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Evolution of the consumption of lorazepam in a rural environment in the Region of Murcia (2012-2018)

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Authorship & contributorship

JA Cano, S Sierra-Alarcón, and A Galindo-Tovar designed the study. JA Cano and P Ballester performed the statistical analyzes of the data and interpreted the results obtained. JA Cano wrote the first version of the manuscript. Finally, all the authors contributed to the critical review of the consecutive versions of the document, made contributions and approved the final version for publication. All signatories are responsible for all aspects of the study.

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ABSTRACT

Objective: To evaluate the consumption of lorazepam in the Region of Murcia, specifically in the district of Mula, during the period 2012-2018, considering age and sex variables.

Method: Cross-sectional descriptive study, where the use of benzodiazepines in a specific population during the period 2012 - 2018 is investigated. The variables collected were sex, age and the prescribed Defined Daily Dose. The data correspond to the dispensations of Lorazepam in the pharmacy offices of the district of Mula, provided by the Health Assistance General Directorate. Daily dose per inhabitant and per 1000 inhabitants were calculated and the groups median and interquartile ranges were established p25 and p75 for later comparisons.

Results: Overall consumption over the period increased by 0.42%. In men it increased by 21.4%, while in women it decreased by 7.5%. However, in women, consumption was at higher doses, between significant differences were found in lorazepam consumption in groups when analyzed by sex. The analysis by age showed a significant increase in consumption as the age of the patients increased.

Conclusion: The consumption of benzodiazepines is high with increasing age, more so in women, and this may have an impact on the adverse effects associated with this group of drugs and present an important public health problem.

Key Words: Benzodiazepines, Pharmaceutical care, Primary Health care, Anxiolytic, Anxiety.

RESUMEN

Objetivo: Evaluar el consumo de lorazepam en la Región de Murcia, concretamente en el municipio de Mula, durante el periodo 2012-2018, considerando las variables edad y sexo.

Método: Estudio descriptivo trasversal, donde se investiga el consumo de Benzodiazepinas en una población concreta durante el periodo 2012 - 2018. Las variables recogidas fueron el sexo, la edad y la Dosis Diaria Definida prescrita. Los datos corresponden a las dispensaciones de Lorazepam en las oficinas de farmacia del municipio de Mula, facilitados por la Dirección General de Asistencia Sanitaria. Se calcularon las Dosis diaria por habitante y día por 1000 habitantes y se establecieron mediana y rangos intercuartílicos p25 y p75 los grupos para posteriores comparaciones.

Resultados: El consumo global durante el periodo estudiado aumentó un 0,42%. En los hombres se incrementó un 21,4%, mientras que en las mujeres disminuyó un 7,5%. Sin embargo, en las mujeres el consumo se produce a dosis más elevadas, encontrándose diferencias significativas en el consumo de lorazepam entre grupos al analizar por sexo. El análisis por edades mostró un aumento significativo de consumo conforme aumentaba la edad de los pacientes.

Conclusión: El consumo de benzodiazepinas es elevado a medida que avanza la edad, de manera más acuciante en las mujeres, pudiendo esto incidir sobre los efectos adversos asociados a este grupo de fármacos y presentando un importante problema de salud pública.

Palabras Clave: Benzodiazepinas, Atención farmacéutica, Atención primaria, Ansiolíticos, Ansiedad.

Introduction

Benzodiazepines (BZP) are widely used for the treatment of anxiety disorders and sleep disorders^(1, 2). They emerged as an alternative to barbiturates, as a safer group, with fewer associated adverse effects and less capacity to produce dependence⁽³⁾. They depress the central nervous system by acting at the level of the gamma aminobutyric acid (GABA) neurotransmitter receptor, specifically in the GABA_A subunit⁽⁴⁾. BZPs have a quadruple therapeutic effect: anxiolytic, sedative-hypnotic, anticonvulsant and muscle relaxant⁽⁵⁾. These effects do not occur equally or simultaneously in all BZP⁽⁶⁾.

