

Clinical and epidemiological analysis of hospitalizations of elderly due to poisoning and adverse effects of medications, Brazil from 2004 to 2008

Análise clínica e epidemiológica das internações hospitalares de idosos decorrentes de intoxicações e efeitos adversos de medicamentos, Brasil, de 2004 a 2008

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Abstract

The elderly are more susceptible to adverse drug effects due to a variety of factors, such as excessive and concomitant use of several drugs, administration errors, physiological changes in the body that alter the pharmacodynamics and pharmacokinetics. In order to determine the main therapeutic classes involved in hospital admissions of elderly people due to intoxication and adverse drug effects, as well as major health problems related to these events, 9,793 hospitalizations of people aged 60 or over registered in the Hospital Information System of the Unified Health System (SIH-SUS) in the period of 2004 to 2008 were analyzed. Unspecified drugs, systemic antibiotics, psychotropics, psychoactives, antiepileptics, sedatives, hypnotics and antiparkinsonians accounted for 57% of the total of admissions analyzed. Injuries and falls were the main health problems related to intoxication and adverse drug effects. Hospitalizations due to injuries were associated with analgesic, antipyretic and antirheumatic non-opioid. Falls were associated with systemic antibiotics, contradicting studies which point out psychotropic drugs as the main drug involved in these events. The results reflect the growing trend of problems associated with drug use by elderly people. It was verified that the consumption profile alone is not sufficient to explain the concentration of cases of the major therapeutic classes. We suggest the adoption of more effective programs of pharmacovigilance, capable of intervening at different stages of drug use: prescribing, dispensing, marketing, administration and compliance.

Keywords: Elderly. Intoxications. Hospitalizations. Therapeutic classes. Fractures. Falls.

Resumo

Os idosos são mais suscetíveis aos efeitos adversos dos medicamentos devido a uma diversidade de fatores, tais como o uso excessivo e concomitante de diversos fármacos, erros de administração, alterações fisiológicas no organismo que alteram a farmacodinâmica e a farmacocinética. Com o objetivo de determinar as principais classes terapêuticas envolvidas nas internações hospitalares de idosos decorrentes de intoxicação e efeito adverso de medicamentos, bem como os principais agravos relacionados a esses eventos, foram analisadas 9.793 internações hospitalares de pessoas com 60 anos ou mais, registradas no Brasil pelo Sistema de Internações Hospitalares do SUS (SIH-SUS), no período de 2004 a 2008. Medicamentos não especificados, antibióticos sistêmicos, psicotrópicos, psicoativos, antiepilépticos, sedativos, hipnóticos e antiparkinsonianos, responderam por 57% do total de internações analisadas. Traumatismos e quedas foram os principais agravos relacionados a intoxicação e efeito adverso de medicamentos. As internações por traumatismo apresentaram relação com analgésicos, antitérmicos e antirreumáticos não opiáceos. Já as quedas estavam associadas aos antibióticos sistêmicos, contrariando os estudos que apontam os psicotrópicos como os principais medicamentos envolvidos nesses eventos. Os resultados encontrados refletem a tendência crescente dos problemas associados ao uso de medicamentos por idosos. Verificou-se que o perfil de consumo não é suficiente para explicar as concentrações de casos nas principais classes terapêuticas. Na busca pelas causas, sugere-se a adoção de programas mais efetivos de farmacovigilância, capazes de monitorar as diferentes etapas do processo de uso de medicamentos: prescrição, dispensação, comercialização, administração e adesão ao tratamento.

Palavras-chave: Idosos. Intoxicações. Internações. Classes terapêuticas. Fraturas. Quedas.

Introduction

The Brazilian population is aging. In 1980 the elderly – individuals aged 60 years old or over¹ – accounted for 6% of the population; in 2010, they already added up to 11%². For 2025, they are estimated to reach 15%, making Brazil the country with the 6th largest population of elderly people in the world^{3,4}.

The natural aging process generates structural and functional changes in the human body. A direct consequence of this is an increase in the prevalence of diseases that are characteristic of the elderly. This age group shows a high prevalence of chronic diseases, particularly neurodegenerative, psychiatric, cardiovascular and metabolic diseases^{5,6}.

Since the elderly are more likely to have a higher number of diseases, they are also exposed to higher consumption of therapeutic drugs⁷⁻¹² and, consequently, to the risks of over utilization. In addition, characteristic changes in the aging process, which can jeopardize action and metabolization of drugs in the body, allied to lack of awareness about the efficacy and safety of many drugs for the delicate bodies of the elderly, increase the likelihood of drug intoxications and adverse events in this age group^{13,14}.

Intoxication data registered in the country by the National System of Toxic-Pharmacological Information (SINITOX)¹⁵ could challenge previous findings. In fact, when we calculate morbidity rates for the elderly we attain lower values compared to other age groups. However, although they do not raise our attention in number of cases, the elderly have the highest mortality and fatality rates, which would be indicators of higher severity of events.

The higher susceptibility of the elderly population to more severe adverse drug reactions was registered by different international studies that observed a higher frequency in this age group, by analyzing data on hospital admissions related to the condition¹⁶⁻²¹. A meta-analysis based on 64 papers concluded that the elderly are

four-fold more likely to be hospitalized by problems related to adverse drug reactions than the remainder of the population²².

Given the importance of adverse reactions in this age group, studies from different countries started to focus on hospitalized elderly patients. Some studies considered adverse reactions only, that is, undesired effects resulting from the correct use of medication²³⁻²⁵, and showed that there are a large number of severe adverse reactions, even when the drugs are correctly prescribed and administered. Other studies worked with a broader concept, that of an adverse event in which medication errors (any error in the process of prescription, transcription, dispensation, administration and treatment follow-up)²⁶ were also taken into account²⁶⁻³². Avoidability of such events has been approached by several authors^{19,26,28-31}. Some will say a large part of adverse reactions can be prevented by means of simple improvements in the prescription process (regular review of prescription, use of electronic prescription and participation of pharmacists in prescription evaluation), since drug interactions were present in almost 17% of these events^{20,31}. Others pointed out to problems related to patient adherence to treatment and self-medication²⁶. However, the most surprising data came from the fact that the drugs most involved in hospitalizations of elderly patients resulting from adverse events were those typically used by this population and not those considered to pose a higher risk^{20,27-30}.

