

Supplementary Materials: Trends and Geographic Variabilities in Benzodiazepines Prescription in Primary Care to Older Adults: A 3-year Population-based Ecological Study in Portugal

Table S1: Excluded benzodiazepines (N05BA and N05CD groups) with reasons (n=20).

ATC Code	Benzodiazepine	Reason of exclusion
N05BA03	Medazepam	(a) BZD without Marketing Authorization (MA) or had lost MA in Portugal during the study period
N05BA07	Adinazolam	
N05BA13	Halazepam	
N05BA14	Pinazepam	
N05BA15	Camazepam	
N05BA16	Nordazepam	
N05BA17	Fludiazepam	
N05BA19	Etizolam	
N05BA21	Clotiazepam	
N05BA23	Tofizopam	
N05BA24	Bentazepam	
N05CD02	Nitrazepam	
N05CD03	Flunitrazepam	
N05CD06	Lormetazepam	
N05CD10	Quazepam	
N05CD12	Doxefazepam	
N05CD13	Cinolazepam	
N05CD15	Nimetazepam	
N05BA10	Ketazolam	(b) without a defined daily dose, accordingly to the SIM@SNS online platform and to the ATC/WHO Index
N05CD14	Remimazolam	(c) exclusively used in a hospital setting

Table S2: Demographic data of study population in 2019.

ARS/Sex/Age group	Male		Female		Total Male	Total Female	Total
	65-74 y	≥ 75 y	65-74 y	≥ 75 y			
ARSN	192926	144787	233886	233514	337713	467400	805113
ARSC	97257	86499	116017	139950	183756	255967	439723
ARSLVT	179604	146041	225182	232645	325645	457827	783472
ARSALE	25946	25437	29830	41220	51383	71050	122433
ARSALG	22356	19261	25718	28718	41617	54436	96053
Total	518089	422025	630633	676047	940114	1306680	2246794

Table S3: Demographic data of study population in 2020.

ARS/Sex/Age group	Male		Female		Total Male	Total Female	Total
	65-74 y	≥ 75 y	65-74 y	≥ 75 y			
ARSN	184555	136395	222341	217495	320950	439836	760786
ARSC	101226	89265	120469	145101	190491	265570	456061
ARSLVT	179663	149744	225566	237389	329407	462955	792362
ARSALE	26182	25023	30011	40659	51205	70670	121875
ARSALG	22488	19431	26097	28990	41919	55087	97006
Total	514114	419858	624484	669634	933972	1294118	2228090

Table S4: Demographic data of study population in 2021.

ARS/Sex/Age group	Male	Female	Total
	≥ 65 y	≥ 65 y	
ARSN	348774	459350	808124
ARSC	216461	284064	500525
ARSLVT	328745	456804	785549
ARSALE	56085	73681	129766
ARSALG	50932	60048	110980
Total	1000997	1333947	2334944

Table S5: Female and Male Relation for every BZD, in every ARS, over the last 3 years
(Intermediate Calculations).

