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

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**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, and 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) to improve treatment for these groups, especially outside the Global North.

**Aims:** To estimate the association between reporting PSU at admission and treatment non-completion among patients with more than one treatment episode.

**Methods**: Retrospective cohort study based on adult treatment records from the Chilean National Substance Use Agency from 2010 to 2019. SUT is available at no cost through Chile’s publicly funded healthcare and is provided in ambulatory and residential modalities in public and private centers. A total of 13,317 individuals with multiple treatment episodes were analyzed from the 70,854 individuals who received their first SUT between 2010 and 2019. SUT completion status was categorized as completed or non-completed. Primary outcomes focused on treatment non-completion. We used Poisson general estimating equations controlling for several covariates of each patient to measure the relative risk (RR) and 95% confidence intervals (95% CI) of non-completion by reporting PSU. Sensitivity analyses used also weighted for the inverse intensity of treatments.

**Results**: The risk of non-completion was significantly 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, the association was not consistent across all treatment settings (Cochran's Q = 14.49, p-value = 0.0059). Sensitivity analyses were consistent with main results in direction and magnitude.

**Conclusions**: Reporting PSU at admission was modestly associated with a higher risk of treatment non-completion. The analysis, adjusted for various covariates and accounting for irregular observation times, highlights the association between PSU reporting and treatment outcomes in specific settings. This underscores 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.

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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 and unnoticedly (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 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 it is related to a higher mortality rate (Gjersing & Bretteville-Jensen, 2018), a higher risk of relapse (Chen et al., 2019; Hassan & Le Foll, 2019), less responsive 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 (H. J. Choi et al., 2022; Steele & Peralta, 2020), and psychiatric comorbidities (Mefodeva et al., 2022). Over the last three decades, evidence has shown that the rate of people with PSU has significantly increased, at least 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 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 (N. G. 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 because most studies have focused on individual substances in isolation and have considered a multiple substance use history as an exclusion criterion for clinical studies on treatment effectiveness, which raises the problem of its translatability to real health contexts (Bonfiglio et al., 2022). Regarding the treatment outcomes, some studies report a lower likelihood of treatment completion among people with PSU (Andersson et al., 2021; Levola et al., 2021), while others find no association (Andersson et al., 2018) or higher completion rates (Basu et al., 2017). In any case, 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 focused on patients who experience multiple and recursive treatments (Bórquez et al., 2024). People with persistent SUD show different characteristics than patients with no longer a disorder after a single or without any treatment.

Given that SUD is understood as a chronic condition (Fleury et al., 2016), the association between reporting PSU and treatment completion on first SUD treatment alone requires accounting that some patients may be readmitted to treatment through the follow-up period. Thus, checking for group biases and adjusting for confounders is needed (Griffin et al., 2014; Hansen et al., 2020). Additionally, these treatments are irregularly spaced, nevertheless, not at random, as the time between treatments might be related to biopsychosocial and treatment-related factors. Thus, 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).

Additionally, 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. In turn, these characteristics are highly dependent on treatment settings (Fiestas & Ponce, 2012; Reif et al., 2021; Tiet et al., 2007). Olivari and colleagues found that women-specific (WO) treatment settings had different readmission and treatment completion than patients in general population programs in Chile. In a similar vein, Ruiz-Tagle et al. found that completion was less likely among ambulatory settings (Olivari, González-Santa Cruz, et al., 2022; Ruiz-Tagle Maturana et al., 2023).

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

Moreover, as many studies in the Global North have often overlooked high-risk populations, there are reasons to believe that is also the case in Latin America, where the prevalence of individuals with PSU is notably high (Reyes et al., 2013). A meta-analysis focusing on Global North studies on 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 between 47% and 66% of users had simultaneous substance use (Olivari, Gaete, 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, Gaete, et al., 2022; Santis B et al., 2007; Vilugrón et al., 2022).

Chile is an interesting case, allowing for an examination of a context outside the Global North. It has a robust public treatment system that produces 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 address characteristics such as PSU behaviors effectively in a context where 2 out of 3 reported PSU (DIPRES, 2017). Understanding the PSU-treatment completion relationship could inform effective prevention and intervention strategies adapted to patients' needs. Moreover, expanding the 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 aims to address this gap by estimating the association of having reported PSU and treatment completion among adult patients admitted to multiple SUD treatment programs in Chile from 2010-2019.

