

RESEARCH ARTICLE

Fatal Intoxications in the North of Portugal: 12 Years of Retrospective Analysis

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Abstract: Background: Fatal intoxications are a topic of great relevance in today's society. They typically occur by accidental or voluntary ingestion, but its characterization by a forensic perspective was not fully explored.

Objective: This study retrospectively reviews fatal intoxication cases autopsied at the northern forensic medicine services of Portugal, between 2001 and 2013.

Method: For this purpose, we analyzed *postmortem* forensic medical reports with positive qualitative analysis for xenobiotics.

Results: A total of 27,778 autopsy reports were analyzed, of which 1,269 cases fulfilled the selection criteria, representing 4.6% of total number of individuals autopsied during the period under analysis. Men were involved in most of the cases (73.8%) and most individuals were adults with ages between 36 and 65 years old (57.0%). The highest incidences were medicines (22.9%) and alcohol (15.8%), followed by their association. Cases of fatal intoxications involving opioids come on fifth place (5.8%) namely due to accidental overdoses. Moreover, intoxications appeared as the leading cause of death in reports concerning accidental etiology, with drugs and alcohol associations having a great expression.

Conclusion: Due to morbidity and relevant number of fatal cases, risk prevention measures, such as public health policies should be implemented to reduce the number of intoxications.

Keywords: Alcohol, fatal intoxications, forensic autopsy, medicines, xenobiotics.

INTRODUCTION

Intoxications represent a significant public health threat [1]. In the United States of America, intoxications appear as the second leading cause of injury-related death, only surpassed by motor vehicle collisions [2]. The World Health Organization (WHO) considered poisoning amongst the top 15 causes of death for individuals ages 5-44 years old and estimated that 99% of the intoxication related fatalities occur in developing countries [1, 3]. According to the 2013 Annual Report of the American Association of Poison Control Center, 2,113 cases of fatal intoxications were registered. Of these, 1,710 were caused by medicines and 40.9% were opioids positive [2]. Opioids have a great role in fatal

intoxications in Europe, as reported in the European Report about Drugs [4]. In 2013, a decrease of heroin consumption was observed, but several other opioids showed increasing use, such as methadone [4].

Between 2001 and 2011 the Portuguese Center for Intoxication Information (CIAV) had received 77 calls per day and registered 8,973 intoxication cases in adolescents and 12,621 in adults [5]. The substances that had a great role in intoxications cases were medicines and drugs of abuse.

In Portugal, according to the law n°45/2004 of August 19th, when there is a suspicion of violent death (e.g., intoxications), the Public Prosecutor Office requests a forensic autopsy to the National Institute of Legal Medicine and Forensic Sciences (INMLCF) [6, 7]. However, until now only one study published in 1989, retrospectively analyzed substances detected in fatal intoxications cases in Portugal [8]. The goal of this work is to uncover this reality about fatal intoxications in Portugal in a forensic perspective.

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All the positive cases for xenobiotics in autopsies performed by the North Branch of the INMLCF between 2001 and 2013 were reviewed and intoxications were characterized according to different parameters (*i.e.*, age, gender, marital status, professional activity, circumstances of death and forensic findings).

METHODOLOGY

Cases selection

A retrospective study was conducted based on the analysis of forensic reports related to intoxication cases autopsied between January 2001 and December 2013 in the northern services of INMLCF of Portugal. The only criterion for case selection was the *postmortem* analysis positive for the presence of xenobiotic(s) in the body. Labor and traffic accident related deaths that occurred under influence of xenobiotics were considered as accidental deaths, since that was how they were classified in the forensic reports. For this study, labor and traffic accident related deaths under the influence of alcohol and psychotropic drugs were not considered, since in most of these cases full toxicological analysis are not performed. The selected cases ($n=1,269$) represented 4.6% of the total of autopsies performed in the region during this period. Data collection was made by the same investigator, to guarantee data repeatability and reproducibility.

