific treatment settings had different readmission and treatment completion rates than general population programs in Chile. Similarly, Ruiz-Tagle et al. found that completion was less likely in ambulatory settings (Olivari et al., 2022; Ruiz-Tagle Maturana et al., 2023).

Most research on PSU comes from the Global North, where treatment settings are usually specialized for particular substances (Babor, 2021; Körkel, 2021). This is not the reality in other contexts, such as Latin America, where treatment is mostly delivered in non-specialized settings or long-term psychosocial interventions outside hospital facilities (i.e., therapeutic communities), in part due to scarce resources and a shortage of the mental health and medical workforce. Studying the role of PSU in treatment outcomes in Latin America is challenging because of limited local data (Lalwani et al., 2022). Furthermore, using evidence from the Global North is not straightforward, as it focuses on methamphetamines, opioids and injecting drug use, which are epidemiologic features that are not prevalent in the Latin American context (Castaldelli-Maia et al., 2023). In contrast, alcohol consumption is

predominant in Latin America, as it is one of the regions with the highest associated morbidity worldwide in absolute numbers (Degenhardt et al., 2018), and it is increasing among youth and women (Diaz et al., 2020). Also, the treatment gap for people meeting SUD criteria and reporting attending treatment in national population surveys of Uruguay, Argentina and Chile is lower among those meeting alcohol dependence criteria vs. cocaine-related substances and marijuana (Mauro et al., 2022). In Chile, evidence among SUD treatment population has shown that alcohol use as a primary substance of admission had a lower risk of treatment readmission (Ruiz-Tagle et al., 2023). Hence, its presence among people reporting PSU may deserve special attention.

Moreover, because many studies in the Global North have often overlooked high-risk populations, there are reasons to believe that this is also the case in Latin America, where the prevalence of PSU is notably high (Reyes et al., 2013). A meta-analysis focusing on Global North studies of cocaine found that more than 70% of people who use cocaine have concurrent alcohol consumption. In addition, between 38% and 64% of the participants had concurrent marijuana use (Liu et al., 2018). A recent study conducted in a Chilean hard-to-reach population that used cocaine base paste found that 47–66% of users had simultaneous substance use (Olivari et al., 2022). Similarly, an analysis of data from studies conducted in six Latin American countries found that 21% of the participants reported PSU (Vilugrón et al., 2022), which was more frequent among males and young adults (18-34) from Chile, Uruguay, and Argentina. In addition, PSU is related to school dropout, unemployment, and sexual and antisocial risk behaviors (Olivari et al., 2022; Santis et al., 2007; Vilugrón et al., 2022).

Chile is an interesting case that allows for an examination of a context outside the Global North. It has a robust public treatment system that has produced a large and high-quality dataset that includes all treatment episodes of people with public health insurance (~80% of the population) since its creation in 2010 (Mateo Pinones et al., 2022). Findings from the Chilean Budgetary Office study support the need for further research to determine whether treatments effectively address characteristics such as PSU behaviors in a context where two out of three reported PSU (DIPRES, 2017). Understanding the PSU-treatment completion relationship could inform effective prevention and intervention strategies adapted to patients' needs. Moreover, expanding knowledge about patients' needs and inequalities in access to health services in the Global South context can serve as an input for developing local policies and actions to reduce health inequities. Thus, this study aimed to address this gap by estimating the association between having reported PSU and treatment non-completion (i.e., treatment dropouts or spelled by misconduct) among adult patients admitted to multiple SUD treatment programs in Chile from 2010 to 2019.

2. MATERIAL AND METHODS

2.1. Setting and participants

We included adult patients (+18 years old) with ongoing treatments from 2010 to 2019. Censoring occurred after the date of data retrieval (November 13, 2019), after an outcome event, or when a patient left the cohort with no other outcomes. Patients with only one treatment episode were excluded. To account for variability by treatment setting, we stratified the analysis by baseline treatment: basic ambulatory (n= 4,360), intensive ambulatory for the general population (GP) (n= 4,998), GP residential (n= 2,178), women-specific/only intensive ambulatory (n= 745), and WO residential (n= 1,036). After excluding records of

ongoing treatments and referrals outside the treatment network, 72,404 patients with 90,075 treatments were selected. In the total sample, 82% had one treatment episode, whereas 1% had more than three treatment episodes. We focused on patients who received more than one treatment, identifying 13,317 patients and 30,988 observations. This study was approved by the Griffith University Human Research Ethics Committee (GUHREC GU Ref. No: 2022/919).

2.2. Variables

The exposure variable was PSU at admission, a self-reported answer to using more than one main substance among alcohol and illicit drugs at admission for SUD treatment, whether sequential or concurrent (Crummy et al., 2020; Font-Mayolas & Calvo, 2022).