In Spain, a study conducted over fifteen years (1992 - 2006) by the Spanish Agency of Medicines and Health Products (AEMPS) showed an increase in consumption of this group of drugs of 113.6% in that time period⁽⁷⁾. In 2011, the EDADES Spanish survey about the consumption of psychoactive substances estimated that 11.4% of the general population (15 - 64 years) were consumers of anxiolytic and hypnotic drugs⁽⁸⁾. Despite these national data, data on consumption per autonomous communities is unknown, since most studies focus on national analysis of consumption.

The risk associated with an acute use of BZP is low compared to long-term use (more than 3 months). In this group, the shorter duration of usage, the greater efficacy and safety achieved. It is not recommended to exceed more than 4 weeks for insomnia treatment, and 12 weeks for the treatment of anxiety disorder⁽⁹⁾. However, in clinical practice there is a trend to make these treatments chronic⁽¹⁰⁾.

Mainly, population over 65 years of age are at risk of chronic BZP prescription, their prolonged use triggers important, and worrying adverse effects, with a positive relationship between chronic consumption and falls with bone fractures^(11,12). In addition, this consumption pattern leads to memory impairment⁽¹³⁾. Other studies have proven that prolonged consumption of BZP is associated with impaired psychomotor performance, decreasing time reaction⁽¹⁴⁾.

Considering that in Spain the prevalence data in provinces is unknown, and the described growing risk of developing adverse events due to chronic treatment with BZP, especially in senior patients, the aim of this work is to evaluate the consumption of lorazepam in the municipality of Mula (Murcia) during the period 2012 - 2018, considering the variables age and sex in the analysis.

Methods

Cross-sectional descriptive study, based on data collected from prescriptions dispensed in pharmacy offices, in the Municipality of Mula, charged to the National Health System (SNS) during 2012-2018.

The data were requested and obtained through the Service of Pharmaceutical Management, which reports to the General Health Assistance Registry (DGAS)⁽¹⁵⁾ of Murcia Health Service (SMS)⁽¹⁶⁾. Medications purchased with private prescriptions or any mutual insurance companies were not included in this study. Anonymized data disaggregated by sex and age were provided for each year.

The annual consumption in defined daily doses (DDD) for each active ingredient and presentation of lorazepam was provided. Defined Daily Doses per thousand inhabitants per day (DDD) were calculated by conversion from the DDD provided: no. of DDD= (DDD x 1000 inhabitants)/(no. of inhabitants by sex and age x 365 days)⁽¹⁷⁾. Each year population was obtained from the population census, through the National Institute of Statistics (www.ine.es).

Quantitative variables were expressed as mean \pm standard deviation, or median (DHD) with interquartile ranges (p and p. The data dispensations were grouped into five year intervals: 9-25 years; 26-40 years; 41-55 years; 56-74 years; >75 years to investigate the relationship between DHD consumption and age groups. Analyses performed were Pearson's Chi-square statistical test, using the IBM SPSS Statistics package for Windows version 28.0. Given the multiple comparisons done, a p value of $p < 0.001$ was set for significant differences.

The present study has the favorable report of the ethics committee of Universidad Católica San Antonio de Murcia (UCAM), code CE021908.

Results

In the period from 2012 to 2018, 98249 packages of lorazepam were dispensed in the pharmacy offices of Mula. A total of 1581 patients, whose age ranged from 9 to 101, were included in the analysis, the mean age was 57 ± 22 years old, and 54% were females.

The average age for each of the five groups was as follows: 20 ± 4 years old youngest group; 34 ± 4 years old for the group of 26-40 years; 48 ± 4 years old for the third group; 65 ± 6 years old in the 56-74 years range; and finally, 85 ± 7 years old for the fifth group.

Overall lorazepam consumption (Figure 1) increased a total of 0.42% (4073 DHD/2012 and 4090 DHD/ 2018). The consumption increased between 2012 and 2013 a 26.46% (4,073 DHD/2012 and 5,151 DHD/2013) notably,

compared to the rest of the years, where consumption kept levels within a similar trend to 2012. Splitting the consume by sex, consumption in men increased a 21.4% (1116.4 DHD/2012 and 1355.2 DHD/ 2018), and in women it decreased a 7.5% (2956.8 DHD/2012 and 2734.8 DHD/2018) over the years.

