

## Benzodiazepines Drug Consumption Trends in a Community Pharmacy. Assessment of the Dispensed Daily Dose

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### Abstract

The present study evaluates the use and the correspondence between the Defined Daily Dose (DDD) set by the WHO Collaborating Center for Drug Statistics Methodology database with the Prescribed Daily Doses (PDD) that are dispensed of seven Benzodiazepines (BZD) in a Community Pharmacy (Tenerife, Spain) from 2015 to 2018 using a retrospective descriptive observational cross-sectional study. A total of 15489 BZD dispensations were recorded and assessed.

Lormetazepam (DDD: 1 mg): the PDD of 2 mg accounts for 71% of the dispensations compared to 29% of the dose of 1 mg. Lorazepam (DDD: 2.5 mg): the PDD of 1 mg (89% of the total Lorazepam dispensed). Alprazolam (DDD: 1 mg): 0.50 mg PDD (55% of the dispensations); 0.25 mg PDD (29% of the dispensations); 1 mg PDD (11% of the dispensations); 2 mg PDD (4% of the dispensations). Diazepam (DDD: 10 mg): 5 mg PDD (51%); 10 mg PDD (27%); 2.5 mg PDD (21%); 2 mg PDD (0.39%). Bromazepam (DDD: 10 mg): 1.5 mg PDD (61%); 3 mg PDD (39%); 6 mg PDD (0.41%).

A substantial discrepancy between the PDD and the DDD has been observed for Lormetazepam where the most prescribed and dispensed dose (2 mg) is double the DDD. Based on these results, a more frequent follow up of all 2 mg lormetazepam prescriptions is suggested. This fact justifies and encourages the provision of Pharmaceutical Care services in coordination with other health professionals to ensure safe use, optimize the therapeutic objectives of BZD and reduce drug-related problems while BZD are being used.

**Keywords:** Benzodiazepines; Lormetazepam; Dose; Pharmacy; Pharmaceutical Care

### Introduction

Benzodiazepines (BZD) are psychotropic drugs that enhance the inhibitory action of the GABA neurotransmitter and are prescribed for severe muscle spasms, tremors, acute seizures and alcohol and drug withdrawal symptoms but their main uses are still in the treatment of anxiety and insomnia [1,2].

Since the 1990s, there has been a progressive increase in the consumption of anxiolytics worldwide and the BZD have stood out for their high rates of prescription [14,15]. Between 2000 and 2007, Spanish consumption of anxiolytics was 37% higher than the European average, ranking fifth after Portugal, France, Luxembourg and Hungary [16,17]. The report of the Spanish Agency for Medicines and Health Products (AEMPS) on the use of anxiolytic and hypnotic drugs in the Spanish population during the period 2000 - 2012, reports an

increase of 46.8% in the group of anxiolytics and 81.8% in the group of hypnotics and sedatives [18,19]. Furthermore, in Spain, the latest National Health Survey suggests that 1 in 10 people take BZD [20]. According to the survey on alcohol and drugs (EDADES 1995 - 2017) of the Spanish National Plan on Drugs (PNSD), the population of hypnotosedants declined in 2015 (18.7%) compared to 2013 (20.8%). Undoubtedly, the most remarkable fact of the study is that 7.5% of patients aged 15 to 64 had consumed hypnotic patients in the previous 30 days, of which 80% consumed them daily (5.9%) [21,22].

BZD are considered safe drugs for use in short periods of time, however, with prolonged use and at doses higher than those recommended in the Clinical Practice Guidelines and technical data sheets of the medications, tolerance, dependence and adverse effects are observed such as falls associated with hip fractures [9], traffic accidents and cognitive impairment, among others [10-12]. The duration of treatment with BZD should be less than 8 - 12 weeks, including the period of gradual withdrawal, when used as anxiolytics, and less than 4 weeks in sleep disorders, however, it is common for treatment plans with BZD to exceed the recommended treatment time [13].

According to the WHO Collaborating Centre for Drug Statistics Methodology [3,4], the Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) as a measuring unit have become the gold standard for international drug utilization monitoring and research. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults and it is sometimes, a "dose" that is rarely if ever prescribed, because it might be an average of two or more commonly used doses [7,8]. DDDs are only assigned to drugs with an ATC code and DDDs for single substances are normally based on monotherapy.

