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Medicine poisoning mortality trend by gender and age group, São Paulo State, Brazil, 1996-2012

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Abstract *This study looked into mortality due to medicinal drug poisoning by age, gender and intent among the population of the state of São Paulo. The adjusted time sequence of mortality due to drug poisoning was developed based on data available in the DATASUS Mortality Data System for 1996 to 2012. We checked the variables for magnitude and trends. We found an increase in adjusted mortality starting in 2005, and more so as of 2009, confirmed by a 95% CI for the average annual rate of change. (AARC) We did not find the same trend in overall mortality in the state (AARC = -0.22%, 95% CI = -1.12 - 0.69) for specific, external cause mortality (AARC = -3.14%, 95% CI = -4.75 - -1.49) and for mortality due to accidental drug poisoning (AARC=+9,76%, 95% IC = -12.16 – 37.14). The largest increase was found in intentional self-poisoning with medicinal drugs (AARC = +10.64%, 95% CI = 6.92 - 14.40), and among the younger subjects (largest magnitude). The trend in mortality due to drug poisoning in the State of São Paulo, the importance of intent and mortality among the younger population reiterate the need to implement control measures.*

Key words *Mortality, Intoxication, Drugs*

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Introduction

Medicinal drugs are essential for healthcare services[1], and are associated with prophylactic, curative, palliative and diagnostic purposes[2]. The widespread use of medicines fuels the emergency of problems related to them[3]. Between 1986 and 2006, SINITOX, the National System for Toxic-Pharmacology Information, recorded 1,220,987 cases of poisoning, and 7,597 deaths (0.06%). In 1994, medicinal drugs took over as the leading cause of poisoning among the toxic agents investigated, accounting for 24.5% of all cases recorded in the country[2]. Consequently, drug poisoning has become a public health challenge, as is the case in other developed and emerging nations[3,4].

Deaths due to drug poisoning are considered a public health issue[5]. Such deaths are primarily the result of intentional (homicide or suicide)[6,7] and accidental (abuse and/or associations, non-medical/recreational use of prescription drugs) misuse[8]. Mortality due to drug poisoning may be a reflection of the pattern of use of medication, and to social phenomena such as inequality, poverty and unemployment[2]. Studies describing fatal intentional poisoning with drugs may help plan and implement programs to prevent such incidents, and also call the attention of healthcare professionals to the importance of the rational use of drugs[9].

Despite the importance of this theme, in Brazil there is a dearth of studies on drug poisoning deaths based on vital statistics[2]. Published studies are based on data provided by SINITOX and state or city toxicology center data (CIAT)[3,10,11]. The aim of this study is to provide an assessment of the magnitude and the trend for deaths due to drug poisoning in the state of São Paulo, Brazil between 1996 and 2012, and analyze the differences in mortality by gender, age group and intent, and include a description of the drugs involved.

Methods

Study design and population

This is an exploratory, time series ecological study. The state of São Paulo has the second highest HDI (Human Development Index) in Brazil[12]. Twenty percent of the nation's population lives in the state[13,14]. According to data from the 2008 National Sample-Based Household Survey - Access and Use of Services, Health Condition, Risk Factors and Health Protection, 72.7% of the population in the State had been to a doctor in the 12 months prior to the survey interview. This same percentage is only 67.7% nation-wide[15]. Data on access to services suggests that access is better in the state of Sao Paulo than elsewhere in the country.

Data regarding deaths due to medicinal drug poisoning in the state comes from the SIM/SUS (Unified Healthcare System Mortality Data System) for 1996 - 2012. Data were stratified by age group and sex (the word used for gender in the DATASUS database). In this study, we use gender, as making this a cross-sectional dimension of healthcare investigation means betting on the possibility that evidence will emerge of inequality between men and women due to gender biases, capable of impacting public policies focused on reducing such inequalities[14].

This study was approved by the University of São Paulo School of Public Health Ethics Committee.

Data Gathering

This time series of death data starts in 1996, when ICD-10 (10th Review of the International Classification of Diseases and Health-Related Problems). 2012 is the last year because it is the last year for which SIM had published data at the time of this study. For analysis purposes we selected and stratified deaths due to drug poisoning, where records show as the basic cause of death the following ICD-10 codes: X40-X44 (accidental poisoning); X60-X64 (intentional self-poisoning - suicide); X85 (aggression using drugs, medicines or other biological substances); Y10-Y14 (poisoning due to unknown cause)[16].

