

Original Article

Benzodiazepine poisoning in Morocco: epidemiological study.

Aicha Detsouli¹, Naïma Rhalem², Zakaria Abidli³, Sara JADDA⁴, Mohamed Fekhaoui⁵, Latifa Amiar⁶, Abdelmajid Soulaymani⁷, Rachida Soulaymani-Bencheikh⁸, Abdelrhani Mokhtari⁹

Abstract:

Objective: This study aims to describe the main epidemiological characteristics of benzodiazepine intoxication in Morocco. **Methods:** This is a retrospective study of cases of benzodiazepine poisoning reported at the Poison Control and Pharmacovigilance Center of Morocco between 2012 and 2016. **Results:** During the period 2012-2016, 1,544 cases of benzodiazepine poisoning were recorded in Morocco. The average age of the addicts is 21.68 ± 14.41 years. According to the data of the study, 70% are Female, with a sex ratio of 2.25. The suicidal act represents a significant percentage with 31.5% of cases. Almost all patients were orally intoxicated with 97.1%. The signs presented are various according to the quantity ingested and the time elapsed before the treatment in particular the psychiatric, neurological, digestive and cardiovascular disorders. Unfortunately, three cases died. The other cases survived with or without sequelae.

Conclusion: benzodiazepines are drugs used in the treatment of several disorders such as anxiety, insomnia and psychomotor agitation. Unfortunately, many people do not know how to use this type of medicine which exposes them to poisoning, for this reason it is necessary to carry out sensitization campaigns for the good use of benzodiazepines at the national level.

Keywords: Poisoning; Benzodiazepines; Epidemiology; Morocco.

Bangladesh Journal of Medical Science Vol. 20 No. 02 April'21. Page : 396-400

DOI: <https://doi.org/10.3329/bjms.v20i2.51555>

Introduction

Benzodiazepines (BZDs) are molecules that act on the central nervous system. They are indicated for the treatment of anxiety, severe sleep disorders and epilepsy because of their sedative, hypnotic, anxiolytic, anticonvulsant and muscle relaxant properties¹. However, when patient doses of benzodiazepines

are used exceed the doses usually prescribed benzodiazepine poisoning, irrespective of the nature of this poisoning voluntary or accidental. In France, the BZD is the first cause of voluntary poisoning in adults with a prevalence of the order of 60 to 80%². Unfortunately, there is little epidemiological study that focuses on benzodiazepine poisoning in Morocco.

1. Aicha Detsouli, Agronomic and vétérinaire Institute, Hassan II Rabat, Morocco and Scientific Institute of Rabat, Mohammed V University Morocco.
2. Naïma Rhalem, Anti-Poison and Pharmacovigilance Center, Rabat, Morocco and Faculty of Medicine Rabat, Mohammed V University, Rabat, Morocco
2. Zakaria Abidli, PPR-B-Mokhtari-FS-UIT-Kenitra.Laboratory of Genetics and Biometry, Faculty of Science, IbnTofail University, Kenitra, Morocco.
3. Sara JADDA, PPR-B-Mokhtari-FS-UIT-Kenitra.Laboratory of Genetics and Biometry, Faculty of Science, IbnTofail University, Kenitra, Morocco.
4. Mohamed Fekhaoui, Scientific Institute of Rabat, Mohammed V University Morocco.
5. Latifa Amiar, Faculty of Science and Technology, University AbdelmalekEssaadi, Tangier, Morocco.
6. Abdelmajid Soulaymani, PPR-B-Mokhtari-FS-UIT-Kenitra.Laboratory of Genetics and Biometry, Faculty of Science, IbnTofail University, Kenitra, Morocco,
7. Sara JADDA, PPR-B-Mokhtari-FS-UIT-Kenitra.Laboratory of Genetics and Biometry, Faculty of Science, IbnTofail University, Kenitra, Morocco.
8. Rachida Soulaymani-Bencheikh.Moroccan Anti-Poison and Pharmacovigilance Center, Rabat, Morocco and Faculty of Medicine Rabat, Mohammed V University, Rabat, Morocco.
9. Abdelrhani Mokhtari, PPR-B-Mokhtari-FS-UIT-Kenitra.Laboratory of Genetics and Biometry, Faculty of Science, IbnTofail University, Kenitra, Morocco.