Intoxications were characterized according to different parameters: age and gender distribution, professional activity, circumstances of death and forensic findings.

Research was approved by the Council of Ethics of the Hospital de São João Center/Faculty of Medicine, University of Porto. According to the current Portuguese Law, for medico-legal autopsies, and following the ethical principles of Declaration of Helsinki, no informed written or oral consent of the victim family is required for scientific research [5, 9]. Therefore, it is foreseen by the law to obtain data regarding forensic cases.

Statistical analyses were performed using the IBM® SPSS® (Statistical Package for Social Sciences) Statistics version 21 software, the Microsoft Windows Excel Office 2010 and Prism GraphPad version 6. A descriptive study was performed.

RESULTS

In the first years of analysis, the percentage of cases that fulfilled the selection criteria was well below 1% due the lack of information about all the autopsied cases. It was only in 2008 that an increase in the number of cases for the presence of xenobiotics was recorded, decreasing again in 2011, and starting to increase by the last years of this study, with an outstanding value of 15.5% of all the *postmortem* toxicological analysis performed being positive for the presence of xenobiotics in the year of 2013 (Fig. 1).

Characterization of Victim

Analyzing the gender distribution of victims, the highest number of intoxication cases were males ($n=936$; 73.8%; females $n=333$; 26.2%).

The cases were divided into five age groups according to the WHO classification: 0-12 for children, 13-18 adolescents, 19-25 young adults, 26-35 adults, 36-65 middle aged adults and, more than 65, elderlies [10]. Of all cases, 0.63% was children (mostly accidental intoxications), 1.50% adolescents, 4.41% young adults, 16.31% adults, 56.97% middle-aged adults and 19.94% elderlies (Fig. 2).

Twenty-one victims had no information about marital status. Most of intoxication victims were married (467 cases, 36.80%), followed by single (453 victims, 35.70%) including 75 cases attributed to children, adolescents and young adults. Divorced and widowers corresponded to 139 (10.95%) and 114 (8.98%) of the total intoxications cases, respectively.

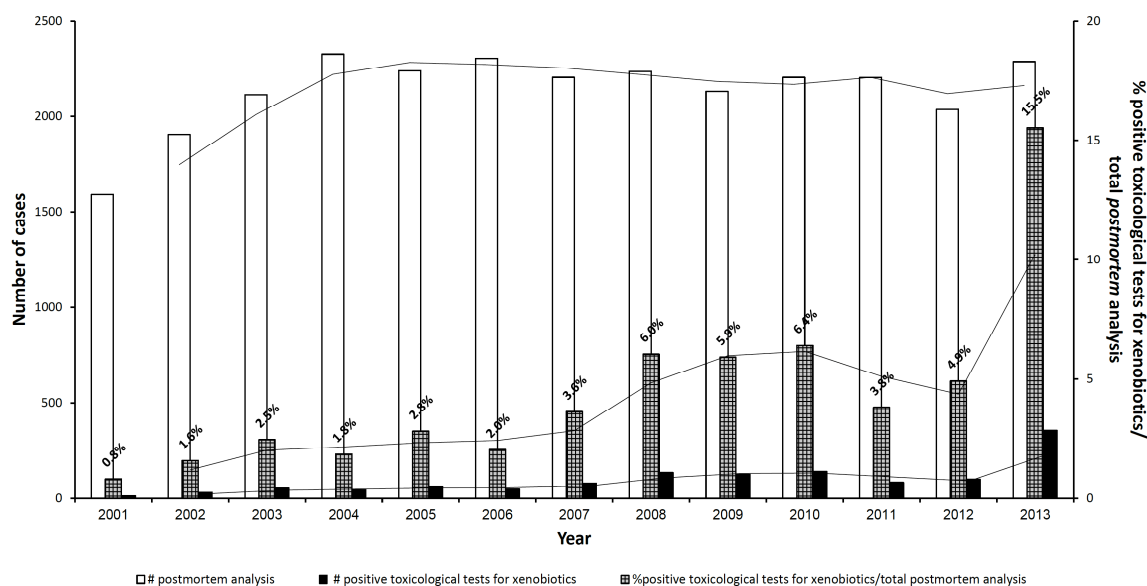


Fig. (1) Results of toxicological *postmortem* analysis.

