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Article

Identification and characterisation of potential drug interaction in a Hospital in Jundiai, Sao Paulo State

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To identify and characterize the most frequent Drug Interaction (DI) in a Jundiaí Hospital. Exploratory, descriptive, and analytical cross-sectional study with a quantitative approach. The source of the study is 100 prescriptions made by the medical service of a hospital in Jundiaí, dispensed from August to October 2018, by the pharmacy of the mentioned hospital for palliative care, mental health, and emergency care. Data plotting in Excel. Of the 100 prescriptions analyzed 60 had at least one type of interaction, 164 DI were found, 14.6% severe, 67.7% moderate, 17.1% minor and 0.6% unspecified. The mechanism of interaction that most appeared in the study was pharmacodynamics, 54.3%, pharmacokinetics were present in 34.1% of DI and 11.6% were not specified. The group most affected by DI was male 33% of prescriptions, female 27%, and 40% showed no interactions. The age group with the most interactions was from 50 to 59 years old. Of the prescriptions that had MI, those with 4 or more interactions were the ones that prevailed. The class of drugs that presented the most interactions was psychotropic drugs. A relevant frequency of interactions was identified by the present study, being the class of psychotropic drugs the most evident and interactions of medium severity the most found, which may be responsible for lowering the clinical condition of patients and the need of possible additional interventions. The data presented may contribute as epidemiological indicators, guiding corrective actions, aiming at the welfare of patients.

Keywords: Drug Interaction. Polypharmacy. Medicine interaction.

INTRODUCTION

The use of several drugs together, known as polypharmacy, is a reality. The use of various drugs in combination, whether prescribed by professionals, self-medication, or the use of drugs with food and beverages may generate drug interaction (DI) (Cedraz, Santos Junior, 2014).

Drug interaction (DI) is the change that occurs in the effect of a drug due to its previously or simultaneously use of other substances, whether pharmacological or not. This means that the change in the expected outcome of the drug administered may occur due to its use with other drugs, food, alcohol, herbs and even the body itself when taking into account the patient's health condition (Preston, 2016; Bushra, Aslam, Khan, 2011; Cedraz, Santos Junior, 2014).

Potentiation of the therapeutic effect may occur if the drug administered together is synergistic, or a reduction in therapeutic efficacy occurs when an antagonist is administered together. Drug interactions may be pharmacokinetic, pharmacodynamics, or pharmacotechnical. When they affect the absorption, distribution, metabolization, and excretion of drugs, they are pharmacokinetics. When there is a change in the effect of a drug due to the presence of another, it is a pharmacodynamic interaction, and pharmacotechnical, when there is an alteration of the drug still outside the patient's organism, being the interaction between drugs inside containers or with external means (Buajordet *et al.,* 2001; Bushra, Aslam, Khan, 2011; Cedraz, Santos Junior, 2014; Prueksaritanont *et al.,* 2013).

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The effects caused by pharmacodynamic DI may be adverse when they have detrimental effects, or side effects, when they cause purposeful and expected changes in the effect, aiming at a result that may be beneficial (Vieira *et al.,* 2012).

Drug interaction is shown to be a variable that affects therapeutic outcomes and may lead to negative interference with the patient's health. The adverse effects resulting from DI are a concern and should be given special attention, as they are responsible for increased length of stay, impact on morbidity and mortality, and cause about 21% of hospitalizations for adverse events, according to world reports. Therefore, it is shown as a public health problem (Secoli, 2010; Vonbach *et al.,* 2008).

The patient's prescription, administration, and condition are relevant factors that induce MI. According to a study by the American Medical Association, 56% of medication errors occur during the prescription phase, besides the increase of the risk of DI which is directly in proportion to the amount of medication prescribed. (Leão, Moura, Medeiros, 2014; Wachter, 2013).

Regarding the patient's condition, there are reports of serious adverse effects caused by the joint administration of many drugs to patients with glaucoma, cancer, heart disease, kidney and liver disorders, and in elderly patients, children, pregnant women. Such groups are more likely to suffer interactions and complications due to a large number of medications they use and the fragility of health. However, deliberate polyprescription and self-medication are also facilitating factors of this occurrence (Bojita, Farcas 2009; Cassiani, 2010; Huber *et al,* 2013).

In addition to interaction with other therapeutic compounds, drug action mechanisms depend on other factors such as receptor affinity, tissue drug concentration and pharmacogenetics (Relling, Giacomini, 2006).

Pharmacogenetics is the study of the influence of genetic bases on pharmacological responses. The observation of a genomic polymorphism, that is, a variation in the genome that directly impacts the pharmacokinetic and pharmacodynamic responses of drug treatment. Knowledge of pharmacogenetics enables drug therapy to be individualized according to patient characteristics, due to the knowledge of the metabolism response and therapeutic effect, and may thus maximize therapeutic outcomes and minimize the risk of toxicity or pharmacological interactions. However, pharmacogenetics is still a new concept that is not inserted in hospital reality, so there is no way to distinguish idiosyncratic pharmacological changes (Relling, Giacomini, 2006).

The route of administration should also be taken into consideration when it comes to drug interaction, it may be oral, intravenous, and even utopian and will determine the speed in which DI will occur, as well as its relevance to the patient's health (Mazzola *et al.,* 2011).

Records regarding drug interaction are usually defined as adverse events and are stored in databases such as Stockley's Drug Interactions and DrugBank, for example. These data can be collected from sources such as the FDA's Adverse Events and Notification System, but such organization is hampered by barriers to manual information gathering, as well as relying on large financial and time expenditures, which underscores the importance of related researches (Preston, 2016; Law *et al.,* 2014; Segura *et al.,* 2013).

For health professional practice, knowledge about (DI) is one of the most important themes, being paramount for the quality of prescription, time and route of administration, as well as educating the population about the use of medicines, leading us to reaffirm how important the multidisciplinary team is in this process (Cassiani, 2010; Mazzola *et al,* 2011).

