Revista de Ciências
Farmacêuticas
Básica e Aplicada
Journal of Basic and Applied Pharmaceutical Sciences

Rev Ciênc Farm Básica Apl., 2017;38
ISSN 1808-4532

Pharmacotherapy of adolescents in the use of psychoactive substances

Sandra Hernandez Morais de Araújo[1]; Renato Rocha Martins[2]; Flavio Marques Lopes[3]; Nathalie de Lourdes Souza Dewulf [3]*

[1] Center for Psychosocial Care of Aparecida de Goiânia
[2] Clinical Hospital of Federal University of Goiás
[3] Research Laboratory in Pharmaceutical Education and Services, Faculty of Pharmacy, Federal University of Goiás.

ABSTRACT

The use of Psychoactive Substances brings problems in several areas of the subject's life such as: health, psychological and social. It´s necessary evaluate the factors involved in drug use and potential drug interactions (PDI) in adolescents using psychoactive substances. It was a Cross-sectional, analytical and quantitative study. The research was carried out at the Center for Psychosocial Care and other drugs for children and adolescents 24h, with adolescents under 18 years of age, using medication. The data were obtained by reviewing the charts and the potential interactions were evaluated through the database *Micromedex*® and *Medscape*®. Of the 159 records used, there were 815 PDI. By gravity were 59.4% moderate, 23.8% secondary, 15.7% severe and 1.1% contraindicated. The drugs that presented the most PDI were Chlorpromazine (32.3%) and Diazepam (19.6%). The factors involved in polypharmacy were total PDI and those involved in the occurrence of total PDI were studying and the quantity diagnostic hypotheses. Due to the high PDI index, the relationship with polypharmacy and a high number of diagnostic hypotheses, it is necessary to increase the attention of health professionals regarding the topic and the development of protocols to support decision making.

Keywords: Drug therapy. Drug interactions. Psychotropic Drugs.

Corresponding author: Nathalie de Lourdes Souza Dewulf. Universidade Federal de Goiás - Faculdade de Farmácia - Rua 240, esquina com 5ª Avenida, s/n, Setor Leste Universitário – CEP: 74605-170 – Goiânia – Goiás – Brasil. E-mail: nlsdewulf@ufg.br

INTRODUCTION

The consumption of psychoactive substances is one of the problems with the greatest impact on world public health among young people. The estimates released by the United Nations Office on Drugs and Crime (UNODC) are that more than 29 million people have mental illness related to drug use (Bousoño *et al.*, 2017). Whether it is sporadic or regular use, drug use can pose health risks, with 200 million people being killed each year for causes attributed to drug use (United Nations Office on Drugs and Crime, 2016). Psychoactive substances (PS) act in the Central Nervous System altering cognitive functions, sense perception and consciousness. The PS are categorized according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) in alcohol, marijuana, hallucinogens, amphetamines, cocaine, caffeine, inhalants, nicotine, opioids, sedatives, hypnotics and anxiolytics (American Psychiatris Association, 2012).

The use of alcohol and other drugs causes problems in several areas of the subject's life, such as health, psychological and social (Jhanjee, 2014). These problems can be effectively dealt with in most cases when access to health services is available in a timely manner (United Nations Office on Drugs and Crime, 2012). In the health services that serve PS users, it is necessary to keep records of the users, indicating the main substances consumed by them, as well as treatment protocols for drug addiction and guidelines for the use of drugs (United Nations Office on Drugs and Crime, 2012).

There are treatments that seek rehabilitation, prevention and social reintegration of the chemical dependent, and this assistance is provided by both the Family Health Teams (FHT) and the Centers for Psychosocial Care Alcohol and Drugs (CPCAD ad) (Brasil, 2004; Silva *et al.*, 2016). In Brazil, the PS user's treatment is preferably done in CPCAD. Psychosocial, pharmacological interventions and their combination are offered in them.

It is recommended that pharmacological interventions be accompanied by psychosocial intervention, considering the needs and risks for each patient, not following a

pattern model. In children and adolescents, it should be also considered the existence of differences between adults and children, as well as among children of different ages. Those differences should be always based on the best available evidence of cost-effectiveness and safety, including, when appropriate, drugs that are not licensed for the age group or the (off-label) (Gilvarry & Jill, 2009).

In view of this, it is necessary to know the drugs that are most used in Brazil and in the world for the treatment of children and adolescents with PS, with their adverse effects and potential drug interactions. However, few studies have already elaborated on the use of drugs in Brazil, especially in children and adolescents, regardless of that, they reveal an important identification of intervention planning, with better use of therapeutic resources by both the user and the prescribers (Storpirtis *et al.*, 2008).

This study aims to evaluate the factors involved in the use of drugs and the possible drug interactions in adolescents using Psychoactive Substances (PS).

MATERIAL AND METHODS

Outline and data collection

This is a cross-sectional, quantitative and analytical study. The research environment is the Center for Psychosocial Care Alcohol and other drugs for children and adolescents 24 h (CPCAD adi-III) located in the city of Aparecida de Goiânia, Goiás.