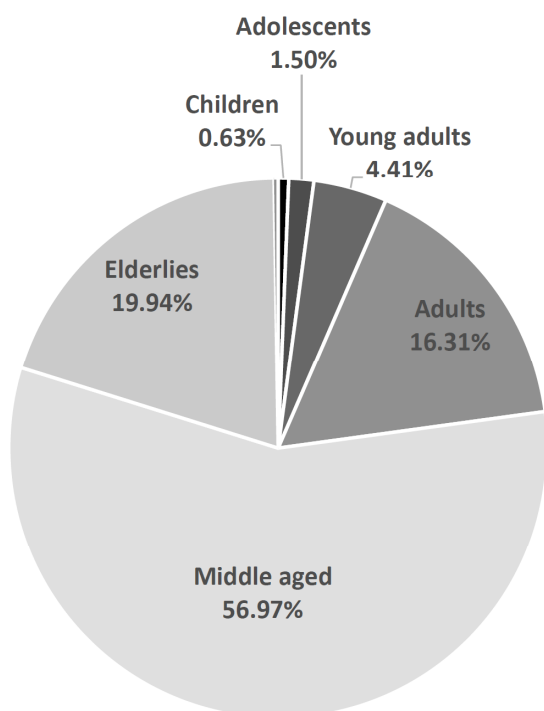


Fig. (2). Age distribution regarding fatal intoxication cases.

From total cases analyzed, 452 victims (35.62%) had no information about their occupation status. Unemployed, employed and retired persons were respectively 180 (14.18%), 344 (27.11%) and 220 (17.34%) of the total number of cases. The minor percentage of occupations were priests (2 cases, 0.39%), housewives (27 cases, 2.13%), students (32 cases, 2.52%), prisoners (7 cases, 0.55%) and others (5 cases, 0.39%). On the students group there was predominance of adolescents with 14 cases (43.75% of total student's cases), followed by graduate students with 10 cases (31.25%) and postgraduate students (8 cases, 25%).

Characterization of Fatal Cases

According to the etiology, intoxications may be intentional, when someone is intoxicated on purpose; accidental, when is a result of an accident, error, carelessness, or an unexpected situation; or homicides, when the intention is to cause the death of other person [5, 11-13]. When a fatal intoxication occurs, it is important to define the medico-legal etiology of the death (*i.e.* suicide, homicide and accident) and forensic toxicology has a great role on these cases [14]. From all cases studied that presented positive toxicological results, 482 cases were accidental deaths (37.98%), followed by suicide (347 cases, 27.34%), natural deaths (253, 19.93%) and homicide (13 cases, 1.02%). 174 cases (13.71%) had no information about the medico-legal etiology.

Suicide Cases

More than 75% of suicide cases were attributed to two major death causes: intoxications (183 cases, 52.73%) and hanging (89 cases, 25.65%). The following causes were trauma by different factors, such as firearm or as a consequence of intoxication, with a total of (47 cases, 13.54%) of the situations. Analyzing the distribution of the forensic death etiology throughout the years (Fig. 3), it is remarkable the relevance that suicide had acquired over the second half period under study. In fact, 85.59% of all suicide cases were registered between 2007 and 2013. Within 2013, 105 suicide cases were registered (30.26% of the total number of suicides), representing more than threefold when compared to the previous 6 years.

