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The role of first use of inhalants within sequencing pattern of first use of drugs among Brazilian university students

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Abstract

The present study investigated the role of first use of inhalants within a first drug sequencing pattern. In a representative sample of university students from 27 Brazilian capitals (n=12,711), we analyzed the patterns of transition from/to first use of inhalants to/from the first use of alcohol, tobacco, cannabis, cocaine, hallucinogens, ecstasy, amphetamines, prescription opioids, and tranquilizers. Cox proportional hazards models were used to analyze data. Drugs that were not specified as the pair of drugs tested in each model were included as time-varying covariates in all models. In this sample, first use of inhalants was preceded only by the first use of alcohol and tobacco. However, first use of inhalants preceded first use of cannabis, amphetamines, cocaine, and tranquilizers. First use of inhalants preceded the first use of prescription opioids, and vice versa. This study highlights the need to intervene early with youths who are at risk of or just beginning to use inhalants, since this class of drugs seems to be the first illegal drug in Brazil to be experimented by respondents in our sample. There is also a call for attention to individuals who have already first used inhalants because of their higher chance to experiment with other drugs such as cannabis, cocaine, and prescription drugs. All these findings show an in-transition culture of drug use, which should be tracked through the time, since some classical models (i.e., gateway model) might be outdated and might also not fit within different settings.

Keywords

inhalants; Brazil; transition; experimentation; gateway; university students

1. Introduction

Inhalants are one of the most popular drug classes throughout the world. Inhalant abuse, which is also referred to as volatile substance abuse or solvent abuse, is a worldwide

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problem with major consequences for abusers, their families and society (Balster et al., 2009), yet it is one of the least-understood and poorly studied substance abuse problems (Balster et al., 2009). Despite the substantial prevalence and serious toxicities of inhalant use, it has been termed “the forgotten epidemic”, and remains as the least studied form of substance abuse, although research on its epidemiology, neurobiology, treatment, and prevention has accelerated in recent years (Howard et al., 2011). The high prevalence of lifetime use of inhalants is also evident in the general population of Brazil, as inhalants are the fourth most widely used drug (Fonseca et al., 2010). Considering these statements, the present study sought to investigate the role of first use of inhalants within sequencing pattern of first use of drugs among Brazilian university students.

Kandel (1975) and Kandel & Faust (1975) proposed a gateway model that attempts to explain the passage from the first contact with a drug to the first contact with a second drug. In this model, the user would go through four stages of involvement with psychoactive substances. There was no special attention to inhalants in this proposed model despite their high prevalence of use. At first, usually individuals use beer and wine. Then, individuals could use tobacco and/or strong drinks (liquor, spirits). From the second stage the person could go to a third stage, in which use of cannabis can happen. The gateway hypothesis implicitly assumes a causal chain sequence in which: (a) alcohol and/or tobacco use preceed cannabis use; (b) cannabis is used prior to the onset of other illegal drugs (including inhalants); and (c) the use of cannabis increases the likelihood of using other illegal drugs (Fergusson et al., 2006).

Alcohol and tobacco are indeed the first drugs that adolescents experiment with according to several international studies (Van Etten et al., 1997, Wagner & Anthony, 2002, Herrera-Vazquez et al., 2004, Wells & McGee, 2008, Caris et al., 2009, Mayet et al., 2010), which may be due to the fact that these two drugs have the highest prevalence of use throughout the lifespan in most countries. However, there are a considerable number of individuals who experiment with cannabis before alcohol and/or tobacco depending on neighborhood (Tarter et al., 2006) and ethnic factors (Vaughn et al., 2008). Regarding sequence of first use of drugs other than alcohol and tobacco, data is more controversial (Castaldelli-Maia et al., 2014a). In countries with a high prevalence of cannabis use, such as Germany, Ukraine and New Zealand, the first use of cannabis precedes the first use of drugs other than alcohol and tobacco (Degenhardt et al., 2010). This pattern was indeed the case for Brazilian university students in a previous study (Castaldelli-Maia et al., 2014b).

However, there are few studies (Ding et al., 2009; Sanchez et al., 2013) focusing on inhalants within drug first use sequencing pattern. In the U.S., Ding et al. (2009) found that inhalants are more commonly used before other illicit drugs in a large sample of inhalant users. Within the Brazilian university student population, the prevalence of lifetime use of inhalants was relatively high (24.6%) according to a survey conducted during this decade (Wagner et al., 2007). Based on this data of relatively high prevalence of lifetime use of inhalants, one can hypothesise that inhalants could be commonly used before illegal drugs, occupying a similar role to cannabis. Sanchez et al. (2013) analysed data from a representative sample of 8th to 12th grade students (middle school = 8th- 9th grade; high school = 10th-12th grade) from private schools (n = 5,226) in São Paulo, Brazil, to test for

sequencing patterns among alcohol, tobacco, cannabis and inhalants. In their study, inhalants were characterized as an intermediate drug class between legal (alcohol and tobacco) and illegal (cannabis) drugs. But this previous study (Sanchez et al., 2013) did not investigate: (i) the sequencing patterns involving inhalants and other important drugs to the Brazilian context (Castaldelli-Maia et al., 2013), such as crack/cocaine (Moreira et al., 2014), prescription drugs (Opaleye et al., 2014), hallucinogens (Castaldelli-Maia et al., 2012) and ecstasy (Remy et al., 2013), and (ii) older students from college years in private and public settings. Considering that adolescence is a period of experimentation with various drugs (Malta et al., 2010), the subsequent period (university or college years) may be of interest to access the sequence of experimentation of with these drugs. In a previous analysis using the sample of the present study, the average age of first use of each of the nine drugs analyzed in this study was between 15.2 and 21.2 years (Castaldelli-Maia et al., 2014b).

This study investigated the role of first use of inhalants within a drug use sequencing pattern in a large representative sample of Brazilian university students. It is also important to consider the first use of drugs other than inhalants as time-dependent variables, as they may have a mediating role in the sequence of drug use.

2. Methods

Data comes from an epidemiological study conducted in 27 Brazilian state capitals. The general objective of this epidemiological study was to evaluate the socio-demographic characteristics, drug use and mental health aspects of a nationally representative sample of university students (n=12,711). The project was previously evaluated and approved by the Ethics Committee for the Analysis of Research Projects at the School of Medicine of the University of São Paulo. Data collection was completed between May and December of 2009.

2.1. Sample

The target population of this study were university students enrolled in undergraduate programs in Higher Education Institutions (HEIs), both public and private, in the 27 Brazilian state capitals (Brazil is comprised by 27 states). The undergraduate programs can last from 4 to 6 years in Brazil. A random sample was stratified and recruited by unequal size clusters. Sampling was conducted in two stages; a sample of HEIs was selected, followed by the selection of classes of students was chosen from this sample. Since the size of the HEIs and the classes (in terms of number of universities) were not always the same, these conglomerates were of unequal sizes.