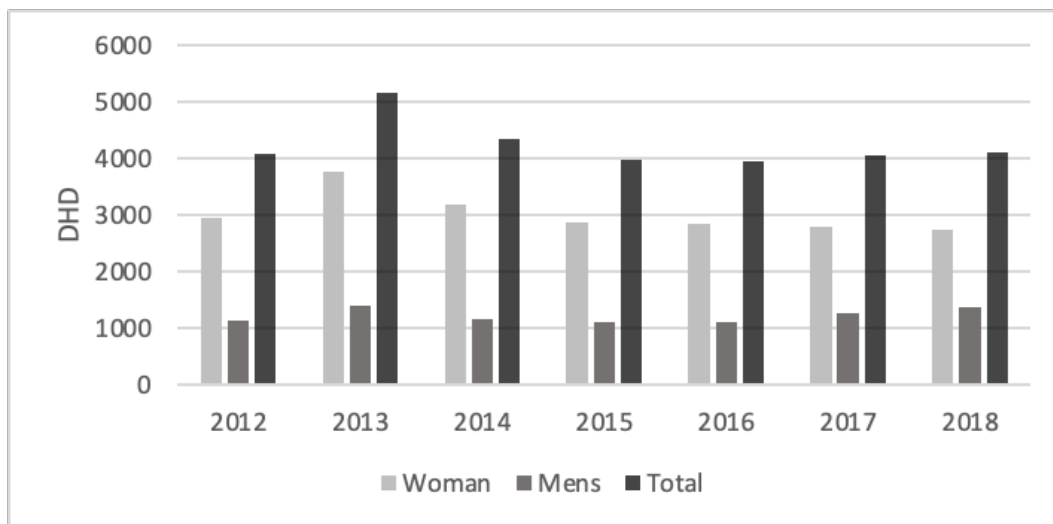


Figure 1: Consumption in DHD during the 2012 - 2018 study period.

Yearly, consumption was analyzed by sex (Figure 2), establishing intervals with the p50, p75 and p100, p25 was not used since until p50 the DHD values were 0. During the first five years of the study (2012-2016), significant differences were observed in the distribution of men and women according to DHD across the percentile intervals analyzed, with a p-value<0.001. There were still differences in 2017 with a p-value<0.005, however, in 2018, there were no significant differences. In the analysis, it was observed that consumption in men is in first DHD interval (p0-p50), and in women in the higher dose intervals. The DHD data indicate that women have a higher dose of lorazepam consumption than men.

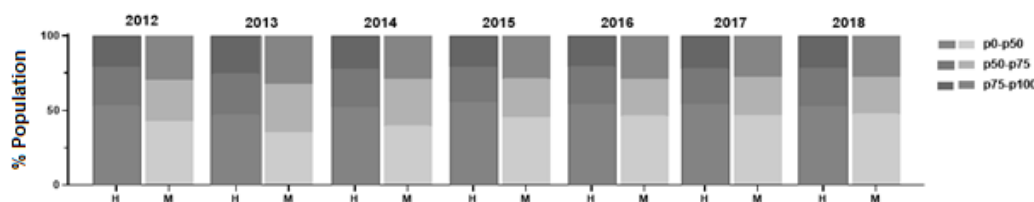


Figure 2: Figure 2. Percentage of lorazepam-consuming population during the period 2012-2018 distributed by DHD intervals and separated by sex and year of study. [p 0; 50; 75; 100]: alludes to percentile 0; 50; 75; 100 respectively; [M]: male; [F]: female *p-value<0.001. **p-value<0.005.