Data analysis

Mortality coefficients were calculated using official population data for the state of São Paulo, taken from data published by the IBGE Fundation[13]. This data is estimated each year based on general population censuses. Annual mortality coefficients are calculated per 1,000,000 inhabitants for each year. Population data in the state is stratified by age as follows: ≤5 years, 5 - 9 years, 10 - 14 years, 15 - 19 years, 20 - 29 years, 30 - 39 years, 40 - 49 years, 50 - 59 years, 60 - 69 years, ≥70 years.

Data on the global population was researched to adjust mortality coefficients due to drug poisoning using the direct method[17] for gender and

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age. We designed a time series running from 1996 through 2012, based on estimates of the adjusted coefficients for mortality due to drug poisoning[18]. Non-adjusted annual coefficients for mortality due to accidental drug poisoning (X40-X44), intentional self-poisoning / suicide (X60-X64) and undetermined intent (Y10-Y14) were estimated to provide a subsidy for the analysis of intent to poison. We analyzed trends over the period, differences by gender and the contribution of each intent to mortality.

Annual coefficients of mortality due to drug poisoning were also estimated by age group. The trend in each age group was analyzed over the study period, bearing in mind also differences in distribution by gender. The magnitude of mortality by age group and gender was also assessed.

We looked at data on total deaths and deaths due to external causes in the state of São Paulo over the study period, and used this data to estimate mortality coefficients.

We calculated the average annual rate of change (AARC) to check trends for all of the mortality coefficients estimated[19].

Data on deaths due to drug poisoning was stratified to subsidize the analysis of the drugs involved in the deaths. Stratification followed the following criteria: X40, X60 and Y10 correspond to deaths due to analgesic, antipyretic, antirheumatic (non-opioid) drug poisoning X41, X61 and Y11 correspond to deaths due to anticonvulsive, sedative, hypnotic, anti-Parkinson and psychotropic drug poisoning; X42, X62 and Y12 correspond to deaths due to narcotic and psychodysleptic drug poisoning; X43, X63 and Y13 correspond to deaths due to poisoning by autonomous central nervous system drugs; X44, X64 and Y14 correspond to deaths due to unspecified drug poisoning.

We used Excel®2013 to calculate mortality coefficients, adjustments to mortality due to drug poisoning, AARC and the frequency at which drug groups are involved in deaths. To analyze trends, we used Stata10.0 (Stata Corporation, College Station, Texas, 2007) to calculate the 95% Confidence Intervals (95% CI) for the AARC.

Results

Between 1996 and 2012, 4,170,358 deaths were recorded in the state of São Paulo. Of these, 0.04% were due to drug poisoning (1,760 cases). External causes accounted for 491,040 of the deaths, 0.4% of which were due to drug poisoning. Of these, 58.8% were males. In 0.3% of the cases age was not reported, all of them male.

Figure 1 shows adjusted data for death due to drug poisoning for the State of São Paulo between 1996 and 2012. Mortality rates were stable through 2004, but started to go up in 2005. The largest growth was in 2009. An analysis of the 95% CI for the average annual rate of change (AARC) in adjusted mortality due to drug poisoning shows a growing trend (AARC = +8.2% with a 95% CI of 0.6 - 16.4).

Table 1 shows the variation in all-cause mortality and specific mortality from external causes in the state of São Paulo between 1997 and 2012. Analysis of the AARC and 95% CI suggest that all-cause mortality remained stationary over the study period (AARC = -0.22%, 95% CI = -1.12 - 0.69), while external cause mortality declined (AARC = -3.14%, 95% CI = -4.75 - -1.49). This means that the trend mortality due to drug poisoning is different from that found for overall mortality (growing vs. constant), and from mortality due to external causes (decreasing) in this period.

Table 2 shows the AARC and 95% CI for mortality due to accidental, intentional and undetermined drug poisoning in the State of São Paulo over the study period. Although the AARC suggests an increase in mortality due to accidental drug poisoning in both genders and the entire study population, the confidence intervals 995% IC calculated for the AARC suggest that the trend in mortality due to accidental drug poisoning over the period is actually stable (AARC = 9.76%, 95% CI = -12.16 - 37.14). We found higher rates of accidental mortality among males in each year of the study period (Table 2). Most of the deaths due to drug poisoning among males were classified as accidental and involved the use of narcotics and psychodysleptics (ICD-10 X42), corresponding to 27.7% of all of the deaths we investigated in this gender.

