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ORIGINAL PAPER

Use transition between illegal drugs among Brazilian university students

João Mauricio Castaldelli-Maia · Silvia S. Martins · Lúcio Garcia de Oliveira · Margriet van Laar · Arthur Guerra de Andrade · Sergio Nicastri

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Abstract
Purpose The aim of the present study was to test whether the first use of an illicit drug increases the chance of first use of other illicit drugs.
Method The transitions from the first use of a drug to the first use of another drug were analyzed. Comparisons were made between first drug users and non-users. Survival analysis methods were used to compare the cumulative probability of second drug use after adjusting for socio-demographic covariates and the intermediate use of alcohol and/or tobacco. A total of 12,721 Brazilian university students participated in this study.
Results Inhalants and marijuana were used prior to the use of several other drugs, whereas the opposite pattern was not found. Ecstasy was used before other drugs in several instances. Other well-examined drugs, such as amphetamines, cocaine and hallucinogens, were used both before and after other illicit drugs without any marked predominance for either of the two roles.
Conclusions This study supports the role of the use of marijuana and inhalants almost exclusively before the use of other illicit drugs, whereas the use of ecstasy has an opposite role. These roles could be linked to the prevalence of lifetime use and whether individuals were at an earlier or later age during experimentation.

Keywords Use transition · Illegal drugs · University students · Cox survival regression

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J. M. Castaldelli-Maia · L. G. de Oliveira · A. G. de Andrade · S. Nicastri
Interdisciplinary Group of Studies on Alcohol and Drugs (GREA), Institute of Psychiatry, Medical School, University of São Paulo, Rua Dr. Ovídio Pires de Campos, 785 (GREA), São Paulo, SP 05403-903, Brazil

J. M. Castaldelli-Maia (✉) · A. G. de Andrade
Disciplines of Psychiatry and Medical Psychology, Medical School, Fundação do ABC, Avenida Lauro Gomes, 2000 (Psiquiatria), Santo André, SP 09060-870, Brazil
e-mail: jmcmaia2@gmail.com

S. S. Martins
Department of Epidemiology, Mailman School of Public Health, Columbia University, 722 West 168th street, Rm. 509, New York, NY 10032, USA

M. van Laar
Trimbos Institute, Netherlands Institute of Mental Health and Addiction, Da Costakade 45, 3521 VS Utrecht, The Netherlands

Introduction

Nowadays, there is a general tendency to consider the predisposition for illicit drug use as the result of various factors [1] that mutually interact (e.g., genetics [2], personality [3] and environment [4]), but the initial use of a drug is still considered a voluntary behavior and could be an interesting focus of prevention [1]. In that sense, many studies found an increased chance of experimentation with one drug before first use of a different one [5–11]—called transition from one drug to another. However, these transitions[1] between illegal drugs have yet to be well examined, despite an estimated 149–271 million people using an

[1] Many authors have used the term 'transition' to describe the transition from the first use of a drug to addiction [17] or to designate the transition from non-use to use of drugs with a high potential for addiction, especially injected drugs [18]. For the purposes of this paper, we define transition as the first use of one drug after the first use of other drug.

illicit drug worldwide in 2009 [12]. Levels of illicit drug use seem to be the highest in high-income countries and in countries near major drug production areas, but data for their use in low-income countries are poor [12].

Within the drug use transition literature, Wagner and Anthony [13] initially studied mechanisms that could link alcohol, tobacco, cannabis and cocaine, based on Kandel's "gateway" theory or "stepping-stone" model [14, 15].[2] Their study attempted to introduce disorders related to drug use into a medical model of disease.[3] However, some authors [5, 16] have stated that the gateway model merely suggests that the use of a particular drug leads to the future use of another drug, yet they have also argued that this model may simply result from a common underlying vulnerability or from common risk factors (e.g., genetic and environmental) to all drug experimentation. However, many steps must occur from the first use of a drug to the first use of another drug, and the predisposition would have to be equal to the exposure occurrence rate and should be followed by a transitional rate of use. Research has yet to clarify how this predisposition is important for individuals who come into contact with a drug [6].