There is still much work to be done in Brazil in this regard. Some studies based on Hospital Information System of the Unified Health System (SIH-SUS) have focused on morbidity by lesions and poisoning in the country³³, external causes³⁴ and overall morbidity³⁵ among the elderly in Brazil, drug related problems in hospitals in Rio de Janeiro³⁶ and drug intoxications and adverse events in children under one year old in Brazil³⁷. More specific studies, approaching hospitalized elderly patients due to drug intoxications and adverse reactions were

conducted locally only, based on data from a few hospitals^{38,39}.

Thus, to expand awareness on the impact of the use of drugs by the elderly population, we analyzed hospital admissions of patients aged 60 or more related to drug intoxication and adverse effects in the country, identifying the key therapeutic classes and problems involved.

Methods

The study was designed as a retrospective study, and covered hospital admissions recorded in the whole of Brazil by the SUS Hospital Information System (SIH-SUS) between 2004 and 2008. Data source comprised CD-ROMs from the SUS Hospitalization Authorization Records⁴⁰⁻⁴⁴.

The study population consisted of elderly patients, that is, individuals aged 60 years old or older, according to the country's Statute of the Elderly, Law 10,741 of October 1, 2003.

The codes of the 10th Review of the International Classification of Diseases (ICD-10)⁴⁵ identify both adverse drug events and drug intoxications. According to the World Health Organization⁴⁶, adverse drug reactions are defined as any unintentional and undesirable noxious effect of a drug that occurs in doses used in human beings for prophylaxis, diagnosis or therapy. In the ICD-10⁴⁵, this definition is adopted for adverse drug effects and the respective codes are: T80.5, T80.6, T88.6, T88.7, Y40 to Y57. As for drug intoxications, the ICD-10 corresponding codes are: F11.0, F13.0, F15.0, F19.0, F55, T36-T39, T40.2, T40.3, T40.4, T41-T50, X40, X41, X43, X44, X60, X61, X63, X64, X85, Y10, Y11, Y13, Y14, that encompass therapeutic failures, accidental and intentional events, abuse and other problems related to drug misuse or irrational use.

"Cases" considered included hospital admissions of elderly patients who had, as a primary and/or secondary diagnosis, one of the codes defined for drug intoxications or adverse events. It is important to highlight that the same codes were adopted by Lessa

et al.³⁷ in the study on hospital admissions of under one year old children related to drug intoxications and adverse events.

As adopted by Rozenfeld³⁶ and Lessa et al.³⁷, the X42, X62 and Y12 codes were suppressed to avoid the selection of ICD-10⁴⁵ codes that would not allow us to discern intoxications due to the use of medication to those associated to the use of legal or illegal drugs.

According to the method proposed by Lessa et al.³⁷, four situations were considered as a result of combinations between primary and secondary diagnoses. Situation 1 identifies hospitalizations in which the drug intoxication or adverse effect, that is, the event of interest, appears in the secondary diagnosis and not in the primary diagnosis. This situation is the only one in which the event of interest is not the reason for hospital admission. It may, however, have started the chain of pathologic events that led directly to the primary diagnosis⁴⁷. The event of interest may also develop during hospitalization, thus affecting the patient's condition⁴⁸. Situation 2 identifies drug intoxication or adverse effects as the primary diagnosis, and other problems as secondary diagnoses. Situations 1 and 2 enable us to analyze the main problems related to drug intoxication or adverse effects. Situation 3 identifies codes related to drug intoxication or adverse effects both in the primary and secondary diagnosis. This is the situation which, in theory, should have more information on the event of interest, specifically on the circumstances in which it occurred. Situation 4 only identifies the primary diagnosis by drug intoxication or adverse effects, and leaves the secondary diagnosis blank.

For intoxication-related hospital admissions, we were able to determine the associated causes based on the codes in chapter 20 of ICD-10⁴⁵. Codes X40-X44 refer to accidental causes; X60-X64 to self-intoxication; X85 to aggression and Y10-Y14 to undetermined causes. Thus, only admissions related to intoxication with a primary or secondary diagnosis defined by these

codes could have their cause described by one of the categories presented. The cause was considered unknown for all others.

Further details on the therapeutic classes involved in cases of drug intoxication and adverse effects were attained from hospital admissions in which the primary or secondary diagnosis had been filled with the four digits provided for the codes in chapter 19 and for the Y40 to Y57 groups in chapter 20 of ICD-10⁴⁵. However, as digits 8 and 9, related to the categories "others" and "unspecified" are used very much, the results found for most substances are not representative. For the T50 category, it was important to consider the fourth digit to separate intoxication cases by other drugs and unspecified (T50.9) from those regarding diuretics.

Population data regarding the years of 2004 to 2008 were attained from the IBGE estimates informed by Datasus² and used to calculate hospitalization rates per 100 thousand inhabitants based on case classification (drug intoxication or adverse effects), gender and on each of the age groups, 60 to 64, 65 to 69, 70 to 74, 75 to 79 and 80 years old and over.

To identify problems related to drug intoxications and adverse events, we analyzed the primary diagnoses involved with situation 1 and the secondary diagnoses involved with situation 2.

To test independence between specialties of care, gender and age groups, as well as between therapeutic classes and situation variables, case classification and causes of intoxication, we used the chi-square test, with a 5% level of significance⁴⁹.

To test if there were differences between situations, as well as between causes of intoxication, based on age and length of hospital stay, we used the Kruskal-Wallis non-parametric test, since assumptions of normality and homogeneity of variances were not met. These are necessary requirements to apply a more renowned and powerful parametric test, such as Analysis of Variance (ANOVA)⁴⁹.

To test if there were differences between

genders, as well as between case classification in “intoxication” or “adverse effect”, based on age and length of hospital stay, we used the Wilcoxon-Mann-Whitney non-parametric test, since assumptions of normality and homogeneity of variances were not met. These are necessary requirements to use the parametric test t^{49} .