The outcome variable was SUD treatment outcome/non-completion status (1=dropout or spelled by misconduct; 0=completed treatment). In addition, the models were adjusted for various baseline confounding variables related to substance use, demographics, and social factors.

The following covariates were included in the model of the association between reported substance use and treatment non-completion status: biopsychosocial compromise (severe status) at admission to treatment, age at admission to treatment, birth year, primary substance of the initial diagnosis (cocaine hydrochloride, cocaine base paste, marijuana, and other substances), psychiatric comorbidity (confirmed comorbidity and diagnosis unknown or under study), daily frequency of primary substance use at admission, occupational status (inactive and unemployed), and primary substance at admission to treatment (cocaine hydrochloride, cocaine base paste, marijuana, and other substances). For further information, please review Supplemental Section 1.

2.3. Missing data

Given the complex longitudinal structure of the data, we conducted a random-forest-based imputation using the *missRanger* package. We used 300 trees with five candidate values of predictive matching (thus aiming for plausible imputations given predictor values), with a maximum of 50 iterations per chaining step. This imputation procedure may circumvent the specification of interactions or nonparametric relationships and handle collinearity between imputation variables (Hong & Lynn, 2020; Sheetal et al., 2023).

2.4. Bivariate analyses

Characteristics of the study sample were summarized by the median (Q2) and percentiles 25 and 75 in brackets for continuous variables, while categorical variables are represented in frequencies and percentages (%) in parenthesis. Differences between people reporting and not reporting PSU at baseline were quantified using standardized mean differences (SMD).

Incidence rates (IR) were calculated per 1,000 person-months to explore the crude association between reporting PSU and treatment non-completion while accounting for heterogeneous follow-up times.

2.5. Model adjustment

We fitted marginal regression models to estimate the relative risk (RR) of people with or without PSU at admission to non-completion status treatment (Grafféo et al., 2018) using generalized estimating equations, assuming a Poisson distribution with a log-link function and an independent structure. Heterogeneity tests were conducted in different strata of the treatment settings for the ratio effect measures (Kaufman & MacLehose, 2013).

2.6. Sensitivity analyses

Given that the study design was based on the administrative records of patients entering and re-entering treatment at varying frequencies and follow-up times, we explored the irregularity of assessment times during which reported patient substance use was captured (See Supplemental Section 2). To address the irregular patterns of admission to treatment and the informative differences therein, marginal structural models were employed and weighted using inverse intensity weights (IIW) by modelling the time to be observed (i.e., stay in treatment or being readmitted) as a counting process (See Supplemental Section 3).

An additional sensitivity analysis to account for differences between the variance and the mean of PSU reports using Negative Binomial distributions was tested using the Quasi-likelihood Information criterion for model selection (See Supplemental Section 4).

A third sensitivity analysis distinguished patients showing PSU with alcohol as their secondary substance at admission to treatment, PSU without alcohol as their secondary substance, and patients without PSU (See Supplemental Section 5).

2.7. Data and code availability

Code & markdowns are available here: bit.ly/4cE8gyf.

3. RESULTS

This section is organized into distinct subsections that detail the specific aspects of our analysis.

3.1. Characteristics of the study sample

Several key differences were notable among the individuals who reported polysubstance use. In terms of demographics at baseline, people with PSU, when compared to people who reported single substance use, had their first admission to treatment earlier in

life. In addition, a higher percentage of the participants were unemployed. Regarding substance use at baseline, people with PSU were more likely to report using cocaine paste and hydrochloride cocaine instead of alcohol as the primary substances that led them to treatment. In terms of the type of initiation substance, fewer started with alcohol, whereas more began with marijuana. In terms of other health information at baseline, severe biopsychosocial compromise was more frequent among patients with PSU. These differences led us to adjust for covariates to estimate the relative risk of treatment non-completion between patients who reported PSU and those who did not (Table 1).

3.2. Prevalence and incidence of PSU and treatment completion

Interestingly, among the patients who received only one treatment, 72% reported PSU. However, when examining patients with multiple treatment episodes, 91% reported PSU in at least one treatment episode. This association is also evident when comparing the number of treatments to the proportion of incomplete treatments. Specifically, 71% of patients with only one treatment did not complete it, whereas 92% of the patients had at least one treatment episode with a non-completion status. According to Figure 1, patients reporting PSU had a slightly lower non-completion than patients without PSU, this difference being more notable among patients in women-specific residential settings (74% vs. 63%), while patients in baseline basic ambulatory settings showing the highest percentages of non-completion.