Alcohol and/or tobacco use are clearly followed by a transition to the use of other drugs [5–11]. However, this statement could not be made about the transitions between illegal drugs, because there are just a few studies [10, 20–23] that only investigate transitions from one drug per sample. It is not possible to compare the role[4] of illicit drugs in these transitions. One study, conducted with 268 young adult ecstasy users in the United States, found evidence that previous marijuana use increased the likelihood of the subsequent use of cocaine and heroin [10]. In the same study, the results of a logistic regression suggested that the age of onset for ecstasy use influenced the age of onset for cocaine use. However, in Taiwan, where marijuana use is much less popular than ecstasy use, a multistage probability survey of adolescents attending school found that the majority of ecstasy users were involved in polydrug use [20]. Changes in the popularity of drug use, such as the recent emergence of ecstasy use, may alter the sequential progression proposed in the gateway literature [10]. Another study did not find evidence to support the transition from inhalants to other drugs, despite a high prevalence of lifetime inhalant use in the United States [21].

Some other studies have focused on a different question—the increased risk of having the opportunity to use an illegal drug after the first use of other illegal drug. For example, the prior use of marijuana and the subsequent opportunity to use hallucinogens were investigated in self-reported data from more than 40,000 young participants in the 1991–1994 National Household Surveys on Drug Abuse (NHSDA) [22]. Youths who had used marijuana were substantially more likely to have the opportunity to use hallucinogens than non-users. In London, data from 200 young [23] marijuana users from special schools (Further Education Colleges) were analyzed to examine the potential opportunities for heroin use based on the design features of Kandel's gateway theory. All individuals who had injected drugs or heroin were excluded from this study. A significant percentage (36 %) of marijuana users had been present when others were using heroin, and 35 % had been offered the drug. A small percentage (12 %) had witnessed someone inject a psychoactive drug. However, this study did not investigate how many of the participants eventually used heroin.

A recent multicentre study revealed that the sequence of drug experimentation might be linked to issues related to alcohol and drug use in specific countries [24]. Violations of the classic gateway sequence (alcohol and/or tobacco → marijuana → other drugs) seem to be more common in countries with a low lifetime use of gateway substances, such as alcohol, tobacco and marijuana. For instance, cannabis was rarely used before other illicit drugs by most other illicit substance users in countries where cannabis use was rare (e.g., Japan and Nigeria). However, in countries where rates of cannabis use were highest, violations to the gateway sequence were uncommon (e.g., US and New Zealand). In addition, the classic model of transition may vary between ethnic groups; in the United State, for instance, African–American youth were significantly more likely to begin marijuana use before cigarette use than their Caucasian peers [25].

As regards the Brazilian context, we do not find studies on first use of drugs sequencing pattern. A recent study [26] with a representative sample of university students from the 27 Brazilian capitals found that the three drugs with the highest prevalence of lifetime use were alcohol, tobacco and marijuana (86.2, 46.7, and 26.1 %, respectively). Other drugs such as cocaine, hallucinogens and ecstasy have quite similar lifetime use prevalence (7.5–7.7 %), but these are very far from the three most used substances during

[2] The gateway hypothesis, as initially formulated by Kandel [14, 15], assumed a causal sequence in which (a) marijuana is used after legal drugs and prior to other illegal drugs, and (b) the use of marijuana increases the likelihood of using other illegal drugs [19].

[3] Based on the "gateway" theory or "stepping-stone" model of Kandel and on the idea of "exposure opportunity" derived from the exposure model of the epidemiology of infectious diseases described by Wade Hampton Frost, Wagner & Anthony [13] studied two mechanisms that could link alcohol, tobacco, cannabis and cocaine. A history of drug use would increase the chance of opportunity to use a second drug. This was an attempt to introduce disorders related to drug use into a medical model of disease, following the epidemiological model of infectious diseases.

[4] In the present study, the term 'role' refers to the position of first use of a drug within a first use of drugs sequencing pattern.

lifetime [26]. The lifetime prevalence of non-prescribed medications[5] [26] is also very different from alcohol, tobacco and cannabis. These findings would suggest that, in this population, violations of the gateway model would be less common, as supported by cross-national findings from Degenhardt et al. [24]. However, Andrade et al. [26] also found that the lifetime use prevalence of inhalants at 20.4 % is quite high and close to that of marijuana. This finding is in line with those from a recent study [27] that used a probabilistic sample of urban secondary schools from nine South American countries. In this study [27], Brazil had the highest inhalants lifetime use prevalence among these countries (16.6 %). Therefore, it would be interesting to investigate inhalants role within illicit drug first use sequencing pattern.