The assigned DDD is based on the average adult dose recommended for the main indication as reflected by the ATC code. When setting the DDD, the recommended maintenance dose (long term therapeutic dose) is usually preferred. DDDs provide a fixed unit of measurement enabling the researcher to assess trends in drug consumption and to perform comparisons between population groups [16,17].

The DDD is a unit of measurement and does not necessarily reflect the recommended or Prescribed Daily Dose (PDD) that is defined as the average dose prescribed according to a representative sample of prescriptions [5,6]. In the case of therapeutic guidelines with more than one dose per day, the DDD would not coincide with the PDD but would be the result of the addition of the different daily doses. The PDD can be determined from studies of prescriptions or medical or pharmacy records and may vary according to both the illness treated and national therapeutic traditions and it is always important to relate the PDD to the diagnosis on which the dosage is based [32].

Although the prescription of BZD corresponds to the medical professional, the dispensation of BZD is performed in the Community Pharmacy after verification by the Community Pharmacist of the prescription. It is worth mentioning that the doses dispensed in the Community Pharmacy must coincide with the doses prescribed by the medical professional. The dispensing of benzodiazepines in the Community Pharmacy provides valuable information and the act of dispensing should be understood as a further step in the healthcare process that reinforces and promotes the health education of the BZD user and their pharmacovigilance.

### Objective of the Study

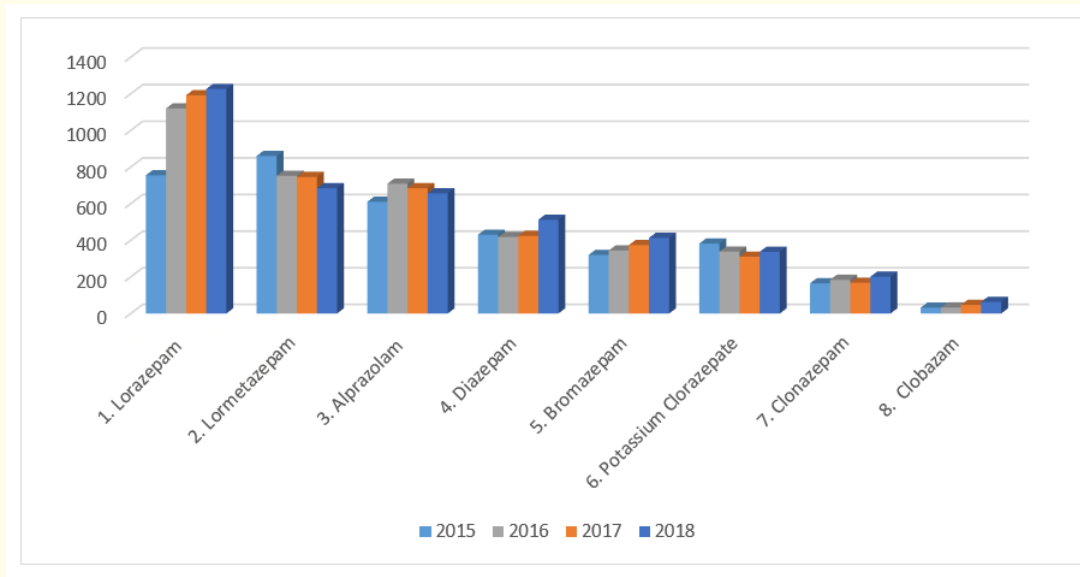
The main objective of the present work is to analyze the evolution of the dispensation of BZD in a Community Pharmacy on the island of Tenerife during the period 2015 - 2018 and to evaluate the doses dispensed and prescribed with the DDD recommended by the WHO for those BZD of greater dispensation.