If we look at the AARC for mortality due to intentional drug poisoning (suicide) in the state of São Paulo over this period shows a growing trend (AARC = 10.64%, 95% CI = 6.92 - 14.49) in both genders, although it is slightly higher among males. We found a higher rate of intentional mortality among females in all years except 1997, 2005, 2008, 2009, 2011 and 2012 (Table 2). Among females, most deaths due to drug poisoning were classified as intentional and the result of anti-convulsives, sedatives, hypnotics, anti-parkinson drugs and psychotropics (ICD-10 X61).

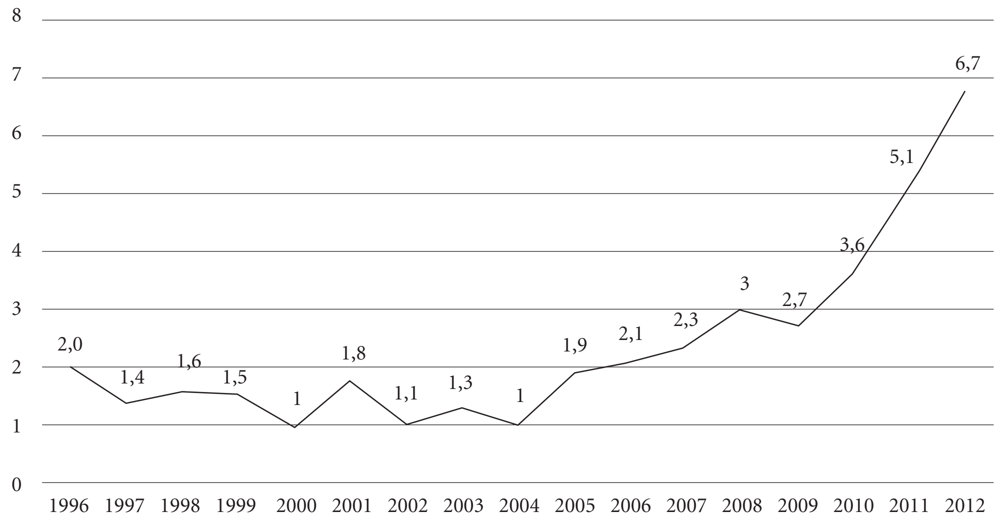

Figure 1. Death due to medicinal drug poisoning in the state of São Paulo (1992-2012): adjusted mortality coefficients (annually per 1,000,000 inhabitants).

Source: Mortality Information System and AHMAD et al. (2001) - world population.

Note: The average annual rate of change (AARC) in adjusted mortality due to drug poisoning was +8.2%, with a 95% CI of 0.6 - 16.4, suggesting it is on the rise.

These amounted to 28.9% of the deaths we investigated for this gender.

The AARC for all mortality due to drug poisoning of undetermined cause in the State of São Paulo grew among both genders over this period, slightly more among females than males. The 95% CI confirmed this upwards trend. Mortality due to drug poisoning of undetermined intent was higher among males in all years except 1997, 2002, 2003, 2004, 2005, 2007 and 2008.

If we consider total variation by intent (Table 2), we find that intentional drug poisoning (suicide) grew faster than other types over the study period (+10.64%).

Figure 2 shows mortality due to drug poisoning rates by age group. We see an increase in mortality among adolescents (15-19) and adults (20-40) starting in 2009. The largest increases were found among adolescents (15-19) and young adults (20-29), followed by adults (30-40) and the elderly (over 70).

Stratification of cases in terms of the drugs involved in these deaths shows a gender difference (Table 3). Among males, narcotics and psychodysleptics accounted for 40.5% of the deaths due to drug poisoning (ICD-10X42, X62 and Y12), while the use of unspecified drugs accounted for 35.7% of the cases (ICD-10 X44. X64 and Y14). Among females, 45.6% of the deaths due to drug poisoning were unspecified in terms of the drugs involved (ICD-10 X44, X64 and Y14). In 40.4% of the cases, the drugs involved were anticonvulsants, sedatives, hypnotics, anti-Parkinson and psychotropics (ICD-10 X44, X64 and Y14).