Thus, there is a potential interest in analyzing a representative sample of Brazilian university students to assess their illegal drug use transitions. In a population like this, one could expect that gateway model violations would be uncommon. In the present study, this specifically refers to the Kandel [14, 15] statement that marijuana is used prior to other illegal drugs. Considering that adolescence usually involves the first use of several drugs [28], the subsequent period, during which many individuals attend university, is an interesting time to assess the age of first use of these drugs, given that most drug use initiations have occurred recently, which minimizes memory bias. The aim of the present study was to test whether the first use of an illicit drug increased the chance of the first use of other illicit drugs. Statistical analyses were performed after adjusting for the possible intermediate first use of alcohol and/or tobacco and the following covariates: gender; age; socioeconomic status; year of course; whether practicing religion or not; happiness with undergraduation choice; ethnic group; marital status; employment status; concurrent drug use; and type of educational institution (private or public). There is no study that analyzes so many transitions between illicit drugs as ours in the literature.

Methods

The data were taken from an epidemiological study conducted across 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 at the University of São Paulo. Data collection was completed between May and December of 2009.

Sample

The target population of this study was university students who were enrolled in undergraduate courses at Higher Education Institutions (HEIs), both public and private, in the 27 Brazilian state capitals. Undergraduate degrees take approximately 4–6 years to complete in Brazil. A random sample was stratified and recruited with clusters of unequal sizes. The sampling was conducted in two stages, such that, a sample of HEIs was selected, and a sample of student classes was chosen from this selection. Given that the sizes of the HEIs and the classes (in terms of the number of universities) were not always the same, the conglomerates were of unequal sizes.

Given that all of the 27 state capitals were included with representatives from public and private HEIs, sample stratification was conducted based on the two variables of capital and type of institution, for a total of 54 levels. However, this stratification was only used for operating purposes. During the data analysis stage, only the five administrative regions (including the 27 state capitals) and the two HEI types were considered for stratification, for a total of 10 levels. To make the fieldwork economically feasible, a sample of HEIs was selected, and within each one of these, a sample of classes was selected. Therefore, the primary sampling unit for this study was the HEI, and the secondary sampling unit was the class. At the end of the data collection, 100 out of 114 HEIs participated in this study (88 % of the estimated size), with 654 student classes (70.6 % of the estimated size), for a total sample size of 12,721 college students throughout Brazil. Although the participants' response rate was 95.6 % for the college students who were in classes at the time of the interview, the final response rate for this study was approximately 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 (a fictitious drug). Thus, the data were analyzed from 12,711 college students from across the nation.

Weighting factors

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. The dissimilar selection probability was one aspect of the sampling plan that was considered when analyzing the data. This dissimilarity

[5] In the present study, the non-prescribed use of prescription medications (amphetamines, tranquilizers, prescription opioids, anticholinergics, steroids and ketamine) is also considered an illicit drug use.

stemmed from the following two issues: (1) a disproportionate allocation of the sample for the state and type of HEI strata, and (2) the use of sampling by multiplicity and the structure of the target population, which made students who attended more subjects more likely to be selected than students who attended fewer subjects. To correct this imbalance and obtain unbiased estimates of the population parameters, the sample data were weighted. Two weighting factors were obtained that were combined by multiplying them to build a single final weight. All estimates and analyses of the survey data factor in this final weight into obtain unbiased results. It was also necessary to consider the use of clustering and stratification (in the sampling plan) to estimate variability measures (such as standard error) to perform analyses involving the use of these measures (such as hypothesis testing).

Measures

A structured, self-administered, anonymous questionnaire consisting of 98 closed questions was developed with an emphasis on drug use and related disorders, risky behaviors and the existence of psychiatric comorbidity (e.g., depressive symptoms and psychotic and nonspecific psychological complaints). The content of this questionnaire was based on the World Health Organization's research questionnaire, which was previously adapted by Andrade et al. [29] and Stempliuk et al. [30] for use with undergraduate students.

Drug use

The data on drug use were collected through a series of questions with multiple response options. First, students reported whether they had ever used the following drugs ("Have you ever tried *NAME OF THE DRUG* without a doctor's prescription?"): alcohol, tobacco, marijuana, inhalants and solvents, cocaine, "merla" (a cocaine by-product), crack, hallucinogens, ketamine, ayahuasca (Santo Daime), ecstasy (3-4 methylenodioxymethamphetamine, MDMA), anabolic steroids, tranquilizers, prescription opioids, anticholinergics, heroin, amphetamines, and synthetic drugs (methamphetamines and GHB). In the second part of the questionnaire, students reported the age that they first used each of the previous drugs ("How old were you when you first tried *NAME OF THE DRUG*?"). For this study, cocaine, merla and crack were combined in the same group (named cocaine). The youngest age reported for cocaine, merla and crack was selected for the analyses.