Since all 27 state capitals had to be covered, including public and private HEIs, sample stratification was carried out based on these two variables (public and private), namely, by capital and by type of institution, a total of 54 levels. However, this stratification was used only for operating purposes. At the data analysis stage, only the five administrative regions (including the 27 state capitals) and the two HEI types were considered for stratification, generating a total of 10 levels. To make the field work economically feasible, it was decided to select a sample of HEIs and, within each one of these, select a sample of classes: the primary sampling unit considered for this study was the HEI, and the secondary sampling

unit was the class. Thus, sampling selection was made in two stages, in which the clusters considered included both HEIs and student groups. Since the sizes (in relation to the number of students) of the HEIs and the groups are not always the same, these clusters are, in fact, of different sizes. Thus, in general, the sampling design consisted of a random sample, stratified by clusters of different sizes, selected in two stages. However, this sampling selection method posed a challenge because of the structure of the population under review. In conventional sampling, the clusters form a disconnected division, i.e., the population elements are related to a single cluster, which is not true for higher education. Within a HEI, student groups are not disconnected, and there may be an overlap between groups of students, since a single student can be enrolled in more than one subject. To get around this issue, we used the multiplicity-based sampling method, enabling the individuals to be included in more than one cluster. However, it was necessary to obtain information about the number of clusters to which the elements selected for the sample were related, for later use in the statistical analysis stage. At the end of the data collection, one hundred out of 114 HEIs accepted to take part in this study (88% of the estimated size), as well as 654 student classes (70.6% of the estimated size), with a total participation of 12,721 college students throughout Brazil. Although the response rate of participation was 95.6% among the college students who were inside classes at the time of the interview, the final response rate for this study was around 72.1% when the estimated size of the college student sample was taken into consideration (12,721/17,651). Finally, of these students (12,721), 10 were excluded because they claimed to use Relevin (ficticious drug); thus, the data from 12,711 nationwide college students were analyzed. More details about this survey could be found in Andrade et al. (2012).

Part of the 12,711 individuals was excluded from the present study. Respondents older than 40-years (n = 548) were excluded because of the high probability of memory bias. In addition, those with missing data on the variables of interest - age (n = 141), whether they used the some of the drugs tested (n = 149 (cannabis); 183 (inhalants); 228 (opioid analgesics); 174 (tranquilizers); 206 (ecstasy); 191 (amphetamines); 190 (cocaine); 165 (hallucinogens)), alcohol (n = 3203) or tobacco (n = 0), those who did not answer the age of first use of some of the drugs tested (n = 476 (cannabis); 625 (inhalants); 670 (opioid analgesics); 602 (tranquilizers); 316 (ecstasy); 430 (amphetamines); 284 (cocaine); 298 (hallucinogens); alcohol (n = 3,203) or tobacco (n = 985) - were excluded. Sample size varied according to the transition considered.

2.2. Measures

A structured, self-administered, and anonymous questionnaire of 98 closed questions was developed with an emphasis on drug use and related disorders, risky behaviours and the existence of psychiatric comorbidity (depressive symptoms and psychotic and nonspecific psychological complaints). The content of this questionnaire was based on the World Health Organisation research questionnaire, which was previously adapted by Andrade et al. (1997) and Stempliuk et al. (2005) for use with undergraduate students.

The present study used part of these data, which focused on drug use. This section was collected in a series of questions with multiple response options. In the first part, the

students reported whether they had ever used the following drugs ("Have you ever tried *NAME OF THE DRUG* without a doctor's prescription? Answer: Yes or No"): inhalants, alcohol, tobacco, cannabis, cocaine, "merla" (a cocaine by-product), crack, hallucinogens, ketamine, ayahuasca (Santo Daime), ecstasy (3-4 methylenodyoximethamphtamine, MDMA), anabolic steroids, tranquilizers, prescription opioids, anticholinergics, heroin, amphetamines, and synthetic drugs (methamphetamines and GHB). In the second part of the questionnaire, we asked for the age of the initial use of each of these drugs ("How old were you when you first tried *NAME OF THE DRUG*? Answer: XX years"). For this study, cocaine, "merla" and crack were combined in the same group (named cocaine).

Our survey instrument included questions that asked all respondents about the use of 'inhalants or solvents' giving as examples: "loló", glue, paint thinner, benzene, enamel, gasoline, and "lança-perfume". All these examples of inhalants or solvents cover the vast majority of types of substances of this class of drugs used in Brazil (Mesquita et al., 1998; Hynes-Dowell et al., 2011; Sanchez et al., 2013; Silva-Oliveira et al., 2014)

2.3. Statistical analysis

• **Time-dependent variables—**Because the aim of this study was to assess the whether the transition from the first use of one drug to the subsequent use of another drug occurred or not – always involving inhalants in one of the two roles – these comparisons were always performed between users and non- users groups (e.g., investigating the transition from inhalants to cocaine – we tested inhalants users versus inhalants nonusers - these groups were defined based on three options available in these two parts of the following question: if the subject had already used inhalants, if the subject had already used cocaine, and whether the subject had used the inhalants before, in the same year, or after cocaine. Inhalants users – if s/he just used cannabis or cocaine after inhalants. Inhalants non-users – if s/he did not use both drugs, or used just cocaine, or inhalants before cocaine. If s/he used both in the same year, s/he was classified as a 'drug seeker'). Users and non-users were assembled for each transition to perform analyses of the transitions from the first use of a drug to the first use of another drug. Analyses focused on transitions of first use of inhalants with first use of alcohol, amphetamines, cannabis, cocaine, ecstasy, hallucinogens, prescription opioids, tobacco, and tranquilizers. Figure 1 depicts the division between users and non-users. The drug seekers were considered drug users with the response (the use of the subsequent drug tested in the model) of event censored. With this we have tried to avoid loss of important data on other socio-demographic variables included in the regression models.

• **Time-dependent covariates—**Drugs other than the pair of drugs tested in each survival model were included as time-varying dependent covariates in all models. (e.g. in the model testing the the pathway from cannabis to inhalants – if the individual first used alcohol after first using cannabis and before first trying inhalants, s/he was classified as alcohol user in the alcohol use time dependent variable of this model).

All analyses were performed using the survey settings commands with weights, strata and primary sampling units. The analysis of the survey data complied with the following characteristics of the sampling plan: (a) a complex sample, (b) the use of stratification, (c)

clustering and (d) dissimilar selection probabilities. Survival analysis methods were used to compare between one type of drug users and non-users the cumulative prevalence of other type of drug use. We chose to use Cox Regression Survival Models (Cox, 1972), following an important framework (Singer & Willett, 1994). We used the statistical package STATA version 11 to run the models with time dependent covariates (as described above) and non-time dependent covariates (these 14 sociodemographic covariates are presented in Table 1) adjustment. The Kaplan-Meier curves were plotted without any adjustment for other variables, and without the exclusion of individuals with more than 40-years. We chose to use a link test to test for proportional-hazards assumption (Cleves et al., 2010). These re-estimation tests were carried out to test for the validity of each Cox model. It searches for variables to add to the model. Under the assumption that the Cox model is correctly specified, the added variables will add little or no explanatory power, so it tests that these variables are insignificant. The Cox model reaches validity with $p > 0.05$ in this link test. Cox models with $p < 0.05$ in link test were not considered for discussion.