Homicide Cases

Between 2001 and 2004 and in the years 2006, 2007 and 2011, no homicide casualties were reported. In the years 2005, 2009 and 2012, one homicide situation was reported in each year. In 2010, two situations were reported and in 2008 three cases occurred. The highest number of homicides was

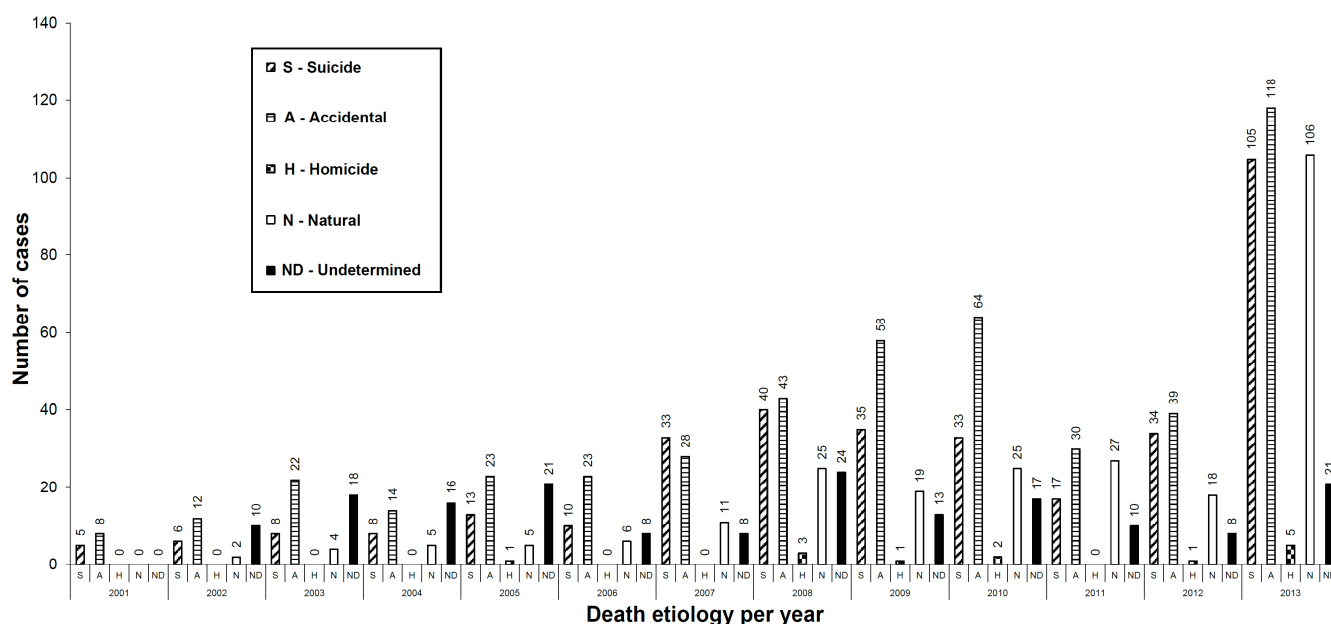


Fig. (3). Death etiology of intoxication cases.

observed in the year of 2013, with five cases (corresponding to 38.46% of all the homicides in the studied period). Concerning the homicides analyzed in this study (13 cases), the main cause of death was trauma by different factors (e.g., single trauma, multiple trauma or firearm trauma), with a total of 8 cases out of the 13 cases evaluated (61.54%). Just one case (7.69% of the situations) was reported as homicide by intoxication.

Accidental Cases

Concerning accidental deaths, the numbers recorded showed an increasing tendency between 2001 and 2010 (with a maximum of 64 cases in 2010), followed by a decrease in 2011, to increase again in 2012 and reaching the maximum value of the entire study in 2013, with 117 cases (24.27% of all the cases). Of all accidental reported deaths (482 cases), intoxications appear in the first position, with 53.32% (257 cases) of the *postmortem* analysis. The other main causes detected in this study for accidental deaths were trauma, single or multiple (105 cases, 21.78%), and suffocation (39 cases, 8.09%).