The population of this study was composed of adolescents under 18 years of age in use / abuse / dependents of PS, who were at treatment, by the time of the collecting data / follow-up at CPCAD adi-III and who had prescribed medications, 159 medical records met these specifications. The data were obtained by retrospective review of medical records, from July 2012 to August 2016.

Variables

The variables were: Age that began the medical care in CPCAD adi III; Sex; Schooling; If he/she was studying; Type of referral; Follow-up time in CPCAD adi III; Total Diagnostic Hypotheses: according to the International Classification of Diseases and Related Health Problems, also known as International Classification of Diseases - ICD 10 (Organização Mundial de Saúde, 1993); Drugs in use: last medical prescription with total medications in use: quantity of drugs prescribed per patient and the drugs which were categorized by the ATC (World Health Organization, 2015) system and used up to the 3rd level. The use of 5 or more drugs was adopted as polypharmacy (Jörgensen *et al.*, 2001).

The potential drug interactions (PDI) were evaluated according to the *Micromedex* database (Drugdex System, 2016) and classified according to the database as the type of interaction (drug-food, drug-ethanol, drug-drug, drug-tobacco), severity of Interaction as described in Board 1. And the PDI between *Cannabis* (Marijuana) and Cocaine were evaluated in the *Medscape* database (Drug checker interaction, 2017) and are classified according to severity described in Board 1.

The total PDI variable is the sum of the following: Potential drug-food interactions, Drug-cocaine, drug-*cannabis*, drug-ethanol, drug-drug, and drug-tobacco.

The variables related to the use of PS are: Which PS already used.

Statistical analysis

The collected data were recorded and stored using the Epi-infoTM program, version 7.1.5.2, created by the CDC (Centers for Disease Control and Prediction) in the public domain (available at http://wwwn.cdc.gov/epiinfo/7/) They were also analyzed with the Statistical Package for Social Sciences (SPSS) 15.0. The outcome variables studied were the number of drugs used and the total number of potential drug interactions. Bivariate analyzes were performed using the logistic regression model to estimate the effect of the other variables on the occurrence of total potential drug interactions and the occurrence of polypharmacy. In the binary logistic regression, all the variables that presented values of $p \leq 0.20$ were included and in the final model only those with $p \leq 0.05$ remained.

Ethical Aspects

It was approved by the Research Ethics Committee of the Federal University of Goiás CEP-UFG through opinion no. 1,727,585, 06/07/2016.

RESULTS

Of the medical records used in the study, 71.7% were male; average age of 16 ± 1.9 years; Incomplete Elementary School (88%), with 67.9% declaring that they are not studying, being on average 19 months out of school at the time of the reception. Regarding the search for care, it was found that in 55.3% of cases were by a judicial measure; 25.1% by order of the Guardianship Council and only 14.4% by spontaneous demand.

There were 290 diagnostic hypotheses according to the ICD-10 (Organização Mundial de Saúde, 1993)10 classifications. The mean values obtained were of 1.8 / patient, with a range between 1 and 6. Those who presented the highest proportion (34.9%) were mental and behavioural disorders due to the use of multiple drugs and the use of

Board 1. Classifcation of PDI regarding the gravity

Gravity	Potential Risk *Micromedex®*	Potential Risk *Medscape®*
Contraindicated	Medications are contraindicated for concomitant use.	Simultaneous use is contraindicated.
Severe	Interaction may be life-threatening and / or require medical intervention to reduce or avoid serious adverse effects.	It should be avoided. An alternative medication should be emploied.
Moderate	The interaction may lead to exacerbation of the patient's health problem and / or require a change in treatment.	The use of medication should be monitored and if necessary modify the treatment.
Secundary	The interaction may lead to limited clinical effects, which may include an increase in the frequency or severity of side effects, but usually without the need for a major change in treatment.	Monitor the therapy as it may increase the side effects.

Source: *Micromedex®* E *Medscape®*, 2017.
Acronyms: PDI - Potential drug interactions.

other PS (F19), mental and behavioural disorders associated with the use of cannabinoids (F12) with 17.2%; Bipolar Affective Disorder (F31) with 12.6%; Specific personality disorders (F60) with 4.1%; Mental and behavioural disorders resulting from cocaine use (F14) with 3.8%; and depressive episodes (F32) with 3.4%.

In relation to previous experiences of treatments, it was verified that 18.2% of the users had already undergone previous treatment. In the CPCAD adi-III, the average follow-up time was 188 days, with records of patients who did not complete the day of medical care and others with 1400 days of follow-up. The age of first use of drugs was on average 12.4 ± 1.90 years, ranging from 6 to 17 years. The most used drugs were *Cannabis* (37.2%), Tobacco (13.2%), Solvents (12.9%) and Cocaine (7,6%).

In the sample, prescriptions of 12 pharmacological groups were found, with 327 drugs prescribed, mean of 1.8 / patient, ranging from 1 to 9 medications. The most prescribed were N03A (antiepileptic) (39.9%) and N05A (antipsychotic) (34.8%) (Table 1).