Considering that drug interactions may cause irreparable damage to patients' health, added to the importance that knowledge about DI represents for health professionals, it is shown as pertinent, study about the most common possible drug interactions in hospitals, aiming at enriching scientific knowledge and, consequently, aiming at population safety (Becker *et al*., 2007; Secoli, 2010).

Therefore, the objective of this study is to identify and characterize the most frequent drug interactions (DI) in a hospital in the city of Jundiaí, São Paulo.

MATERIAL AND METHOD

This study was approved by the Research Ethics Committee of the Padre Anchieta University

Center under protocol number: 008/2018. CAAE: 91092718.1.0000.5386.

Area of study

Hospital located in the city of Jundiaí, Sao Paulo.

Study source

Prescriptions made by the medical service of a hospital in the city of Jundiaí - SP. Collection of prescriptions at the hospital pharmacy from August to October 2018.

Study variables

Dependent variable

Prescription of more than one drug per prescription

Sample size determination

In this study, 100 medical prescriptions were collected and analyzed. Factors such as the size of the city where the data collection field is located and the duration of the project were considered when determining the sample quantity.

Study design

An exploratory, descriptive, and analytical cross-sectional study with a quantitative approach.

The data collection took place at the pharmacy of the Central Emergency Room in the mentioned Hospital, which serves besides the emergency care service, palliative care, and mental health too. The days and times were defined by the Hospital responsible staff. The prescriptions were collected by the researcher student, according to the order issued by the medical professionals.

A hundred prescriptions were analyzed. In order to avoid retention of prescriptions by the researcher, they were scanned through the CamScanner application, available for mobile devices. The data was stored in a cloud created specifically for the project's development.

The prescriptions were enumerated maintaining the confidentiality of the patients. From them, the following data were collected: gender, age, medication route of administration, and name of medications. After data collection, the interactions were classified as pharmacokinetics and/or pharmacodynamics, being excluded from the pharmacotechnical evaluation due to the impossibility of access to the preparation of medications, only to medical prescriptions. They were also classified as severe, moderate, or minor and recorded the most prominent class of drug in number of interactions. At the end of the analysis of all prescriptions, the data were plotted in graphs and analyzed as percentages. Data analysis through Excel.

Data processing and analysis

Data analysis was performed through consulting drug leaflets, the book "Drug Interactions" by Almir L. da Fonseca, through the American Drugs.com online drug consultation page, as well as DI guides and articles. The data was plotted in Excel spreadsheets and charts.

RESULTS AND DISCUSSION

A hundred medical prescriptions were collected at the pharmacy of the hospital in Jundiaí-SP, the pharmacy serves besides the emergency care service, palliative care, and mental health. The prescriptions were chosen randomly and enumerated, hiding the identity of the patients, subdividing them according to gender, being F the representation of females and M the representation of males. From the total of 100 prescriptions collected, 60 presented at least one type of drug interaction (DI), in the 60 prescriptions in question, 164 DI were registered with 72 different combinations, presenting statistically 2.73 DI per prescription. The IDs found and their characteristics may be observed in the chart in the appendix of this article.

The Table I and Figure 1 below represent the total number of prescriptions divided by gender and the number of drug interactions that occurred, also divided by gender, in which we can observe that even the sample of men being smaller than the sample of women, the amount of ID appears mostly in males, which differs

from the studies by Varallo, Costa, Mastroianni, 2013, and Silva *et al.,* 2018, in which the gender that presented more DI was female in both studies.

TABLE I - Percentage of Gender-Related Prescriptions and Drug Interactions

GENDER	Number of Prescriptions (%)	Prescriptions DI (%)
Male	48%	33%
Female	52%	27%

Note: Table based on a sample of 100 medical prescriptions, divided according to female F and male M. Representing percentage of prescriptions and Drug Interactions (DI) according to gender.

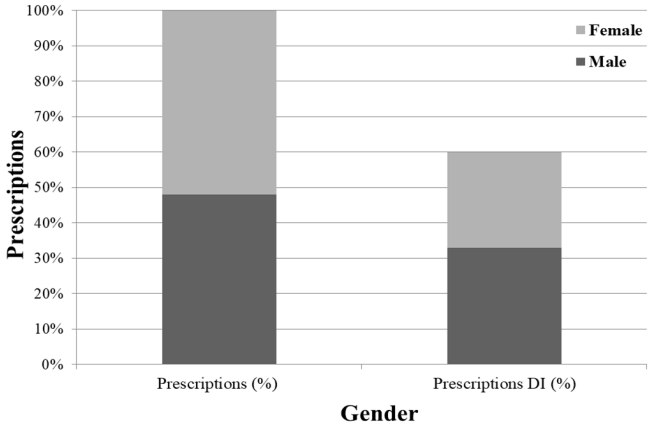

FIGURE 1 - Data of Drug Interactions (DI) Corresponding To Gender.

in the hospital, which ranges from 25.3% to 72.5%, according to data from Leão, Moura, Medeiros, 2014.

TABLE II - Amount of DI by Prescription

Amount DI by Prescription	Frequency in Prescriptions	Frequency in Prescriptions (%)
0	40	40%
1	18	18%
2	8	8%
3	10	10%
≥4	24	24%
DI TOTAL	60	60%

Note: Table representing the frequency and percentage (%) of drug interactions (DI) present per prescription in total medical prescriptions.

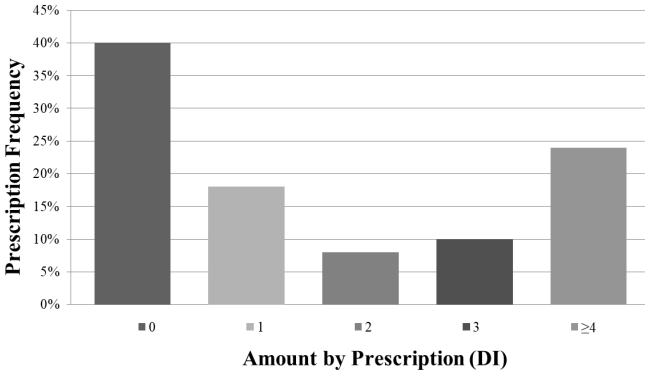

FIGURE 2 - Drug Interactions (DI) Per Prescription.