However, a lower incidence of non-completion was observed in patients who reported PSU at admission. Specifically, the incidence of at least one non-completion episode per patient, followed from the first admission until the censoring date (November 2019), was lower in patients reporting PSU at admission to the first treatment (11.6 95% CI 11.3-11.8 per 1,000 person-months) compared to patients who did not report PSU (13.2 95% CI 12.6-

13.8). Similarly, the incidence of non-completion at the first admission was lower among patients reporting PSU at admission to the first treatment (9.9 95% CI 9.7-10.1) versus patients who did not report PSU (11.3 95% CI 10.8- 11.9). When focusing more longitudinally on patients who had at least one treatment in which they reported PSU, we see that rates of at least one non-completion are lower in this group (11.6 95% CI 11.4-11.9) compared to patients who did not report any PSU (13.9 95% CI 13.1-14.8). This trend was also observed when looking at the incidence of non-completion at the first treatment episode alone (10.0 95% CI 9.8-10.2 versus 11.9 95% CI 11.1-12.6) (Table 2).

3.3. Marginal longitudinal association between Polysubstance use at admission and treatment outcome

According to Table 3, we found a modest association between polysubstance use at any admission to treatment among users in intensive ambulatory settings for the general population (RR= 1.04 95% CI 1.01-1.07). Also, the risk was 14% higher for residential settings exclusive to women (RR= 1.14 95% CI 1.06-1.23). The association between polysubstance use and treatment non-completion varied significantly across the treatment settings (Cochran's Q= 14.5, p= 0.0059).

3.4. Sensitivity analyses

The associations between polysubstance use (PSU) and treatment non-completion were stable across models, with null intervals for intensive ambulatory settings for women and residential settings for the general population. One model for basic ambulatory settings showed a modest significant association (RR= 1.04 95% CI 1.01-1.07). The association weakened in general population intensive ambulatory settings, especially with marginal

models with inverse intensity weights from an intensity model with stratified follow-up and lagged covariates at 1 (RR= 1.01 95% CI 0.98-1.05). In women-specific residential settings, only the marginal model with inverse intensity weights from an intensity model stratified by follow-up with lagged covariates at 1 overlapped the null (RR= 1.09 95% CI 0.99-1.20), although both settings maintained a positive direction (See Table S5).

Distinguishing between patients reporting PSU with and without alcohol as a substance of concern at admission showed similar results (See Table S6). Patients in residential settings exclusive to women showed associations for both patients reporting PSU with (RR= 1.14 95% CI 1.06-1.23) and without (RR= 1.14 95% CI 1.05-1.24) alcohol. However, patients in intensive ambulatory settings for the general population only showed associations among people with alcohol use as a secondary substance (RR= 1.10 95% CI 1.07-1.14) but people that reported PSU without alcohol showed positive associations but with confidence intervals that crossed the null (1.02 95% CI 0.99-1.05). These associations also occurred for patients in basic ambulatory settings reporting PSU with alcohol (RR= 1.08 95% CI 1.05-1.12) but did not occur in those without alcohol (1.01 95% CI 0.98-1.04). Interestingly, reporting PSU with alcohol as a secondary had a protective role among people in residential treatments for the general population (RR= 0.89 95% CI 0.83-0.94).

4. DISCUSSION

Our findings revealed a significant association between reporting PSU at admission and the risk of treatment non-completion among patients admitted to SUD treatment programs in Chile between 2010 and 2019. Specifically, the risk of non-completion was modestly higher in intensive ambulatory settings for the general population (RR= 1.04 95% CI 1.01-1.07) and in women-only residential settings (RR= 1.14 95% CI 1.06-1.23). However, this association was not consistent across all treatment settings, indicating variability in how PSU influences treatment outcomes, depending on the type of treatment program (Cochran's Q= 14.5, p= 0.0059). Sensitivity analyses supported these findings, showing stability in the associations across the different model specifications and treatment settings. After comparing patients reporting PSU versus those reporting single substance use regarding treatment completion, we found notable differences in treatment outcomes. The association between reporting polysubstance use and treatment non-completion seems robust to different model specifications, suggesting that despite their complex clinical profiles, patients with PSU may benefit from repeated treatment engagements. A more detailed analysis distinguishing between PSU with alcohol and PSU without alcohol as a secondary substance allowed us to observe that PSU with alcohol as a secondary substance showed associations for every treatment setting at baseline, excepting women-specific intensive-ambulatory settings. Furthermore, for those individuals who had alcohol as a secondary substance, PSU might play a protective role against treatment non-completion among patients in residential treatments for the general population. This last result does not align with those of recent studies, suggesting that PSU generally complicates treatment retention

in specific settings (Andersson et al., 2021; Levola et al., 2021). Regarding the reasons for non-completion, a study conducted in Latin America found that the main reasons for abandonment were “not accepting the rules of the institution,” “lack of money”, and “not feeling comfortable with the facilities” (Gómez-Restrepo et al., 2017). An impact evaluation of treatment conducted in Chile found a lack of time to assist (in ambulatory treatments) and a sense of well-being (DIPRES, 2017) as the main reasons for non-completion.