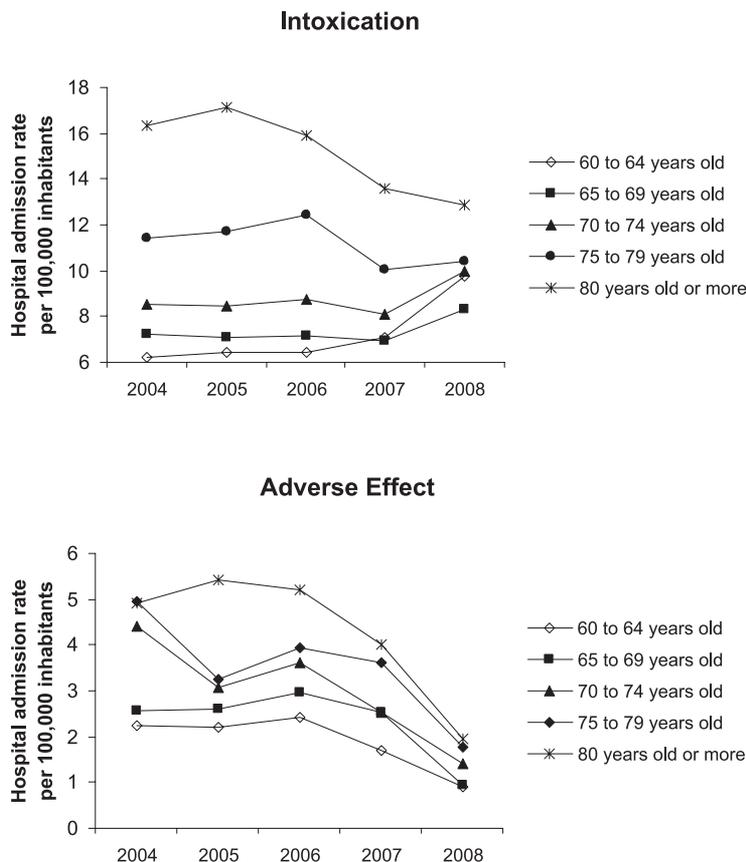
The project was approved by the Ethics Committee in Research in Human Beings of the Institute of Clinical Research Evandro Chagas (IPEC) of the Oswaldo Cruz Foundation (Fiocruz), with report nº 020/2009.

Results

The SUS Hospitalization System (SIH-SUS) recorded 9,793 hospital admissions of elderly patients related to drug intoxications and adverse events in Brazil between 2004 and 2008. In the period, these events showed a 13.6% growth, going from 1,857 cases in 2004 to 2,109 in 2008. The number of hospital admissions related to intoxications grew in all age groups in a different way, ranging from 9.9% for the elderly aged 80 years old and over to 88.7% for those aged 60 to 64 years old. On the other hand, the number of hospitalizations due to adverse events decreased more homogeneously in all age groups, ranging from 44.7% for the elderly aged 80 years old and over to 61.1% for those aged 70 to 74 years old.

Figure 1 shows a decreasing trend for all age groups regarding adverse effects, and an increasing trend regarding cases of intoxication for patients aged 60 to 64, 65 to 69 and 70 to 74 years old. Hospital admission rates increased as age advanced, both in cases of intoxication and in cases of adverse effects. The exception to this was observed in the years of 2007 and 2008 for intoxications, when the rate of elderly patients aged 60 to 64 years old (7.08 and 9.75) was higher than for those aged 65 to 69 years old (6.93 and 8.33), and in the year of 2004 for adverse events, when the rate of elderly patients aged 75 to 79 years old (4.95) was very close to that of patients aged 80 years old and over (4.91).

Data in Table 1 show the four situations, based on the combination of diagnoses. We can see they differ significantly in the proportion of each of the specialties of care (chi-square test, p -value = 0). The percentage regarding surgery for situation 1 is as high as 48.6%, whereas it is no higher than 0.6% in the other situations. Situation 4, in turn, shows 17.3% of hospital admissions in psychiatry, whereas the category does not reach 0.2% in other situations. The younger and older age groups, 60 to 64 years old, and 80 years old and over, respectively, had the highest concentrations of cases, 24.4% and 21.5%, respectively. The four situations differ significantly in the proportion of age groups (chi-square test, p -value = 2.22389 E-23). Situation 4 features the highest proportion of elderly patients aged 60 to 64 years old (41.3%) and the lowest proportion of elderly patients aged 80 years old and over (12.7%). When we observe total admissions, the female population contributed with the highest absolute number and the male population with the highest hospital admission rate, 12.11 and 11.41 per 100 thousand inhabitants, respectively. The four situations differ significantly in the proportion of each gender (chi-square test, p -value = 9.43234 E-37). Situations 1 and 4 show higher proportions for males (50.6% and 66.4%, respectively) whereas in situations 2 and 3 female patients were more frequent (56.2% and 60.6%, respectively). Hospital admission rates per age group for males were higher than females among elderly patients aged 60 to 64 years old (10.36 and 8.05); 65 to 69 years old (10.66 and 8.78) and 70 to 74 years old (12.23 and 11.29). As of 75 years old, we observed an inversion, and rates regarding females were higher than those of males; from 75 to 79 years old we have 14.81 and 14.18, and from 80 years old and over the numbers are 20.01 and 17.65, respectively. There was also more drug intoxications (77.3%) compared to adverse effects (22.7%). The four situations differ significantly in the proportion of these events (chi-square test, p -value = 0). The percentage regarding adverse drug effects,



Fonte/Source: SIH-SUS

Figure 1 - Rates of hospitalization per 100,000 inhabitants related to drug intoxication and adverse effects distributed by age group. Brazil, 2004 to 2008.