	<i>Mulheres</i>					<i>Homens</i>				
	Alentejo	Algarve	Norte	Centro	LVT	Alentejo	Algarve	Norte	Centro	LVT
<i>Midazolam</i>	522680	226713	1083398	561606	1552419	182709	118774	532216	238398	646178
<i>Temazepam</i>	82936	55916	201684	60648	456191	24836	18760	56154	21462	123438
<i>Triazolam</i>	198740	136580	848760	240180	1079220	57260	60740	342140	102040	307400
<i>Estazolam</i>	484111	195049	1971770	793193	2820675	157901	81229	866068	318659	1028151
<i>Flurazepam</i>	189340	76893	1103591	304569	1033614	71828	45497	476762	138764	419926
<i>Cloxazolam</i>	405190	164735	3578155	2017650	2391650	153930	65305	1464715	683345	908230
<i>Ethyl Loflazepate</i>	1021940	760320	10224400	4282520	8619940	321660	233580	3828640	1457940	2870320
<i>Alprazolam</i>	5704255	3016795	43277505	29277115	33944515	1738865	1219150	16509195	10427580	12011745
<i>Clobazam</i>	122410	83695	1731785	544555	985195	49875	27535	795575	250490	414085
<i>Bromazepam</i>	1156890	870312	8008239	3452202	8044782	366417	325449	2619726	1150407	2551647
<i>Potassium Clozepamate</i>	322690	156310	2124440	1368855	1754525	90720	61335	720745	445465	585185
<i>Chlordiazepoxide</i>	2760	950	3993	633	2303	1000	290	2303	403	1163
<i>Diazepam</i>	1927097	816383	11813788	8685364	12176502	793779	287032	4841784	3258322	4666546
<i>Prazepam</i>	520	1880	23773	3313	5920	347	573	8553	1520	1140
<i>Oxazepam</i>	98034	90060	1077177	1541994	688461	69126	70671	1606068	1341534	527391
<i>Lorazepam</i>	3642170	2060188	47619206	23890720	23928480	1245136	805362	19788884	9189372	8591362
<i>Cetazolam</i>	0	0	0	0	0	0	0	0	0	0
<i>Brotizolam</i>	574728	273756	2462866	642292	2457266	197232	98812	1903930	254940	936922
<i>Loprazolam</i>	331080	74430	1133280	304635	826725	112485	37740	518580	143205	309780
<i>Mexazolam</i>	2431	2183	10415	8549	13707	766	729	3651	2715	4529
TOTAL	16790002	9063148	1.38E+08	77980593	102782090	5635872	3558563	56885689	29426561	36905138

Table S6: N05B and N05C National Percentage (%), over the last 3 years.

Grupos ATC 3rd level	N05C	N05B
Total 3 anos	35477073	441125565
%	7.4%	92.6%

Table S7: N05B-Top5 National Percentage (%), over the last 3 years.

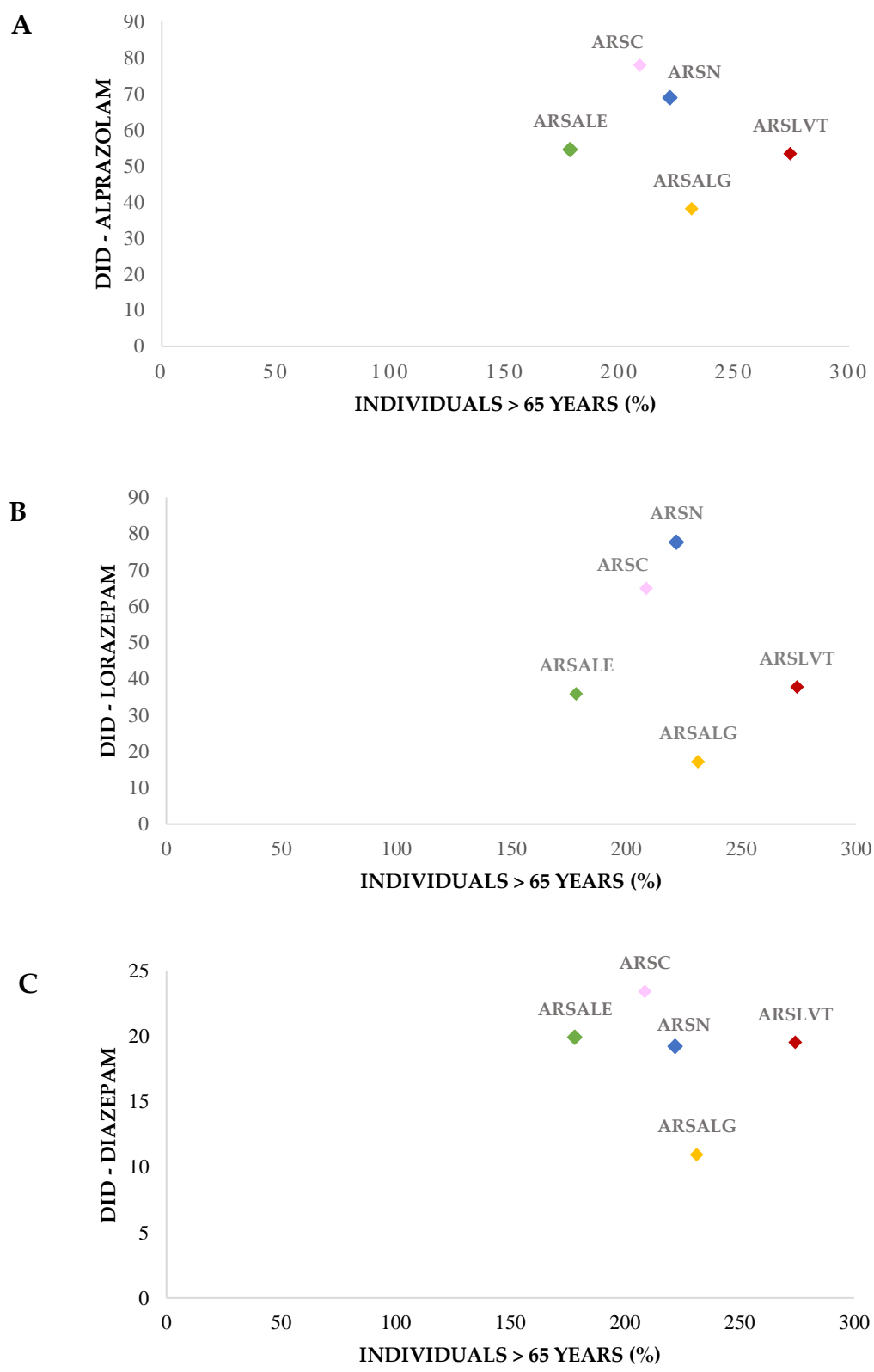
	Alprazolam	Lorazepam	Diazepam	Ethyl Loflazepate	Bromazepam	TOTAL
Top 5	N05BA12	N05BA06	N05BA01	N05BA18	N05BA08	
Total	157126720	140760880	49378727	33621260	28546071	
% do total	33.0%	29.5%	10.4%	7.1%	6.0%	