Natural Deaths

The number of deaths by natural causes (253 cases) with positive toxicological analysis was also not constant throughout the period in study. From 2001 until 2006, the number of *postmortem* analysis reported as natural deaths were always under 10 cases. In 2007, eleven cases were registered. From that point onward, until 2012, the number of reported cases increased, between 17 and 27 cases each year. These cases were classified as consequence of major organ failure, such as myocardial infarction (59 cases, 23.32%), pneumonia (41 cases, 16.20%), cardiorespiratory arrest (27

cases, 10.67%), cardiac arrhythmia (25 cases, 9.88%) and brain hemorrhage (15 cases, 5.92%).

Undetermined

Cases for which the forensic report did not allow the establishment of the death etiology were classified as undetermined (174 cases). The main causes were intoxication (68 cases, 39.08%), trauma (15 cases, 8.62%), cardiorespiratory arrest (9 cases, 2.87%) and drowning (8 cases, 4.59%). It is important to notice that in 30 cases (17.24%), there was no establishment of a specific cause of death.

Seasonality

The 1,269 cases were organized according to the month of death during the period under analysis. The month with the highest number of occurrences was April, with 116 deaths (9.14%). In the range between 8.5% and 9.0% of deaths were the months January, February, August, October and December. In the interval between 8.0% and 8.5% of cases we could find the months of June, July and September. Ranging from 7.0% and 8.0% were the months of March, May and November, being the last one the month with the lowest number of situations (93 cases, 7.33%).

Results of Toxicological Analysis

A total of 509 deaths reported were caused by fatal intoxications (40.11% of the entire *postmortem* analysis positive for the presence of xenobiotic(s)). The numbers of different substances groups and their associations detected in the deceased are presented in the Fig. (4). The substances detected in the toxicological reports were divided in nine groups: ethanol, opioids, amphetamines, medicines (psy-