### Method

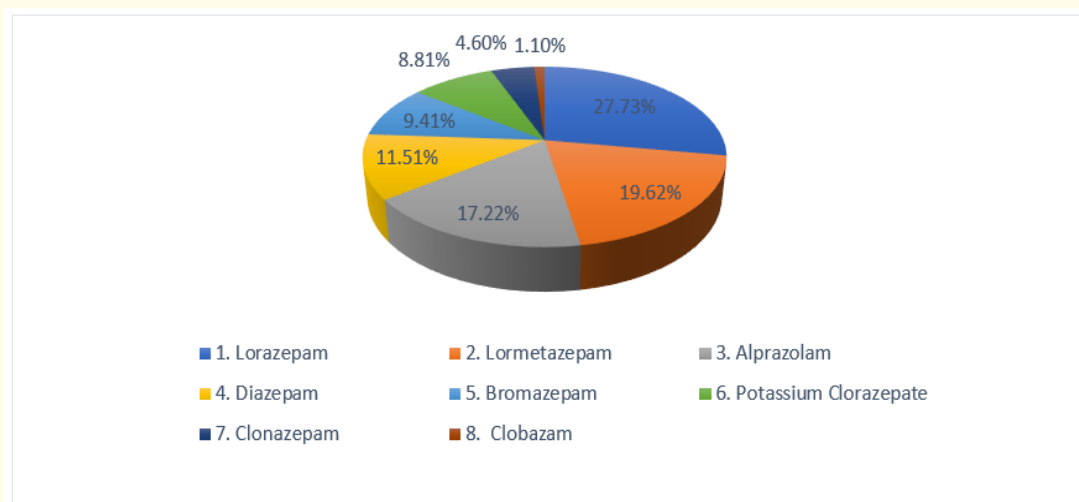
The study is a retrospective observational, descriptive and cross-sectional study of the dispensation of the seven active principles of the therapeutic group N05BA (anxiolytic indication BZD) and group N05CD (hypnotic and sedative indication BZD) of the WHO ATC classification that have a DDD (Table 1). The active substances of these groups that do not have a DDD set by the WHO have been excluded from the study. The ATC/DDD Index 2019 (WHO Collaborating Center for Drug Statistics Methodology) relationship has been used for oral administration. The dispensing data have been grouped by molecule, dose and presentation.

**Results and Discussion**

Figure 1, 2 and table 1 show the recorded dispensations of BZD between 2015 and 2018 that show the characteristics of the 15489 dispensations of pharmaceutical specialties based on BZD.



**Figure 1:** Community Pharmacy 2015-2018 dispensed packets evolution.



**Figure 2:** Percentage of the different BZD molecules prescribed and dispensed in the Community Pharmacy.

	BZD	ATC Group	Half-Life	Defined Daily Dose (DDD)	Prescribed Daily Dose (PDD)	Total units by Dose	Total Percentage by Dose	No. Dispensed Packets	Percentage of No. Dispensed Packets
1	Lorazepam	N05BA	Intermediate	2.5 mg	1 mg	3812	89%	4293	27.7%
					2 mg	166	3.9%		
					5 mg	315	7.3%		
2	Lormetazepam	N05CD	Short	1 mg	1 mg	883	29%	3042	19.6%
					2 mg	2159	71%		
3	Alprazolam	N05BA	Intermediate	1 mg	0.25 mg	779	29.3%	2659	17.2%
					0.50 mg	1466	55%		
					1 mg	302	11.4%		
					2 mg	112	4.2%		
4	Diazepam	N05BA	Long	10 mg	2.5 mg	376	21%	1784	11.5%
					2 mg	7	0.4%		
					5 mg	913	51%		
					10 mg	488	27.4%		
5	Bromazepam	N05BA	Intermediate	10 mg	1.5 mg	881	61%	1451	9.4%
					3 mg	564	38.9%		
					6 mg	6	0.41%		
6	Potassium Clorazepate	N05BA	Long	20 mg	2.5 mg	19	1.4%	1367	8.8%
					5 mg	798	58.4%		
					10 mg	321	23.5%		
					15 mg	180	13.2%		
					50 mg	49	3.6%		
7	Clonazepam	N05BA	Long	8 mg	2.5 mg/ml	121	16.9%	718	4.6%
					0.50 mg	418	58%		
					2 mg	179	24.9%		
8	Clobazam	N05BA	Intermediate	20 mg	10 mg	151	86%	175	1.1%
					20 mg	24	13.7%		

PDD coincides with the dispensed dose.