Bivariate analyses highlight the various demographic and clinical characteristics that differentiate patients reporting PSU from those using a single substance. Patients with PSU tended to be younger, with a median age of 31.4 years at admission, compared to 37.1 years for single-substance users, and were more likely to be unemployed. Additionally, the expansion of treatment supply, the broader reach of SENDA into more sectors and the healthcare network, and a gradual reduction in the stigma associated with returning to treatment could also contribute to this pattern. Additionally, the primary substances leading to treatment admission differed significantly, with PSU patients reporting cocaine hydrochloride and base paste as their main substances compared with alcohol. Moreover, severe biopsychosocial compromise is more prevalent among patients with PSU, underscoring the complex clinical profiles that require tailored interventions. Despite these differences, the incidence rates of non-completion were paradoxically lower among patients with PSU in certain contexts, suggesting that repeated treatment engagements might influence their overall treatment trajectory. These findings differ from studies that have observed lower treatment responsiveness among patients with PSU (Bonfiglio et al., 2022).

We focused on people with a persistent pattern of substance use disorder rather than a transient substance use disorder. These patients are characterized by repeated treatment

episodes, varying periods of abstinence, and relapses leading to the resumption of moderate or problematic substance use, as highlighted in the literature (Beaulieu et al., 2022). Our results indicate that while PSU poses challenges, the specific context and characteristics of the treatment setting play a critical role in determining outcomes, highlighting the need for tailored interventions.

Regarding secondary analyses, we observed that accounting for irregular assessment of people with multiple treatments (i.e., different frequency of treatments and time between treatments) through inverse intensity weighting did not change associations between reporting PSU and treatment non-completion substantially. Interestingly, some factors that we expected to be influential, such as polysubstance use in previous treatments, specific primary substances at admission, and certain psychiatric comorbidities (Passos & Camacho, 2000), were found to have negligible or non-significant effects on treatment return rates. We suspect adjusting for biopsychosocial compromise and stratification by treatment setting would have captured the variability attributed to these factors and substantially attenuated these associations. Future studies should explore whether a causal conclusion can be drawn from these associations by employing other advanced causal inference methods.

This study had some limitations. First, the proportional intensity model that calculates IIWs imposes a proportional hazard assumption on assessment intensity. However, this assumption is debatable. Diagnosing proportionality in a Cox model with recurrent events can be quite challenging, and statistical tools might not account for changes in intensities due to possible changes in baseline risks for cumulative events, making interpretations of nonproportionality less straightforward (Royston & Altman, 2013). Tests based on Schoenfeld residuals are insufficient because contrasting the null hypothesis for changes as

a function of time may not be entirely indicative of nonproportional hazards (Dickman, 2023). Even small violations can become apparent because of sample size (Keele, 2010). Additionally, given that the intensity model has prediction purposes (i.e., readmission), it can still be used effectively even if hazards are not proportional (Jardillier et al., 2022). However, the association described here may lack causal interpretation, given that the recurrent event process might be associated with the right censoring mechanism. For example, patients admitted for treatment on dates closer to administrative censorship or in ongoing treatments might have different characteristics that may change the inverse of susceptibility to recurrent treatments (Rytgaard & van der Laan, 2024).

5. CONCLUSION

Our study showed that PSU at admission was associated with higher treatment non-completion rates in specific settings, notably in intensive ambulatory and women-only residential programs. These findings underline the need for tailored interventions to address the unique challenges of PSU patients with PSU. Additionally, demographic factors such as age and birth cohort significantly influenced treatment outcomes. This study provides valuable insights for improving SUD treatment programs in Latin America, emphasizing the importance of comprehensive data collection and personalized treatment strategies to enhance patient retention and completion rates.

6. BIBLIOGRAPHY

Andersson, H. W., Lauvsnes, A. D. F., & Nordfjærn, T. (2021). Emerging Adults in Inpatient Substance Use Treatment: A Prospective Cohort Study of Patient

Characteristics and Treatment Outcomes. *European Addiction Research*, *27*(3), 206–215. https://doi.org/10.1159/000512156

Andersson, H. W., Steinsbekk, A., Walderhaug, E., Otterholt, E., & Nordfjærn, T. (2018). Predictors of Dropout From Inpatient Substance Use Treatment: A Prospective Cohort Study. *Substance Abuse: Research and Treatment*, *12*, 1178221818760551. https://doi.org/10.1177/1178221818760551

Andersson, H. W., Wenaas, M., & Nordfjærn, T. (2019). Relapse after inpatient substance use treatment: A prospective cohort study among users of illicit substances. *Addictive Behaviors*, *90*, 222–228. https://doi.org/10.1016/j.addbeh.2018.11.008