Discussion

Estimates of mortality based on secondary death data showed an increasing trend in adjusted mortality due to drug poisoning in the state of São Paulo, starting in 2005. This is different from the trend in all-cause mortality and external cause mortality. These findings agree with a study using the same data source to describe mortality due to drug poisoning in Brazil between 1996 and 2005[2]. The authors found a 17.8% rate of increase in drug poisoning mortality, and 8.7% increase in all-cause mortality[15]. However, comparing this data to those of the present study must be made with reservations, as the method used by those authors to calculate AARC is different from the one used in the present study, as is the population (all of Brazil) and the period (1996 - 2005).

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Table 1. Overall and specific external cause mortality. State of São Paulo, 1997 - 2012.

Year	Overall mortality (per 1,000 inhabitants)	Specific external cause mortality (per 10,000 inhabitants)
1997	6.7	9.4
1998	6.6	9.1
1999	6.6	9.5
2000	6.6	9.3
2001	6.3	9.0
2002	6.2	8.6
2003	6.2	8.1
2004	6.1	7.4
2005	5.8	6.8
2006	5.9	6.1
2007	6.1	5.8
2008	6.1	5.8
2009	6.2	5.8
2010	6.4	5.9
2011	6.5	5.8
2012	6.5	6.0
AARC	-0.22%	-3.14%
(95% CI)	(-1.12 – 0.69)	(-4.75 – -1.49)

Sources of data for calculations: DATASUS and IBGE.

Note: While the AARC for mortality is negative, the 95% CI suggests an downwards trend in specific external cause mortality (negative values), and stable for overall mortality (zero is part of the interval).

According to DATASUS, in 2011 the content of Death Statements (DS) changed to include more detail. The SIM CGIAE, the Agency that Coordinates Epidemiological Data and Analyses, points out that the more detailed forms led to a drop in poorly defined cause of death or death due to undetermined intent. This, in turn, led to an increase in other causes of death; the decrease in deaths due to undetermined intent resulted in an increase in the number of cases considered accidental or intentional. It is important to note that DS forms changed in 2011, and that both forms were used simultaneously for that entire year. The new form could partly explain the increase in mortality due to drug poisoning as of 2011. However, according to the SIM CGIAE, the state of São Paulo used the new form in only 58% of the deaths in 2011, a percentage the coordinators consider to be small[20]. We also found that the trend in mortality due to drug poisoning differs from the trend for all-cause mortality and specific mortality for external causes, reinforcing the hypothesis of growth in adjusted mortality due to drug poisoning in the state of São Paulo over the study period.

ICD-10 categories X42, X62 and Y12 codify circumstances involving the use of hallucinogenics in general, and is not restricted to medicinal products. This results in inaccuracy regarding the number of drug poisonings, which may actually be smaller, and inaccurate numbers for medicinal drug poisonings, which could be smaller. This should be taken into account, especially when considering deaths due to drug poisoning among males, where these codes were more significant.

On the other hand, data on drug poisoning refers primarily to situations where exposure and outcome come close together in time (acute poisoning). Therefore, these estimates may be low by not including cases of continued drug use. Even cases of acute poisoning may occur without a diagnosis of poisoning as the cause of death, as often the poisoning is unclear, there is no confirmed diagnosis and patients receive only symptomatic treatment[21]. Many drugs and poisons produce no characteristic pathology, and the symptoms of poisoning or overdose are often non-specific[22]. For this reason, deaths due to poisoning could be mistakenly assigned to other causes.

This incidence refers to the speed at which new events happen within a given population, bearing in mind the time during which individuals are free of the problem or, in other words, at risk of developing it[23]. Therefore, for calculating the incidence of a problem we use the number of new cases over a certain period of time within a specific population at risk of developing the problem. Considering this definition, mortality due to drug poisoning does not correspond to the incidence of poisoning, as we do not know the number of people exposed to drugs (at risk of poisoning), necessary for the correct calculation. We used the total population instead, which shows that an estimate of incidence, had it been possible, would have resulted in higher values for these coefficients than those found. Other studies on the theme also used the total population[2].