3. Results

Table 1 depicts the socio-demographic information of the sample. Table 2 presents the results of the transitions analyzed and Figure 2 highlights all the transitions that did not violate the Linktest of proportional hazard-assumptions (LHPA) and could be taken into account. Figure 3 depicts all Kaplan Meier curves of the transitions which had significant differences that did not violate the LHPA. Overall, the first use of inhalants was subsequent to first use of alcohol (n = 1,181), tobacco (n = 655) and prescription opioids (n = 64), and preceded the subsequent first use of prescription opioids (n = 181), cannabis (n = 409), cocaine (n = 271), tranquilizers (n = 165) and amphetamines (n = 363).

3.1. Transitions from first use of inhalants to first use of other drugs

Seven of nine models did not violate the LHPA. Within the valid models, the cumulative prevalence of first use of amphetamines (aHR = 2.59, 95% CI = 1.65-4.07, $p < 0.001$), cannabis (aHR = 1.56, 95% CI = 1.26-1.93, $p < 0.001$), cocaine (aHR = 4.33, 95% CI = 3.08-6.09, $p < 0.001$), prescription opioids (aHR = 29.39, 95% CI = 7.17-120.54, $p < 0.01$) and tranquilizers (aHR = 2.10, 95% CI = 1.05-4.18, $p < 0.05$) were significantly higher among those that had first initiated inhalant use as compared to inhalants non-users. Regarding gender, there was higher cumulative prevalence of alcohol and cannabis first use among men as compared to women (aHR = 0.70, 95%CI = 0.53-0.93, $p < 0.05$, and aHR = 0.56, 95%CI = 0.39-0.80, $p < 0.01$, respectively), adjusting for previous use of inhalants. However, regarding amphetamine and tranquilizer first use, an opposite situation occurred. The cumulative prevalence of first use in these cases were higher among women compared to men (aHR = 5.51, 95%CI = 3.72-8.15, $p < 0.001$, and aHR = 2.28, 95%CI = 1.48-3.50, $p < 0.001$, respectively), adjusting for previous use of inhalants. There were no gender differences in regards to cocaine, prescription opioid, and tobacco first use.

3.2. Transitions from first use of other drugs to first use of inhalants

All models did not violate the LHPA. The cumulative prevalence of first use of inhalants was significantly higher among alcohol (aHR = 1.41, 95% CI = 1.09-1.81, $p < 0.01$),

prescription opioids (aHR = 3.51, 95% CI = 1.14-10.82, $p < 0.05$) and tobacco (aHR = 2.70, 95%CI = 1.92-3.79, $p < 0.001$) first users as compared to non-users of these drugs. In addition, the cumulative prevalence of first use of inhalants was significantly lower in cocaine (aHR = 0.06, 95%CI = 0.01-0.23, $p < 0.001$) first users as compared to cocaine non-users. Within all the transitions, there was a higher cumulative prevalence of inhalant first use among men as compared to women, adjusting for other drugs previous use.

4. Discussion

The main aim of the present study was to conduct an analysis of the role of first use of inhalants within the sequence of first drug use, and we found that it was preceded by the first use of alcohol, tobacco and prescription opioids. However, the first use of inhalants preceded the first use of amphetamines, cannabis, cocaine, prescription opioids and tranquilizers. These findings place inhalants into the position that is typically ascribed to cannabis, as its first use is more common after the first use of legal drugs and before the first use of illegal drugs. Additionally, cannabis first use did not precede inhalants first use; rather, the opposite pattern was evident.

A global debate on the validity of studying the transition of various drug use (Van Etten et al., 1997, Wagner & Anthony, 2002, Herrera-Vazquez et al., 2004, Wells & McGee, 2008, Caris et al., 2009, Mayet et al., 2010) was revived due to the results of a study investigating epigenetic alterations related to drug experimentation in laboratory animals (Levine et al., 2011). Pre-treatment of mice with nicotine increased their responses to cocaine, as assessed by addiction-related behaviours and synaptic plasticity in the striatum, a brain region critical for addiction-related rewards. The responses to cocaine were altered only when nicotine was administered first, and then nicotine and cocaine were administered concurrently. Reversing the order of the drug administration was ineffective, as cocaine had no effect on nicotine-induced behaviours and synaptic plasticity (Levine et al., 2011). There is also fresh epidemiologic data on this field. A recent multicentre study revealed that the sequence of drug experimentation may be linked to particular issues related to alcohol and drug use in a specific country (Degenhardt et al., 2010) and that violations of the classical sequence of drug experimentation (i.e., alcohol/tobacco → cannabis → other drugs) seem to be more common in countries with low lifetime use of alcohol, tobacco, and cannabis. Thus, it is important to study first use sequencing patterns in other less developed settings, such as Brazil, where there is different prevalence of lifetime drug use (e.g., higher levels of lifetime prevalence of inhalant use).

Ding et al. (2009) studied the position of inhalants in the sequence of drug use in U.S. using data from the 2003 National Survey on Drug Use and Health (NSDUH). The age of first inhalant use was compared with the age of onset of other drug use among 6,466 inhalant users who also used at least one of 14 other drugs. The findings indicated that only 4.2% of multiple drug users had used inhalants prior to using other drugs, in particular, alcohol, tobacco, and cannabis. Thus, the theory that first use of inhalants is more common before the first use of illegal drugs was not supported in this study. Comparing this study (Ding et al., 2009) design with the current one, we have found many differences. In the present study, we used survival analysis methods to compare drug users and non-users while taking into

account the cumulative prevalence of other drug use across time. We chose to use Cox regression survival models following an important framework (Singer & Willet, 1994, Wagner & Anthony, 2002). Another explanation for the differences between the two studies could be trends over time. That is, inhalants can be more commonly used in 2009 in Brazil as compared to U.S. in 2003. However, recent U.S. data shows that 17% of youths initiated inhalants during middle school (Ober et al., 2013) – a considerable high rate of initiation.

Our findings are in line with those from Sanchez et al. (2013) in their study with a younger sample of private school high- and middle-school students in São Paulo, Brazil. We also found that inhalants use preceded the cannabis use. In addition to that transition, our study expand this role of inhalant use - preceding the use of other illicit drugs – in a large and representative sample of Brazilian urban university students. Considering that, a number of classical statements should be reconsidered in light of findings such that in our country. First, if there is a more common sequence of drug experimentation, then inhalant use should be placed in the same step of (or even before) cannabis - after legal drug use and before illegal drug use. There are few studies regarding drug transitions that take the position of inhalants in this sequence into account.

The first use of inhalants preceded the first use of amphetamines, cannabis, cocaine, prescription opioids and tranquilizers. However, the magnitude of the association between prior use of inhalants and subsequent use of these drugs varied a lot, which leads us to believe that the chance of using some drugs may be greater than others after using inhalants. Surely this is the case of prescription opioids and cocaine, with the highest adjusted hazard ratios (aHR). However, the absolute number of individuals that first used a drug after using inhalants was highest for cannabis and amphetamines, which should also call for the attention of police makers.

The transition to/from inhalants use seems to be a confounding factor in the association between gender and drug use. In all transitions tested from other drugs first use to inhalants first use, there was higher prevalence of inhalants first use in men compared to women, what is in line with previous findings of the prevalence of inhalants use in this sample (Andrade et al., 2012). Regarding the use of other drugs, there was higher cumulative prevalence of alcohol and cannabis first use among men, and of amphetamines and tranquilizers first use among women, that is also in line with previous findings (Andrade et al., 2012). However, the present study did not confirm higher prevalence of tobacco and cocaine first use among men, and first use of tranquilizers among women, as previously found in this sample (Andrade et al., 2012). This leads us to believe that the adjusting for previous inhalant first use made the gender differences in cocaine and tranquilizers first use disappear, positing first use of inhalants as a confounding factor. Other studies could investigate the role of inhalants previous use as a confounding factor for associations between gender and drug use.