Time-dependent drug use variable

Because the aim of this study was to assess the transition from the first use of one illicit drug to other illicit drug, we compared the rates of first use of a drug B between two groups: drug A users and drug A non-users. These groups were defined based on the age of first use of drug A and drug B. The individuals could be classified in three categories per transition: (1) if the subject had already first used the drug A, (2) if the subject had already first used the drug B and (3) whether the subject had first used the drug A before, in the same year or after first used the drug B. If the subject had first used both in the same year, he/she was classified as a drug seeker.

Statistical analyses

We tested all the illegal drugs that had at least 400 users as possible first drugs (described as drug A above). Many of the drug A users groups included less than 400 people because some drug A users had first used the drug B before the drug A in the analyzed transition and thus qualified as drug A non-users. For comparison purposes, all the illegal drugs that could be at least three times as the second drug (described as drug B above) were tested. We analyzed the transition data only when the transition had occurred in 5 % or more of the drug A users.

We used survival analysis methods to compare the cumulative probability of drug B use between the drug A users and drug A non-users groups; these methods produced odds ratios and a 95 % confidence interval. The level of statistical significance chosen was 0.05, and we chose to use Cox Regression Survival Models [31], following previous studies on this subject [13, 32]. All the analysis was performed within the survey option with weights, strata and primary sampling units. We used the STATA version 11.2 (Statacorp, Texas, US, 2009), to run the models with adjustment for covariates (gender; age; socio-economic status; year of course; whether practicing religion or not; happiness with undergraduation choice; ethnic group; marital status; employment status; concurrent drug use; and type of educational institution, and intermediate first use of alcohol and/or tobacco). We chose to use a link test to test for proportional-hazards assumption [33]. This test is based on re-estimation. 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 ($p > 0.05$). Thirteen transitions could not be analyzed since violated this test (i.e., all the seven transitions from other illicit drugs to tranquilizers; the three transitions from inhalants, prescription opioids and cocaine to synthetic drugs; the two transitions from tranquilizers to marijuana and amphetamines, and the transition from cocaine to marijuana).

We excluded the respondents who were over 40 years old ($n = 548$), those who did not indicate their age ($n = 141$), those who did not report whether they used the

drug A or the drug B ($n = 149$ (marijuana), 183 (inhalants), 228 (opioids), 174 (tranquilizers), 206 (ecstasy), 191 (amphetamines), 190 (cocaine), 165 (hallucinogens), 3,203 (alcohol) and 0 (tobacco)), and those who did not report the age of their first use of drug A or drug B ($n = 476$ (marijuana), 625 (inhalants), 670 (prescription opioids), 602 (tranquilizers), 316 (ecstasy), 430 (amphetamines), 284 (cocaine), 298 (hallucinogens), 3,203 (alcohol) and 985 (tobacco)). These exclusions were only used when the given information was necessary to identify the drug's role in the studied transition. Thus, the sample size varied according to the transition considered. The drug seekers (people who used the drug A and the drug B in the same year) were considered drug A users, with the response of the event censored. The number of cases in this group ranged from 0 (from opioids to ketamine) to 288 (from marijuana to inhalants and the opposite transition).

Results

The main results are displayed in three tables. Table 1 shows the socio-demographic characteristics of the sample. Table 2 lists the mean ages at experimentation, median age at experimentation, and the prevalence of lifetime use of all the licit and illegal drugs tested. Table 3 presents the results of the unadjusted and adjusted Cox models.

With regard to the age of first use for the illegal drugs that were tested as "drug A" in this study, we found that the mean age for the onset of inhalants and marijuana use was lower than for the other illegal drugs (17.0 and 17.6 years, respectively). Furthermore, the rates of lifetime use of inhalants and marijuana were the highest of the illegal drugs (16.6 and 19.8 %, respectively). The mean age of first use varied from 19.1 to 19.5 years for the following drugs: cocaine, hallucinogens, and ecstasy (lifetime use prevalence varied from 4.8 to 5.9 %). We observed a higher mean age for the first use of amphetamines and prescription opioids (21.3–21.4 years, respectively) than for cocaine, hallucinogens, and ecstasy.

Marijuana and inhalants

The survival regression models showed that the first use of inhalants was correlated with the subsequent first use of illicit drugs in four of the five potential transitions analyzed and that the first use of marijuana was correlated with the subsequent first use of illicit drugs in four of the six potential transitions analyzed. The marijuana non-users had significant low cumulative probability of the first use of inhalants (aHR = 0.63; 95 % CI = 0.42–0.95; $p = 0.031$).