**Table 1:** Dispensation of BZD (2015-2018) in the Community Pharmacy.

Of all the BZD, Lorazepam is the one with the highest number of prescriptions and consequent dispensations (4293 packets, 27.7%). The dispensation in our Pharmacy Office is line with the trends observed in Spain (2000 - 2010) [21] and in Canada (2000 - 2016) where Lorazepam was also the most consumed molecule among all BZD [23]. Lorazepam 1 mg (89% of the total Lorazepam dispensed) is the BZD with the highest number of prescriptions and dispensations (3812) over the four-year period of study. The PDD for this BZD is below the DDD recommended by WHO of 2.5 mg.

Between 2015 and 2018, 3042 packets of Lormetazepam were dispensed after the presentation of their corresponding prescriptions. Lormetazepam 2 mg accounts for 71% of the prescriptions and dispensations of this molecule with 2159 packets dispensed compared to 29% of prescriptions and dispensations of Lormetazepam 1 mg (883 packets). Given that it is a short half-life molecule and its main indication is insomnia, its most common schedule is 1 tablet every 24 hours, preferably at night. This study shows that Lormetazepam is being used in our health area at doses that double the 1 mg DDD recommended by the WHO Collaborating Center for Drug Statistics Methodology. There is a discrepancy between DDD and PDD of Lormetazepam 2 mg which is the more dispensed form. It might be advisable to use the lowest marketed dose of Lormetazepam for patients with insomnia treated with a single dose of Lormetazepam (1 mg). This not only coincides with the DDD recommended by the WHO, but it would also avoid possible drowsiness and daze of the patient the morning after. Similar figures were found when comparing our results with the total data (not differentiated by dose) observed for Lormetazepam on a national level [21].

Over the 4-year study period, a total of 2659 Alprazolam packets were dispensed in this Community Pharmacy. Alprazolam 0.50 mg accounted for 55% of the total dispensations of this molecule with 1466 packets followed by Alprazolam 0.25 mg (29.3%), Alprazolam 1 mg (11.4%) and Alprazolam 2 mg (4.2%). All Alprazolam pharmaceutical specialties present lower prescribed and dispensed doses than the DDD set at 1 mg. A study carried out in the Valencian Community (Spain) [3] over a 10-year period reported higher figures (29.8%) of total Alprazolam dispensations than those reported here (17.2%).

Diazepam (DDD: 10 mg) is prescribed and dispensed in doses of 5 mg (51%); 10 mg (27.4%); 2.5 mg (21%) and 2 mg (0.4%). The most dispensed dose (5 mg) is below the DDD. As this is a molecule with a long half-life, its main indication is as an anxiolytic, since if it was used for insomnia it would cause rebound drowsiness in the morning. The highest prescription dose (5 mg) is usually used in a single nocturnal dose.

Bromazepam (1451 packets dispensed) comes in three commercial presentations (1.5 mg, 3 mg and 6 mg). Bromazepam 1.5 mg accounts for 61% of the prescriptions of this molecule followed by Bromazepam 3 mg (38.9%) and Bromazepam 6 mg (0.41%). All prescribed and dispensed doses (PDD) are below the 10 mg DDD set by the WHO. This active substance usually includes several day administrations. Thus, patients who use 1.5 mg usually take the medication twice a day (1 every 12 hours) and therefore, their daily dose would be 3 mg. Only patients under treatment with Bromazepam 6 mg who have been prescribed 2 doses/day would be exceeding the DDD by 2 mg/day, although the time between taking the medication allows the metabolization and elimination of the active ingredient.

A total of 1367 dispensations have been recorded for the five doses of Potassium Clorazepate marketed in Spain. The most prescribed dose is 5 mg accounting for 58.4%, followed by 10 mg (23.5%), 15 mg (13.2%), 50 mg (3.6%) and 2.5 mg (1.4%). If these PDDs are compared with the DDD, all of them are lower than the 20 mg DDD except the 50 mg dose that is reserved for very specific cases of generalized resistant anxiety or insomnia cases and in a nighttime dose because it is a molecule with long half-life. In addition, the 5 mg dose usually includes taking the medication several times per day although the DDD would not be exceeded even in patients with 3 daily doses.