Figura 1 - Taxas de internação hospitalar por 100.000 hab. relacionadas a intoxicação e efeito adverso de medicamentos distribuídas por faixa etária. Brasil, 2004 a 2008.

among cases related to situation 1, was practically double of that presented for the total of cases (42.6% and 22.7%, respectively), whereas for situations 2 and 4 this percentage is not higher than 3% and, for situation 3, it is around the overall value, 27.2%. The causes of intoxication are often unknown (51.0%). Accidents accounted for 17.3%, followed by self-intoxication (15.6%) and undetermined (14.6%) causes. Aggressions accounted for only 1.5% of intoxications. The four situations differed significantly in the proportion of these events (chi-square test, p -value = 0). Situations 2 and 4 barely discriminate the causes of intoxications; situation 3 shows the highest percentage for accidental causes (45.6%) and situation 1

shows self-intoxication as the most frequent cause (33.7%). As for the key therapeutic classes involved in hospitalizations of elderly patients, other drugs and unspecified accounted for the highest number of cases, with 24.0% of hospital admissions; systemic antibiotics rank second, with 17.0%, followed by psychotropic, psychoactive, antiepileptic, sedative, hypnotic and anti-Parkinson drugs, with a 16.2% share. These three groups account for 57.2% of the total hospital admissions analyzed. The four situations differ significantly in the proportion of therapeutic classes (chi-square test, p -value = 0). Highlights in situation 1 include non-opioid analgesic, antipyretic and anti-rheumatic drugs with a 25.4% share.

Situation 2 shows systemic antibiotics with 32.4%. Other drugs and unspecified prevail in situation 3, with 27.7%. In situation 4, a large concentration of cases was due to psychotropic, psychoactive, antiepileptic, sedative, hypnotic and anti-Parkinson drugs with 43.5%.

In Table 2, *injuries in general* stand out in situation 1, especially in the lower limbs (42%). As for situation 2, falls concentrate one third of events. Most of these events take place at patients' homes (24%). Females have a higher share of injuries in general than males, accounting for 59%, with even higher rates for fractures in the forearm (76%), femur (69%) and shoulder and arm (69%).

Figure 2 shows that injuries and falls differ significantly in the proportions of therapeutic classes (chi-square test, p -value = 2.145E-270). For injuries, non-opioid analgesic, antipyretic and anti-rheumatic drugs stand out (44.8%), whereas for falls, the higher concentration of cases was associated with systemic antibiotics (37.8%). The proportion of hormones, synthetic substitutes and antagonists is eight times higher for injuries compared to falls. In turn, despite showing values lower than 10%, the proportion of substances that primarily act on the circulatory system and on the cardiovascular system, as well as the proportion of substances that act on the gastrointestinal tract regarding falls are ten and twenty-one times higher than those regarding injuries, respectively.

Figure 3 shows that systemic antibiotics and analgesics presented quite larger shares in intoxication-related hospital admissions, 20% and 11%, in comparison to those related to adverse effects, 7% and 5%, respectively. The opposite occurs, however, for hormones, synthetic substitutes and antagonists, for substances of essentially systemic action and hematologic substances and for the drugs that particularly affect the autonomic nervous system. Hospitalizations related to adverse effects have higher rates than those related to intoxications, 12.3%, 10.7% and 10.6%

against 1.3%, 2.4% and 4.4%, respectively. With regard to the causes of intoxication, 41% of hospitalization-related accidents were caused by other drugs and unspecified. Non-opioid analgesic, antipyretic and anti-rheumatic drugs accounted for 37% of hospitalizations related to self-intoxication. Aggression had 83% of cases related to other non-classified substances, in which code X85 ("aggression by means of drugs, medication and biological substances") applies. There were differences between the percentile distribution of therapeutic classes involved with the "undetermined" and "unknown" categories. Comparatively, systemic antibiotics stand out in the "unknown" category, while non-opioid analgesic, antipyretic and antirheumatic drugs, as well as drugs that particularly affect the autonomic nervous system, showed a higher concentration for the "undetermined" category.

When comparing the 4 situations, the Kruskal-Wallis test showed significant differences among ages (test statistics = 116.769, p -value = 0.0) and length of hospital stay (test statistics = 99.7888, p -value = 0.0). Situation 4 had the lowest mean age, 68.9 years old, followed by situations 1, 2 and 3, with means of 71.8; 72.6 and 72.8, respectively; and the longest mean length of stay, 7.3 days. The other situations showed much lower means, around 4.5 days. Situation 4 was the one that featured the higher proportion of intoxications related to mental and behavioral disorders (55.4%), in that most of them were related to sedatives, hypnotics and other psychoactive substances, F11.0 = use of opioids (67); F13.0 = use of sedatives and hypnotics (81); F15.0 = use of other stimulants, including caffeine (37); F19.0 = use of multiple drugs and other psychoactive substances (115).

Comparison of causes of intoxication by the Kruskal-Wallis test also showed significant differences among ages (test statistics = 19.577, p -value = 0.00149995) and length of hospital stay (test statistics = 55.2633, p -value = 1.15228E-10). Accidental causes showed the highest age mean (72.9), in that the lowest mean length of stay was observed

Table 1 - Cases of hospitalization related to drug intoxication and adverse effects in elderly distributed by specialty care, age group, sex, classification case, intoxication cause and therapeutic classes by situation. Brazil, 2004 to 2008.

Tabella 1 - Casos de internação hospitalar em idosos decorrentes de intoxicação e efeito adverso de medicamentos distribuídos por especialidade do atendimento, faixa etária, sexo, classificação do caso, circunstância da intoxicação e classe terapêutica segundo situação. Brasil, 2004 a 2008.

Variables	Cases				Total
	Situation				
	1	2	3	4	
Service specialty					
Surgery	1,664	7	1	3	1,675
Medical Clinic	1,745	3,250	2,548	440	7,983
Psychiatry	2	2	1	94	99
Others	13	14	4	5	36
Age Group					
60 to 64	870	728	569	224	2,391
65 to 69	714	662	475	104	1,955
70 to 74	664	592	471	94	1,821
75 to 79	474	551	440	51	1,516
80 or more	702	740	599	69	2,110
Gender					
Female	1,693	1,840	1,548	182	5,263
Male	1,731	1,433	1,006	360	4,530
Case classification					
Intoxication	1,967	3,218	1,859	528	7,572
Adverse Effect	1,457	55	695	14	2,221
Cause of Intoxication					
Unknown	123	3,202	12	521	3,858
Accidental	455	8	847	1	1,311
Self-Intoxication	662	5	515	1	1,183
Undetermined	632	3	464	5	1,104
Aggression	95	-	21	-	116
Therapeutic Class					
Other drugs and unspecified (T50.9, T88.7, X44, X64, Y14, Y57.8, Y57.9)	784	827	708	32	2,351
Systemic antibiotics (T36, Y40)	39	1,062	524	43	1,668
Antiepileptic, sedative, hypnotic, antiparkinsonian, psychotropic and psychoactive drugs(F13.0, F19.0, T42, T43, X41, X61, Y11, Y46, Y47, Y49)	456	363	532	236	1,587
Non-opioid analgesic, antipyretic and anti-rheumatic drugs (T39, X40, X60, Y10, Y45)	871	38	39	5	953
Substances that act primarily on the circulatory and on the cardiovascular system (T46, Y52)	45	246	409	37	737
Drugs primarily affecting the autonomic nervous system (T44, X43, X63, Y13, Y51)	465	60	34	8	567
Substances of essentially systemic action and hematologic substances (T45, Y43, Y44)	183	107	117	10	417
Other not classified above	581	570	191	171	1,513
Total	3,424	3,273	2,554	542	9,793

