**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. 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 70,854 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, 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 the treatments.

**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 and magnitude.

**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.

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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, 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 opioids and injecting drug use, which are epidemiologic features that are not prevalent in the Latin American context (Castaldelli-Maia et al., 2023).

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.

1. **MATERIAL AND METHODS**
   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).

* 1. 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.

* 1. 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).

* 1. 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.

* 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) 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).

* 1. 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).

* 1. Data and code availability

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

1. **RESULTS**

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

* 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 substanceuse 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).

* 1. 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, 80–88% reported PSU. This suggests 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 incomplete treatments. Specifically, 71% of patients with only one treatment did not complete it, whereas 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 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).

* 1. 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).

* 1. 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).

1. **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. Sensitivity analyses supported these findings, showing stability in the associations across the different model specifications and treatment setting. 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. These results 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).

The secondary results 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. Age at admission to treatment and recent birth years may suggest the presence of an age-cohort effect, in which younger individuals might be less reluctant to seek subsequent treatment. 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.

This study 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). Interestingly, we also noted that some factors expected to influence treatment outcomes, such as previous PSU, specific primary substances at admission, and certain psychiatric comorbidities, had negligible or nonsignificant effects on treatment return rates (Passos & Camacho, 2000). This is in contrast to studies that have observed lower treatment responsiveness among patients with PSU (Bonfiglio 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

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. Adjusting for biopsychosocial compromise and stratification by treatment setting would capture the variability attributed to these factors.

This study had some limitations. First, the proportional intensity model used to calculate 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 fully 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).

1. **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.

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