There is a consensus among the few studies regarding inhalants from across all of the areas in the addiction field (Howard et al., 2011, Konghom et al., 2010), and our results support the implication that more attention to inhalant use and in its consequences and correlates are needed, especially in Brazil. Nonnemaker et al. (2011) suggested a strong relationship

between inhalant use, other problem behaviors and sensation-seeking. These results highlight the need to intervene early with youths who are at risk of or just beginning to engage in inhalant use, given that low-frequency inhalant users report predominately hedonic experiences during inhalant intoxication that are not aversive (Garland & Howard, 2010). Even non-persistent use of inhalants is associated with a greater risk for nonmedical opioid and stimulant use and is a strong predictor of non-persistent opioid and stimulant use (Nakawaki & Crano, 2012).

4.1. Limitations

An important limitation of this study is the recall bias, which is inherent in cross-sectional studies (Raphael, 1987). In addition, it is also difficult to extrapolate from data obtained from university students to the Brazilian general population. College students in this country are not representative of the general population as only 13.9% of young adults have access to higher education. Almost 50% of university students study in private institutions, which sets them apart from the general population. However, we did use a representative sample from all of the Brazilian capitals, thus providing balanced data from this large country, with various social, cultural and economic differences (Victora et al., 2010, Parayba & Veras, 2008). In addition, 8 of 36 transitions tested violated the linktest for the proportional hazard assumption LPHA), which implies the absence of important transitions (i.e., between cannabis and tobacco).

Another limitation is that if a respondent did not provide the age of first use of a drug, we could not use this individual data to perform any analysis of a transition that involved this drug. In view of the large number of people who did not remember at least one of the ages of experimenting with some of the drugs, we decided to carry out a comparative analysis between individuals who remembered all the ages of experimentation with drugs and those who did not remember at least one of the ages (missing group). To this end, we analyzed the sub-sample of those individuals who used drugs at least 1 drug of all the following three groups: (i) alcohol and/or tobacco; (ii) marijuana and/or inhalants; (iii) cocaine and/or hallucinogens and/or ecstasy and/or amphetamine and/or prescription opioids and/or tranquilizers. From this analysis (Appendix 1), individuals who: were older; had a religion; not practiced their religion; used hallucinogens; used ketamine; did not use tranquilizers; did not use barbiturates; and did not use codeine syrup; were associated with the missing group. Therefore, one should take care when extrapolating our findings to these sub-populations. Future analyses on first drug use sequencing patterns involving hallucinogens and tranquilizers would be interesting to better evaluate these transitions.

4.2. Conclusion

This study highlights the need to intervene early with youths who are at risk of or just beginning to engage in inhalant use, since this class of drugs seems to be the first to be experimented with in our sample. There is also a call for attention to individuals who have already first used inhalants because of their higher chance to experiment with other drugs such as cannabis, cocaine, and prescription drugs. It was also interesting to find that cannabis were subsequent compared to inhalants within first use sequencing pattern. All these findings show an in-transition culture of drug use among young adults in Brazil.

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Appendix

Appendix 1

Results of logistic regression comparing individuals used at least 3 drugs and were reminded of all the ages of exeprimentation of these drugs and those who any age of experimentation was missing among Brazilian university students, 2009.

Variable	aOR	SE	*p*	[95%	CI]
Age	**1.92**	**0.51**	**0.018**	**1.12**	**3.28**
Gender	1.01	0.23	0.936	0.64	1.61
Type of religion	**1.27**	**0.11**	**0.008**	**1.06**	**1.52**
Praticing the religion	**0.64**	**0.12**	**0.023**	**0.44**	**0.94**
Scholarity of the head of the family	0.81	0.12	0.177	0.60	1.09
Socioeconomic status	1.04	0.03	0.238	0.97	1.11
Ethnic group	0.69	0.16	0.125	0.43	1.10
Civil status	0.78	0.20	0.364	0.46	1.32
Children	0.56	0.27	0.250	0.21	1.50
Currently working	1.22	0.17	0.166	0.91	1.63
Driver license	0.56	0.16	0.056	0.31	1.01
University course area	1.18	0.17	0.244	0.88	1.58
Semester of the course	0.96	0.09	0.735	0.79	1.17
All-day course	0.98	0.31	0.954	0.51	1.86
Happy with the course choice	0.81	0.33	0.607	0.36	1.82
Alcohol use	0.90	0.86	0.918	0.13	6.06
Tobacco use	0.83	0.15	0.330	0.57	1.20
Cannabis use	1.19	0.38	0.591	0.62	2.27
Inhalants use	0.99	0.33	0.979	0.50	1.95
Cocaine use	1.23	0.38	0.498	0.66	2.30
Hallucinogens Use	**2.59**	**1.20**	**0.044**	**1.02**	**6.55**
Ketamine use	**20.85**	**25.32**	**0.014**	**1.86**	**233.25**
Ayahuasca use	1.49	0.85	0.486	0.47	4.65
Ecstasy use	0.62	0.23	0.217	0.29	1.32
Steroids use	0.59	0.27	0.259	0.24	1.46
Tranquilizers use	**0.54**	**0.11**	**0.005**	**0.35**	**0.83**
Sedative/Barbiturates use	**0.17**	**0.13**	**0.028**	**0.03**	**0.82**
Opioid analgesics use	0.45	0.19	0.070	0.18	1.06
Codein syrup use	**0.05**	**0.04**	**0.002**	**0.01**	**0.33**
Anticholinergics use	2.00	1.83	0.452	0.32	1.23
Heroin use	6.63	11.47	0.277	0.21	206.65

Variable	aOR	SE	*p*	[95%	CI]
Amphetamine use	0.69	0.28	0.391	0.30	1.59
Synthetic drugs use	1.97	1.93	0.490	0.28	1.39

References

Andrade AG, Duarte P. do C. Barroso LP, Nishimura R, Alberghini DG, Oliveira LG. Use of alcohol and other drugs among Brazilian college students: effects of gender and age. Revista Brasileira de Psiquiatria. 2012; 34:294–305. [PubMed: 23429775]

Andrade AG, Queiroz S, Villaboim RCM, César CLG, Alves MCGP, Bassit AZ. Uso de álcool e drogas entre alunos de graduação da Universidade de São Paulo. Revista ABP-APAL. 1997; 19:53–9.

Balster RL, Cruz SL, Howard MO, Dell CA, Cottler LB. Classification of abused inhalants. Addiction. 2009; 104:878–82. [PubMed: 19215599]

Castaldelli-Maia JM, Bhugra D, de Andrade AG, Lotufo-Neto F. Substance use and misuse in Brazilian Movies (2000- 2008). Substance Use and Misuse. 2013; 48:248–57. [PubMed: 23302060]

Castaldelli-Maia JM, Martins SS, de Oliveira LG, de Andrade AG, Nicastri S. The role of drug use sequencing pattern in further problematic use of alcohol, tobacco, cannabis, and other drugs. Journal of Mental Health. 2014a [in press].