Source/Fonte: SIH-SUS

Event of Interest = drug intoxication or adverse drug effect

Situation 1 = Main Diagnosis not related to the Event of Interest and Secondary Diagnosis related to the Event of Interest.

Situation 2 = Main Diagnosis related to the Event of Interest and Secondary Diagnosis not related to the Event of Interest.

Situation 3 = Main and Secondary diagnoses are related to the Event of Interest.

Situation 4 = Main Diagnosis related to the Event of Interest and Secondary Diagnosis not filled.

Evento de Interesse = Intoxicação ou Efeito Adverso de Medicamentos

Situação 1 = Diagnóstico Principal não relacionado ao Evento de Interesse e Diagnóstico Secundário relacionado ao Evento de Interesse.

Situação 2 = Diagnóstico Principal relacionado ao Evento de Interesse e Diagnóstico Secundário não relacionado ao Evento de Interesse.

Situação 3 = Diagnósticos Principal e Secundário relacionados ao Evento de Interesse.

Situação 4 = Diagnóstico Principal relacionado ao Evento de Interesse e Diagnóstico Secundário não preenchido.

Table 2 - Cases and percentage associated to main and secondary diagnosis related to situations 1 and 2. Brazil, 2004 to 2008.

Tabela 2 - Casos e percentuais associados aos Diagnósticos Principal e Secundário relacionados às Situações 1 e 2. Brasil, 2004 a 2008.

Main Diagnosis related to Situation 1	Cases	%
S00-T14 General injury	1,363	39.8
T51-T65 Toxic effects from substances of predominantly non medicinal origin	734	21.4
T80-T88 Complications from non-classified medical and surgical care	591	17.3
C00-C97 Malignant neoplasm [tumors]	166	4.8
T66-T78 Other effects from external causes and unspecified	163	4.8
I00-I99 Circulatory system diseases	132	3.9
T20-T32 Burns and corrosions	39	1.1
J00-J99 Respiratory system diseases	33	1.0
T15-T19 Effect from penetration of foreign body through natural orifice	30	0.9
T40-Intoxication by narcotics and psychodysleptic drugs (except for T40.2, T40.3, T40.4)	28	0.8
T90-T98 Sequelae from injuries, intoxications and other consequences	22	0.6
L00-L99 Skin and subcutaneous skin diseases	18	0.5
N00-N99 Genitourinary system diseases	15	0.4
K00-K93 Digestive system diseases	14	0.4
R00-R99 Abnormal symptoms, signs and findings in clinical and lab tests	14	0,4
Others	62	1.8
Total	3,424	100.0
Secondary diagnosis related to Situation 2	Cases	%
W00-W19 Falls	1,082	33,1
X58-X59 Accidental exposure to other and unspecified factors	317	9.7
Y10-Y34 Events whose intention is undetermined (except drugs)	262	8.0
X86-Y09 Aggressions	231	7.1
V01-V99 Transportation accidents	179	5.5
X40-X49 Accidental event or intoxication due to exposure to noxious substances (except drugs)	169	5.2
Y40-Y84 Complications from medical and surgical care	144	4.4
W20-W64 Exposure to mechanical forces	142	4.3
W85-W99 Exposure to electric current, radiation & extreme temperatures and pressures	135	4.1
X60-X84 Intentionally self-provoked lesions (except drugs)	112	3.4
Y85-Y89 Sequelae from external morbidity and mortality causes	109	3.3
Y90-Y98 Supplemental factors related to external morbidity and mortality causes	101	3.1
X20-X29 Contact with poisonous animals and plants	88	2.7
X00-X09 Exposure to smoking, fire and flames	68	2.1
X10-X19 Contact with source of heat or with hot substances	52	1.6
Others	82	2.5
Total	3,273	100.0

Source/Fonte: SIH-SUS

Event of Interest = drug intoxication or adverse effect

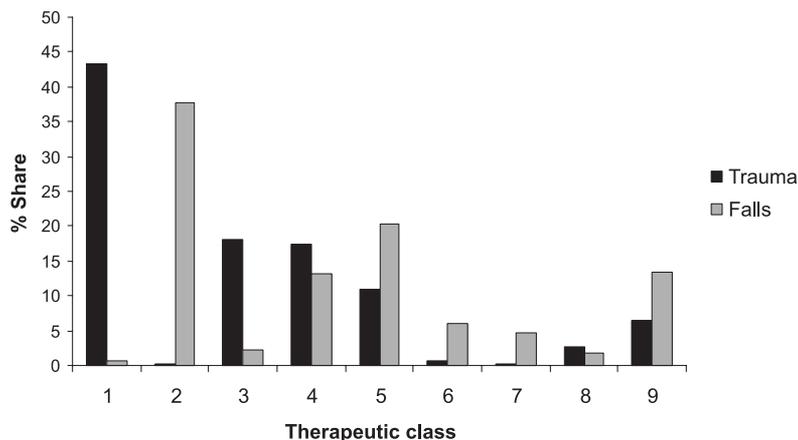
Situation 1 = Main Diagnosis not related to the Event of Interest and Secondary Diagnosis related to the Event of Interest.