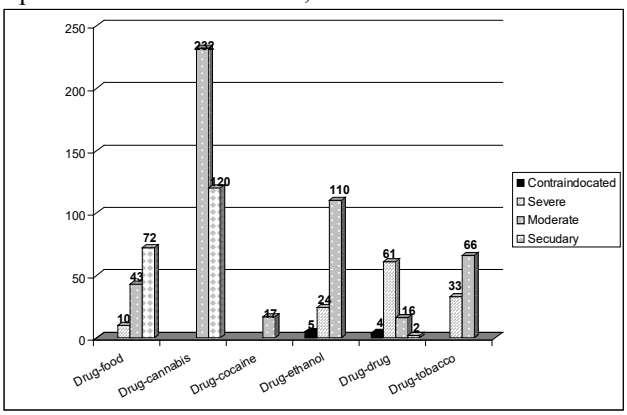
It was verified the existence of 815 PDI, with a mean of 5 / patient, ranging from 0 interaction to 24 PDI. PDI by type and severity can be visualized in Graph 1.

Being listed by gravity, the PDI were 59.4% moderate, 23.8% secondary, 15.7% severe and 1.1% contraindicated. The drugs that presented the most potential interactions were Chlorpromazine (32.3%), Diazepam (19.6%), Haloperidol (7.5%), and Risperidone (4.3%).

The Valproic Acid presented itself as the safest drug, with only 1.5% of the PDI. On the other hand, Topiramate and Bromopride are the drugs that demand greater caution in prescription, accounting for 1.1% of the total PDI, but all are contraindicated. The main PDI drug-drug, the drugs involved the severity of the interaction, the potential risk, the suggested clinical management and the frequency can be visualized in Table 2.

Among the PDI drug-food, the most frequent drugs were Diazepam 81 (64.8%) and Clonazepam 18 (14.4%),

Graph 1. PDI by type of interaction and severity found in prescriptions of the Psychosocial Child Care Center, Aparecida de Goiânia-Goiás, Brazil 2017



Source: From the author, 2017.
Acronyms: PDI - Potential drug interactions.

and the most frequent drugs in the PDI and PS were analyzed in Table 3.

In the bivariate analysis of the factors involved in the occurrence of polypharmacy, the variables that showed association were number of drugs used (p = 0,019) and Total PDI (p = 0,001). In the bivariate analysis of the factors involved in the occurrence of Total PDI, the variables that presented association were: Being studying (p = 0,008) and Total diagnostic hypothesis (p = 0,001) and can be visualized in Table 4.

The results of the multivariate regression analysis of the Factors involved in the occurrence of polypharmacy have that the total of PDI increases by 1.5 the chance of the patient to make use of polypharmacy and can be visualized in Table 5. And multivariate regression analysis of the factors involved in the occurrence of Total PDI, whoever is studying the chance of occurrence of the total PDI is 68.0% lower than those who are not studying, and that with each additional diagnostic hypothesis increases the chance of occurrence of total PDI by 2.84 and may be observed in Table 5.

Table 1. Drugs used according to ATC of the Child Psychosocial Care Center, Aparecida de Goiânia-Goiás Brazil, 2017

Medications by group ATC (Anatomical Therapeutics Chemistry) and DCB (Brazilian Common Denomination)	Frequency (%)
A02B – DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	
Omeprazole	0.3
Ranitidine	0.6
A03F (PROPULSIVES)	
Bromopride	1.5
J01F (MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS)	
Azitromycin	0.3
N03A (ANTIEPILEPTICS)	
Valproic Acid	30.6
Carbamazepine	2.4
Clonazepam	5.4
Topiramate	1.5
N04A (ANTICHOLINERGIC AGENTS)	
Biperiden	0.6
N05A (ANTIPSYCHOTICS)	
Lithium	0.9
Chlorpromazine	20.7
Haloperidol	6.3
Haloperidol Depot	0.3
Olanzapine	0.6
Quetiapine	0.6
Risperidone	5.4
N05B(ANXIOLYTICS)	
Diazepam	9.0
N06A (ANTIDEPRESSANTS)	
Amitriptyline	1.5
Bupropion	0.3
Fluoxetine	5.4
Imipramine	1.2
Nortriptyline	0.3
Sertraline	0.6
N06B (Psychostimulants, agents used for ADHD and nootropics)	
Methylphenidate	0.3
M01A (Anti-inflammatory and Non-Steroidal Anti-Rheumatics)	
Diclofenac	0.3
Nimesulide	0.3
R03A (Adrenergic, inhalants)	
Salbutamol	0.3
R06A Systemic antihistamine	
Promethazine	2.4

Source: From the author, 2017.

Table 2. Characterization of PDI drug-drug, according to the severity of the interaction, potential risk, clinical management, and frequency, of the Center for Psychosocial Children and Adolescent Care, Aparecida de Goiânia-Goiás.Brazil, 2017