Correspondence to: Zakaria Abidli, PPR-B-Mokhtari-FS-UIT-Kenitra.Laboratory of Genetics and Biometry, Faculty of Science, IbnTofail University, Kenitra, Morocco. Email: abidli@outlook.fr

In this sense, this study describes the epidemiological, clinical and evolutionary aspects of benzodiazepine poisoning in Morocco between 2012 and 2016 with a view to promoting actions for their medical care and prevention.

Data and Methods

This is a retrospective epidemiological study of all cases of benzodiazepine poisoning collected by the Poison Control Center of Morocco (CAPM) reported to the toxicological information unit of CAPM over a period of five years. From January 2012 to December 2016. The variables studied concern the characteristics of the intoxicated population (year, sex, age, type of intoxication and circumstance), clinical characteristics (symptomatology and evolution and clinical signs). The age was analyzed according to the distribution of the IPCS (WHO)³ The evaluation of the gravity was done by the poisoning score severity (PSS) (Person 1998) (Table 1)⁴.

Indeed, the statistical methodology was based on two axes: descriptive statistics and analytic statistics. In a first part, we have to identify the frequencies and

the characteristics of each variable studied which allowed us to draw up an epidemiological profile of all cases of intoxication. The results were expressed as a percentage for the qualitative variables and as an average \pm standard deviation for the quantitative variables. Secondly, the χ^2 test was used to determine whether a significant difference exists between certain variables studied.

Ethical clearance:

Results

During the period 2012 and 2016, 1544 cases of benzodiazepine poisoning were reported to the Anti Poison Center and Pharmacovigilance of Morocco from the various administrative regions. The incidence of cases increased significantly in 2014, reaching the maximum value of cases registered (354 cases), then a downward trend in 2016 (309 cases) and in 2016 (209 cases), with a coefficient 40% overall R2 determination (FIG. 1).

The distribution of our sample according to the age of the addicts shows that the average age is 21.68 ± 14.41 years and a median of 20 years. The most

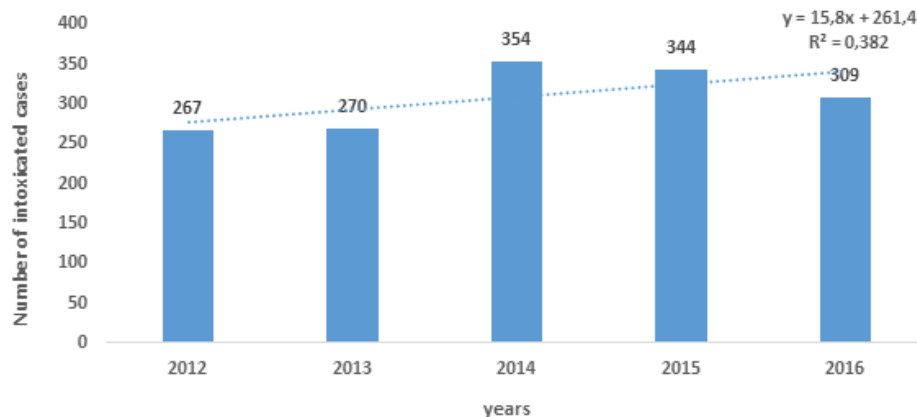


Figure 1: Distribution of cases of benzodiazepine poisoning by year (2012-2016)

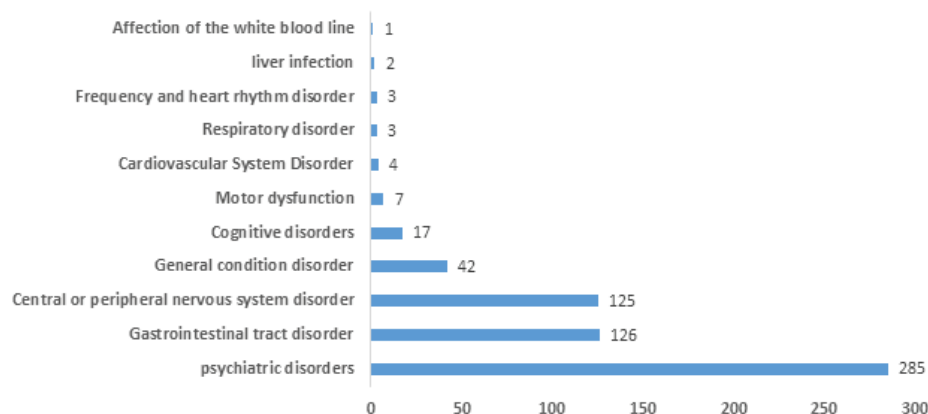


Figure 2: Distribution of intoxicated cases according to the clinical signs that appeared during intoxication