The yearly analysis of consumption by age group is shown in Table I. This analysis proved significant differences, between the different age intervals and lorazepam consumption, with a p -value <0.001 for all years of the study. In the table it can be shown how the percentage by age group and year of consumption is reflected in DHD intervals, P0-50 and P50-75. For the first two age groups, more than 70% of the consumption was distributed in the first DHD interval. Percentages above 50 in the group of 26-40 years and reaching a percentage above 30% in the DHD interval P75 -P100 for the last two age groups. We could affirm that there was a increase in percentages as we increased age. As can be seen in Figure 3, for the first age group, 9-25 years, consumption was observed mainly in p0-p50 and P50-P75, then, up to the 41-55 years age group, the most prevalent consumption was observed in the first two DHD intervals. However, in the next two age groups, 56-74 years and >75 years, consumption was higher, in p75-p100 interval. In general, a trend of higher DHD consumption observed after the 41 years of age, increasing as age increases, while at ages below 40, consumption was higher in DHD doses in the first group (P0-P50).

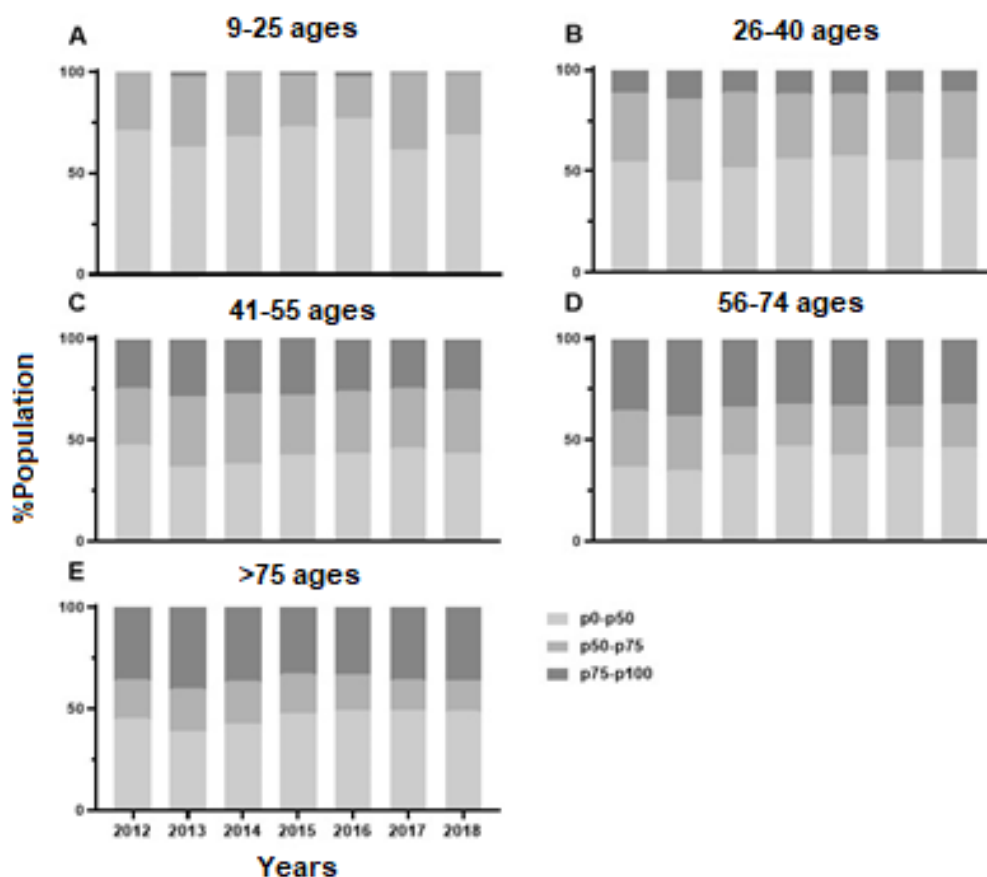


Figure 3: Percentage of lorazepam consuming population during the period 2012-2018 in Mula, separated by age interval and DHD range for each year of the study. [p 0; 50; 75; 100]; alludes to percentile 0; 50; 75; 100 respectively. * p -value <0.001 .