Babor, T. F. (2021). Treatment Systems for Population Management of Substance Use Disorders: Requirements and Priorities from a Public Health Perspective. In N. el-Guebaly, G. Carrà, M. Galanter, & A. M. Baldacchino (Eds.), *Textbook of Addiction Treatment: International Perspectives* (pp. 553–567). Springer International Publishing. https://doi.org/10.1007/978-3-030-36391-8_39

Basu, D., Ghosh, A., Sarkar, S., Patra, B. N., Subodh, B. N., & Mattoo, S. K. (2017). Initial treatment dropout in patients with substance use disorders attending a tertiary care de-addiction centre in north India. *The Indian Journal of Medical Research*, *146*(Supplement), S77–S84. https://doi.org/10.4103/ijmr.IJMR_1309_15

Beaulieu, M., Tremblay, J., & Bertrand, K. (2022a). Adjustments to Service Organization in Specialized Addiction Services and Clinical Strategies for Better Meeting the Needs of People with a Persistent Substance Use Disorder. *International Journal of Mental Health and Addiction*. https://doi.org/10.1007/s11469-022-00982-z

Beaulieu, M., Tremblay, J., & Bertrand, K. (2022b). Adjustments to Service Organization in Specialized Addiction Services and Clinical Strategies for Better Meeting the

Needs of People with a Persistent Substance Use Disorder. *International Journal of Mental Health and Addiction*. https://doi.org/10.1007/s11469-022-00982-z

Bhondoekhan, F., Li, Y., Gaither, R., Daly, M. M., Hallowell, B. D., Chambers, L. C., Beaudoin, F. L., & Marshall, B. D. L. (2023). The impact of polysubstance use patterns on engagement of substance use disorder treatment among emergency department patients at high risk of opioid overdose. *Addictive Behaviors Reports*, *18*, 100512. https://doi.org/10.1016/j.abrep.2023.100512

Bonfiglio, N. S., Portoghese, I., Renati, R., Mascia, M. L., & Penna, M. P. (2022). Polysubstance Use Patterns among Outpatients Undergoing Substance Use Disorder Treatment: A Latent Class Analysis. *International Journal of Environmental Research and Public Health*, *19*(24), Article 24. https://doi.org/10.3390/ijerph192416759

Bórquez, I., Cerdá, M., González-Santa Cruz, A., Krawczyk, N., & Castillo-Carniglia, Á. (2024). Longitudinal trajectories of substance use disorder treatment use: A latent class growth analysis using a national cohort in Chile. *Addiction (Abingdon, England)*, *119*(4), 753–765. https://doi.org/10.1111/add.16412

Bunting, A. M., Shearer, R., Linden-Carmichael, A. N., Williams, A. R., Comer, S. D., Cerdá, M., & Lorvick, J. (2023). Are you thinking what I'm thinking? Defining what we mean by "polysubstance use." *The American Journal of Drug and Alcohol Abuse*, *0*(0), 1–7. https://doi.org/10.1080/00952990.2023.2248360

Castaldelli-Maia, J. M., Wang, Y.-P., Brunoni, A. R., Faro, A., Guimarães, R. A., Lucchetti, G., Martorell, M., Moreira, R. S., Pacheco-Barrios, K., Rodriguez, J. A. B., Roever, L., Silva, D. A. S., Tovani-Palone, M. R., Valdez, P. R., Zimmermann, I. R., Culbreth, G. T., Hay, S. I., Murray, C. J. L., & Bensenor, I. M. (2023). Burden of disease due to amphetamines, cannabis, cocaine, and opioid use disorders in South America, 1990–2019: A systematic analysis of the Global Burden of

Disease Study 2019. *The Lancet Psychiatry*, *10*(2), 85–97. https://doi.org/10.1016/S2215-0366(22)00339-X

Chen, T., Zhong, N., Du, J., Li, Z., Zhao, Y., Sun, H., Chen, Z., Jiang, H., & Zhao, M. (2019). Polydrug use patterns and their impact on relapse among heroin-dependent patients in Shanghai, China. *Addiction*, *114*(2), 259–267. https://doi.org/10.1111/add.14451

Choi, H. J., Grigorian, H., Garner, A., Stuart, G. L., & Temple, J. R. (2022). Polydrug Use and Dating Violence Among Emerging Adults. *Journal of Interpersonal Violence*, *37*(5–6), 2190–2217. https://doi.org/10.1177/0886260520934427

Choi, N. G., & DiNitto, D. M. (2020). Older-Adult Marijuana Users in Substance Use Treatment: Characteristics Associated with Treatment Completion. *Journal of Psychoactive Drugs*, *52*(3), 218–227. https://doi.org/10.1080/02791072.2020.1745966