Table II and Figure 2 represent the number of interactions in each patient's prescription, with zero representing the absence of interactions, 1, 2, 3, 4, or more according to the number of interactions that occurred in each prescription. According to the sample, 40% of prescriptions had no drug interactions, 18% had a single interaction, 8% had 2, 10% had 3, and 24% had 4 or more DI per prescription. The total amount of interactions found was 60% and is in agreement with Leão, Moura, Medeiros, 2014, where 48.9% of prescriptions had some type of DI, and Silva *et al.,* 2018, where there were 76,1% possible interactions in the studied group. The results also corroborate the estimates of possible drug interactions

Graph III and figure 3 show the amount of drug interactions according to the age range of the prescriptions, which shows that from 19 to 29 years old there are 10% of DI, from 30 to 39 years old there are 18% of DI, from 40 to 49 years old 5% of DI, from 50 to 59 years old 33% of DI, from 60 to 69 years old 20% of DI, from 70 to 79 years old 5% of DI and from 80 to 90 years old 8% of DI. Which leads us to the conclusion that the age group in which the cases of drug interactions prevailed is between 50 and 59 years old, followed by 60 to 69 years old, corroborating the data from Leão, Moura, Medeiros, 2014, a study in which the age group of 50 years old or older presents 80% of the risk of DI for at least one drug

combination. This age group may present changes in pharmacokinetic and pharmacodynamic processes due to aging, intensifying the possibility of DI, and requiring special attention and follow-up on prescriptions (Amaral, Perassolo, 2012).

TABLE III – Drug Interactions Amount Age Range

Age Range	Quantity of DI	Percentage of DI
19-29	6	10%
30-39	11	18%
40-49	3	5%
50-59	20	33%
60-69	12	20%
70-79	3	5%
80-90	5	8%

Note: Table representing age and percentage of drug interactions (DI) present per age group. Based on 60 prescriptions that presented drug interactions and covering the ages of 19 to 90 years old.

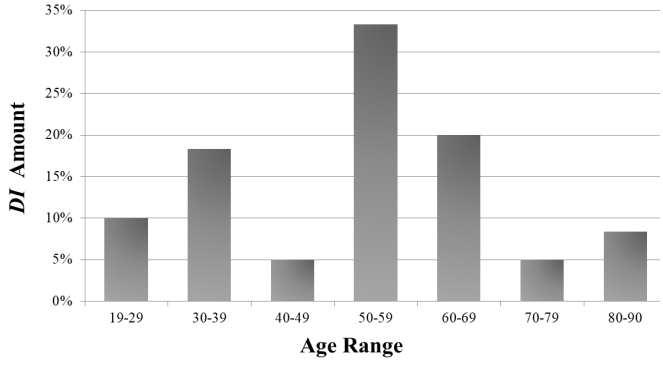

FIGURE 3 - Drug Interactions (DI) By Age.

Regarding the severity level of the interactions, in the 164 DI found, 24 were severe, 111 moderate, 28 minor, and 1 unspecified. Their corresponding percentages follow 14.6% serious, 67.7% moderate, 17.1% minor, and 0.6% unspecified, according to table IV and figure number 4. Moderate interactions were the ones that presented the most in the present work, followed by the light ones and finally by the serious ones. The order of severity level found is consistent with the work of Alves *et al.,* 2019; Iamaguchi *et al.,* 2017; Silva *et al.,* 2018 and Varallo, Costa, Mastroianni, 2013, in which, although they do not present exactly corresponding values, they also brought the moderate interactions as the predominant ones. Moderate level interactions may be responsible for the decrease in the patient's clinical condition, prolonging the time of therapy and even hospitalization, according to Tatro, 2008, and Nobrega, 2013.

TABLE IV - Severity of DI

SEVERITY	Amount of Interactions	Percentage of Interactions
Major	24	14,6%
Moderate	111	67,7%
Minor	28	17,1%
Not Specified	1	0,6%
Total	164	100%

Note: Table representing the severity of Drug Interactions (DI) in percentage. Based on 164 interactions found in 60 prescriptions.

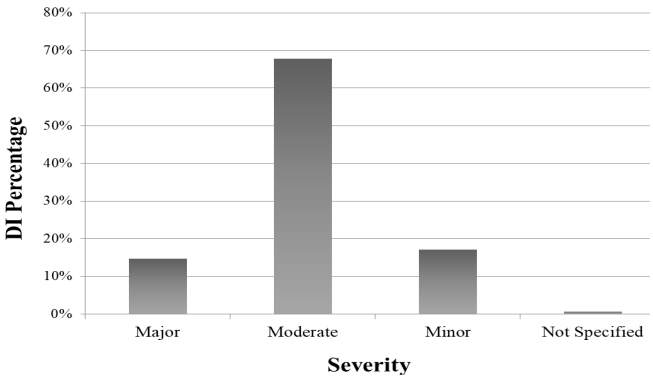

FIGURE 4 - Drug Interactions (DI) By Severity.

According to information present in table V and figure 5, the mechanism that determined the type of interaction that most appeared was the pharmacodynamic, 54.3%, pharmacokinetic 34.1%, and 11.6% were not specified due to the difficulty of gathering information

that would allow the determinant analysis of the mechanism. Silva *et al.,* 2018 and Sousa *et al.,* 2019, also bring pharmacodynamic interactions as the most evident in their studies.