Table 1 Sociodemographic data of university students of 27 Brazilian capitals, 2009

Variable	*n*	%	SE
Individuals			
Total sample	12,711	100.00	
Age			
<22 years	7,206	56.69	0.01
≥22 years	5,505	43.31	0.01
Gender			
Male	5,682	44.82	0.01
Female	6,995	55.18	0.01
Ethnic group			
Caucasian	7,053	56.22	0.01
Black	862	6.87	0.01
Mulatto/brown	3785	30.17	0.01
Asiatic	363	2.89	0.01
Native indians	104	0.83	0.01
Others[a]	378	3.01	0.01
Brazilian region			
North	2,305	18.13	0.01
Northeast	3,200	25.18	0.01
West-centre	2,199	17.30	0.01
Southeast	2,566	20.19	0.01
South	2,441	19.20	0.01
Marital Status			
Single	10,238	81.13	0.01
Married/living together	2,145	17.00	0.01
Divorced/separated	220	1.74	0.01
Widow(er)	16	0.13	0.01
Children			
Yes	1,897	15.04	0.01
No	10,714	84.96	0.01
Field of the course			
Biological	3,212	25.71	0.01
Humanities	3,276	26.22	0.01
Mathematics	6,007	48.08	0.01
Year of the course[b]			
First	4,526	36.00	0.01
Second	2,711	21.56	0.01
Third	2,684	21.35	0.01
Fourth	1,706	13.57	0.01
Fifth	721	5.73	0.01
Sixth	224	1.78	0.01
Institution type			
Public	6,206	48.82	0.01
Private	6,506	51.18	0.01

[a] The person did not include himself/herself in none of the ethnic groups listed above

[b] Failures were not questioned

Table 2 Mean age of first use and prevalence of lifetime use of drugs of university students of 27 Brazilian capitals, 2009

Drug[a]	Mean age at experimentation[c]	t[f]	p	Median age at experimentation[e]
Alcohol	15.26 (15.20–15.33)	–	–	15 (15–15)
Tobacco	16.13 (16.03–16.23)	14.31	<0.001	16 (16–16)
Inhalants	17.00 (16.82–17.17)	8.77	<0.001	17 (16–17)
Marijuana	17.64 (17.51–17.77)	6.05	<0.001	17 (17–17)
Hallucinogens	19.11 (18.88–19.35)	10.57	<0.001	19 (18–19)
Cocaine	19.45 (19.05–19.86)	1.46	0.142	19 (18–19)
Ecstasy	19.50 (19.20–19.81)	0.18	0.855	19 (19–19)
Tranquilizers	21.30 (20.86–21.74)	5.61	<0.001	20 (20–20)
Prescription Opioids	21.33 (20.17–22.50)	0.06	0.950	20 (19–20)
Amphetamines	21.40 (20.95–21.86)	0.13	0.892	20 (20–20)
Drug[b]	Prevalence of lifetime use[d]	t[f]	p	
Alcohol	85.27 (84.65–85.89)	–	–	
Tobacco	38.28 (37.44–39.13)	87.96	<0.001	
Marijuana	19.86 (19.16–20.55)	32.92	<0.001	
Inhalants	16.67 (16.02–17.32)	6.53	<0.001	
Tranquilizers	10.37 (9.83–10.90)	14.65	<0.001	
Amphetamines	8.41 (7.92–8.89)	5.31	<0.001	
Prescription Opioids	5.99 (5.57–6.40)	7.40	<0.001	
Hallucinogens	5.92 (5.50–6.33)	0.23	0.813	
Cocaine	5.15 (4.76–5.53)	2.66	0.007	
Ecstasy	4.80 (4.43–5.18)	1.25	0.208	

[a] The drugs were displayed in crescent mean age at experimentation

[b] The drugs were displayed in decrescent prevalence of lifetime use

[c] In years, 95 % confidence interval between the parentheses

[d] In percent(%), 95 % confidence interval between the parentheses

[e] In years, 95 % confidence interval between the parentheses

[f] t test comparison of the mean age at experimentation/lifetime use prevalence between the drug in row with the drug in the row above

Nonetheless, there was no significant difference in the cumulative probability for the first use of marijuana between users and non-users of inhalants (aHR = 0.95; 95 % CI = 0.80–1.14; $p = 0.640$). When we analyzed whether these drugs acted as second drugs (drug B) in the transition, we noted that the cumulative probability for the first use of inhalants and marijuana was never significantly different between other illicit drug users and non-users.