Connor, J. P., Gullo, M. J., White, A., & Kelly, A. B. (2014). Polysubstance use: Diagnostic challenges, patterns of use and health. *Current Opinion in Psychiatry*, *27*(4), 269. https://doi.org/10.1097/YCO.0000000000000069

Crummy, E. A., O'Neal, T. J., Baskin, B. M., & Ferguson, S. M. (2020). One Is Not Enough: Understanding and Modeling Polysubstance Use. *Frontiers in Neuroscience*, *14*. https://www.frontiersin.org/articles/10.3389/fnins.2020.00569

Daskalopoulou, M., Rodger, A., Phillips, A. N., Sherr, L., Speakman, A., Collins, S., Elford, J., Johnson, M. A., Gilson, R., Fisher, M., Wilkins, E., Anderson, J., McDonnell, J., Edwards, S., Perry, N., O'Connell, R., Lascar, M., Jones, M., Johnson, A. M., … Lampe, F. C. (2014). Recreational drug use, polydrug use, and sexual behaviour in HIV-diagnosed men who have sex with men in the UK: Results from the cross-sectional ASTRA study. *The Lancet HIV*, *1*(1), e22–e31. https://doi.org/10.1016/S2352-3018(14)70001-3

Dickman, P. W. (2023, March 31). *An introduction to flexible parametric survival models and a discussion of the proportional hazards assumption*. Talk at: Department of Statistics and Quantitative Methods, University of Milano-Bicocca.

DIPRES. (2017a). *Informe Final: Evaluación de resultados de los programas de tratamiento y rehabilitación del Servicio nacional para la prevención y rehabilitación del consumo de drogas y alcohol*. SENDA.

DIPRES. (2017b). *Informe Final: Evaluación de resultados de los programas de tratamiento y rehabilitación del Servicio Nacional para la Prevención y Rehabilitación del Consumo de Drogas y Alcohol, SENDA.*

Fiestas, F., & Ponce, J. (2012). Eficacia de las comunidades terapéuticas en el tratamiento de problemas por uso de sustancias psicoactivas: Una revisión sistemática. *Revista Peruana de Medicina Experimental y Salud Publica*, *29*(1), 12–20.

Fleury, M.-J., Djouini, A., Huỳnh, C., Tremblay, J., Ferland, F., Ménard, J.-M., & Belleville, G. (2016). Remission from substance use disorders: A systematic review and meta-analysis. *Drug and Alcohol Dependence*, *168*, 293–306. https://doi.org/10.1016/j.drugalcdep.2016.08.625

Font-Mayolas, S., & Calvo, F. (2022). Polydrug Definition and Assessment: The State of the Art. *International Journal of Environmental Research and Public Health*, *19*(20), Article 20. https://doi.org/10.3390/ijerph192013542

Gjersing, L., & Bretteville-Jensen, A. L. (2018). Patterns of substance use and mortality risk in a cohort of 'hard-to-reach' polysubstance users. *Addiction*, *113*(4), 729–739. https://doi.org/10.1111/add.14053

Gómez-Restrepo, C., Maldonado, P., Rodríguez, N., Ruiz-Gaviria, R., Escalante, M. Á., Gómez, R. Á., de Araujo, M. R., de Oliveira, A. C. S., Rivera, J. S. C., García, J. A. G., Ferrand, M. P., & Blitchtein-Winicki, D. (2017). Quality measurers of therapeutic communities for substance dependence: An international

collaborative study survey in Latin America. *Substance Abuse Treatment, Prevention, and Policy*, *12*(1), 53. https://doi.org/10.1186/s13011-017-0129-y

Grafféo, N., Latouche, A., Geskus, R. B., & Chevret, S. (2018). Modeling time-varying exposure using inverse probability of treatment weights. *Biometrical Journal*, *60*(2), 323–332. https://doi.org/10.1002/bimj.201600223

Griffin, B. A., Ramchand, R., Almirall, D., Slaughter, M. E., Burgette, L. F., & McCaffery, D. F. (2014). Estimating the causal effects of cumulative treatment episodes for adolescents using marginal structural models and inverse probability of treatment weighting. *Drug and Alcohol Dependence*, *136*, 69–78. https://doi.org/10.1016/j.drugalcdep.2013.12.017

Hansen, E. M., Mejldal, A., & Nielsen, A. S. (2020). Predictors of Readmission Following Outpatient Treatment for Alcohol Use Disorder. *Alcohol and Alcoholism*, *55*(3), 291–298. https://doi.org/10.1093/alcalc/agaa018

Hassan, A. N., & Le Foll, B. (2019). Polydrug use disorders in individuals with opioid use disorder. *Drug and Alcohol Dependence*, *198*, 28–33. https://doi.org/10.1016/j.drugalcdep.2019.01.031