Castaldelli-Maia JM, Martins SS, de Oliveira LG, van Laar M, de Andrade AG, Nicastri S. Use transitions between ilegal drugs among Brazilian university students. Social Psychiatry & Psychiatric Epidemiology. 2014b; 49:385–94. [PubMed: 23918195]

Castaldelli-Maia JM, Oliveira HP, Andrade AG, Lotufo-Neto F, Bhugra D. Using selected scenes from Brazilian films to teach about substance use disorders, within medical education. Sao Paulo Medical Journal. 2012; 130:380–91. [PubMed: 23338735]

Caris L, Wagner FA, Rios-Bedoya CF, Anthony JC. Opportunities to use drugs and stages of drug involvement outside the United States: Evidence from Republic of Chile. Drug and Alcohol Dependence. 2009; 102:30–4. [PubMed: 19328635]

Cleves, M.; Gutierrez, RG.; Gould, W.; Marchenko, YV. 3rd edition. Stata Press; Texas: 2010. An Introduction to Survival Analysis Using Stata..

Cochran, WG. Sampling Techniques. Wiley; New York: 1997.

Cox DR. Regression models and life time tables. Journal of the Royal Statistical Society (Series B). 1972; 34:187–202.

Degenhardt L, Dierker L, Chiu WT, Medina-Mora ME, Neumark Y, Sampson N, Alonso J, Angermeyer M, Anthony JC, Bruffaerts R, de Girolamo G, de Graaf R, Gureje O, Karam AN, Kostyuchenko S, Lee S, Lépine JP, Levinson D, Nakamura Y, Posada-Villa J, Stein D, Wells JE, Kessler RC. Evaluating the drug use “gateway” theory using cross- national data: consistency and associations of the order of initiation of drug use among participants in the WHO World Mental Health Surveys. Drug and Alcohol Dependence. 2010; 108:84–97. [PubMed: 20060657]

Ding K, Chang GA, Southerland R. Age of inhalant first time use and its association to the use of other drugs. Journal of Drug Education. 2009; 39:261–72. [PubMed: 20196331]

Fergusson DM, Boden JM, Horwood LJ. Cannabis use and other illicit drug use: testing the cannabis gateway hyphotesis. Addiction. 2006; 101:556–69. [PubMed: 16548935]

Garland EL, Howard MO. Phenomenology of adolescent inhalant intoxication. Experimental and Clinical Psychopharmacology. 2010; 18(6):498–509. [PubMed: 21186924]

Herrera-Vazquez M, Wagner FA, Velasco-Mondragon E, Borges G, Lazcano- Ponce E. Inicio en el consumo de alcohol y tabaco y transición a otras drogas en estudiantes de Morelos, México. Salud Publica de México. 2004; 46:132–40. [PubMed: 15176575]

Howard MO, Bowen SE, Garland EL, Perron BE, Vaughn MG. Inhalant use and inhalant use disorders in the United States. Addiction Science and Clinical Practice. 2011; 6:18–31. [PubMed: 22003419]

Hynes-Dowell M, Mateu-Gelabert P, Barros HMT, Delva J. Volatile substance misuse among high school students in South America. Substance Use and Misuse. 2011; 46(S1):27–34. [PubMed: 21609142]

Kandel DB. Stages in adolescent involvement in drug use. Science. 1975; 190:912–914. [PubMed: 1188374]

Kandel D, Faust R. Sequence and stages in patterns of adolescent drug use. Archives of General Psychiatry. 1975; 32:923–932. [PubMed: 1156108]

Kish, L. Survey Sampling. Wiley-Interscience; New York: 1965.

Konghom S, Verachai V, Srisurapanont M, Suwanmajo S, Ranuwattananon A, Kimsongneun N, Uttawichai K. Treatment for inhalant dependence and abuse. The Cochrane Database of Systematic Reviews 12. 2010:CD007537.

Levine A, Huang Y, Drisaldi B, Griffin EA Jr. Pollak DD, Xu S, Yin D, Schaffran C, Kandel DB, Kandel ER. Molecular mechanism for a gateway drug: epigenetic changes initiated by nicotine prime gene expression by cocaine. Science Translational Medicine. 2011; 3:107–9.

Malta DC, Sardinha LM, Mendes I, Barreto SM, Giatti L, Castro IR, Moura LD, Dias AJ, Crespo C. Prevalence of risk health behavior among adolescents: results from the 2009 National Adolescent School-based Health Survey (PeNSE). Ciencia e Saude Coletiva. 2010; 15:3009–19. [PubMed: 21049138]

Mayet A, Lagleye S, Chau N, Falissard B. The mediation role of licit drugs in the influence of socializing on cannabis use among adolescents: a quantitative approach. Addictive Behaviors. 2010; 35:890–5. [PubMed: 20584572]

Mesquita AM, de Andrade AG, Anthony JC. Use of the inhalant lança by Brazilian medical students. Substance Use and Misuse. 1998; 33:1667–80. [PubMed: 9680087]

Moreira MM, Barbosa GL, Laranjeira R, Mitsuhiro SS. Alcohol and crack/cocaine use in women: a 14-year cross-sectional study. Journal of Addiction Diseases. 2014 [Epub ahead of print].

Morral AR, McCaffrey DF, Paddock SM. Reassessing the marijuana gateway effect. Addiction. 2002; 97:1493–504. [PubMed: 12472629]

Nakawaki B, Crano WD. Predicting adolescents' persistence, nonpersistence, and recent onset of nonmedical use of opioids and stimulants. Addictive Behaviors. 2012; 37:716–21. [PubMed: 22381640]

Nonnemaker JM, Crankshaw EC, Shive DR, Hussin AH, Farrelly MC. Inhalant use initiation among U.S. adolescents: evidence from the National Survey of Parents and Youth using discrete-time survival analysis. Addictive Behaviors. 2011; 37:878–81. [PubMed: 21481544]

Ober AJ, Miles JN, Ewing B, Tucker JS, D'Amico EJ. Risk for inhalant initiation among middle school students: understanding individual, family, and peer risk and protective factors. Journal of Studies on Alcohol and Drugs. 2013; 74:835–40. [PubMed: 24172109]

Opaleye ES, Ferri CP, Locatelli DP, Amato TC, Noto AR. Nonprescribed use of tranquilizers and use of other drugs among Brazilian students. Revista Brasileira de Psiquiatria. 2014; 36:16–23. [PubMed: 24604458]

Parahyba MI, Veras R. Socio-demographic differentials in the functional decline among the elderly in Brazil. Ciencia & Saude Coletiva. 2008; 13:1257–64. [PubMed: 18813625]

Raphael K. Recall bias: a proposal for assessment and control. International Journal of Epidemiology. 1987; 16:167–70. [PubMed: 3610443]

Remy L, Narvaez J, Sordi A, Guimarães LS, Von Diemen L, Surratt H, Kurtz S, Pechansky F. Correlates of unprotected sex in a sample of young club drug users. Clinics (Sao Paulo). 2013; 68:1384–91. [PubMed: 24270948]

Sanchez ZM, Ribeiro LA, Moura YG, Noto AR, Martins SS. Inhalants as intermediate drugs between legal and illegal drugs among middle and high school students. Journal of Addiction Diseases. 2013; 32:217–26.