exposed age group is that of adults with 41.2% of cases, followed by adolescents with 14.3% of cases, then baby walkers with a percentage of 11.7% of cases while infants and elderly represent low percentages of benzodiazepine poisoning, respectively 0.9% and 0.2% of cases.

In our study the female predominance is very clear, with 70% of the cases against 28% of the men ($p < 0.000$), with a sex ratio of 2.25 in favour of the female. Most of the addicts who reported their origins, were urban with 82% of cases, with a difference between the two origins (urban, rural) was highly significant ($p = 0.001$). (Table 2) As far as the circumstance

Table 1: The evaluation of gravity was done by the poisoning score severity (PSS)

Grades	The gines
0	Absence of functional or physical sign
1	Minor symptoms, transient and regressing spontaneously
2	Marked or persistent symptoms
3	Severe or life-threatening symptoms
4	Deadly poisoning

Table 2: Distribution of benzodiazepine poisoning by patient characteristics and intoxication

Variables	N cas	Evolution			P value
		Favorable	Death	Unknown	
Sex					
Female	1088(70%)	843	3	242	0.001***
Male	425(28%)	317	0	108	
Unknown	31(2%)	20	0	11	
Poisoning environment					
Urban	1264(82%)	963	3	298	0.001***
Rural	128(8%)	104	0	24	
Unknown	152(10%)	113	0	39	
Age groups					
Infants	9(0.6%)	7	0	2	0.81 ^{n.s}
Baby walker	181(11.7%)	153	0	28	
Children	137(8.9%)	115	0	22	
Teenagers	221(14.3%)	172	0	49	
Adults	637(41.2%)	466	2	171	
The elderly	4(0.2%)	2	1	1	
Unknown	356(23.1%)	265	0	88	
Circumstance					
Classic accident	281(18.2%)	221	1	59	0.009***
Abortion	1(0.06%)	1	0	0	
Undesirable effect	15(1%)	10	0	5	
Therapeutic error	22(1.4%)	17	0	5	
Suicidal	486(31.5%)	378	0	108	
Substance addiction	4(0.3 %)	3	0	1	
Unknown	735(47.6%)	550	2	183	
Clinical state					
Symptomatic	799(51.7%)	636	2	161	0.001***
Asymptomatic	218(13.9%)	174	0	44	
Unknown	527(34.1%)	370	1	156	

***: Highly significant difference (p <0.001), n.s: not significant.

is concerned, the suicidal act represents a maximum number of intoxicated cases with 31.5% cases, followed by classical accidents with 18.2% cases. Almost all the patients were intoxicated by the oral route with 1500 (97.15%) cases. Intoxication is isolated in 1480 (95.8%) of the reported cases and collective in 25 (1.6%) cases. The clinical state of the addicts was predominantly symptomatic with a 51.7% of cases, with 436 (28.2%) cases of hospitalization versus 330 (21.3%) non-hospitalized cases (p <0.001). Benzodiazepine addicts developed signs as a psychiatric disorder with 285 cases followed by gastrointestinal tract disorder represented by 126 cases, and then central or peripheral nervous system disorder with 125 cases (Figure 2). For the evolution was favourable in 1180 cases (Table 2). Unfortunately 3 people died during this period. The three deceased are adult women and a senior who are hospitalized and symptomatic. Deaths are of urban origin with two deaths accidentally (Table 3).The statements came from all regions of Morocco, the strongest statement was recorded in the Rabat-Salé-Kenitra region with 461 cases followed by Casablanca-Settat with 247 cases and then the Tangier-Tetouan-Al Hoceima region with 161 cases.