Hong, S., & Lynn, H. S. (2020). Accuracy of random-forest-based imputation of missing data in the presence of non-normality, non-linearity, and interaction. *BMC Medical Research Methodology*, *20*(1), 199. https://doi.org/10.1186/s12874-020-01080-1

Jardillier, R., Koca, D., Chatelain, F., & Guyon, L. (2022). Prognosis of lasso-like penalized Cox models with tumor profiling improves prediction over clinical data alone and benefits from bi-dimensional pre-screening. *BMC Cancer*, *22*(1), 1045. https://doi.org/10.1186/s12885-022-10117-1

Karamouzian, M., Cui, Z., Hayashi, K., DeBeck, K., Reddon, H., Buxton, J. A., & Kerr, T. (2024). Longitudinal polysubstance use patterns and non-fatal overdose: A

repeated measures latent class analysis. *The International Journal on Drug Policy*, 104301. https://doi.org/10.1016/j.drugpo.2023.104301

Kaufman, J. S., & MacLehose, R. F. (2013). Which of these things is not like the others? *Cancer*, *119*(24), 4216–4222. https://doi.org/10.1002/cncr.28359

Keele, L. (2010). Proportionally Difficult: Testing for Nonproportional Hazards in Cox Models. *Political Analysis*, *18*(2), 189–205. https://doi.org/10.1093/pan/mpp044

Körkel, J. (2021). Treating patients with multiple substance use in accordance with their personal treatment goals: A new paradigm for addiction treatment. *Drugs and Alcohol Today*, *21*(1), 15–30. https://doi.org/10.1108/DAT-10-2020-0065

Lalwani, K., Whitehorne-Smith, P., Walcott, G., McLeary, J.-G., Mitchell, G., & Abel, W. (2022). Prevalence and sociodemographic factors associated with polysubstance use: Analysis of a population-based survey in Jamaica. *BMC Psychiatry*, *22*(1), 513. https://doi.org/10.1186/s12888-022-04160-2

Levola, J., Aranko, A., & Pitkänen, T. (2021). Psychosocial difficulties and treatment retention in inpatient detoxification programmes. *Nordisk Alkohol- & Narkotikatidskrift : NAT*, *38*(5), 434–449. https://doi.org/10.1177/14550725211021263

Liu, Y., Williamson, V. G., Setlow, B., Cottler, L. B., & Knackstedt, L. A. (2018). The importance of considering polysubstance use: Lessons from cocaine research. *Drug and Alcohol Dependence*, *192*, 16–28. https://doi.org/10.1016/j.drugalcdep.2018.07.025

Mateo Pinones, M., González-Santa Cruz, A., Portilla Huidobro, R., & Castillo-Carniglia, A. (2022). Evidence-based policymaking: Lessons from the Chilean Substance Use Treatment Policy. *International Journal of Drug Policy*, *109*, 103860. https://doi.org/10.1016/j.drugpo.2022.103860

McPherson, C., Boyne, H., & Waseem, R. (2017). Understanding the Factors that Impact Relapse Post-residential Addiction Treatment, a Six Month Follow-up from a

Canadian Treatment Centre. *Journal of Alcoholism & Drug Dependence*, *05*(03). https://doi.org/10.4172/2329-6488.1000268

Mefodeva, V., Carlyle, M., Walter, Z., Chan, G., & Hides, L. (2022). Polysubstance use in young people accessing residential and day-treatment services for substance use: Substance use profiles, psychiatric comorbidity and treatment completion. *Addiction (Abingdon, England)*, *117*(12), 3110–3120. https://doi.org/10.1111/add.16008

Olivari, C. F., Gaete, J., Rodriguez, N., Pizarro, E., Del Villar, P., Calvo, E., & Castillo-Carniglia, A. (2022). Polydrug Use and Co-occurring Substance Use Disorders in a Respondent Driven Sampling of Cocaine Base Paste Users in Santiago, Chile. *Journal of Psychoactive Drugs*, *54*(4), 348–357. https://doi.org/10.1080/02791072.2021.1976886

Olivari, C. F., González-Santa Cruz, A., Mauro, P. M., Martins, S. S., Sapag, J., Gaete, J., Cerdá, M., & Castillo-Carniglia, A. (2022). Treatment outcome and readmission risk among women in women-only versus mixed-gender drug treatment programs in Chile. *Journal of Substance Abuse Treatment*, *134*, 108616. https://doi.org/10.1016/j.jsat.2021.108616

Passos, S. R., & Camacho, L. A. (2000). Factors associated with immediate dropout of outpatient treatment for drug abuse in Rio de Janeiro. *Social Psychiatry and Psychiatric Epidemiology*, *35*(11), 513–517. https://doi.org/10.1007/s001270050273