Sanchez ZM, Noto AR, Anthony JC. Social rank and inhalant drug use: the case of lança perfume use in São Paulo, Brazil. Drug and Alcohol Dependence. 2013; 131:92–9. [PubMed: 23279923]

Silva-Oliveira F, Jorge KO, Ferreira e Ferreira E, Vale MP, Kawachi I, Zarzar PM. The prevalence of inhalant use and associated factors among adolescents in Belo Horizonte, Brazil. Ciencia e Saude Coletiva. 2014; 19:881–90. [PubMed: 24714902]

Singer JD, Willett JB. Designing and analyzing studies of onset, cessation, and relapse: using survival analysis in drug abuse research. NIDA Research Monograph. 1994; 142:196–263. [PubMed: 9243538]

Stempliuk VA, Barroso LP, Andrade AG, Nicastri S, Malbergier A. Comparative study of drug use among undergraduate students at the University of São Paulo-São Paulo campus in 1996 and 2001. Revista Brasileira de Psiquiatria. 2005; 27:185–93. [PubMed: 16224605]

Strang J, Babor T, Caulkins J, Fischer B, Foxcroft D, Humphreys K. Drug policy and the public good: evidence for effective interventions. Lancet. 2012; 379:71–83. [PubMed: 22225672]

Tarter RE, Vanyukov M, Kirisci L, Reynolds M, Clark DB. Predictors of marijuana use in adolescents before and after licit drug use: Examination of the gateway hypothesis. American Journal of Psychiatry. 2006; 163:2134–2140. [PubMed: 17151165]

Van Etten ML, Neumark YD, Anthony JC. Initial opportunity to use marijuana and the transition to first use: United States, 1979-1994. Drug and Alcohol Dependence. 1997; 49:1–7. [PubMed: 9476693]

Vaughn MG, Wallace J, Perron BE, Copeland V, Howard MO. Does marijuana use serve as a gateway to cigarette use for African-Americans? American Journal of Drug and Alcohol Abuse. 2008; 34:782–791. [PubMed: 19016184]

Victora CG, Matijasevich A, Silveira M, Santos I, Barros AJ, Barros FC. Socio-economic and ethnic group inequities in antenatal care quality in the public and private sector in Brazil. Health Policy Planning. 2010; 25:253–61. [PubMed: 20123940]

Wagner FA, Anthony JC. Into the world of ilegal drug use: exposure opportunity and other mechanisms linking the use of alcohol, tobacco, marijuana, and cocaine. American Journal of Epidemiology. 2002; 155:918–925. [PubMed: 11994231]

Wagner GA, Stempliuk VA, Zilberman ML, Barroso LP, Andrade AG. Alcohol and drug use among university students: gender differences. Revista Brasileira de Psiquiatria. 2007; 29:123–9. [PubMed: 17650531]

Wells JE, McGee MA. Violations of the usual sequence of drug initiation: prevalence and associations with the development of dependence in the New Zealand Mental Health Survey. Journal of Studies on Alcohol and Drugs. 2008; 69:789–95. [PubMed: 18925336]

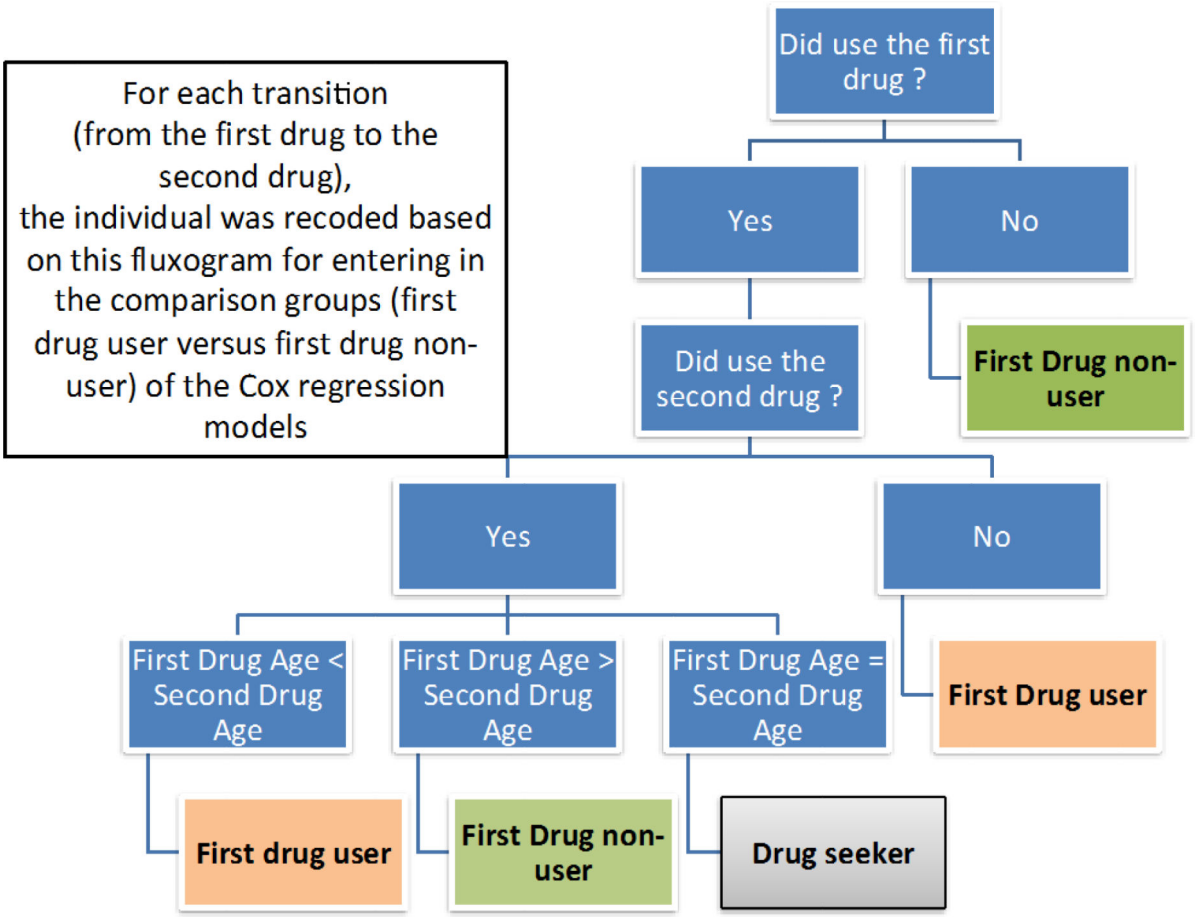

Figure 1.
Fluxogram presenting the division of the individuals between users and non-users, among Braziian university students of the 27 states capitals, 2009.