We found differences in the drugs responsible for the death of males and females. We point out the importance of studies showing the difference in health profiles between men and women, aiming to find possible variations in gender-related perceptions and practices in understanding health-disease processes[24].

The results show that suicides are relevant among the deaths selected for this study. We found that deaths due intentional drug poisoning were the largest contributors to the increase

Table 2. Death due to medicinal drug poisoning by intent (accidental, suicide and undetermined). State of São Paulo, 1996 - 2012.

Year	Mortality due to accidental drug poisoning (per 1,000,000 inhabitants/ year)			Death due to intentional drug self-poisoning (suicide) (per 1,000,000 inhabitants/ year)			Death due to drug poisoning by intent (accidental, suicide and undertermined). (per 1,000,000 inhabitants/ year)		
	F	M	Total	F	M	Total	F	M	Total
1996	0.64	1.01	0.82	0.81	0.71	0.76	0.17	0.65	0.41
1997	0.45	1.23	0.83	0.34	0.58	0.46	0.17	0.12	0.14
1998	0.39	0.81	0.60	0.73	0.58	0.65	0.28	0.40	0.34
1999	0.44	0.79	0.61	0.66	0.62	0.64	0.28	0.45	0.36
2000	0.05	0.11	0.08	0.79	0.39	0.59	0.21	0.50	0.35
2001	0.10	0.43	0.27	1.20	0.76	0.98	0.57	0.65	0.61
2002	0.05	0.16	0.10	0.72	0.53	0.63	0.41	0.37	0.39
2003	0.00	0.05	0.03	0.91	0.53	0.72	0.76	0.26	0.52
2004	0.00	0.00	0.00	0.70	0.52	0.61	0.50	0.42	0.46
2005	0.10	0.25	0.17	0.82	0.86	0.84	1.07	0.81	0.94
2006	0.19	0.70	0.44	1.58	1.14	1.36	0.33	0.60	0.46
2007	0.19	0.49	0.34	1.50	1.48	1.49	0.80	0.69	0.74
2008	0.48	1.20	0.83	1.57	2.50	2.02	0.62	0.60	0.61
2009	0.28	1.04	0.65	1.74	1.79	1.76	0.61	0.65	0.63
2010	0.47	2.09	1.26	2.03	1.99	2.01	0.52	1.10	0.80
2011	0.75	3.80	2.24	2.20	2.57	2.38	0.84	1.33	1.08
2012	0.98	6.38	3.60	2.79	3.14	2.96	0.74	1.32	1.03
AARC (95% CI)	+3.84% (-12.25 – 22.88)	+11.87% (-11.05 – 40.71)	+9.76% (-12.16 – 37.14)	+10.11% (7.52 – 12.77)	+11.35% (5.32 – 17.72)	+10.64% (6.92 – 14.49)	+9.15% (5.45 – 12.97)	+8.76% (4.56 – 13.13)	+8.84% (6.72 – 11.00)

Sources of data for calculations: DATASUS and IBGE.

Note: The AARC is positive for mortality due to accidental, intentional and undetermined drug poisoning, however the 95% CI suggests an upwards trend for intentional and undetermined mortality due to drug poisoning (values higher than zero), and stable for accidental mortality (zero is part of the interval).

F = Female. M = Male.

in mortality during the study period. However, we should point out that the coefficients of mortality due to drug poisoning of undetermined intent were also significant and growing.

The availability of information that is based on solid and reliable data is key for objective analysis of the health situation of any location, and for making evidence-based decisions and program healthcare actions[25]. The category of undetermined events in the data on mortality was classified as such whenever the intent was unknown (accidental or intentional). It is important to realize that knowing the actual cause could increase the number of suicides and accidental deaths[26].

Suicide is a legal term, not a diagnosis[27]. Legal and religious issues involved in intentional poisoning could favor their classification as another intent. Furthermore, a study conducted in England between 1990 and 2005 shows that there are time trends in the verdicts of examiners regarding possible suicides, influenced by an increase in the rulings of accidental or undefined death, especially in cases involving poisoning[28]. Another study found that most of the deaths assigned to substance disorders are considered accidental[29]. These facts point to the possibility that some of the deaths classified as accidental were not, in fact, accidental, resulting in under-reporting and under-estimating the magnitude of mortality due to intentional self-poisoning with drugs.