Situation 2 = Main Diagnosis related to the Event of Interest and Secondary Diagnosis not related to the Event of Interest.

Evento de Interesse = Intoxicação ou Efeito Adverso de Medicamentos

Situação 1 = Diagnóstico Principal não relacionado ao Evento de Interesse e Diagnóstico Secundário relacionado ao Evento de Interesse.

Situação 2 = Diagnóstico Principal relacionado ao Evento de Interesse e Diagnóstico Secundário não relacionado ao Evento de Interesse.



Fonte/Source: SIH-SUS

1 - Nonopioid analgesics, antipyretics and antirheumatics (T39, X40, X60, Y10, Y45).
 2 - Systemic antibiotics (T36, Y40).
 3 - Hormones, their synthetic substitutes and antagonists (T38, Y42).
 4 - Antiepileptics, sedative, hypnotic, antiparkinsonian, psychotropic and psychoactive drugs (F13.0, F19.0, T42, T43, X41, X61, Y11, Y46, Y47, Y49).
 5 - Other and unspecified drugs (T50.9, T88.7, X44, X64, Y14, Y57.8, Y57.9).
 6 - Substances that act primarily on the circulatory system and on the cardiovascular system (T46, Y52).
 7 - Substances of action in the gastrointestinal system (T47, Y53).
 8 - Drugs primarily affecting autonomic nervous system (T44, X43, X63, Y13, Y51).
 9 - Other not classified above (T37, Y41, T45, Y43, Y44, T48, Y55, T49, Y56, T41, Y48, X85, Y500, Y542, Y545, Y549, Y573, Y576)

1 - Analgésicos, antitérmicos e anti-reumáticos não opiáceos (T39, X40, X60, Y10, Y45).
 2 - Antibióticos sistêmicos (T36, Y40).
 3 - Hormônios, seus substitutos sintéticos e seus antagonistas (T38, Y42).
 4 - Antiepilépticos, sedativos, hipnóticos, antiparkinsonianos, drogas psicotrópicas e psicoativas (F13.0, F19.0, T42, T43, X41, X61, Y11, Y46, Y47, Y49).
 5 - Outras drogas e as não especificadas (T50.9, T88.7, X44, X64, Y14, Y57.8, Y57.9).
 6 - Substâncias que atuam primariamente sobre o aparelho circulatório e sobre o aparelho cardiovascular (T46, Y52).
 7 - Substâncias de ação no trato gastrointestinal (T47, Y53).
 8 - Drogas que afetam principalmente o sistema nervoso autônomo (T44, X43, X63, Y13, Y51).
 9 - Outros não classificados acima (T37, Y41, T45, Y43, Y44, T48, Y55, T49, Y56, T41, Y48, X85, Y500, Y542, Y545, Y549, Y573, Y576)

Figure 2 - Percentage participation of therapeutic classes in "Injuries in general" and "Falls". Brazil, 2004 to 2008.

Figura 2 - Percentual de participação das classes terapêuticas nos "Traumatismos em Geral" e nas "Quedas". Brasil, 2004 a 2008.

for self-intoxications (4.1 days).

When comparing gender, the Wilcoxon-Mann-Whitney test concluded that the median age was higher for female elderly patients (72 against 70, p-value = 0.00). Although the median length of hospital stay was the same for both genders—3 days—as the test was built based on the means of different health centers, it concluded that median lengths of stay were higher for male patients (p-value = 0.000650428).

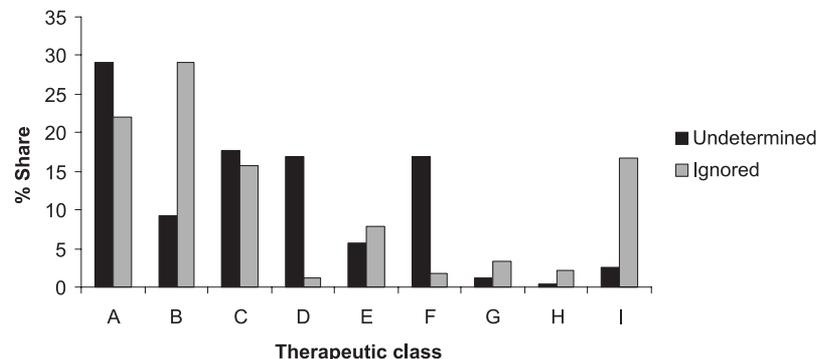
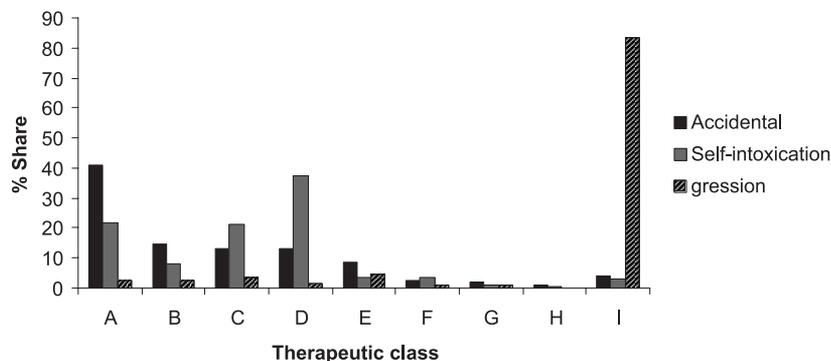
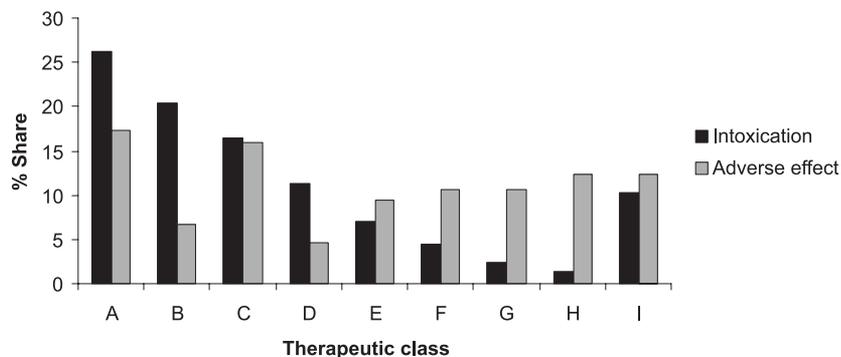
When comparing cases classified as "intoxication" and "adverse effect", the Wilcoxon-Mann-Whitney test concluded that the median ages for intoxication and adverse effect cases are the same (p-value = 0.189475). However, median length of hospital stay is higher for intoxications

compared to adverse effects, although they have the same median (3.0 days) (p-value = 0.000141697).