Price, O., Sutherland, R., Man, N., Bruno, R., Dietze, P., Salom, C., Akhurst, J., & Peacock, A. (2023). Trends and psychosocial correlates of same day polysubstance use among people who inject drugs in Australia, 2012-2022. *International Journal of Drug Policy*, 104150. https://doi.org/10.1016/j.drugpo.2023.104150

Quek, L.-H., Chan, G., White, A., Connor, J., Baker, P., Saunders, J., & Kelly, A. (2013). Concurrent and Simultaneous Polydrug Use: Latent Class Analysis of an Australian Nationally Representative Sample of Young Adults. *Frontiers in Public Health*, *1*. https://www.frontiersin.org/articles/10.3389/fpubh.2013.00061

Reif, S., Stewart, M. T., Torres, M. E., Davis, M. T., Dana, B. M., & Ritter, G. A. (2021). Effectiveness of value-based purchasing for substance use treatment engagement and retention. *Journal of Substance Abuse Treatment*, *122*, 108217. https://doi.org/10.1016/j.jsat.2020.108217

Reyes, J., Perez, C., Colon, H., Dowell, M., & Cumsille, F. (2013). Prevalence and Patterns of Polydrug Use in Latin America: Analysis of Population-based Surveys in Six Countries. *Review of European Studies*, *5*(1), Article 1. https://doi.org/10.5539/res.v5n1p10

Royston, P., & Altman, D. G. (2013). External validation of a Cox prognostic model: Principles and methods. *BMC Medical Research Methodology*, *13*(1), 33. https://doi.org/10.1186/1471-2288-13-33

Ruiz-Tagle Maturana, J., González-Santa Cruz, A., Rocha-Jiménez, T., & Castillo-Carniglia, Á. (2023). Does substance use disorder treatment completion reduce the risk of treatment readmission in Chile? *Drug and Alcohol Dependence*, *248*, 109907. https://doi.org/10.1016/j.drugalcdep.2023.109907

Rytgaard, H. C. W., & van der Laan, M. J. (2024). *Nonparametric efficient causal estimation of the intervention-specific expected number of recurrent events with continuous-time targeted maximum likelihood and highly adaptive lasso estimation* (arXiv:2404.01736). arXiv. https://doi.org/10.48550/arXiv.2404.01736

Santis B, R., Hidalgo C, C. G., Hayden C, V., Anselmo M, E., Rodríguez T, J., Cartajena de la M, F., Dreyse D, J., & Torres B, R. (2007). Consumo de sustancias y conductas de riesgo en consumidores de pasta base de cacaína no consultantes

a servicios de rehabilitación. *Revista Médica de Chile*, *135*(1), 45–53. https://doi.org/10.4067/S0034-98872007000100007

Sewell, J., Miltz, A., Lampe, F. C., Cambiano, V., Speakman, A., Phillips, A. N., Stuart, D., Gilson, R., Asboe, D., Nwokolo, N., Clarke, A., Collins, S., Hart, G., Elford, J., & Rodger, A. J. (2017). Poly drug use, chemsex drug use, and associations with sexual risk behaviour in HIV-negative men who have sex with men attending sexual health clinics. *International Journal of Drug Policy*, *43*, 33–43. https://doi.org/10.1016/j.drugpo.2017.01.001

Sheetal, A., Jiang, Z., & Di Milia, L. (2023). Using machine learning to analyze longitudinal data: A tutorial guide and best-practice recommendations for social science researchers. *Applied Psychology*, *72*(3), 1339–1364. https://doi.org/10.1111/apps.12435

Steele, J. L., & Peralta, R. L. (2020). Are Polydrug Users More Physically and Verbally Aggressive? An Assessment of Aggression Among Mono- Versus Polydrug Users in a University Sample. *Journal of Interpersonal Violence*, *35*(21–22), 4444–4467. https://doi.org/10.1177/0886260517715024

Tiet, Q. Q., Ilgen, M. A., Byrnes, H. F., Harris, A. H. S., & Finney, J. W. (2007). Treatment setting and baseline substance use severity interact to predict patients' outcomes. *Addiction (Abingdon, England)*, *102*(3), 432–440. https://doi.org/10.1111/j.1360-0443.2006.01717.x

Vázquez-Real, M., Talero-Barrientos, E. M., & Franco-Fernández, M. D. (2022). Sociodemographic, clinical and pharmacological factors influencing early readmission in mental health settings. *Actas Espanolas De Psiquiatria*, *50*(6), 248–255.

Vilugrón, F., Molina G., T., Gras-Pérez, M. E., Font-Mayolas, S., Vilugrón, F., Molina G., T., Gras-Pérez, M. E., & Font-Mayolas, S. (2022). Precocidad de inicio del consumo de sustancias psicoactivas y su relación con otros comportamientos de

riesgo para la salud en adolescentes chilenos. *Revista Médica de Chile*, *150*(5), 584–596. https://doi.org/10.4067/s0034-98872022000500584