Non-prescribed medications

We tested prescription opioids in five potential transitions in the role of drug A. The users of prescription opioids had a higher cumulative probability for the first use of only 1 illicit drug (cocaine—aOR = 14.93; 95 % CI = 2.73–81.54; $p = 0.002$) than the non-users. However, there was no chance of testing prescribing opioids in the role of drug B. Regarding amphetamines, we found two instances of four potential transitions, in which the users of this drug had a higher cumulative probability for the first use of other illicit drugs than the non-users (ecstasy and hallucinogens). But there were two instances of five potential transitions in which the users of other illicit drugs (inhalants and hallucinogens) had a higher cumulative probability for the first use of amphetamines than the non-users. All the transitions that involved tranquilizers (in the role of drug A or B) violated the link test to test for proportional hazards assumption.

Cocaine, hallucinogens, and ecstasy

Six potential transitions analyzed hallucinogens as drug A. In three cases, there were statistically significant higher cumulative probabilities for the first use of other illicit drugs (ecstasy, amphetamines, and synthetic drugs) among the hallucinogen users than non-users. Three potential transitions tested cocaine as drug A, and, in two cases, the cocaine users had higher cumulative probabilities for the use of other illicit drugs (hallucinogens and ecstasy) than the cocaine non-users. Ecstasy was tested as the first drug (drug A) in five potential transitions, and significant

Table 3 Results of Cox survival regression models of transitions between illicit drugs among university students of 27 Brazilian capitals, 2009

From	To	*n* (transitions)[c]	HR	95 % CI	*p* value	aHR[a]	95 % CI[a]	*p*-value[a]	*p* (TPHA)[b]
Marijuana	Inhalants**	235	1.49	1.18–1.89	0.001	0.63	0.42–0.95	0.031	0.688
	Cocaine*	346	16.99	11.00–26.24	<0.001	6.38	4.02–10.14	<0.001	0.109
	Hallucinogens*	366	20.86	15.46–28.15	<0.001	7.84	2.86–21.47	<0.001	0.117
	Ecstasy*	345	16.13	13.40–19.41	<0.001	5.33	3.84–7.39	<0.001	0.306
	Amphetamines	180	2.13	1.28–3.55	0.004	2.17	0.93–5.06	0.070	0.064
	Synthetic drugs*	95	13.39	8.24–21.75	<0.001	12.08	6.57–22.20	<0.001	0.876
Inhalants	Marijuana	408	2.56	1.96–3.35	<0.001	0.95	0.80–1.14	0.640	0.663
	Cocaine*	264	14.15	9.83–20.37	<0.001	4.45	3.06–6.45	<0.001	0.952
	Hallucinogens*	377	16.73	12.73–21.98	<0.001	6.88	4.96–9.54	<0.001	0.074
	Ecstasy*	328	15.17	12.40–18.58	<0.001	5.55	2.26–13.64	0.001	0.169
	Amphetamines*	192	2.28	1.73–3.01	<0.001	2.98	1.27–6.97	0.012	0.213
Prescription Opioids	Marijuana	25	0.55	0.33–0.94	0.030	1.04	0.90–1.20	0.581	0.581
	Inhalants	54	2.04	0.87–4.74	0.096	1.97	0.90–4.31	0.089	0.879
	Cocaine*	16	36.96	9.32–154.66	<0.001	14.93	2.73–81.54	0.002	0.975
	Hallucinogens	52	6.48	1.12–37.46	0.037	0.23	0.03–1.50	0.125	0.263
	Ecstasy**	49	11.16	4.06–30.66	<0.001	0.16	0.03–0.84	0.031	0.437
Amphetamines	Marijuana	85	0.86	0.52–1.44	0.579	0.87	0.72–1.05	0.150	0.584
	Inhalants	44	0.70	0.40–1.22	0.210	0.60	0.29–1.22	0.161	0.566
	Hallucinogens*	57	10.40	6.99–15.45	<0.001	5.33	3.70–7.67	<0.001	0.179
	Ecstasy*	56	11.17	4.95–25.24	<0.001	4.72	1.44–15.42	0.011	0.551
Cocaine	Hallucinogens*	78	11.39	5.72–22.64	<0.001	6.90	3.68–12.91	<0.001	0.186
	Ecstasy*	74	7.03	3.96–12.48	<0.001	3.13	1.63–6.00	0.001	0.333
	Amphetamines	54	1.39	0.90–2.14	0.132	2.80	0.88–8.83	0.078	0.486
Ecstasy	Marijuana	30	1.84	0.61–5.49	0.270	1.25	0.85–1.82	0.237	0.613
	Inhalants	34	1.77	0.82–3.81	0.138	0.68	0.22–2.07	0.501	0.818
	Cocaine	31	6.66	3.37–13.18	<0.001	2.23	0.50–9.80	0.283	0.836
	Hallucinogens*	27	17.64	11.79–26.38	<0.001	4.90	2.08–11.56	<0.001	0.208
	Amphetamines	22	2.15	1.58–2.93	<0.001	0.76	0.22–2.52	0.653	0.078
Hallucinogens	Marijuana	31	1.58	0.51–4.85	0.416	1.27	0.80–2.02	0.289	0.644
	Inhalants	49	2.20	1.22–3.98	0.009	0.82	0.27–2.48	0.728	0.767
	Cocaine	47	8.75	4.33–17.65	<0.001	2.68	0.73–9.85	0.135	0.696
	Ecstasy*	92	28.89	14.05–59.40	<0.001	11.27	4.43–28.68	<0.001	0.202
	Amphetamines*	33	2.51	1.61–3.91	<0.001	2.25	1.24–4.10	0.008	0.168
	Synthetic drugs*	22	16.49	11.04–24.63	<0.001	11.08	6.19–19.81	<0.001	0.297