Drugs envolved	Interaction severity	Potential Risk	Clinical management	Frequency n (%)
Chlorpromazine x Haloperidol	Severe	The QT interval prolongation may result in additive effects and increased risk of ventricular arrhythmias, including torsades de pointes and sudden death.	The combination is not recommended.	13(16)
Valproic acid x Risperidone	Moderate	The combination can result in incresed concentrations of Valproic acid	Monitor the increase in ammonia levels and plasma concentrations of Valproic acid with addition medications containing Risperidone or changes in its dosage.	11(13)
Chlorpromazine x Risperidone	Severe	Increased risk of cardiotoxicity (QT prolongation, torsades pointes and sudden death)	The concomitant use is not recommended	7(8)
Haloperidol x Promethazine	Severe	Increased risk of QT prolongation.	Monitor QT interval prolongation.	6(7)
Carbamazepine x Chlorpromazine	Severe	The use of such drugs in liquid form may generate a precipitate.	Do not administer at the same time.	5(6)
Chlorpromazine I x Promethazine	Severe	Increased risk of QT prolongation	Monitor QT interval prolongation.	5(6)
Chlorpromazine x Fluoxetine	Severe	Increased exposure to fluoxetine and increased risk of QT prolongation	Monitor the ECG at the beginning and periodically during the treatment of fluoxetine in patients with risk factors of QT interval prologation and ventricular arrhythmia. If signs or symptoms of ventricular arrhythmia occur, consider the discontinuation of fluoxetine and the follow-up with cardiac evaluation. Consider monitoring the toxicity of fluoxetine	4(5)
Bromopride x Chlorpromazine	Contraindicatd	Increased risk of extrapyramidal reactions	Concomitant use is contraindicated.	3(4)
Other possible interactions				29(35)
Total				**83(100)**

Source: From the author, 2017.

Table 3. The most frequent drugs responsible for the PDI with psychoactive substances analyzed, from the Psychosocial Care Center for Children and Adolescents, Aparecida de Goiânia-Goiás, Brazil 2017

Type of interaction	Responsible Drug	Frequency n (%)
Drug-Cocaine	Fluoxetine	11 (64.8)
Drug-Cocaine	Imipramine	3 (17.6)
Other possible interactions		3 (17.6)
Total		**17 (100)**
Drug-Ethanol	Chlorpromazine	67 (48.2)
Drug-Ethanol	Diazepam	27 (19.4)
Other possible interactions		45 (32.4)
Total		**139 (100)**
Drug-Marijuana	Chlorpromazine	134 (38.0)
Drug-Marijuana	Diazepam	54 (15.3)
Other possible interactions		164 (46.7)
Total		**352 (100)**
Drug-Tobacco	Chlorpromazine	67 (67.7)
Drug-Tobacco	Haloperidol	20 (20.2)
Other possible interactions		12 (12.1)
Total		**99 (100)**

Source: From the author 2017.

Acronyms: PDI - Potential drug interactions.

Table 4. Bivariate analysis of the factors involved in the occurrence of polypharmacy and bivariate analysis of the factors involved in the occurrence of Total PDI from the Children Psychosocial Care Center, Aparecida de Goiânia-Goiás, Brazil 2017

Variable	Factors involved in the occurrence of polypharmacy					Factors involved in the occurrence of total PDI				
	≤ 4 (N=153)		≥ 5 (N=6)		p	Não (N=38)		Sim (N=121)		p
	N	%	N	%		N	%	N	%	
Sex										
Female	43	28.1	2	33.3		11	28.9	34	28.1	
Male	110	71.9	4	66.7	0.781	27	71.1	87	71.9	0.919
Age started treatment at the CPCAD										
11	2	1.3	—	0.0		1	2.6	1	0.8	
12	7	4.6	—	0.0		1	2.6	6	5.0	
13	21	13.7	1	16.7		7	18.4	15	12.4	
14	42	27.5	—	0.0	0.068*	10	26.3	32	26.4	0.288
15	34	22.2	1	16.7		9	23.7	26	21.5	
16	41	26.8	2	33.3		10	26.3	33	27.3	
17	6	3.9	2	33.3		0	0.0	8	6.6	
Schooling										
Illiterate	2	1.3	—	0.0		0	0.0	2	1.7	
Incomplete Elementary School	136	88.9	4	66.7		34	89.5	106	87.6	
Complete Elementary School	1	0.7	—	0.0	0.125*	1	2.6	0	0.0	0.973
Incomplete High School	11	7.2	2	33.3		2	5.3	11	9.1	
Complete High School	3	2.0	—	0.0		1	2.6	2	1.7	
Studies in progress										
No	104	68.0	4	66.7		19	50.0	89	73.6	
Yes	49	32.0	2	33.3	0.946	19	50.0	32	26.4	0.008*
School Grade										
1st High School	10	6.8	1	16.7		3	7.9	8	6.9	
3rd High School	2	1.4	1	16.7		1	2.6	2	1.7	
4th Elementary School	7	4.7	—	0.0		1	2.6	6	5.2	
5th Elementary School	16	10.8	—	0.0	0.532	3	7.9	13	11.2	0.475
6th Elementary School	43	29.1	1	16.7		9	23.7	35	30.2	
7th Elementary School	29	19.6	1	16.7		13	34.2	17	14.7	
8th Elementary School	21	14.2	1	16.7		4	10.5	18	15.5	
9th Elementary School	14	9.5	1	16.7		4	10.5	11	9.5	
Relatioship with school										
Good	60	39.2	5	83.3		19	50.0	46	38.0	
Bad	54	35.3	1	16.7	0.078*	10	26.3	45	37.2	0.375
Not declared	39	25.5	—	0.0		9	23.7	30	24.8	
Have already had a previous treatment										
No	126	82.4	4	66.7		38	100.0	92	76.0	
Yes	27	17.6	2	33.3	0.342	—	0.0	29	24.0	0.998