Higher mortality coefficients were found among adolescents and young adults. Suicide is one of the three leading causes of death among the economically more productive population[30]. One study found that the population groups most susceptible to suicide in Brazil are young

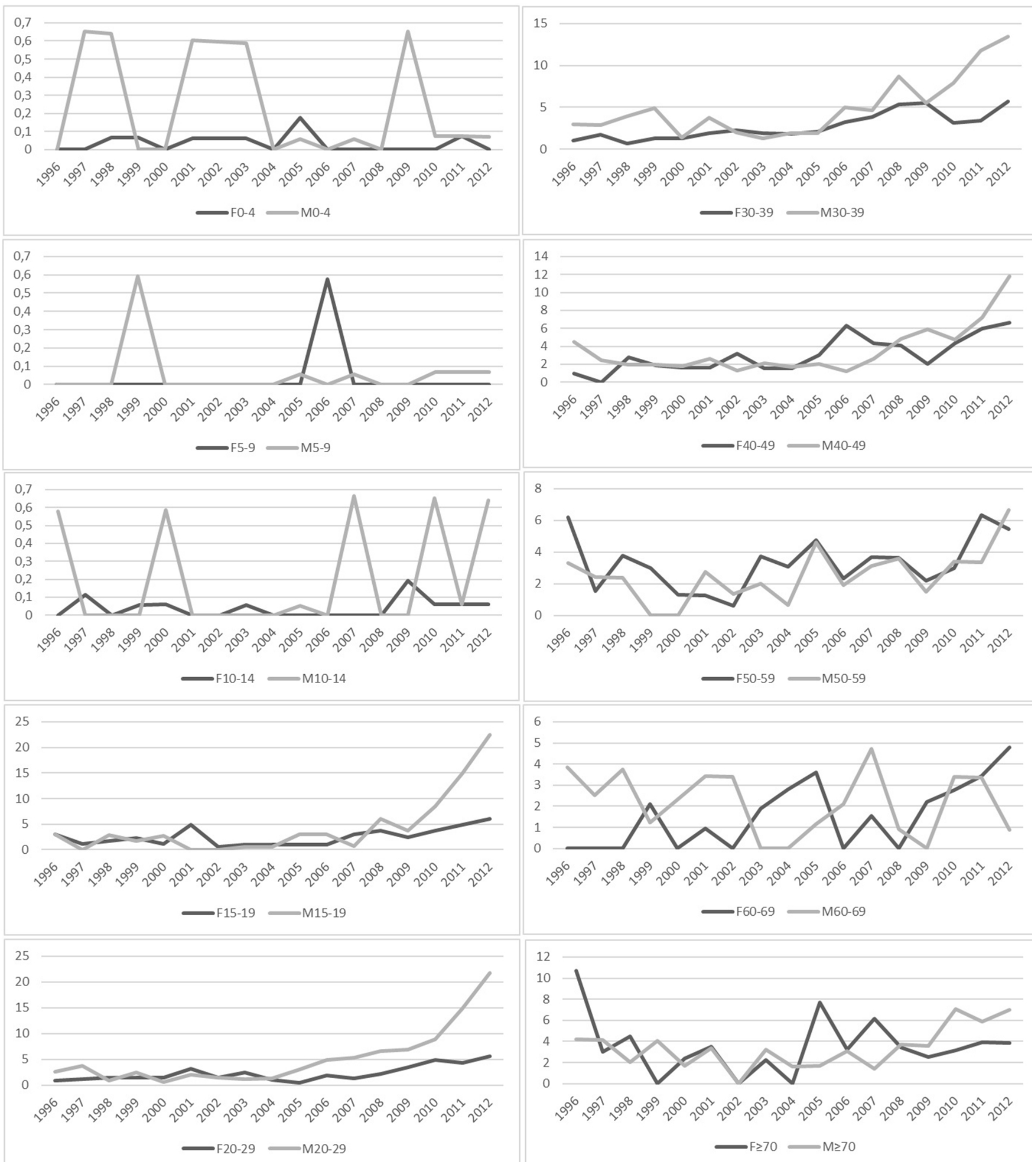

Figure 2. Mortality due to medicinal drug poisoning: mortality coefficients by age group (annual per 1,000,000 inhabitants). State of São Paulo, 1996 - 2012.