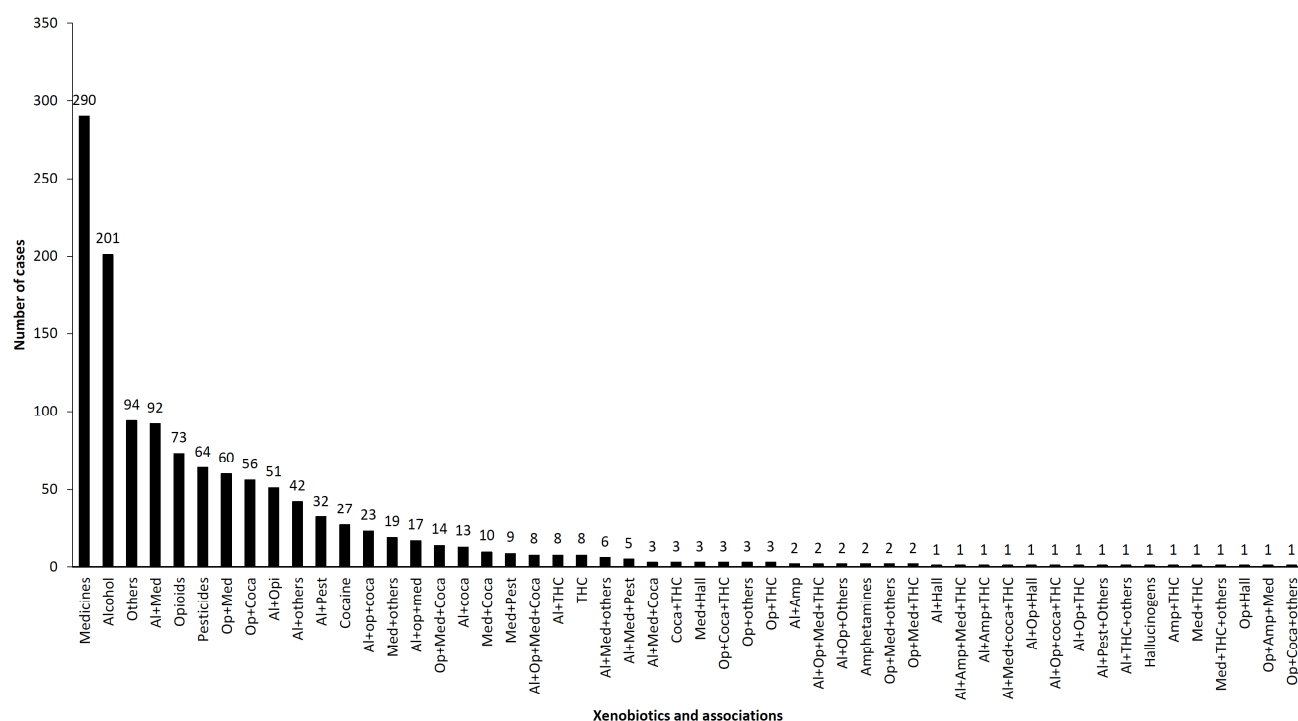


Fig. (4). Xenobiotics in fatal intoxications.

choactive and non-psychoactive), cocaine and its derivatives, cannabinoids, hallucinogens, pesticides and others (e.g., carbon monoxide, strychnine, hydrocarbonated gases, corrosive substances, cyanide, anesthetics and, ethyleneglicol). The highest incidence was medicines (290 cases, 22.85%), alcohol (201 cases, 15.84%) followed by their associations (92 cases, 7.24%) and others (94 cases, 7.25%), a group that englobes eight types of substances. Cases of fatal intoxications involving opioids come on fifth place (73 cases, 5.75%). Considering all different types of xenobiotics and their associations, it was found 51 different associations including a great variety of substances.

Prescription drugs were the most relevant substances involved on fatal intoxications, benzodiazepines being the greatest group with 407 cases (79.96%), including their associations with other substances. Antidepressants presented 194 cases (38.11%) and were mostly related in suicide cases.

DISCUSSION

Forensic Toxicology is the study and practice of the application of toxicology to the purposes of the law. [15, 16]. Toxicologists typically use the word “intoxication”, or poisoning, to describe situations when excessive concentrations of an exogenous compound (*i.e.*, xenobiotic) are present [5].

Intoxications played a major role in the cause of deaths reported in the retrospective *postmortem* analysis of autopsy reports. It also reveals the importance of developing preventive measures towards risk groups.

Prescription drugs revealed the higher incidence in fatal intoxication cases (Fig. 5A). Benzodiazepines had a great role with 407 cases (62.33%), including their association with different substances. This data is in accordance with previous data related with European and American prevalence of xenobiotics intoxication [14, 17, 18]. Antidepressants contributed to 194 cases (29.71%) and were reported as an important substance involved in fatal intoxications [19, 20] and are especially involved on suicides [6]. Of all suicide cases analyzed (347), 80 (23.05%) had toxicological test positive for antidepressant and 31 (8.93%) were considered suicide by poisoning with medicines, including antidepressants. Within these 31 cases, 51.61% were females, confirming the tendency of women to commit suicide by poisoning instead other suicide methods [6]. This is a cultural fea-

ture in southern European countries, since the same kind of results were established in a retrospective study made in the northeast part of Italy. In their study, intoxications by abuse of pharmaceutical substances such as psychoactive drugs, benzodiazepines and tranquilizers, were three times higher in women than in men [21]. Similar results were observed in another retrospective study performed in Spain regarding acute intoxications, which showed that women are using more often drug poisoning to attempt suicide than men (approximately by two fold) [22].