Follow-up time at CPCAD										
<10 days	35	22.9	1	16.7		12	31.6	24	19.8	
10 to 100 days	44	28.8	3	50.0		11	28.9	36	29.8	
101 to 200 days	19	12.4	—	0.0	0.817	6	15.8	13	10.7	0.082*
>200 days	55	35.9	2	33.3		9	23.7	48	39.7	
Age of drug use										
6	1	0.7	—	0.0		—	0.0	1	0.8	
7	2	1.3	—	0.0		1	2.7	1	0.8	
8	6	4.0	—	0.0		—	0.0	6	5.0	
9	2	1.3	—	0.0		—	0.0	2	1.7	
10	9	6.0	1	16.7		3	8.1	7	5.8	
11	18	11.9	—	0.0	0.957	4	10.8	14	11.7	0.429
12	26	17.2	2	33.3		6	16.2	22	18.3	
13	44	29.1	2	33.3		12	32.4	34	28.3	
14	27	17.9	—	0.0		7	18.9	20	16.7	
15	12	7.9	1	16.7		2	5.4	11	9.2	
16	3	2.0	—	0.0		2	5.4	1	0.8	
17	1	0.7	—	0.0		—	0.0	1	0.8	
Number of drugs already used										
0	1	0.7	—	0.0		1	2.6	—	0.0	
1	38	24.8	—	0.0		9	23.7	29	24.0	
2	45	29.4	2	33.3		10	26.3	37	30.6	
3	30	19.6	—	0.0		7	18.4	23	19.0	
4	27	17.6	2	33.3	0.019*	6	15.8	23	19.0	0.886
5	8	5.2	1	16.7		4	10.5	5	4.1	
6	4	2.6	—	0.0		1	2.6	3	2.5	
7	—	0.0	1	16.7		—	0.0	1	0.8	
Total ICD-10 Diagnostic Hipotheses										
1	70	46.4	4	66.7		27	73.0	47	39.2	
2	50	33.1	—	0.0		9	24.3	41	34.2	
3	19	12.6	2	33.3		—	0.0	21	17.5	
4	8	5.3	—	0.0	0.663	1	2.7	7	5.8	0.001*
5	3	2.0	—	0.0		—	0.0	3	2.5	
6	1	0.7	—	0.0		—	0.0	1	0.8	
Total Potential Interactions										
0	38	24.8	—	0.0		—	—	—	—	
1	5	3.3	—	0.0		—	—	—	—	
2	16	10.5	—	0.0		—	—	—	—	
3	15	9.8	—	0.0		—	—	—	—	
4	23	15.0	—	0.0		—	—	—	—	
5	5	3.3	—	0.0		—	—	—	—	
6	3	2.0	1	16.7		—	—	—	—	
7	4	2.6	—	0.0	0.001*	—	—	—	—	
8	11	7.2	—	0.0		—	—	—	—	
9	1	0.7	—	0.0		—	—	—	—	
10	19	12.4	—	0.0		—	—	—	—	
11	3	2.0	—	0.0		—	—	—	—	
12	1	0.7	—	0.0		—	—	—	—	
13	1	0.7	—	0.0		—	—	—	—	
14	4	2.6	1	16.7		—	—	—	—	

15	2	1.3	—	0.0		—	—	—	—	
17	2	1.3	—	0.0		—	—	—	—	
18	—	0.0	1	16.7		—	—	—	—	
19	—	0.0	1	16.7		—	—	—	—	
24	—	0.0	2	33.3		—	—	—	—	
Total Drugs in use										
1	—	—	—	—		38	100	31	25.6	
2	—	—	—	—		—	0.0	42	34.7	
3	—	—	—	—		—	0.0	30	24.8	
4	—	—	—	—		—	0.0	12	9.9	0.993
5	—	—	—	—		—	0.0	4	3.3	
7	—	—	—	—		—	0.0	1	0.8	
9	—	—	—	—		—	0.0	1	0.8	
Forwarded by										
Spontaneous Demand	22	14.4	1	16.7		5	13.2	18	14.9	
Judicial Demand	86	56.2	2	33.3		26	68.4	62	51.2	
Guardianship Council	37	24.2	3	50.0	0.673	6	15.8	34	28.1	0.225
Others	8	5.2	—	0.0		1	2.6	7	5.8	

Source: From the author, 2017.
*Statistically significant; Acronyms: CPCAD adi-III: Center for Psychosocial Care Alcohol and other drugs 24 hours; International Classification of Diseases - ICD -10; CI: Confidence interval; OR: Odds Ratio; PDI: Potential drug interactions.