Discussion

While the total number of hospital admissions recorded in the country by the SIH-SUS decreased by 7% in the period from 2004 to 2008⁵⁰, hospital admissions of elderly patients decreased by 3% and hospital admissions related to drug intoxications and adverse events increased by almost 14%, drawing attention to the importance of the problem among this population.

Increased age-related risk of hospital admission due to drug intoxication and adverse effects was also observed by Burgess



Fonte/Source: SIH-SUS

A - Other and unspecified drugs ((T50.9,T88.7,X44,X64,Y14, Y57.8,Y57.9)
 B - Systemic antibiotics (T36,Y40)
 C - Antiepileptic, sedative-hypnotic, antiparkinsonism drugs, psychotropic and psychoactive drugs (F13.0,F19.0,T42,T43, X41,X61,Y11,Y46,Y47,Y49)
 D - Nonopioid analgesics, antipyretics and antirheumatics (T39,X40,X60,Y10,Y45)
 E - Substances that act primarily on the circulatory system and on the cardiovascular system (T46,Y52)
 F - Drugs primarily affecting autonomic nervous system (T44,X43,X63,Y13,Y51)
 G - Substances of action primarily systemic and haematological substances (T45,Y43,Y44)
 H - Hormones, their synthetic substitutes and antagonists (T38,Y42).
 I - Other not classified above.

A - Outras drogas e as não especificadas (T50.9,T88.7,X44,X64, Y14,Y57.8,Y57.9)
 B - Antibióticos sistêmicos (T36,Y40)
 C - Antiepilépticos, sedativos, hipnóticos, antiparkinsonianos, drogas psicotrópicas e psicoativas (F13.0,F19.0,T42,T43,X41, X61,Y11,Y46,Y47,Y49)
 D - Analgésicos, antitérmicos e anti-reumáticos não opiáceos (T39,X40,X60,Y10,Y45)
 E - Substâncias que atuam primariamente sobre o aparelho circulatório e sobre o aparelho cardiovascular (T46,Y52)
 F - Drogas que afetam principalmente o sistema nervoso autônomo (T44,X43,X63,Y13,Y51)
 G - Substâncias de ação essencialmente sistêmica e substâncias hematológicas (T45,Y43,Y44)
 H - Hormônios, seus substitutos sintéticos e seus antagonistas (T38,Y42)
 I - Outros não classificados acima

Figure 3 - Percentage of participation in therapeutic class Intoxication and Adverse Effect and the categories of Intoxication Cause. Brazil, 2004 to 2008.
Figura 3 - Percentual de participação das Classes Terapêuticas na Intoxicação e no Efeito Adverso e nas categorias da Circunstância da Intoxicação. Brasil, 2004 a 2008.

et al.²³ and Loyola Filho et al.³⁵ for adverse reactions. These results are compatible to the studies that state that the consumption of drugs increases as age advances⁸⁻¹⁰.

The comparison to SINITOX¹⁵ data is compromised because SINITOX shows overall cases of intoxication, which may or may not have led to hospitalizations. Data from the system for the period of the study show the following percentage shares related to the elderly in drug intoxications, decreasing according to the age group: 1.41% (60 to 69 years old), 0.81% (70 to 79 years old) and 0.48% (80 years old and over). Morbidity rates per 100 thousand inhabitants, in turn, show a rising trend, 0.45, 0.46 and 0.64, respectively, thus reiterating that there is an elevated risk of intoxication among the elderly as age increases.

When studying the profile of drug use among the elderly, Coelho Filho et al.¹² observed that there is a higher average number of prescribed drugs in use among females aged 75 years old or older. Loyola Filho et al., also in a similar study, observed that the association between females and the consumption of prescribed drugs persisted even after they adjusted for the number of appointments with a physician and for health status. They also observed an increase in the consumption of prescribed drugs as age advances. These results can explain the inversion by gender observed as of 75 years old in hospital admission rates.

The fact that the median age of females is higher than that of males is a consequence of women's higher longevity. The fact that the median length of hospitalization among males is higher than that of females may be related to greater severity of cases, worse health status, pre-existing co-morbidities and, specially, male-specific behavioral issues. These depend on cultural and social factors, such as behavior towards the disease, looking for healthcare, smoking, drinking, type of diet, work environment, physical activity, body weight, among others⁵¹.

The first category to appear when we search for the key therapeutic classes involved in hospitalizations of elderly patients is

the "other drugs or unspecified" category. Although this should be an exception, and chosen only in a few situations, it is the rule in Brazil, and accounts for almost one fourth of entries. When studying hospital admissions of children under one year of age, Lessa et al.³⁷ also came across this category being involved in most cases. We have to highlight that the ICD-10 code that concentrates most of these observations is T50.9. Category T50 refers to intoxication by diuretics and other drugs, biological substances and medication, and unspecified. Thus, studies that do not take the fourth digit into consideration may be overestimating the cases related to diuretics, creating an important bias that should be more closely observed in pharmaceutical surveillance programs. To improve the quality of data with the decrease of cases assigned as T50.9, we recommend that the teams responsible for filling out Hospital Admission Authorizations (AIH) be trained and made aware of the importance of detailed information for pharmaceutical surveillance programs. However, we are aware that quite often deficiencies in information derive from what is reported by patients and family members.