* Significant adjusted transitions: the previous use of the drug in the first column was correlated with a higher cumulative prevalence of first use of the drug in the second column ($p < 0.05$, aOR > 1)

** Significant inverse adjusted transitions: the previous use of the drug in the first column was correlated with a lower cumulative prevalence of first use of the drug in the second column ($p < 0.05$, aOR < 1)

[a] Adjusted covariates: gender; age; socio-economic status; year of course; whether practicing religion or not; happiness with undergraduation choice; ethnic group; marital status; employment status; concurrent drug use; and type of educational institution (private or public) *HR* unadjusted hazard ratio; *aHR* adjusted hazard ratio; 99 % CI = 99 % confidence interval; *p*-value = Pearson value

[b] Pearson coefficient of Test of Proportional-Hazard Assumption (link test)

[c] Number of individuals who first used the drug in the second column before the drug in the first column. This is an estimated value since it is not possible to calculate the exact number with survey settings

difference in the cumulative probability for the first use of other illicit drugs was found only once (hallucinogens) between the ecstasy users and non-users. In the drug B role, the cumulative probability for the first use of cocaine was higher in other illicit drugs users than non-users in three of five potential transitions, and the first use of hallucinogens was higher in other illicit drugs users than non-users in five of six potential transitions, the same result of ecstasy.

Discussion

The aim of the present study was to examine whether the first use of an illegal drug would increase the cumulative probability of the first use of another illicit drug (the transition of use between two drugs). Seventeen of 34 potential transitions were statistically significant transitions. We identified the following drugs in the role of drug A in these statistically significant transitions: marijuana in 4/6 of the tested transitions, inhalants in 4/5, prescription opioids in 1/5, amphetamines in 2/4, cocaine in 2/3, ecstasy in 1/5, hallucinogens in 3/6. These findings are in line with Palmer et al.'s [34] study examining tobacco, alcohol and marijuana, which identified a generalized risk, namely that when someone uses one of these drugs, he increases his chances of using another of these drugs. Nevertheless, it is true that the first use of marijuana and inhalants never occurs after the first use of other illegal drugs. In general, the first use of both drugs occurred prior to the first use of other illicit drugs, and the first use of other illicit drugs did not take place before the first use of marijuana and inhalants. Ecstasy played the role of drug B in several significant transitions. In contrast, our findings suggest that amphetamines, cocaine and hallucinogens may play a different role compared to other illicit drugs in drug use transitions, as they do not systematically act as drug A or B.

Regarding the role of marijuana and inhalants, our data are consistent with previous findings. Brazilian university students have high rates of lifetime use of marijuana and inhalants (35.4 and 24.6 %, respectively) [35], which was confirmed in the present sample (Table 2). Thus, we can expect [24] the first use of these drugs to occur before the first use of other illicit drugs. In other countries with high rates of marijuana use [11, 13], this role has also been confirmed.

With regard to inhalants, our findings differed from the results of a previous study conducted in the United States [21]. In both the US and Brazil, this class of drugs is the fourth most commonly used during lifetime [36]. It is possible that the correlation of the first use of inhalants with the subsequent use of other illicit drugs could be stronger in Brazil than it is in the US. Findings from the US [21] have indicated that only 4.2 % of multiple drug users used inhalants prior to other drugs: in particular, alcohol, tobacco, and marijuana. However, the design of the US study was quite different from ours, as it compared the age of first time inhalant use with the age of onset for the use of other drugs among 6,466 inhalant users who also used at least one of 14 other drugs.