TABLE V - Mechanism of DI

Mechanism	Amount	Percentage
Pharmacokinetics	56	34,1%
Pharmacodynamics	89	54,3%
Not Specified	19	11,6%
Total	164	100%

Note: Table representing the Drug interaction (DI) mechanism, based on the 164 interactions present in the 60 prescriptions

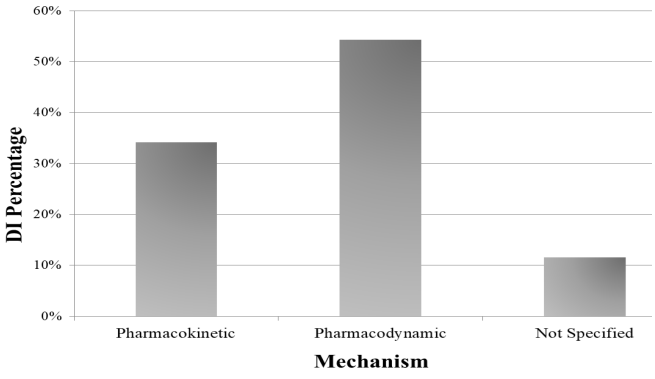

FIGURE 5 - In the first visualization task (control), there was no statistical difference between factors. The fragrance application (test) modified the visual pattern distribution, with a significant concentration on the congruent information (image and fragrance).

The oral route of administration was significantly the most prevalent among the medications that manifested MI, with 92.16% of the time being the route of at least one of the drugs and 81,8% being the route of both drugs. The route of administration is an important data for the study of drug interactions, as it determines the speed of drug absorption, consequently the speed of DI. (Mazzola *et al.,* 2011). However, no study was found to quantify the most prevalent route of administration in its results.

Leão, Moura, Medeiros 2014 readied in their studies that 99.6% of the recipes evaluated in his work did not have the specified route of administration, a fact that prevents the confrontation of the main occurring route and hinders the comparison of data between surveys. Table VI and figure 6 show the percentages found regarding the route of administration.

TABLE VI - DI Administration Routes

Route	Total	(%)
IV + IV	8	4,8%
IV + SC	1	0,6%
IV + PO	4	2,4%
IM + IV	2	1,2%
SC + IV	1	0,6%
PO + IV	11	6,7%
PO + IM	2	1,2%
PO + SC	1	0,6%
PO + PO	135	81,8%
Total	164	100%

Note: Table representing the percentage of routes of administration present in the 60 prescriptions that had Drug Interactions (DI).

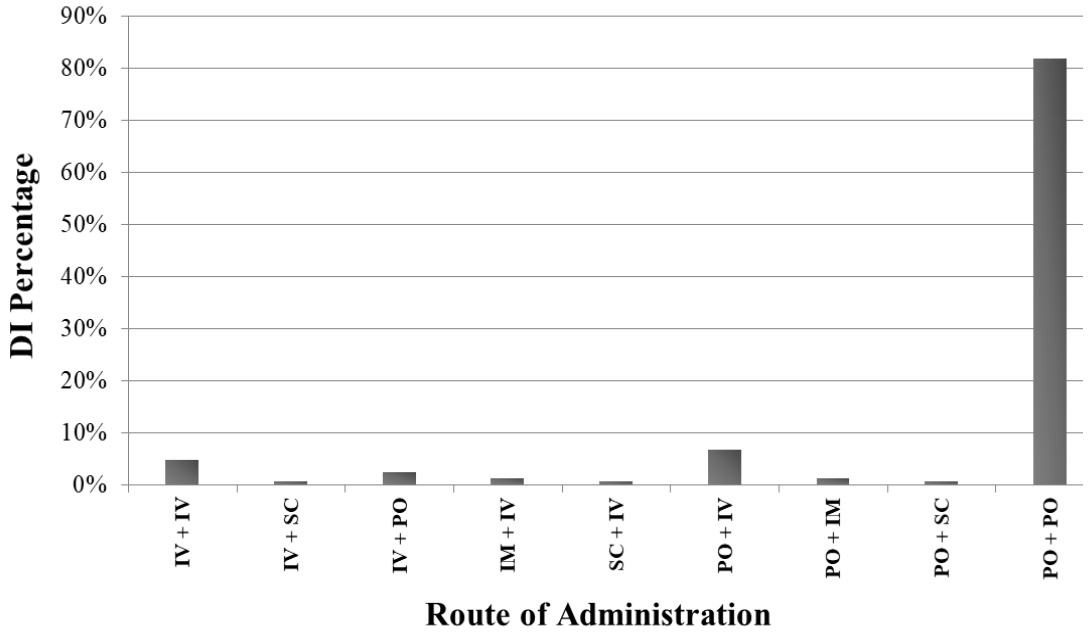

FIGURE 6 - Percentage Of Drug Interactions (DI) By Route Of Administration.

The pharmacological class that stood out the most in the present study was the psychotropics, with interactions with only one psychotropic representing 84% and interactions between psychotropic drugs, 55%, according to what is represented in table VII and figure 7. Balen *et al.,* 2017 brings in his studies 77.9% of DI related to the psychotropic class, a result relatively close to those mentioned here.

Psychotropics are drugs that act directly on the central nervous system and, therefore, the likelihood of possible interactions in this class of drugs is considerably higher. The number of combinations of these drugs for the treatment of disorders is also very large and dissociation is usually not feasible with treatment, which leads to a probable increase if DI and, consequently, the need for great attention to this class of drugs in the stages of prescription, dispensing and administration (Fernandes *et al.,* 2012 Rang *et al.,* 2016;).

TABLE VII - DI Drug Class

DI Total	**164**	**100%**
Presence of at least one Psychotropic	138	84,1%
DI Between Psychotropic	91	55,5%
DI among other categories of drugs	26	15,9%

Note: Table representing the percentage of Drug Interactions (DI) between psychotropics, psychotropics, and other classes of drugs and other categories of drugs.

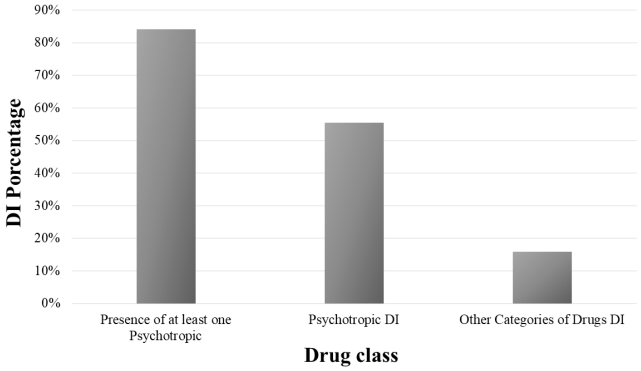

FIGURE 7 - Drug Interactions (DI) By Class.