Table 5. Multivariate Regression Analysis for the factors involved in the occurrence of Polypharmacy and Multivariate Regression analysis for the factors involved in the occurrence of Total PDI of the Children Psychosocial Care Center, Aparecida de Goiânia-Goiás, Brazil 2017

Variables ǂ	**P**	**OR**	**IC OR**	
			Inf.	**Sup.**
Relatioship with the school	0.352	0.392	0.055	2.817
Schooling	0.938	1.078	0.165	7.036
Total of PDI	0.003*	1.558	1.158	2.095
Age of entry into CPCAD	0.287	2.112	0.533	8.358
Number of drugs already used	0.403	1.540	0.560	4.237
Multivariate Regression Analysis for the factors involved in the occurrence of Total PDI				
Variables	**P**	**OR**	**IC OR**	
			Inf.	**Sup.**
1ºStep ǂ				
Studies in progress	0.010*	0.339	0.148	0.772
Follow-up time at CPCAD	0.536	1.118	0.786	1.590
Total ICD-10 Diagnostic Hipotheses	0.002*	2.762	1.470	5.191
2º Step ǂ				
Studies in progress	0.006*	0.321	0.143	0.721
Total ICD-10 Diagnostic Hipotheses	0.001*	2.847	1.519	5.338

Source: From the author, 2017.
ǂ Multivariate Regression Analysis for the factors involved in the occurrence of Polypharmacy;
ǂ Including the variables that presented p <0.20 in the bivariate analysis;
ǂ ǂ Excluded the variable that presented the highest value of p in Step 1;
Acronyms: CI: Confidence Interval; OR: Odds Ratio; PDI: Potential drug interactions; CPCAD adi-III: Center for Psychosocial Care Alcohol and other drugs 24 hours; International Classification of Diseases - ICD -10;
* Statistically significant.

DISCUSSION

The clinical practice for prescribing drugs for users of psychoactive substances requires an evaluation of the full context of the substances used. An approved drug for the treatment of a psychoactive substance may present PDI with other substances that the patient may use and may lead to serious problems such as respiratory depression and increased sedation (Storpirtis *et al.*, 2008). Among the 159 medical prescriptions, 76.1% had at least one PDI.

The drugs with the highest potential for PDI were Chlorpromazine (32.3%) and Diazepam (19.6%). In the study by Viel *et al.* (2014), they analyzed the occurrence of PDI in the hospital environment with the use of benzodiazepines and among the 100 prescriptions analyzed, 93 presented PDI with the other medications used. The use of benzodiazepines requires attention because its pharmacodynamic and pharmacokinetic profile favours the occurrence of PDI with different pharmacological groups, food and PS.

Andrade *et al.* (2016) carried out a study on PDI in alcohol users attended in an emergency, and 496 PDI were found, of which 197 were of the drug-drug type. The drugs involved in 64.6% of the PDI were: diazepam, phenytoin, metoclopramide and prometazine. Co-administration of medications requires adequate risk management in order to avoid adverse reactions and therapeutic ineffectiveness. It is important to know the druds most frequently used and among those with the highest PDI risk.

Cannabis (marijuana) was the PS most used by CPCAD adi III adolescents (37.2%), corroborating the findings of Vilela (40.2%) (Vilela, 2016). The pharmacological treatment for users of *Cannabis* requires attention, since it was the substance with the highest frequency in interactions with 352 PDI. Seen as there is no drug with proven efficacy, anxiolytic and antidepressant medications are used to alleviate withdrawal symptoms (Walther *et al.*, 2016).

Topiramate was the drug indicated as the one that demands greater caution in the prescription, considering that the verified PDI were all contraindicated. It should be noted, however, that, according to the literature, Topiramate as Modafinil is used for the treatment of crack and cocaine users (Associação Brasileira de Psiquiatria, 2012). Although, according to Fonseca *et al.* (2014), there is no well-established pharmacological approach to crack and cocaine, only the control of the symptoms of intoxication, psychiatric comorbidities and withdrawals of the drug.

Among the potential risks of PDI found in the study were: increased extrapyramidal effects, encephalopathy, brain damage, central nervous system depression, respiratory depression, altered drug metabolism, increased toxicity, coma, which could lead to sudden death. The databases researched suggest the clinical management to avoid or prevent the PDI, among them substitution of the medication, monitoring, adjustment in the dosage, change the time of medication administration, among other recommendations (Leão *et al.*, 2014). The main drug-drug PDI are listed in Table 2 with the risks and clinical management suggested for the actual identification of the manifestations of PDI.

Long-term treatments tend to expose more the patient to the occurrence of PDI of clinical importance in so far as, in the course of the treatment, it is possible to appear several clinical conditions that require the use of drugs with a high possibility of drug interactions. Thus, it is necessary to carry out a careful analysis for the prescription and dispensation (Secoli, 2001). Within this context we have Bromopride, indicated to treat symptoms of nausea, vomiting, gastric motility disorders, which presented contraindicated PDI.

As reported by Oliveira and Nappo (2008), the combined use of PS is considered as a strategy to reduce the negative effects caused in the moments of withdrawal. Thus, it is important to carry out an analysis of the pharmacotherapeutic proposal at the time of the choice, verifying if there is presence of PDI with the prescribed drugs and with the PS that is in use, or that it may be used in moments of withdrawal crisis.

The practice of polypharmacy increases the occurrence of PDI, as was observed in the present study. The risk of adverse drug reactions is 6% when two drugs are used simultaneously, and 50% when five drugs are used. There is a linear relationship between the number of drug interactions and the number of drugs used (Broeiro *et al.*, 2008).