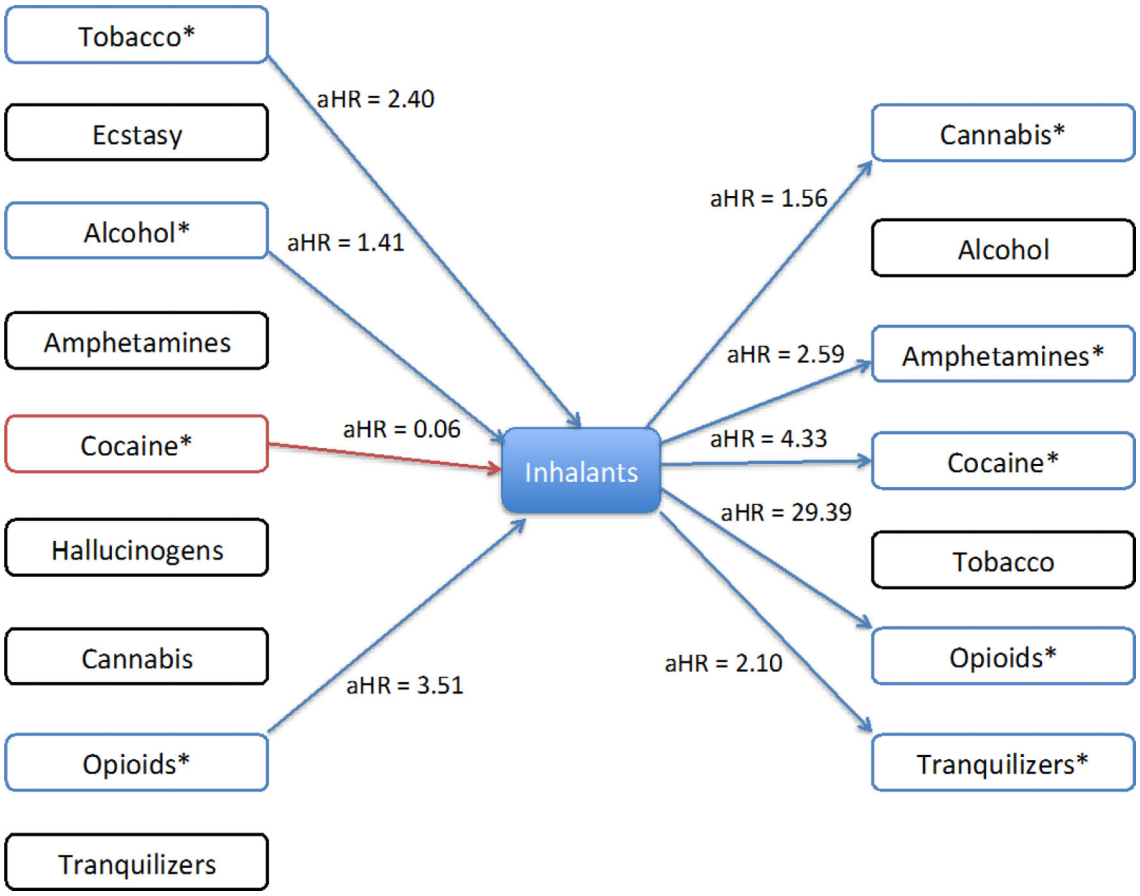

Figure 2.

The scheme highlights all the transitions that did not violate the linktest of proportional hazard-assumptions (LHPA) and could be taked into account (see details in Table 2). The arrows were drawn every time the Cox survival regression model reached significance* ($p<0.05$). If the arrow is blue, the cumulative prevalence of first use of the drug in the lefthead of the arrow was higher in users than non-users of the drug in the righthead of the arrow (aHR > 1). If the arrow is red, the cumulative prevalence of first use of the drug in the lefthead of the arrow was lower in users than non-users of the drug in the righthead of the arrow (aHR < 1).

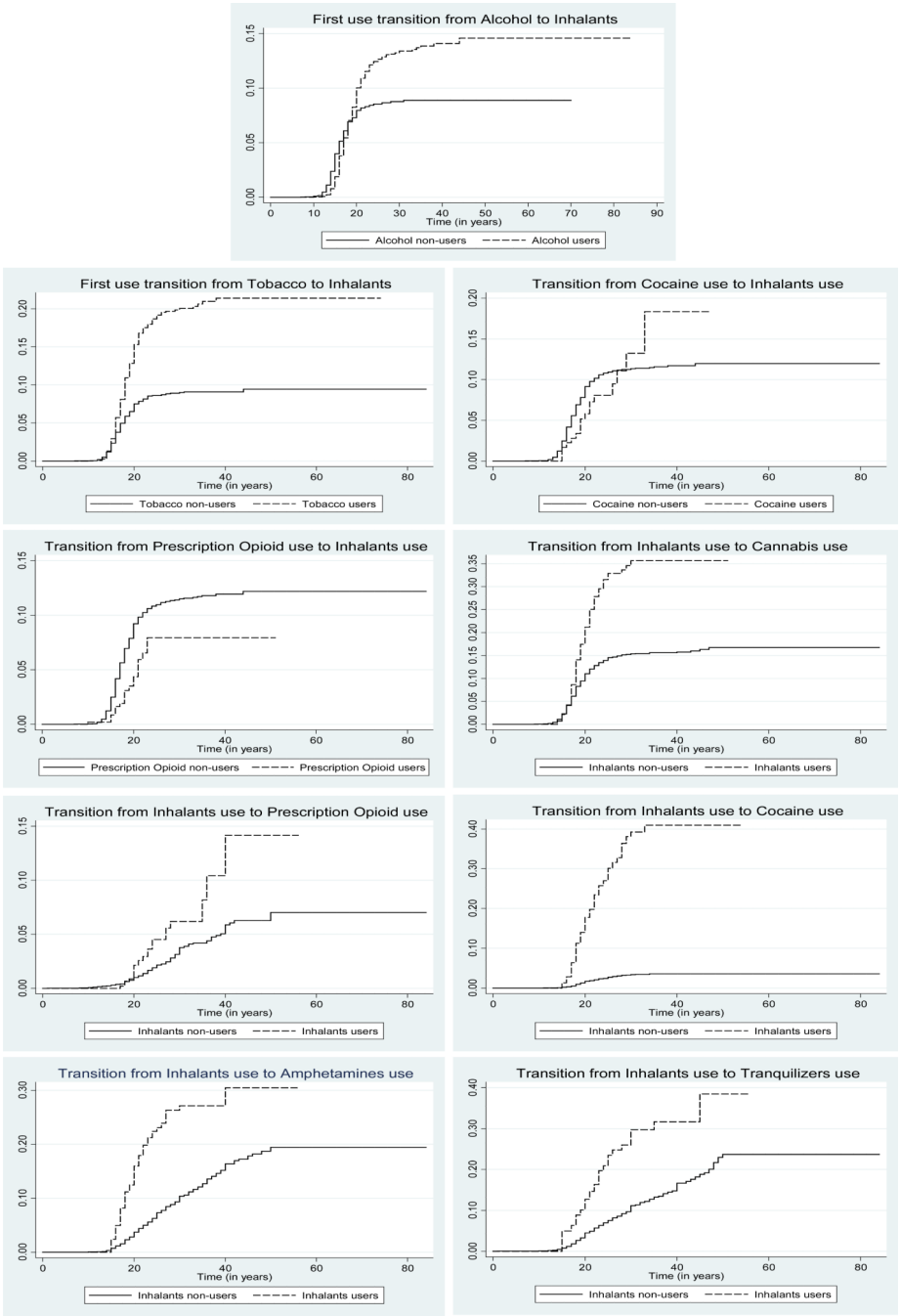

Figure 3.
Kaplan-Meier curves of all transitions which involved inhalants and did not violate LHPA.