1. **MATERIAL AND METHODS**
   1. **Design**

This study was approved by the Griffith University Human Research Ethics Committee (GUHREC GU Ref No: 2022/919).

* 1. **Setting and participants**

Substance use treatment (SUT) is available at no cost through Chile’s publicly funded healthcare and is provided in ambulatory and residential modalities in public and private centers.

We considered adult patients (+18 years old) with ongoing treatments from 2010 until 2019. Censoring occurred after the date of data retrieval (November 13, 2019), after an outcome event occurred, or when a patient left the cohort with no other outcomes. We excluded from the sample patients with only one treatment episode. To account for variability by treatment setting, we stratified the analysis by setting at 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 (WO) intensive ambulatory (n= 745), and WO residential (n= 1,036). After excluding records of ongoing treatments and referred outside the treatment network, 72,404 patients with 90,075 treatments were selected. In the total sample, 82% had one treatment episode, while 1% had more than 3 treatment episodes. We focused on patients with more than one treatment, identifying 13,317 patients and 30,988 observations.

* 1. **Variables**

The exposure variable was PSU at admission, a self-reported answer of using more than one main substance among alcohol and illicit drugs at admission to 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 treatments). Additionally, the models adjusted for various baseline confounding variables related to substance use, demographics, and social factors.

The following covariates for the model of the association between reported substance use and treatment outcome were included: 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 frequence of primary substance use at admission, occupational status (inactive and unemployed), primary substance at admission to treatment (cocaine hydrochloride, cocaine base paste, marijuana, and other substances). For further information, please review Supplemental Section 1.

* 1. **Missing data**

Given the complex longitudinal structure of the data, we conducted random-forest-based imputation using the *missRanger* package. We used 300 trees, using 5 candidate values of predictive matching (thus, aiming for plausible imputations given predictor values), with a maximum of 50 iterations per chaining steps. This imputation procedure may circumvent specification of interactions or nonparametric relationships and can handle collinearity between imputation variables (Hong & Lynn, 2020; Sheetal et al., 2023).

* 1. **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) through generalized estimating equations (GEE) assuming a Poisson distribution with a log link function and an independence structure. Heterogeneity tests in different strata of treatment settings for ratio effect measures were conducted.

* Sensitivity analyses

Given that the study design is based on administrative records with 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, GEE models were employed, weighted using inverse intensity weights (IIW) by modelling the time to being 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 variance and the mean of PSU reports using Negative Binomial distributions were tested using Quasi-likelihood Information criterion for model selection (See Supplemental Section 4).

* 1. **Data and code availability**

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

1. **RESULTS**

This section is organized into distinct subsections, each detailing specific aspects of our analysis.

* Characteristics of the study sample

Several key differences were notable among individuals reporting polysubstance use. In terms of **demographics** at baseline, people with PSU, when compared to people who report single substance use had their first admission to treatment earlier in life. Also, a higher percentage of them were unemployed. Regarding of **substance use** at baseline, people with PSU when compared to people who report single substance use: were more likely to report using cocaine paste and hydrochloride cocaine instead of alcohol as the primary substance that led them to treatment. In terms of the type of initiation substance, fewer started with alcohol, while more began with marijuana. In terms of other **health** information at baseline, severe biopsychosocial compromise was more frequent among people with PSU. These differences led us to adjust for covariates to estimate the relative risk between patients reporting PSU vs. people who do not (See Table 1).

* Prevalence and incidence of PSU and Treatment completion

Interestingly, among patients with only one treatment, 72% reported PSU. However, when examining patients with multiple treatment episodes, from 80% to 88% reported PSU. This suggest that exposure to PSU could be overrepresented in the sample, as readmission is associated with PSU. This association is also evident when comparing the number of treatments to the proportion of non-complete treatments. Specifically, 71% of patients with only one treatment did not complete it, while 79%, 81% and 85% of the treatment episodes of patients with two, three or four treatments and more, respectively, had a non-completion status.

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 dropout 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 is 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) (See Table 2).