The main value of this work is its thorough investigation of drug use transitions between illegal drugs in a specific subpopulation sample, specifically, Brazilian undergraduate students. This analysis was performed with the exclusion of possible confounding factors, such as the intermediate first use of alcohol and/or tobacco, gender, economic status, age, type of educational institution (private or public) and other socio-demographic variables. These results are important given the considerable debate over the validity of the "gateway" theory [11, 16, 19, 24]. One way to build on this classical model [15] is to consider the prevalence of lifetime use and the age of experimentation for each drug. For example, the use of marijuana, inhalants, amphetamines and tranquilizers is moderately high prevalent in this sample, but the first two drugs presented an earlier mean age of experimentation than the latter two in this sample. Furthermore, it may be incorrect to only consider drugs with high prevalence rates that correlate with higher cumulative probabilities for the first use of other illicit drugs.

Based on our study's findings, we can formulate practical implications and recommendations. Brazilian adolescents who use marijuana or inhalants should be provided with targeted guidance to prevent their subsequent use of other drugs, as this is a common transition pathway. Of course, the prevention depends on the nature of the assumed (common) causes. As Degenhardt et al. [24] stated, it is not enough to prevent the use of one drug to prevent the later use of other drugs. For example, prescription opioid users, and perhaps amphetamine users, appear to have no inclination to begin using other drugs, which may be due to these groups experimenting at a later age than other illegal drug users. The population that seeks analgesic effects [37], or appetite suppressers [38], may differ from individuals who are curious [39] about the sensations induced by illegal drugs such as marijuana, inhalants, cocaine and others. During adolescence, people are more likely to engage in risky behaviors, such as drug experimentation, which may result in abuse and dependence [40]. Unlike the US sample, in which most of the nonmedical users of prescription drugs were polydrug users [41, 42], among Brazilian young adults, the trajectory of individuals who begin to use nonmedical legal drugs may be quite different from those who seek out illegal drugs.

Campaigns to prevent drug use tend to have modest results [43, 44]. By identifying the most prevalent trajectories in a population, we can focus on brief interventions with specific goals for small populations at risk [45]. Based on the mean age for first time drug use found in this study, we can observe that the "university years" (approximately 18–24 years) appear to be important for preventing the onset of illegal drug use. Prevention programs could target the Brazilian university students who have already used marijuana or inhalants to discourage their future use of other drugs, such as ecstasy and synthetic drugs. From an individual perspective, health, social and educational professionals could counsel patients and students to prevent future drug use based on the trajectories identified in this study.

Limitations

An important limitation of this study is recall bias, which is inherent in cross-sectional studies [46]. In addition, an important proportion of students have missing information on the age of onset for many drugs and whether they used this drug. It could bias the results mainly in case of some drugs with a proportional high number of missing (e.g., prescription opioids, tranquilizers). Furthermore, we only interviewed university students, so we cannot extrapolate the data to the general Brazilian population. University students in this country are not representative of the general population given that only 13.9 % of young adults have access to higher education. Almost 50 % of university students study in private institutions, which set them apart from the general population. However, the present study used a representative sample from all of the Brazilian capitals provided balanced data from a large country with many social, cultural and economic differences [47]. It is important since these differences play a role in physical and mental health [48].

The present study did not consider the earlier or later use of all of the drugs tested. Premature experimenters with some drugs may be at higher risks for the first use of other drugs than those who experiment later in life [7, 49, 50]. Moreover, this study did not examine the gateway theory, which proposes sequences that are involved in the first use of drugs. To address that theory, we would have had to take into account the mediating role that some drugs might play in some of the transitions. Alcohol and tobacco were not tested, although there are many reverse gateway processes leading from illegal drug use to legal drug use [51]. Previous findings suggest that alcohol and tobacco could have played a mediating role in our study.

Conclusions

This study supports the role of the first use of marijuana and inhalants prior to the first use of other illegal drugs. It also confirms that the first use of marijuana and inhalants rarely occurs after the first use of other illicit drugs that were analyzed in this sample. The first use of ecstasy frequently occurred prior to the first use of other illicit drugs in a Brazilian university population. Other drugs may play a different role compared to other illicit drugs in the drug use transitions, as they did not systematically act as the drug A or drug B.

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Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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