There is also information to be considered, such as the fact that Valproic Acid is one of the drugs that most interacted with other drugs. This condition is due to the fact that this drug is a psychotropic with a low therapeutic index and a potent pharmacological effect. Hypoglycemic agents and digoxins also have a low therapeutic index and, in this study, interactions in which these drugs were present were also identified, reinforcing the importance of careful monitoring of patients who use these medications in particular. (Kawano *et al.,* 2006; Osório-de-Castro, Teixeira, 2004).

CONCLUSION

The result of 60% DI is an important discovery because studies have shown the importance of the low level of interactions. Drug interaction is shown to be a variable that affects therapeutic results, even more, in the case of medium severity, such as those found here, being responsible for possible increase in hospital stay, delay in solving the health problem or adverse effects.

The pharmacological class in which most interactions were found was that of psychotropic drugs, in which there is a known high probability of interactions.

Information regarding the age and gender of patients, the class of drugs, and the mechanism of interactions that most occur are relevant as the construction of epidemiological data that direct the area in which greater attention and interventions should be made, aiming at health and well-being of the patients.

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APPENDICES: SUPPLEMENTARY INFORMATION SESSION

APPENDIX I

Chart of drug interactions identified at Jundiaí-SP hospital

N° REPETITIONS	ADMINISTRATION ROUTE	INTERACTIONS	EFFECT	MECHANISM: DESCRIPTION	MECHANISM	GRAVITY
8	PO + PO	VALPROIC ACID + DIAZEPAM	...	Valproate displaces Diazepam from its plasma albumin binding sites and inhibits its metabolism.	Pharmacokinetics	MODERATE
8	PO + IV	CLONAZEPAM + OMEPRAZOLE	Prolongation of half-life leading to increased sedative effects and ataxia.	Decreased oxidative metabolism of Benzodiazepine.	Pharmacokinetics	MODERATE
7	PO + PO	VALPROIC ACID + CLONAZEPAM	May induce absence status in patients with a history of convulsion.	There may be decreased plasma levels of Clonazepam, inducing its hepatic metabolism.	Pharmacokinetics	MODERATE
6	PO + PO	CLONAZEPAM + RISPERIDONE	Respiratory or central nervous system depressant effects may be increased (synergisms).	Synergisms	Pharmacodynamics	MODERATE
6	PO + PO	DIAZEPAM + HALOPERIDOL	The effects of the central nervous system and respiratory depressant may be increased.	Synergism of the depressant effect on the central nervous system.	Pharmacodynamics	MODERATE
5	PO + PO	VALPROIC ACID + CLOZAPINE	Increased sedation and impairment of the central nervous system.	Valproate may slightly increase serum Clozapine levels and Clozapine metabolite levels.	Pharmacokinetics	MINOR
5	PO + PO	VALPROIC ACID + HALOPERIDOL	Respiratory or central nervous system depressant effects may be increased (synergisms).	Synergism of the depressant effect on the central nervous system.	Pharmacodynamics	MODERATE
5	PO + PO	CHLORPROMAZINE + HALOPERIDOL	Increased plasma levels of Haloperidol may occur leading to side effects such as the risk of arrhythmias.	Decreased CYP2D6 enzymatic activity may cause an increased concentration of Haloperidol. Possibly due to inhibition of Haloperidol metabolism by this route. Also, there is possibly an additive or synergistic effect.	Pharmacokinetics	MAJOR
4	PO + PO	VALPROIC ACID + BIPERIDEN	Respiratory or central nervous system depressant effects may be increased	The central nervous system or respiratory depressant effects may be increased additionally or synergistically.	Pharmacodynamics	MODERATE
4	PO + PO	BIPERIDEN + CLOZAPINE	There is a possibility of an increased risk of adverse effects such as central nervous system depression and tardive dyskinesia. Excessive anticholinergic effects may occur in combination, which may result in paralytic ileus, hyperthermia, heatstroke, and anticholinergic intoxication syndrome.	Centrally acting anticholinergic agents may antagonize the therapeutic effects of neuroleptic agents.	Pharmacodynamics	MODERATE