In the present study, only 3.8% presented polypharmacy, and 83% presented 14 or more PDI, being $p = 0{,}001$, a similar result was found in the study by Leão *et al.* (2014), in which 8.6% presented polypharmacy and presented frequency of interactions higher than 80% of those who did not use polypharmacy with a result of $p < 0{,}001$.

The total PDI presented statistical relationship with the variable being studied, and adolescents who were not studying presented a greater chance of IMP. Among the main consequences of the use of PS is the drop in school performance and remained in school (Horta *et al.*, 2007). The adolescents who attend school present better conditions in relation to the use of PS, because the school is a protection factor through an interdisciplinary and multidisciplinary perspective, in which it can articulate health and education in the promotion of educational lectures on the use of PS and the consequences of the use (D'orazio *et al.*, 2013).

The association between the number of PDI and the diagnostic hypotheses shows that the presence of more than one pathology may require the use of a larger number of medications. Studies show that there is a great association

between the use of PS and the existence of a mental disorder, considering that the use of drugs is a consequence of an existing mental disorder, this condition is called dual pathology and among the mental disorders most found in these situations we have: anxiety disorders, personality disorders, intellectual development disorders and attention deficit hyperactivity disorders (Vilela, 2016). Faced with the difficulty to treat the dual pathologies in Spain is being developed the guidelines for clinical practice for the treatment of this condition (San *et al.*, 2016).

The present study brought important results, being the first in Brazil to consider all the PDI involved in the use of medications and the PS in use, in children and adolescents.

The factor involved in the use of medications was the total of PDI. Among the factors involved in the occurrence of the total PDI were studies in progress and the amount of hypotheses diagnosed. Regarding the high PDI index, the relationship with polypharmacy and a high number of diagnostic hypotheses, it is necessary to increase the attention of health professionals regarding the topic and the development of protocols to support decision making.

RESUMO

Farmacoterapia de adolescentes em uso de substâncias psicoativas

O uso de Substâncias Psicoativas acarreta problemas em diversas áreas da vida do sujeito tais como: na saúde, psicológicos e sociais. Assim, faz-se necessário avaliar os fatores envolvidos na utilização de medicamentos e nas potenciais interações medicamentosas (PDI) em adolescentes em uso de substâncias psicoativas. Este foi um estudo transversal, analítico e quantitativo. A pesquisa foi realizada no Centro de Atenção Psicossocial e outras Drogas Infanto Juvenil 24h, com adolescentes menores de 18 anos, em uso de medicamentos. Os dados foram obtidos por revisão dos prontuários e as PDI foram avaliadas por meio de banco de dados *Micromedex*® **e** *Medscape*®**. Dos 159 prontuários utilizados, verificou-se a existência de 815 PDI. Por gravidade foram 59,4% moderadas, 23,8% secundárias, 15,7% graves e 1,1% contraindicado. Os medicamentos que mais apresentaram PDI foram a clorpromazina (32,3%) e o diazepam (19,6 %). Os fatores envolvidos na polifarmácia foram o total de PDI e os envolvidos na ocorrência do total de PDI foram: estar estudando e a quantidade de hipóteses diagnostica. Diante do alto índice de PDI, a relação com polifarmácia e alto número de hipóteses diagnósticas, faz-se necessário maior atenção dos profissionais de saúde quanto ao tema e desenvolvimento de protocolos para suporte na tomada de decisão.**

Palavras-chave: Tratamento farmacológico. Interações de Medicamentos. Psicotrópicos.

REFERENCES

American Psychiatric Association (APA). Diagnostic and Statistical manual of Mental Disorders. DSM-V Development. [Internet]. 5th. ed. Washington, DC: APA; 2012. [acesso em 10 fev 2017]. Disponível em: http://www.dsm5.org/Pages/Default.aspx.

Andrade JDS, Rocha CE, Maciel MAV, Santana DCAS, Santana FJM. *et al.* Prevalence and risk of potentially adverse drug interactions in the treatment of acute alcohol poisoning. Braz J Pharm Sci. [Internet]. 2016; 52(1):133-41. [acesso em 22 abr 2017]. Disponível em: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S198482502016000100015&lng=en.

Associação Brasileira de Psiquiatria. Abuso e dependência: crack. Rev Assoc Med Bras. [Internet]. 2012; 58(2):138-40. [acesso em 21 abr 2017]. Disponível em: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0104-42302012000200008&lng=en.

Bousoño Serrano M, Al-Halabí S, Burón P, Garrido M, Díaz-Mesa EM, Galván G. *et al.* Uso y abuso de sustancias psicotrópicas e internet, psicopatología e ideacwión suicida en adolescentes. Adicciones, [Internet]. 2016;29(2):97-104. [acesso em 26 mar 2017]. Disponível em: http://www.adicciones.es/index.php/adicciones/article/view/811/846.

Brasil, Ministério da Saúde. Saúde Mental no SUS: Os centros de atenção psicossocial. Brasília-DF. [Internet]. 2004. [acesso em 10 nov 2016]. Disponível em: <http://www.saude.gov.br.

Broeiro P, Maio L, Ramos V. Polifarmacoterapia: estratégias de racionalização. Rev Port Clin Geral. 2008; 24(5):625-31.