		2012	2013	2014	2015	2016	2017	2018
9-25 ages	P0-P50 (%,n)	0-0,17 (71,5%,93)	0-0,31 (63,1%,82)	0-0,18 (68,5%,89)	0-0,12 (73,1%,95)	0-0,10 (76,9%,100)	0-0,06 (61,5%,80)	0-0,06 (69,2%,90)
	P50-P75 (%,n)	0,17-1,89 (28,5%,37)	0,31-2,39 (34,6%,45)	0,18-1,92 (30,8%,40)	0,12-1,70 (25,4%,33)	0,10-1,70 (20,8%,27)	0,06-1,60 (37,7%,49)	0,06-1,58 (30%,39)
	P75-P100 (%,n)	1,89-98,63 (0%,0)	2,40-278,36 (2,3%,3)	1,92-175,34 (0,8%,1)	1,70-87,67 (1,5%,2)	1,70-76,71 (2,3%,3)	1,60-109,59 (0,8%,1)	1,59-109,59 (0,8%,1)
26-40 ages	P0-P50 (%,n)	0-0,17 (54,5%,163)	0-0,31 (45,2%,135)	0-0,18 (51,8%,155)	0-0,12 (55,9%,167)	0-0,10 (57,4%,171)	0-0,06 (55,5%,166)	0-0,06 (55,9%,166)
	P50-P75 (%,n)	0,17-1,89 (34,1%,102)	0,31-2,39 (40,5%,121)	0,18-1,92 (37,1%,111)	0,12-1,70 (32,4%,97)	0,10-1,70 (30,9%,92)	0,06-1,60 (33,4%,100)	0,06-1,58 (33,7%,100)
	P75-P100 (%,n)	1,89-98,63 (11,4%,34)	2,40-278,36 (14,4%,43)	1,92-175,34 (11%,33)	1,70-87,67 (11,7%,35)	1,70-76,71 (11,7%,35)	1,60-109,59 (11%,33)	1,59-109,59 (10,4%,31)
41-55 ages	P0-P50 (%,n)	0-0,17 (47,5%,163)	0-0,31 (37%,127)	0-0,18 (38,2%,131)	0-0,12 (42,9%,147)	0-0,10 (43,4%,149)	0-0,06 (46,1%,158)	0-0,06 (43,7%,149)
	P50-P75 (%,n)	0,17-1,89 (28%,96)	0,31-2,39 (34,4%,118)	0,18-1,92 (35%,120)	0,12-1,70 (29,2%,100)	0,10-1,70 (30,6%,105)	0,06-1,60 (29,4%,101)	0,06-1,58 (31,1%,106)
	P75-P100 (%,n)	1,89-98,63 (24,5%,84)	2,40-278,36 (28,6%,98)	1,92-175,34 (26,8%,92)	1,70-87,67 (28%,96)	1,70-76,71 (25,9%,89)	1,60-109,59 (24,5%,84)	1,59-109,59 (25,2%,86)
56-74 ages	P0-P50 (%,n)	0-0,17 (36,8%,152)	0-0,31 (34,9%,144)	0-0,18 (42,6%,176)	0-0,12 (47,2%,195)	0-0,10 (42,6%,175)	0-0,06 (46,7%,193)	0-0,06 (46,5%,192)
	P50-P75 (%,n)	0,168-1,887 (27,6%,114)	0,310-2,394 (27,1%,112)	0,182-1,923 (23,5%,97)	0,123-1,701 (20,6%,85)	0,098-1,701 (24,3%,100)	0,061-1,6 (20,6%,85)	0,064-1,584 (21,3%,88)
	P75-P100 (%,n)	1,89-98,63 (35,6%,147)	2,40-278,36 (38%,157)	1,92-175,34 (33,9%,140)	1,70-87,67 (32,2%,133)	1,70-76,71 (33,11%,136)	1,60-109,59 (32,7%,135)	1,59-109,59 (32,2%,133)
>75 ages	P0-P50 (%,n)	0-0,16 (45,2%,179)	0-0,31 (39%,154)	0-0,18 (42,4%,168)	0-0,12 (47,5%,188)	0-0,10 (49%,194)	0-0,06 (49,1%,194)	0-0,06 (48,9%,192)
	P50-P75 (%,n)	0,17-1,89 (19,2%,76)	0,31-2,39 (21%,83)	0,18-1,92 (21,2%,84)	0,12-1,70 (19,9%,394)	0,10-1,70 (17,7%,70)	0,06-1,60 (15,2%,60)	0,06-1,58 (15,3%,60)
	P75-P100 (%,n)	1,89-98,63 (35,6%,141)	2,40-278,36 (40%,158)	1,92-175,34 (36,4%,144)	1,70-87,67 (32,6%,395)	1,70-76,71 (33,3%,132)	1,60-109,59 (35,7%,141)	1,59-109,59 (35,9%,141)