Table 1

Sociodemographic data (14 variates included in the Cox survival models) of Brazilian university students from 27 capitals, 2009.

Variable	%	95%CI	SE
Gender			
Female	56.87	53.67-60.00	0.01
Male	43.13	40.00-46.33	0.01
Age*			
< 22 years	38.93	25.69-54.04	0.07
> 21 years	61.07	45096-74.31	0.07
Religion			
None	14.85	12.25-17.90	0.01
Catholic	50.00	45.79-54.22	0.02
Spiritualist	8.90	7.40-10.68	0.01
Umbanda/Candomble	1.77	0.77-4.04	0.01
Jew	0.67	0.37-1.20	0.01
Reformed/Evangelical	17.42	14.17-21.24	0.01
Buddhist/Hindu	0.64	0.40-1.02	0.01
Santo Daime/Vegetal Union	0.20	0.01-0.44	0.01
Other	4.97	3.39-7.24	0.01
Practice of the religion			
Special occasions only	35.26	33.27-37.30	0.01
Montly or more	45.71	43.26-48.19	0.01
No	18.12	16.16-20.26	0.01
Socioeconomic status*			
Low	0.01	0.01-0.29	0.01
Low-average	1.75	0.01-2.37	0.01
Average	25.23	21.64-29.19	0.01
High-average	62.84	58.85-66.66	0.01
High	10.09	7.76-13.02	0.01
Head of the family education			
Zero	7.06	5.45-9.10	0.01
Up to 4 years	7.60	6.01-9.57	0.01
5-8 years	6.02	4.69-7.69	0.01
9-11 years	35.10	31.66-38.71	0.01
12 years or more	42.44	37.39-47.66	0.02
Ethnic group			
Caucasian	62.27	66.05-70.53	0.01

Variable	%	95%CI	SE
African-American	6.50	5.31-7.94	0.01
Mulato	24.71	21.44-28.31	0.01
Oriental	2.45	1.41-4.22	0.01
Indian	0.11	0.57-2.11	0.01
*Other***	2.96	2.37-3.71	0.01
Marital status			
Single	75.68	63.89-84.56	0.05
Married/Living together	20.10	13.50-28.84	0.03
Separated/Divorced	3.57	2.03-6.21	0.01
Widow	0.65	0.14-2.87	0.01
Children			
Yes	19.78	11.82-31.19	0.04
No	79.56	68.38-87.51	0.04
Employment			
No	39.65	34.95-44.54	0.02
Up to 20h/week	17.85	15.12-20.94	0.01
>20h/week	41.85	35.50-48.49	0.03
Driver License			
Yes	61.11	57.62-64.49	0.01
No	38.23	34.97-41.60	0.01
Area of undergraduate studies			
Biological/Health	17.67	10.87- 27.40	0.04
Mathematics	17.01	11.60-24.25	0.03
Humanities	65.33	55.96-73.64	0.04
Current year in college/university**			
First	28.67	21.83-36.65	0.03
Second	26.42	18.19-36.70	0.04
Third	17.00	11.22-24.92	0.03
Fourth	14.33	9.93-20.23	0.02
Fifth	9.64	3.75-22.61	0.04
Sixth	2.13	1.37-3.31	0.01
All-day classes			
Yes	15.05	8.27-25.82	0.04
No	84.95	74.18-91.73	0.04
Happy with the undergraduate choice			
Yes	92.03	88.58- 94.50	0.01
No	7.53	5.20-10.80	0.01

* Included in the Cox survival regression model as continuous measures

** The person does not includ himself/herself within in none of the ethnic groups listed above.

*** We did not ask whether or not students had failed in courses during their studies.

Table 2

Cox survival regression models results of transitions from/to inhalants among university students of 27 Brazilian capitals, 2009.

			Transition*			Gender****			
From	**To**	**Users****	**aHR**	**95%CI**	***p***	**aHR**	**95%CI**	***p***	***p* (TPHA)*****
Alcohol	***Inhalants***	**1181**	**1.41**	**1.09-1.81**	**0.007**	**0.58**	**0.45-0.75**	**<0.001**	**0.236**
Amphetamines		**29**	**0.88**	**0.47-1.64**	**0.700**	**0.60**	**0.47-0.77**	**<0.001**	**0.177**
Cocaine		**20**	**0.06**	**0.01-0.23**	**< 0.001**	**0.67**	**0.56-0.81**	**<0.001**	**0.077**
Ecstasy		**23**	**0.63**	**0.32-1.23**	**0.181**	**0.61**	**0.48-0.78**	**<0.001**	**0.169**
Hallucinogens		**24**	**0.96**	**0.59-1.56**	**0.881**	**0.61**	**0.48-0.78**	**<0.001**	**0.159**
Cannabis		**283**	**0.95**	**0.72-1.24**	**0.729**	**0.56**	**0.44-0.72**	**<0.001**	**0.141**
Prescription Opioids		**64**	**3.51**	**1.14-10.82**	**0.029**	**0.61**	**0.48-0.78**	**<0.001**	**0.160**
Tobacco		**655**	**2.70**	**1.92-3.79**	**< 0.001**	**0.66**	**0.52-0.83**	**0.001**	**0.070**
Tranquilizers		**37**	**1.07**	**0.37-3.10**	**0.892**	**0.67**	**2.55-13.15**	**<0.001**	**0.080**
Inhalants	**Alcohol**	**115**	**0.78**	**0.43-1.43**	**0.426**	**0.70**	**0.53-0.93**	**0.017**	**0.308**
	Amphetamines	**363**	**2.59**	**1.65-4.07**	**< 0.001**	**5.51**	**3.72-8.15**	**<0.001**	**0.354**
	Cocaine	**271**	**4.33**	**3.08-6.09**	**< 0.001**	**0.69**	**0.43-1.11**	**0.131**	**0.461**
	Ecstasy	417	2.12	0.93-4.84	0.071	0.51	0.26-1.01	0.052	0.005
	Hallucinogens	338	6.88	4.14-11.42	<0.001	0.52	0.30-0.93	0.028	0.006
	Cannabis	**409**	**1.56**	**1.26-1.93**	**< 0.001**	**0.56**	**0.39-0.80**	**0.002**	**0.304**
	Prescription Opioids	**181**	**29.39**	**7.17-120.54**	**<0.001**	**1.59**	**0.96-1.86**	**0.068**	**0.246**
	Tobacco	**274**	**1.30**	**0.84-1.99**	**0.224**	**0.85**	**0.69-1.04**	**0.130**	**0.616**
	Tranquilizers	**165**	**2.10**	**1.05-4.18**	**0.035**	**2.28**	**1.48-3.50**	**<0.001**	**0.700**

* All the transitions were adjusted for the intermediate use of the other 8 drugs and to 14 sociodemographic variables

** Individuals that used the drug in the second column before the drug in the first column

*** Pearson coefficient of Test of Proportional-Hazard Assumption (link test). In bold all the transitions which did not violate the test

**** Analysis of the association between the variable gender and the second drug use prevalence, adjusted for each transition. The refence category was male.