N° REPETITIONS	ADMINISTRATION ROUTE	INTERACTIONS	EFFECT	MECHANISM: DESCRIPTION	MECHANISM	GRAVITY
4	PO + PO	BISACODYL + DEXAMETHASONE	Concomitant use with adrenocorticosteroids, such as dexamethasone, may increase the risk of electrolyte imbalance.	The use of laxatives may cause electrolyte loss and increase the risk of hypokalemia associated with corticosteroid therapy. For corticosteroids promote sodium and water retention and potassium excretion. Particularly if administered systemically for longer than short periods.	Pharmacodynamics	MODERATE
3	PO + PO	AMITRIPTYLINE + BACLOFEN	The effects of the central nervous system may be increased. Muscle hypotonia, CNS depression.	Amitriptyline is a tricyclic antidepressant. Potentiates the effect of Baclofen causing a depressing effect on the central nervous system.	...	MODERATE
3	PO + PO	AMITRIPTYLINE + METHADONE	...	Methadone may cause QT interval prolongation. Theoretically, coadministration with other agents that may prolong the QT interval may result in additive effects.	...	MAJOR
3	PO + PO	AMITRIPTYLINE + MORPHINE	May cause irritability, altered consciousness, confusion, and hallucination. Neuromuscular abnormalities and gastrointestinal symptoms such as abdominal cramps, nausea, vomiting, and diarrhea.	Significant increase in plasma morphine.	Pharmacokinetics	MODERATE
3	PO + PO	BIPERIDEN + BUTYLSCOPOLAMINE	...	Agents with anticholinergic properties may have additive effects when used in combination.	Pharmacodynamics	MODERATE
3	PO + PO	BIPERIDEN + CHLORPROMAZINE	The therapeutic effects of Chlorpromazine may be diminished by centrally acting anticholinergics such as Biperiden.	Anticholinergics antagonize the effects of phenothiazines directly in the central nervous system.	Pharmacodynamics	MODERATE
3	PO + PO	BUTYLSCOPOLAMINE + CLOZAPINE	Increase anticholinergic action, such as dry mouth and constipation.	Increased anticholinergic action.	Pharmacodynamics	MODERATE
3	IV + IV	BUTYLSCOPOLAMINE + DIPYRONE	Risk of severe pressure drop (shock) and agranulocytosis (decreased platelet count).	Difficult assessment due to restriction of studies on Dipyrone	Difficult assessment due to restriction of studies on Dipyrone	MINOR
3	PO + PO	LITHIUM CARBONATE + CLONAZEPAM	The effects of the central nervous system or respiratory depressant may be increased.	The central nervous system or respiratory depressant effects may be increased additionally or synergistically.	Pharmacodynamics	MODERATE
3	PO + PO	CHLORPROMAZINE + DIAZEPAM	Increased effects of the central nervous system and respiratory depressant. Acute dystonic reactions, tardive dyskinesia, and akathisia may occur.	Addiction or synergism.	Pharmacodynamics	MODERATE
3	IV + PO	HALOPERIDOL + METOCLOPRAMIDE	...	Additive anti-dopamine effects.	Pharmacodynamics	MAJOR
3	IV + IV	HALOPERIDOL + ONDANSETRON	Risk of ventricular arrhythmias.	Haloperidol may cause QT prolongation. Extending the QT interval may result in additive effects.	Pharmacodynamics	MAJOR

N° REPETITIONS	ADMINISTRATION ROUTE	INTERACTIONS	EFFECT	MECHANISM: DESCRIPTION	MECHANISM	GRAVITY
2	PO + PO	VALPROIC ACID + CHLORPROMAZINE	...	Valproic Antidopaminic Acid Antagonist.	Pharmacodynamics	MINOR
2	PO + PO	VALPROIC ACID + FLUOXETINE	Fluoxetine may increase Valproate levels.	Possible inhibition of hepatic metabolism of Valproate.	Pharmacokinetics	MINOR
2	PO + PO	VALPROIC ACID + RISPERIDONE	...	Co-administration with Risperidone may alter serum Valproic Acid concentrations, although data are conflicting. The mechanism is unknown but may be related to the displacement of Valproate Risperidone from plasma proteins.	Pharmacokinetics	MODERATE
2	PO + PO	AMITRIPTYLINE + CLONAZEPAM	Sedation and increased central nervous system effects, respiratory depressant may be increased.	Synergism.	Pharmacodynamics	MODERATE
2	PO + PO	AMITRIPTYLINE + METRONIDAZOLE	...	Metronidazole may rarely prolong the QT interval of the electrocardiogram. Theoretically, coadministration with other agents that may prolong the QT interval may result in additive effects.	Pharmacodynamics	MINOR
2	PO + PO	BACLOFEN + PHENYTOIN	The effects of the central nervous system or respiratory depressant may be increased.	The central nervous system or respiratory depressant effects may be increased additionally or synergistically.	Pharmacodynamics	MODERATE
2	PO + PO	BIPERIDEN + DIAZEPAM	The effects of the central nervous system or respiratory depressant may be increased.	The central nervous system or respiratory depressant effects may be increased additionally or synergistically.	Pharmacodynamics	MODERATE
2	PO + PO	BIPERIDEN + PROMETHAZINE	The decreased therapeutic effect of Promethazine (phenothiazine) by the central action of anticholinergic(Biperiden).	Probable antagonistic action.	Pharmacodynamics	MODERATE
2	PO + PO	LITHIUM CARBONATE + HALOPERIDOL	...	Haloperidol may cause prolongation of the QT interval.	Pharmacodynamics	MAJOR
2	PO + PO	CLONAZEPAM + ENALAPRIL	The possible hypotensive effect, in case of initiation of treatment and increase of dose.	...	...	MODERATE
2	PO + PO	CLONAZEPAM + METHADONE	Concomitant use of opioids with benzodiazepines or other central nervous system depressants may result in sedation and respiratory depression. There is also a risk of hypotension.	...	...	MAJOR

N° REPETITIONS	ADMINISTRATION ROUTE	INTERACTIONS	EFFECT	MECHANISM: DESCRIPTION	MECHANISM	GRAVITY
2	PO + IV	POTASSIUM CHLORIDE + BUTYLSCOPOLAMINE	Concomitant use of agents with anticholinergic properties may potentiate the risk of high gastrointestinal injury associated with solid oral potassium chloride formulations.	The mechanism involves increased gastrointestinal transit time due to the reduced stomach and intestinal motility by anticholinergic agents, creating a high concentration of potassium ions in the region of a dissolving tablet or capsule and increasing contact time with the gastrointestinal mucosa.	Pharmacodynamics	MAJOR
2	PO + PO	CHLORPROMAZINE + PROMETHAZINE	Excessive parasympatholytic effects may result in paralytic ileus, hyperthermia, heatstroke, and anticholinergic intoxication syndrome.	Anticholinergic agents may have additive effects when used in combination.	Pharmacodynamics	MODERATE
2	PO + PO	DEXAMETHASONE + METHADONE	...	Co-administration with inducers of various CYP450 isoenzymes may decrease plasma concentrations of Methadone, which is metabolised by CYP450 3A4, 2B6, 2C19, 2C9 and 2D6.	Pharmacokinetics	MAJOR
2	PO + PO	DIAZEPAM + CHLORPROMAZINE	Possible respiratory depression.	The effects of the central nervous system and respiratory depressant may be increased additionally or synergistically.	Pharmacodynamics	MODERATE
2	PO + PO	DIAZEPAM + PROMETHAZINE	Increased effects of the central nervous system and respiratory depressant.	synergism	Pharmacodynamics	MODERATE
2	PO + PO	ENALAPRIL + RISPERIDONE	Orthostatic hypotension and syncope associated with vasodilation may occur during initial dosing or parenteral administration.	Phenothiazines and neuroleptic agents may potentiate the hypotensive effect of some medicinal secondary to peripheral alpha-1 blocking activity.	Pharmacodynamics	MODERATE
2	PO + PO	PHENYTOIN + RANITIDINE	The toxic pharmacological effect may occur due to increased phenytoin plasma concentration.	Possible inhibition of hepatic metabolism of phenytoin.	Pharmacokinetics	MODERATE
2	PO + PO	METHADONE + METRONIDAZOLE	...	Metronidazole may rarely prolong the QT interval of the electrocardiogram. Theoretically, coadministration with other agents that may prolong the QT interval may result in additive effects.	Pharmacodynamics	MINOR
1	PO + PO	PHENITOYNE + PARACETAMOL	Increases risk of liver damage.	Induction of paracetamol metabolism and a consequent increase of hepatotoxic metabolites.	Pharmacokinetics	MODERATE
1	PO + PO	ACETYLSALICYLIC ACID + ATENOLOL	Antihypertensive effects of Betablocker may be diminished by Salicylates.	PGs inhibition, and consequent increase in blood pressure	Pharmacodynamics	MODERATE
1	PO + SC	ACETYLSALICYLIC ACID + ENOXAPARIN	May affect hemostasis	...		MAJOR