D'orazio WPS, Carvalho SA, Lima TH, Borges AAT, Picoli MC, Marques ACL, *et al.* Uso de drogas e desempenho escolar entre jovens e adolescentes do ensino médio de uma escola pública de Pires do Rio – GO. Holos; 2013; 5:305-14. Disponível em: http://www2.ifrn.edu.br/ojs/index.php/HOLOS/article/view/1479/745

Drug checker interaction. *Medscape*. [acesso em 29 mar 2017]. Disponível em: http://www.*Medscape*.com/druginfo/druginterchecker.

Drugdex System [Internet]. Greenwood Village (Colorado): Thomson *Micromedex*; 1974-2016. [Internet]. [acesso em 6 out 2016]. Disponível em: http://www.periodicos.capes.gov.br

Fonseca FN da, Gondim APS, Fonteles MM de F. Influência dos grupos terapêuticos em Centro de Atenção Psicossocial entre usuários com dependência de cocaína/crack. Saúde debate. 2014; 38(102):551-61.

Gilvarry E, Jill B. Guidance for the pharmacological management of substance misuse among young people in secure environments. London: Department of Health. 2009.

Horta RL, Horta BL, Pinheiro RT, Morales B, Strey MN.

Tabaco, álcool e outras drogas entre adolescentes em Pelotas, Rio Grande do Sul, Brasil: uma perspectiva de gênero. Cad Saúde Pública 2007; 23(4):775-83.

Jhanjee S. Evidence based psychosocial interventions in substance use. Indian J Psychol Med [Internet]. 2014;36:112-8. [acesso em 15 mar 2017]. Disponível em: http://www.ijpm.info/text.asp?2014/36/2/112/130960

Jörgensen T, Johansson S, Kennerfalk A, Wallander M, Svärdsudd K. Prescription drug use, diagnoses, and healthcare utilization among the elderly. Ann Pharmacother 2001;35(9):1004-9.

Leão DFL, Moura CS, Medeiros DS. Evaluation of potential drug interactions in primary health care prescriptions in Vitória da Conquista, Bahia (Brazil). Ciênc Saúde coletiva [Internet]. 2014 Jan; 19(1):301-318. [acesso em 14 mai 2017]. Disponível em: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S141381232014000100311&lng=en.

Oliveira LG, Nappo SA. Caracterização da cultura de crack na cidade de São Paulo: padrão de uso controlado. Rev. Saúde Pública, São Paulo, 2008;42(4):664-671.

Organização Mundial de Saúde (OMS). Classificação estatística internacional de doenças e problemas relacionados à saúde. 10. rev., 1989, São Paulo: EDUSP; 1993.

San L, Arranz B, Arrojo, M, Becoña E, Bernardo M, Caballero L, Garriga M. Guía de práctica clínica para el tratamiento de la patología dual en población adulta. Adicciones, [Internet]. 2016;28(1):1-3. Disponível em: http://www.adicciones.es/index.php/adicciones/article/view/784/759

Secoli SR. Interações medicamentosas: fundamentos para a prática clínica da enfermagem. Rev Esc Enf USP. [Internet]. 2001; 35(1):28-34.

Silva AB, Pinho LB, Olschowsky A, Siniak DS, Nunes CK. O cuidado ao usuário de crack: estratégias e práticas de trabalho no território. Rev. Gaúcha Enferm. [Internet]. 2016. 37(esp):e68447. [citado 2017 Abr 08]. Disponível em: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S198314472016000500404&lng=pt.

Storpirtis S, Mori ALPM, Yochiy A, Ribeiro E, Porta V. Farmácia Clínica e Atenção Farmacêutica. Rio de Janeiro: Guanabara Koogan; 2008. 489 p.

United Nations Office on Drugs and Crime (UNODC). TREATNET. Quality Standards for Drug Dependence Treatment and Care Services. New York, NY: UNITED NATIONS; 2012. [acesso em 10 jan 2017]. Disponível em: http://www.unodc.org/docs/treatment/treatnet_quality_standards.pdf

United Nations Office on Drugs and Crime (UNODC). World Drug Report 2016. Vienna, Austria: United Nations publication, 2016. (United Nations publication, Sales No. E.16.XI.7).

Viel AM, Ribeiro-paes JT, Stessuk T, Santos L. Interações medicamentosas potenciais com benzodiazepínicos em prescrições médicas de pacientes hospitalizados. Journal of Basic and Applied Pharmaceutical Sciences, 2014; 35(4):589–96.

Vilela ACM. Perfil epidemiológico e psiquiátrico de crianças e adolescentes dependentes químicos hospitalizados no Brasil Central (manuscrito). [Dissertação]- (Mestrado) – Universidade Federal de Goiás, Faculdade de Medicina, Goiânia; 2016, 47 f.

Walther L, Gantner A, Heinz A, Majic T. Evidence-based Treatment Options in *Cannabis* Dependency. Deutsches Ärzteblatt International, 2016;113(39):653–9. Disponível em: http://doi.org/10.3238/arztebl.2016.0653

World Health Organization (WHO). Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment, 2015. Oslo, Norway: WHO; 2014.

Received on November 17th 2016

Accepted for publication on July 25th 2017