Note: F = Female; M = Male.
Source: Mortality Information System.

people living in large cities, the native Indians of the middle-west and north, and rural workers in the interior of Rio Grande do Sul[31]. Different results have been found in other contexts. According to a study conducted in Brazil[32], smaller cities and native Indian communities show a standardized death by suicide rate that is higher than larger cities. Higher suicide rates in smaller cities have also been found in Finland[33]. One of the hypotheses raised is that the differences in mortality due to suicide may reflect the aggregate risk of a concentration of people at higher risk (composition effect0, and/or the influence of economic, social and cultural aspects on mental health (context effect)[32]. The numbers for Brazil should, therefore, be analyzed with caution, as the number of suicides may be under-reported[31,34] and rates vary by region[31].

Table 3. Deaths grouped by ICD-10 code, number and frequency State of São Paulo, 1996 - 2012.

Year	X40+X60+Y10			X41+X61+Y11			X42+X62+Y12			X43+X63+Y13			X44+X64+Y14		
	F	M	T	F	M	T	F	M	T	F	M	T	F	M	T
1996	0	1	1	7	4	11	0	4	4	0	0	0	21	31	52
1997	0	0	0	3	5	8	2	11	13	0	0	0	12	17	29
1998	1	0	1	10	5	15	1	1	2	0	1	1	13	24	37
1999	0	0	0	8	5	13	0	4	4	0	1	1	17	23	40
2000	1	0	1	7	5	12	2	2	4	0	0	0	10	11	21
2001	0	0	0	19	5	24	1	4	5	1	0	1	15	25	40
2002	1	0	1	11	7	18	0	3	3	1	0	1	10	10	20
2003	0	0	0	7	7	14	1	1	2	0	0	0	25	8	33
2004	0	0	0	11	10	21	0	0	0	0	0	0	13	8	21
2005	0	0	0	11	13	24	1	9	10	0	1	1	29	15	44
2006	0	0	0	20	13	33	1	13	14	0	0	0	23	23	46
2007	0	3	3	22	15	37	4	18	22	4	2	6	23	16	39
2008	2	0	2	24	16	40	8	35	43	3	1	4	19	34	53
2009	3	4	7	24	21	45	8	27	35	1	1	2	20	17	37
2010	0	1	1	20	19	39	12	44	56	1	1	2	31	39	70
2011	2	1	3	41	21	62	16	98	114	0	2	2	22	34	56
2012	2	3	5	47	45	92	21	139	160	0	4	4	27	30	57
Total	12	13	25	292	216	508	78	413	491	11	14	25	330	365	695
(%)	(2)	(1)	(1.5)	(40)	(21)	(29)	(11)	(41)	(28)	(1)	(1)	(1.5)	(46)	(36)	(40)

Note: F = Female; M = Male; T = Total.

The high frequency of deaths among both genders, where the drug involved is unknown (X44, X64 and Y14), reported in this study points to a lack of suitable description of the agents involved in the death. Furthermore, the other categories of the ICD-10 do not allow looking at anything other than the group of drugs described. Among females, the most important drugs for the deaths in this study were anti-convulsants, sedatives, hypnotics, anti-Parkinson drugs and psychotropics (ICD-10 X41, X61 and Y11), but there is no way to get a more stratified view of the importance of each type of drug. Using the ICD to classify ATC, often used in studies on drug use, favors the suitable description of the drug involved in these cases.

Statistics on mortality have been, and still are an important source of data to understand the epidemiological profile of a given area, analyze trends, indicate priorities and assess programs, among other purposes, helping develop indicators and plan healthcare actions[35]. Educational and regulatory measures should be implemented for continued awareness of healthcare professionals, thus ensuring that the data generated is complete and of as good a quality as possible, and that they are committed to following their patients and correctly using drugs, providing suitable prescriptions and combining drug and non-drug based therapies. Such measures would contribute to improving the impact of drugs on healthcare and notification of poisoning as an important health issue.

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Collaborations

JMF Oliveira designed and planned the study, gathered data, ran calculations and designed figures and tables, analyzed and interpreted the data and drafted the final version. GA Wagner and NS Romano-Lieber planned the study, contributed to a critical review of the content and helped approve the final version of the manuscript. JLF Antunes planned the study, ran calculations and data analysis, contributed to a critical review of the content, and helped approve the final version of the manuscript.

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