N° REPETITIONS	ADMINISTRATION ROUTE	INTERACTIONS	EFFECT	MECHANISM: DESCRIPTION	MECHANISM	GRAVITY
1	PO + IV	ENOXAPARINA + HYDROCORTISONE	Decreased glomerular filtrate, ulcerations, and gastrointestinal bleeding may occur.	Corticosteroids (enzyme inducers) stimulate the hepatic metabolism of salicylates and may increase acetylsalicylic acid metabolism.	Pharmacokinetics	MODERATE
1	PO + PO	ACETYLSALICYLIC ACID + OMEPRAZOLE	Increased gastric side effects.	The increase in gastric pH mediated by proton pump inhibitors results in faster dissolution and release of salicylate from the enteric-coated product. Increased ionization, reduced absorption, higher concentration of local acetylsalicylic.	Pharmacokinetics	MINOR
1	PO + IV	AMLODIPINE + HYDROCORTISONE	...	Corticosteroids may antagonize the effects of antihypertensive drugs, inducing sodium, and fluid retention.	Pharmacodynamics	MODERATE
1	PO + IM	ATENOLOL + KETOPROFEN	The combination of these medicines may reduce the effects of Atenolol in lowering blood pressure.	Non-steroidal anti-inflammatory drugs may attenuate the antihypertensive effect of beta-blockers. The proposed mechanism is induced inhibition of renal prostaglandin synthesis by Non-steroidal anti-inflammatory, which results in unopposed pressor activity producing hypertension. In addition, Non-steroidal anti-inflammatory may cause fluid retention, which also affects blood pressure.	Pharmacodynamics	MODERATE
1	PO + IV	ATENOLOL + FUROSEMIDE	Diuretics and beta-blockers may increase the risk of hyperglycemia and hypertriglyceridemia in some patients, especially in patients with diabetes or latent diabetes.	...	...	MODERATE
1	PO + PO	BIPERIDEN + HALOPERIDOL	The development of tardive dyskinesia and the worsening of schizophrenia-related symptoms are reported when anticholinergic agents are used with Haloperidol.	Decreased serum Haloperidol concentration.	Pharmacokinetics	MODERATE
1	IV + PO	BUTYLSCOPOLAMINE) + PHENYTOIN	Reduced therapeutic efficacy of Buscopan.	Phenytoin and other hydantoins may induce hepatic metabolism of corticosteroid CYP450 3A4 and increase their clearance and decrease half-life.	Pharmacokinetics	MODERATE
1	PO + PO	BUTYLSCOPOLAMINE + BIPERIDEN	...	Agents with anticholinergic properties may have additive effects when used in combination.	Pharmacodynamics	MODERATE

N° REPETITIONS	ADMINISTRATION ROUTE	INTERACTIONS	EFFECT	MECHANISM: DESCRIPTION	MECHANISM	GRAVITY
1	PO + IM	CAPTOPRIL + KETOPROFEN	The combination of these drugs may reduce the effects of captopril on the action of lowering blood pressure.	Non-steroidal anti-inflammatory drugs may mitigate the anti-hypertensive effects of ACE inhibitors. The mechanism is the induced inhibition of the synthesis of renal prostaglandins by NSAIDs, which results in pressure activity without opposition producing hypertension. In addition, NSAIDs may cause fluid retention, which also affects blood pressure.	Pharmacodynamics	MODERATE
1	PO + PO	CARVEDILOL + DIPIRONE	Decreases antihypertensive effect.	Difficult assessment due to restriction of studies on Dipyrone	Difficult assessment due to restriction of studies on Dipyrone	MINOR
1	IM + IV	KETOPROPHEN + FUROSEMIDE	It may affect renal function, the hypotensive effect of diuretics may be reduced and, consequently, increased blood pressure. Diuretic effects may be reduced, risk of congestive heart failure associated with the combination.	Concomitant use of non-steroidal anti-inflammatory drugs and diuretics may adversely affect renal function due to inhibition of prostaglandin synthesis by non-steroidal anti-inflammatory drugs that help maintain renal perfusion in dehydrated states. The risk may be increased in patients with dietary sodium restriction. At the same time, the hypotensive effect of diuretics may be reduced because inhibition of prostaglandins may lead to unopposed pressor activity and hence elevation of blood pressure. Natriuretic and diuretic effects may also be reduced as NSAIDs cause sodium and water retention, which may be responsible for the increased risk of congestive heart failure associated with the combination.	Pharmacodynamics	MODERATE
1	IM + IV	KETOPROPHEN + HYDROCORTISONE	The use of hydrocortisone in combination with ketoprofen may increase the risk of side effects on the gastrointestinal tract, such as inflammation (ulceration and bleeding).	The combined use of oral corticosteroids and non-steroidal anti-inflammatory may increase the potential for severe gastrointestinal toxicity, including inflammation, bleeding, ulceration, and perforation.	Pharmacodynamics	MODERATE
1	PO + PO	CLONAZEPAM + LOSARTAN	May result in additive effects on blood pressure and orthostasis.	Many CNS-active psychotherapeutic agents (anxiolytics, sedatives, hypnotics, antidepressants, antipsychotics, opioids, muscle relaxants) exhibit hypotensive effects, especially during initiation of therapy and dose escalation. Concomitant administration with antihypertensive agents and other hypotensive agents, in particular vasodilators and alpha-blockers, may result in additive effects on blood pressure and orthostasis.	Pharmacodynamics	MODERATE