718 packets of Clonazepam were dispensed in the study period. Clonazepam 0.50 mg accounts for 58% of prescriptions while Clonazepam 2 mg represents 24.9%. Clonazepam 2.5 mg/mL is marketed in a pharmaceutical form in drops and is 16.9% of the total dispensations of this molecule. All doses are lower than the 8 mg DDD recommended by the WHO. In this active principle it is common for the guidelines to include several daily administrations. While patients who take 0.5 mg twice a day (1 every 12 hours) would be exposed to 1 mg/day (< DDD) and patients treated with 2 mg and 2 doses/day would be exposed to 4 mg/day. Both situations are below the DDD. In patients who take the medication at night, it should be taken into account that due to its long elimination half-life the patient would wake up with excessive sedation and it is, therefore, preferable to use the 0.50 mg dose.

Only 175 packets of Clobazam were dispensed in the study period. The 10 mg PDD (50% of the DDD set by the WHO) predominates with 86% versus the Clobazam 20 mg (13.7%) dispensations that coincide with the DDD.

If we exclude the Lormetazepam indicated for insomnia, the results of our health area concerning the consumption of the active ingredients of these ATC groups show the same trend as those published for Spain in 2013 [14] with Lorazepam, Alprazolam and Diazepam as the three most dispensed anxiolytic molecules.

Another Spanish study in 2019 analyzed the consumption of BZD in a Primary Care center [16] and found that the most prescribed BZD were Diazepam (46.15%), Alprazolam (21.22%), Bromazepam (20.69%), Lormetazepam (15.91%) and Lorazepam (12.20%). The results of the present study, however, are nearly two times higher than the dispensing data for Lorazepam as it accounts for 27.7% of the total of the BZD dispensed and the prescription and dispensing figures are lower for Alprazolam (17.2%), Bromazepam (9.4%) and Diazepam (11.5%). Therefore, there is a discrepancy between the data on the use of BZD in Primary Care and the dispensing data in the Community Pharmacy, possibly due to the fact that the Primary Care center uses BZD in on-site treatments for specific emergencies that mean that Diazepam is most used active ingredient.

### Conclusion

The DDD is a unit of measurement and does not necessarily correspond to the recommended or Prescribed Daily Dose (PDD). Therefore, the PDD should always be related to the diagnosis on which the dosage is based (in the case of studied BZD the diagnosis could either be anxiety or insomnia). A substantial discrepancy between the PDD and the DDD has been observed for Lormetazepam where the most prescribed and consequently, dispensed dose of Lormetazepam (2 mg) is double the DDD established by WHO Collaborating Center for Drug Statistics Methodology database. Based on these results, we suggest a more frequent follow up that all 2mg lormetazepam prescriptions. The follow up of all BZD treatments BZD will not only make a reduction of the overall consumption of these therapeutic groups possible but will also seek to optimize their use and their therapeutic objectives by adapting them to the maximum recommended duration for the different indications which they are marketed for. This will also prevent all drug related problems associated with their use. This fact justifies and encourages the provision of Pharmaceutical Care services in coordination with other health professionals (health team) to ensure safe use of BZD. The community pharmacist, during the dispensation, may also contribute to improving the knowledge that patients using BZD have about their drug's use and risks, especially when the treatments are long term. Despite the limitations in this study that may affect the generalizability of the results, this study demonstrates the need for interventions based on the Pharmaceutical Care model which are capable of reducing drug-related problems while BZD are being used.

### Author Statement

Conception and design of the study: All authors. Carmen Rubio Armendáriz, Daida Alberto Armas, María Avelina Pérez Dieppa, Arturo Hardisson de la Torre.

Data collection: Daida Alberto Armas, María Avelina Pérez Dieppa.

Analysis and interpretation of the data: Carmen Rubio Armendáriz, Daida Alberto Armas, María Avelina Pérez Dieppa, Arturo Hardisson de la Torre.

Preparation of the manuscript: Edition of the manuscript: Carmen Rubio Armendáriz, Daida Alberto Armas.

Review of the manuscript: the final version of the article has the approval of all the authors.

### Transparency Statement

Carmen Rubio Armendariz, the author for correspondence on behalf of the rest of the signatories, guarantees the accuracy, transparency and honesty of the data and information contained in the study sent to this journal; that no relevant information has been omitted; and that all discrepancies between authors have been adequately resolved and described.

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## Conflict of Interest

The authors declare that they have no conflicts of interest.

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