Discussion

The analysis of the global data on the prevalence of lorazepam usage indicates that, overall, there was an increase in the use of lorazepam during the time studied, data that agreed with the growing use described in similar studies carried out in Spain ^(7,18,19). After a thorough review of the literature, it was not possible to find studies that yielded consumption data presented in our format.

However, it is comparable with the results of the study of consumption by years of the AEMPS about the use of anxiolytic and hypnotic drugs in Spain ⁽²⁰⁾, which highlighted an increase of 7.79% in the consumption of lorazepam between 2012-2018, whereas our study shows a lower increase of that active ingredient being 0,42%, this may be due to the fact that the study conducted by the AEMPS takes into account the consumption of official and mutual prescriptions, the latter not being included in our study, also in the AEMPS study are included all the active principles of the therapeutic group N05B, and all ages.

Table 1: Distribution of the population by age groups and DHD interval for each year of study.

The analysis by sex highlights that women have higher DHD values than men, as described in other studies carried out in Spain⁽²¹⁻²³⁾ and outside Spain^(24,25). These results can be attributed to a greater concern for their state of health and greater frequency of medical visits compared to men^(26, 27), and a higher prevalence of psychiatric diseases in this group^(28, 29).

In relation to the consumption of BZP by age groups, we have observed that it is in the last age intervals where the consumption of lorazepam is increasing, coinciding with the highest DHD. That agreed with the trend of different studies carried out in our country about the consumption of BZP that point to a higher consumption in older groups of population^(21, 23). The fact that older patients are those who consume more of these drugs is worrying, since they present a greater risk of adverse effects associated with BZP consumption⁽³⁰⁾.

Among the limitations of this study, it should be noticed that we have little information on the patient; we only know the sex and age, but not the treatment indication. In addition, our data come from prescriptions dispensed and billed to the SMS from 2012 to 2018, not including data from the corresponding private prescription dispensations or those charged to any other mutual insurance company rather than the SMS. The data refer to dispensations in the municipality of Mula, but we cannot ensure that the prescriptions come all in their origin from the primary care centers of Mula, being able to collect disperse data of dispensations from patients who live outside the municipality but withdraw their medication in Mula, just as we cannot ensure that everything prescribed in this health area is dispensed in this same municipality.

Among the strengths we can highlight that this is a pioneering and novel analysis of the DHD that allows a better reflection of the population consuming this type of medication, and also that the study time is extense, allowing a long follow-up time duration of these treatments. On the other hand, this work leaves open the possibility of new lines of research, extending the years of study, carrying it out in the whole Region of Murcia and including more active ingredients to the therapeutic group analyzed. It is important to develop a new line of research to analyze the impact of different strategies to reduce the consumption of these drugs, promote their rational use, and try to reduce their consumption rates, through the development multidisciplinary protocols uniting pharmacist and primary care providers. In addition, it would be interesting to extend the study sample both in terms of population and the number of active ingredients to be analyzed in order to observe whether consumption behavior is similar to what has been described in our study.

In conclusion, the consumption of lorazepam is high in the municipality of Mula, Region of Murcia, even higher as patients' age increases, mostly in women, which aggravates the risk of the appearance of adverse effects that they produce.

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