N° REPETITIONS	ADMINISTRATION ROUTE	INTERACTIONS	EFFECT	MECHANISM: DESCRIPTION	MECHANISM	GRAVITY
1	IV + IV	DEXAMETHASONE + MIDAZOLAM	...	Certain corticosteroids may decrease the plasma concentration of some benzodiazepines. The mechanism is related to the induction of cytochrome P450 liver enzymes responsible for benzodiazepine metabolism.	Pharmacokinetics	MODERATE
1	PO + PO	DIAZEPAM + FLUOXETINE	...	The mechanism may be related to CNS additive depressive effects and/or inhibition of Benzodiazepine metabolism by CYP450 2C19 and/or 3A4 by fluoxetine.	Pharmacokinetics	MODERATE
1	PO + PO	DIPYRONE + FUROSEMIDE	Decreases diuretic and antihypertensive effect	UNKNOWN	Difficult assessment due to restriction of studies on Dipyrone	NOT SPECIFIED
1	IV + PO	SCOPOLAMINE + PARACETAMOL	Absorption of paracetamol is slower, so it may take longer to start pharmacological action (which may be less than expected).	Decreased gastrointestinal motility caused by the action of Anticholinergics.	Pharmacodynamics	MINOR
1	PO + PO	FLUOXETINE + HALOPERIDOL	...	Haloperidol is metabolised by many routes, including glucuronidation and by enzymes from the cytochrome P450 system (particularly CYP3A4 or CYP2D6). The inhibition of these metabolism routes by other drugs or the decrease in the enzymatic activity of CYP2D6 may result in an increase in haloperidol concentrations and an increased risk of adverse events, including prolongation of the QT interval. medicines characterized as substrates or inhibitors of CYP3A4 or CYP2D6 isoenzymes.	Pharmacokinetics	MODERATE
1	IV + PO	HYDROCORTISONE + PHENYTOIN	Decreased therapeutic efficacy.	Phenytoin and other Hydantoins may induce the hepatic metabolism of CYP450 3A4 in corticosteroids and increase its clearance and shorten its half-life, possibly reducing its therapeutic efficacy.	Pharmacokinetics	MODERATE
1	IV + SC	HYDROCORTISONE + SALBUTAMOL	...	Concomitant use of beta-2 adrenergic agonists and corticosteroids may result in hypokalemia effects. Since beta-2 agonists may sometimes cause prolongation of the QT interval	Pharmacodynamics	MINOR
1	PO + PO	LEVOTHYROXINE + SIMVASTATIN	Possible increase or decrease in thyroid hormone.	...		MINOR

N° REPETITIONS	ADMINISTRATION ROUTE	INTERACTIONS	EFFECT	MECHANISM: DESCRIPTION	MECHANISM	GRAVITY
1	PO + PO	LOSARTAN + PREDNISONE	...	Corticosteroids may antagonize the effects of antihypertensive drugs, inducing sodium, and fluid retention. These effects may be more common with natural corticosteroids (cortisone, hydrocortisone) because they have greater mineralocorticoid activity. On the other hand, some calcium channel blockers, such as Diltiazem and verapamil, may increase plasma levels and the effects of corticosteroids, inhibiting their clearance through the metabolism of CYP450 3A4.	Pharmacokinetics	MODERATE
1	PO + PO	LOSARTAN + RISPERIDONE	...	Phenothiazines and neuroleptic agents may potentiate the hypotensive effect of some drugs secondary to peripheral alpha-1 adrenergic blocking activity. Orthostatic hypotension and syncope associated with vasodilation may occur, particularly during initial dosing or parenteral administration of phenothiazine or neuroleptic.	Pharmacodynamics	MODERATE
1	IV + PO	METOCLOPRAMIDE + MORPHINE	Increased sedative effects.	Metoclopramide potentiates CNS depression caused by morphine. The effect of metoclopramide on gastric motility is reduced by morphine.	Pharmacodynamics	MODERATE
1	IV + IV	MIDAZOLAM + MORPHINE	The effects of the central nervous system or respiratory depressant may be increased.	The effects of the central nervous system or respiratory depressant may be increased additionally or synergistically	Pharmacodynamics	MODERATE
1	IV + IV	MIDAZOLAM + OMEPRAZOLE	It prolongs the sedative effect and may cause ataxia.	Omeprazole may increase the pharmacological effects and the serum levels of certain Benzodiazepines through hepatic enzyme inhibition.	Pharmacokinetics	MODERATE
1	PO + PO	OMEPRAZOLE + SIMVASTATIN	Increased adverse effects of simvastatin. Risk of liver and kidney damage.	Omeprazole increases the plasma concentration of simvastatin.	Pharmacokinetics	MODERATE
1	PO + PO	RISPERIDONE + SERTRALINE	Doses greater than 100 mg/ day of Sertraline may increase the concentrations of the active antipsychotic fraction of Risperidone.	...		MODERATE

Note: (...) Not found; (IV) Intravenous; (IM) Intramuscular; (PO) Per Os\Oral; (SC) Subcutaneous.

APPENDIX II

Chart references

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