Systemic antibiotics rank second. The large share of these drugs in hospitalizations of elderly patients (17%), particularly in those related to situations 2 (32%) and 3 (21%), was not found in the studies on hospitalizations we analyzed. What could be observed in studies conducted in the United States²⁷ on adverse events, and in the Netherlands²¹, Italy²⁵, Spain¹⁷, Great Britain¹⁸ and Australia²³ on adverse reactions were much lower percentages: 3.8%²⁷, 4.1%²¹, 5.7%²⁵, 6.3%¹⁷ and 9.0%^{18,23}, indicating an important difference that may be explained by the higher control those countries have in the sale of such products. During the study period, drugs that should be only sold under prescription were being sold over-the-counter in Brazil^{52,53}. These included antibiotics, which only in May 2011, upon adoption of Resolution 20 of the National Sanitation Surveillance Agency (ANVISA)⁵⁴, started to be sold upon

retention of the prescription. This measure represents an important step in the fight for rational drug use, because in addition to inhibiting self-medication, it enables pharmacists to supervise prescriptions and guide consumers on the correct use of a drug. New studies should be performed to assess the impact of the law on intoxications and adverse events among elderly patients.

The third class of drugs to appear includes psychotropic, psychoactive, antiepileptic, sedative, hypnotic and anti-Parkinson drugs with a 16.2% share. The high prevalence of neurodegenerative disorders, like Parkinson and Alzheimer, and mood disorders, like depression, insomnia and anxiety, may explain the use of these drugs by this population group⁵. Thus, the high share of these drugs in situation 4 (43.5%) can be explained by the prevalence of mental and behavioral disorders observed. However, some of these drugs are potentially counter indicated for the elderly⁵⁵⁻⁵⁷.

Therapeutic classes of broader use (non-opioid analgesic, antipyretic and antirheumatic drugs^{52,58}) and the most prescribed drugs (drugs with cardiovascular action^{9-12,55,59-61}) did not appear as the most involved in hospital admissions resulting from drug intoxications and adverse events, ranking fourth and fifth, respectively.

Separating hospital admissions in 4 situations enabled us to outline a profile for each one of them, which can favor analysis and direct studies and specific control measures. Situation 1 is characterized by a higher proportion of adverse events than the others. The specialties of care related to this situation are mostly clinical and surgical. With a higher male population, the key therapeutic class consists of non-opioid analgesic, antipyretic and antirheumatic drugs. Trauma is the main problem related to it. Situation 2 is characterized by intoxications. The specialty of care related to this situation is mostly clinical. With higher female population, the key therapeutic class consists of systemic antibiotics. Falls are the main problem related to it. Situation 3 is characterized by intoxications. The specialty

of care related to this situation is mostly clinical. With higher female population, the key therapeutic class consists of other drugs or unspecified. Situation 4 is characterized by a higher proportion of intoxications, and concentration of mental and behavioral disorders. The specialties of care related to this situation are mostly clinical and psychiatric. With a larger male population, lower mean age, longer mean length of hospital stay, the key therapeutic class consists of psychotropic, psychoactive, antiepileptic, sedative, hypnotic and antiparkinsonian drugs.

The method also enabled us to identify the main problems related to drug intoxications and adverse events. Injuries and falls were identified as the main problems related to these events, which is compatible to the results attained by Hamra et al.⁶. The authors suggest that patients on medication have a higher risk of suffering fall-related fractures.

Trauma was related to primary diagnoses and drug intoxication or adverse effects to secondary diagnoses, which corresponds to situation 1. The drugs most involved with such hospitalizations were non-opioid analgesic, antipyretic and antirheumatic drugs, accounting for almost 45% of cases. In this situation, since intoxications or adverse effects were not the main reason for hospital admission, part of these cases may have taken place in the hospital environment. Although the study database does not allow us to infer the exact number of such events, we believe that analysis of situation 1 may indicate some of the problems caused by drugs to elderly patients in the hospital environment. We should thus review the use of non-opioid analgesic, antipyretic and antirheumatic drugs in elderly patients with trauma to avoid problems resulting from use of multiple drugs, prescription errors and iatrogenic effects.

In the case of falls, intoxication and/or adverse drug effects were associated with primary diagnoses and falls to secondary diagnoses, which corresponds to situation 2. The key therapeutic classes involved in these hospital admissions were systemic

antibiotics, challenging studies that point out psychotropic drugs as the main drugs involved in these events^{5,62-64}.

The relation between falls and antibiotics was also referred to by Lessa et al.³⁷ when studying hospital admissions of children under one year old resulting from drug intoxications and adverse events. A possible explanation may come from the study recently published by Wright et al.⁶⁵, which says that for those elderly patients treated with calcium-channel blockers, the use of antibiotics like erythromycin or clarithromycin was associated to an increased risk of hypotension or shock and required hospitalization.

The present study shares the limitations of those studies based on secondary data coming from SIH-SUS³⁵. In the present study, particularly, the large use of digits 8 (others) and 9 (unspecified) for the fourth digit of codes in chapter 19 (T36 to T50) and chapter 20 (Y40 to Y57) prevented detailing 57% of the drugs within a given therapeutic class. The different methods adopted in the several existing studies on hospitalization to measure hospital admissions resulting from adverse drug reactions¹⁶⁻²⁵ and adverse drug-related events²⁶⁻²⁹ compromise comparisons with the results of this study. Some of these studies^{16,18} considered as adverse reactions those cases that in their primary diagnosis ICD-10 codes included the words "induced by" or "due to" drugs, and left details of the therapeutic class with

codes described in this study for secondary diagnosis. Since we know that information on secondary diagnosis is not always thorough, adverse effect cases may have been underestimated. Despite the method adopted with separation into 4 situations, among the cases in situation 1, we were not able to tell apart the intoxication or adverse effect present at the moment of hospital admission from those in which these events occurred during hospitalization. However, different from the work of Rozenfeld³⁶, it was possible for us to get a sample closer to the events that take place in the hospital environment, which enabled us to suggest more surveillance in the utilization of pain killers. Stausberg et al.³² used a similar procedure by considering the secondary diagnosis as a "proxy" for adverse reactions acquired in the hospital.

Conclusion

The results found reflect the growing trend of problems associated with utilization of drugs by the elderly. We observed that the consumption profile alone is not sufficient to explain the concentrations of cases in the key therapeutic classes. In search for causes, we suggest the adoption of more effective pharmaceutical surveillance programs capable of monitoring the different stages of drug use: prescribing, dispensing, marketing, administration and compliance to treatment.

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