Alcohol is the oldest and the most diffuse substance of abuse [23]. One of the highest volumes of alcohol consumption occurs in the established markets of Western Europe [24]. In our target population, alcohol intoxication cases corresponded to the second highest incidence, with 201 cases, and from these, 52 (25.87%) were fatal intoxications caused only by alcohol. Thirty-nine cases of fatal alcoholic intoxications were considered accidental and may reflect the high rates of alcohol consumption in Portugal. The Portuguese *per capita* alcohol consumption is among the highest in Europe [25, 26] and there is evidence of a correlation between the higher overall level of consumption in a population and a larger number of chronic abusers [26]. Alcohol appears usually associated with medicines (92 cases) and opioids (51 cases). These associations are 71.14% of all cases of alcohol intoxications. The great problem is the pharmacological mechanism of action of all of them. The three are potent central nervous system depressants and may cause respiratory depression [23, 27]. Respiratory depression was the cause of death of 26 positive cases with presence of alcohol.

A previous study regarding a population of the center of Portugal concluded that pesticides were especially involved in cases of suicide and workplace intoxications of agricultural workers [28]. In the present study, pesticides corresponded to 110 cases from all the intoxication reports analyzed (Fig. 5B). Eighty-two cases were suicides, one was accidental and twenty-seven presented undetermined etiology of death. Pesticides are used in most countries to protect agricultural crops against damage. Most poisoning cases by pesticides occur as a result of misuse, accidental exposure and, in cases of accidental or suicidal exposure by oral ingestion [28]. Pesticide poisoning is also one of the most common methods of suicide in developing countries [29]. Although some authors [30, 31] had studied new pesticide for-

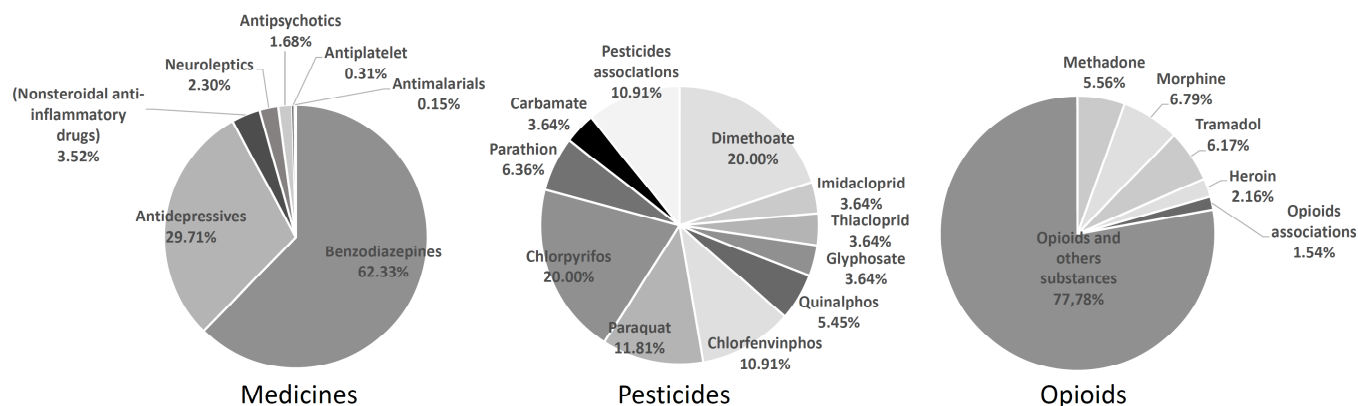


Fig. (5). Fatal intoxications cases for medicines (A), pesticides (B) and opioids (C).

mulation, in order to make them safer or with disgusting flavor, the incidence of pesticide intoxication is preoccupant. Teixeira and colleagues [28] also reported higher intoxication cases in men, which is in agreement with the results obtained on our study (69.44% were males and 30.56% were females).