* 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 (95% CI 1.06-1.23). The association between polysubstance use and treatment noncompletion varies significantly across the treatment settings (Cochran's Q = 14.5, p-value = 0.0059).

* 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 stratified follow-up and lagged covariates at 1 (1.01 95% CI 0.98-1.05). In women-specific residential settings, the only model overlapping with the null was stratified by follow-up with lagged covariates at 1 (1.09 95% CI 0.99- 1.20), though both settings maintained a positive direction (See Table S5). Hence, the association between reporting polysubstance use and treatment noncompletion seems robust to different model specifications.

1. **DISCUSSION**

Our findings show that the incidence of PSU according to treatment completion is…

After comparing patients reporting PSU vs. single substance regarding treatment completion, we found…

Additionally, the association between PSU reported at admission and treatment non-completion is restricted to intensive ambulatory settings and women-specific residential treatments…

This study is focused on people who had a persistent pattern of substance use disorder rather than 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). The results of the inverse intensity model also provide unique insights into patient characteristics associated with increased readmissions to SUD treatments. Age at admission to treatment and recent birth years may suggest the presence of an age-cohort effect, where younger individuals might be less reluctant to seek subsequent treatment. Additionally, the expansion of treatment offerings, the broader reach of SENDA into more sectors and the healthcare network, or a gradual reduction in the stigma associated with returning to treatment could also contribute to this pattern. Interestingly, some factors that we expected to be influential, such as polysubstance use in the previous treatment, specific primary substances at admission, and certain psychiatric comorbidities, were found to have negligible or non-significant effects on treatment return rates. Possibly, adjusting for biopsychosocial compromise and stratifying by treatment settings would have captured the variability attributed to these factors.

Limitations

The proportional intensity model to calculate IIWs impose a proportional hazards assumption on the 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 the intensities due to possible changes in baseline risks for cumulative events, making interpretations of nonproportionality less straightforward (Royston & Altman, 2013). Tests such based on Schoenfeld residuals are insufficient as contrasting for the null for changes as a function of time may not be fully indicative of nonproportional hazards. Even small violations can become apparent due to the 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 might not be proportional (Jardillier et al., 2022).

However, the association described here may lack a causal interpretation, given that the recurrent event process might be associated with the right censoring mechanism. For example, patients admitted to treatment on dates closer to administrative censorship or in ongoing treatments might have different characteristics that may change the inverse of the susceptibility of having recurrent treatments.

1. **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. (2022). 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

Carrero, J. J., Fu, E. L., Vestergaard, S. V., Jensen, S. K., Gasparini, A., Mahalingasivam, V., Bell, S., Birn, H., Heide-Jørgensen, U., Clase, C. M., Cleary, F., Coresh, J., Dekker, F. W., Gansevoort, R. T., Hemmelgarn, B. R., Jager, K. J., Jafar, T. H., Kovesdy, C. P., Sood, M. M., … Nitsch, D. (2023). Defining measures of kidney function in observational studies using routine health care data: Methodological and reporting considerations. *Kidney International*, *103*(1), 53–69. https://doi.org/10.1016/j.kint.2022.09.020

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

Cole, S. R., & Hernán, M. A. (2008). Constructing Inverse Probability Weights for Marginal Structural Models. *American Journal of Epidemiology*, *168*(6), 656–664. https://doi.org/10.1093/aje/kwn164

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

DIPRES. (2017). *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

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

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

Lokku, A., Lim, L. S., Birken, C. S., Pullenayegum, E. M., & on behalf of the TARGet Kids! Collaboration. (2020). Summarizing the extent of visit irregularity in longitudinal data. *BMC Medical Research Methodology*, *20*(1), 135. https://doi.org/10.1186/s12874-020-01023-w

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

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

Pullenayegum, E. (2022). *IrregLong: Analysis of Longitudinal Data with Irregular Observation Times* [Computer software]. https://cran.r-project.org/web/packages/IrregLong/index.html

Pullenayegum, E. M., Birken, C., Maguire, J., & TARGet Kids! Collaboration. (2023). Causal inference with longitudinal data subject to irregular assessment times. *Statistics in Medicine*, *42*(14), 2361–2393. https://doi.org/10.1002/sim.9727

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

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