Discussion

Drug poisoning is a major public health problem around the world. They are at the origin of an important activity at the level of the services of medical emergencies and resuscitation⁵. Benzodiazepines are among the most represented drugs in cases of drug poisoning in the world. A French study, on the change of profile of acute auto-intoxications over a period of 10 years, showed that 67.2% are intoxicated by BZD in the first period between 1992-1993, while 54.7% are intoxicated in the period 2001-2002 by the BZD⁶. In Morocco, a study carried out by the anti-poison and pharmacovigilance center for drug poisoning, has shown that the most incriminated drug families in the study are those of the central nervous system with bromazepam (benzo), which occupies the 2nd place in sales of benzodiazepines in Morocco⁷. which explains the large number of poisoning by BZD in our series with 1544 intoxicated. Benzodiazepines rank third as the most misused prescription drug by adolescents⁸ and adults⁹. In our study, for example, adults followed by adolescents are the most exposed to benzodiazepine poisoning with a percentage of (41.2%) and (23.1%) respectively.

Table 3: Distribution of the deceased cases poisoned according to the sociodemographic and clinical parameters

	Sex	Age	Region	Service	Circumstances	Clinical signs	Hospitalisation
Death 1	Female	Adults	Rabat-Salé-Kénitra	Emergency	Accidental	Coma	Hospitalized
Death 2	Female	The elderly	Marrakech-Safi	Emergency	Suicidal	Coma	Hospitalized
Death 3	Female	Adults	Tanger-Tétouan-Al Hoceïma	Emergency	Accidental	Nausea, vomiting And vertigo	Hospitalized

A study in the Taiwanese health insurance database, which included 184,509 outpatients with psychiatric illnesses, showed an increase in suicide attempts by intoxication (aOR = 2.44, after adjusting for age, gender, age and sex). anxiety, sleep disorders, depression, schizophrenia and a history of auto-intoxication)¹⁰. Benzodiazepines still represent the first drug class of voluntary poisoning with a frequency of between 20 and 67%¹¹⁻¹²⁻¹³⁻¹⁴⁻¹⁵⁻¹⁶. These studies are in agreement with our result, because the suicidal act by the administration BZD represents a very important percentage by bringing other circumstances with 31.5% intoxicated.

On the other hand, a Swedish study has focused on the role of benzodiazepines in suicides in the elderly, this study showed that benzodiazepines were involved in 39% of suicides (216 of 548 cases)¹⁷, therefore conclude that benzodiazepines are pharmaceutical molecules commonly used in voluntary drug poisoning. However, in our series four people are addicted to the BZD whose addictive purpose (drug addiction). At an international scale several researchers have made alarmingly, patients already at risk of becoming dependent on benzodiazepines, substance abuse problems and overdose, receive

them more frequently and more frequently at higher doses¹⁸. Evidence suggests that the use of benzodiazepines for greater than four weeks results in the appearance of some form of psychological or physiological impairment in approximately 50% of patients¹⁹. This explanation is approved in our study that 46.3% of the benzodiazepine addicts have developed signs in the form of psychiatric disorder. In terms of pharmacovigilance, at the level of the literature review, several studies link the use of BZDs to adverse effects. A meta-analysis performed on the impact of BZDs on cognitive functions, demonstrated that BZDs have side effects on cognitive functions such as memory and attention²⁰. For this reason, a French study focuses on the feast of good use of benzodiazepines²¹.

Conclusion: benzodiazepines are drugs used in the treatment of several disorders such as anxiety, insomnia and psychomotor agitation. Unfortunately, many people do not know how to use this type of medicine. Which exposes them to poisoning, for this reason it is necessary to carry out sensitization campaigns for the good use of benzodiazepines at the national level.

Reference:

1. Griffin C., Kaye A., Bueno F., Kaye A., Benzodiazepine Pharmacology and Central Nervous System-Mediated Effects, *The ochsner journal*. 2013. P 214-222.
2. Guillaume Hoizey, Hélène Marty, Denis Lamiable, Richard Vistellea. Intoxications aiguës par les benzodiazépines. *Revue Française des Laboratoires*.2000;**2000** (322):47-52 [https://doi.org/10.1016/S0338-9898\(00\)80476-X](https://doi.org/10.1016/S0338-9898(00)80476-X)
3. International Programme on Chemical Safety (IPCS). Guidelines on Poisoning Prevention and Management, Harmonized data collection, Definitions. <http://www.who.int/ipcs/poisons>
4. Person HE, Sjöberg GK, Haines JA, et coll. Poisoning severity score. Grading of acute. *Poisoning Clin Toxicol* 1998;**36**(3):205-13 <https://doi.org/10.3109/15563659809028940>
5. Lambert H, Manel J, Bellou A, El Kouch S. Morbidité et mortalité par intoxications médicamenteuses aiguës en France. *Rev Prat*.1997; **47**:716-20
6. Staikowsky F, et al. Change in profile of acute self drug-poisonings over a 10-year period. *Human & Experimental Toxicology* 2004; **23**:507-11. <https://doi.org/10.1191/0960327104ht487oa>
7. Badrane N , Abadi F , Ouammi L , 2 , Soulaymani-Bencheikh R. Intoxications médicamenteuses au Maroc Données du Centre Anti Poison du Maroc (1980-2008). N° 7 - 4ème trimestre 2010 Publication officielle du Centre Anti Poison du Maroc Ministère de la santé
8. Johnston, L.D., O'Malley, P.M., Miech, R.A., Bachman, J.G., Schulenberg, J.E. Monitoring the Future national survey results on drug use, 1975-2016: Overview, key findings on adolescent drug use. Ann Arbor Institute for Social Research, The University of Michigan, Ann Arbor
9. Center for Behavioral Health Statistics and Quality, 2016. Results from the 2015 National Survey on Drug Use and Health: Detailed tables. Substance Abuse and Mental Health Services Administration, Rockville, MD
10. Shih H-I, Lin M-C, Lin C-C, Hsu H-C, Lee H-L, Chi C-H, et al. Benzodiazepine therapy in psychiatric outpatients is associated with deliberate self-poisoning events at emergency departments-a population-based nested case-control study. *Psychopharmacology (Berl)* 2013;**229**:665-71. <https://doi.org/10.1007/s00213-013-3127-4>
11. Billy F, Montaz L, Perault MC, Vandel B. Étude des intoxications médicamenteuses volontaires reçues dans une unité d'accueil des urgences. *Thérapie* 1998;**53**:553-8.
12. Atout S. Evolution des intoxications médicamenteuses volontaires entre 1994-1995 et 1999-2000. *Thèse de Médecine*. Paris 7. 2004
13. Lapostolle F. Les intoxications médicamenteuses aiguës. *Rev Prat* 1997;**47**:760-2.
14. Bismuth C, Baud F, Leporc P, Naguib S, Sato T. Épidémiologie et coût des intoxications hospitalisées. *Rev Fr Lab* 1985;**140**:106-10.
15. Wink P. Les facteurs sociofamiliaux et médicosychiatriques dans les tentatives de suicide. Étude épidémiologique. Thèse de Médecine -Nancy 1996:112 pages.
16. Adnet F, Atout S, Galinski M, Lapostolle F. Evolution des intoxications médicamenteuses volontaires en France. *Réanimation* (2005);**14**: 721-6. <https://doi.org/10.1016/j.reaurg.2005.10.023>
17. Carlsten A, Waern M, Holmgren P, Allebeck P. The role of benzodiazepines in elderly suicides. *Scand J Public Health* 2003; **31**: 224-8. <https://doi.org/10.1080/14034940210167966>
18. Kroll, D.S., Nieva, H.R., Barsky, A.J., Linder, J.A. Benzodiazepines are prescribed more frequently to patients already at risk for benzodiazepine-related adverse events in primary care. *J. Gen. Intern. Med.* 2016;**31**, 1027-1034 <https://doi.org/10.1007/s11606-016-3740-0>
19. de las Cuevas, C., Sanz, E., de la Fuente, J. Benzodiazepines: More "behavioural" addiction than dependence. *Psychopharmacology*. 2003;**167**, 297-303 <https://doi.org/10.1007/s00213-002-1376-8>
20. Lapeyre-Mestre M. Impact des benzodiazépines sur les fonctions cognitives et le risque de démence. Revue des arguments de causalité issus des études observationnelles Benzodiazépines, cognitive decline and dementia: A review of causality criteria from published observational studies. *Thérapie* Available online 3 October 2018, In Press. <https://doi.org/10.1016/j.therap.2018.09.071>
21. A , Yroni A, Montastruc F. *La Presse Médicale*. 2018;**47**(10):872-877 <https://doi.org/10.1016/j.lpm.2018.10.008>