Prescription drugs overdose deaths are rising worldwide as both the medical and the illicit use of prescription drugs, particularly narcotic pain relievers [32]. Nonmedical use of prescription drugs increased 81% during 1992-2003 in the United States [33]. Opioids are important substances involved in this type of intoxication cases. In our study, 325 cases (25.61%) were claimed to be positive for opioids, a high percentage considering that these substances are available only by prescription or, in the worst scenario, their source is illicit (Fig. 5C). Of all opioids cases, 147 (45.23%) were positive for morphine, which does not exclude heroin cases once the heroin metabolism is very fast and leads to morphine formation [34]. Autopsies reports with positive result for 6-monoacetylmorphine was considered as a positive result for heroin use once 6-monoacetylmorphine is the marker for the presence of heroin in the body. The heroin ester bonds are quickly hydrolyzed in aqueous solution to produce 6-monoacetylmorphine in plasma, and it is that metabolite which is detected on toxicological assays [34].

Opioids are analgesic substances with a psychoactive mechanism of action. They act as ligands on opioids receptors at central nervous system and are capable to produce analgesia, strong decrease of the respiratory function and sedation [27, 34]. The cases in which the cause of death was assigned to opioids were analyzed, from these 8.66% were associated to cardiorespiratory failure, and among these, 53.57% were accidental overdoses.

The criteria of cause of death classification may be biased by some personal opinion of the professional responsible for the autopsy. As a matter of fact, it has been reported disagreement between medical examiners and forensic toxicologists regarding the cause of death in intoxication situations. Some epidemiologic studies showed that the assessment made by the medical examiner in intoxication cases is considered reliable as gold standard [1, 35]. Cordner [36] stated that to determine a cause of death, a technically perfect *postmortem* analysis is required, but not sufficient [36, 37]. For all these reasons, certifying the cause of death when it is unclear or controversial remains one of the most daunting tasks in forensic medicine [37].

This retrospective study presents some limitations. In some cases, information on the forensic reports, especially related to social information, was missing. Moreover, there were reports for which the cause and etiology of death was not fully obtained/described. This might have some impact in the perception of casuistic. Nevertheless, the goal of this study was to analyze the forensic reports without introducing further interpretations (and therefore to possible bias) raised by authors regarding described conclusions. In addition the high prevalence of undetermined cause of death can be due to different factors. The lack of information about the individual clinical past, use of prescription drugs and use of illicit drugs, makes sometimes difficult/impossible to establish death etiology by the medical examiners and forensic toxicologists.

By analyzing a long period as 12 years, it was possible to minimize the interference of highlighted limitations.

CONCLUSIONS

A total of 27,778 autopsies reports between 2001 and 2013 were analyzed. From all the cases studied, 1,269 were related with the presence of xenobiotics. It was observed a high number of intoxications caused by prescription drugs, and alcohol was the second most important substance. Associations between alcohol and drugs were problematic due to its high frequency. Opioids showed a great participation on deaths usually claimed to be accidental overdoses. These evidence points to the establishment and development of preventive measures towards some target populations, such as patients whose treatments require the use of benzodiazepines, antidepressants and/or opioids, alcoholics and drug abusers, in order to decrease the prevalence of fatal intoxications.

Further studies on the impact of cultural, psychological, social and economic factors on the different cases would enable the establishment of the cause of death with a higher degree of confidence. The assessment of the cause and death etiology would also benefit by the implementation of a standard procedures aiming autopsy reports better harmonized and repeatable. Therefore the influence of personal factors on such evaluation will certainly decrease.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest, particularly any financial and personal relationships with other people or organizations that could inappropriately influence (bias) this work.

ACKNOWLEDGEMENTS

Emanuele Alves acknowledges Brazilian agency Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (process 245844/2012-0) for research grants and scholarship. Ricardo Dinis-Oliveira acknowledges Fundação para a Ciência e a Tecnologia (FCT) for his Investigator Grant (IF/01147/2013). Authors also acknowledge to Forensic Pathologists and Forensic Toxicologists of the North Branch of the National Institute of Legal Medicine and Forensic Sciences for allowing data access of intoxications cases from 2001 and 2013.

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