Table S8: Gender and Age Group differences in Alprazolam, Lorazepam, Diazepam, Ethyl Loflazepate and Bromazepam prescription according to each ARS and over the years.

DDD/ 1000 inhabitants ^a /day (DID)		2019				2020				2021*		Δ 2019-2021	
		Female		Male		Female		Male		Female	Male	Female	Male
		65-74	≥ 75	65-74	≥ 75	65-74	≥ 75	65-74	≥ 75				
ARSN	Alprazolam	83.7	73.7	41.1	41.8	94.3	85.4	46.2	49.2	91.8	45.8	86.7	44.9
	Lorazepam	75.1	99.6	42.9	59.1	84.7	113.3	48.4	67.0	100.3	55.2	95.4	53.8
	Diazepam	24.2	20.0	12.9	12.0	27.1	22.3	14.4	13.5	24.2	13.0	23.7	13.2
	Ethyl Loflazepate	25.0	17.2	12.2	9.6	19.7	13.6	9.8	7.8	23.5	11.1	20.5	10.4
	Bromazepam	14.2	15.8	6.2	7.8	15.4	17.9	6.5	8.8	16.5	7.0	16.0	7.1
ARSC	Alprazolam	98.1	101.4	45.7	53.7	98.3	102.5	45.5	55.4	98.0	45.7	99.5	48.3
	Lorazepam	68.0	91.6	34.7	52.5	68.2	92.8	36.3	52.9	81.0	40.9	81.2	42.6
	Diazepam	34.1	28.1	16.2	15.6	32.6	28.2	16.1	15.5	27.7	13.8	29.5	15.1
	Ethyl Loflazepate	19.8	13.9	8.6	7.0	13.4	9.3	6.1	4.7	15.9	5.0	14.6	6.8
	Bromazepam	10.2	13.4	4.5	6.7	10.0	13.5	4.4	6.9	11.4	7.0	11.7	5.3
ARSLVT	Alprazolam	61.2	66.3	29.0	34.4	64.6	69.0	31.3	36.9	71.7	34.9	67.5	33.4
	Lorazepam	34.0	56.9	17.0	29.8	35.5	58.3	18.4	31.2	49.8	24.8	47.6	23.9
	Diazepam	24.9	23.7	12.8	13.3	24.9	23.6	12.8	13.4	24.1	12.9	24.2	13.0
	Ethyl Loflazepate	20.1	15.7	9.0	7.6	15.0	11.1	6.6	5.9	20.6	9.4	17.1	8.0
	Bromazepam	13.6	17.4	5.8	8.2	13.6	17.8	6.1	8.4	16.7	7.3	16.0	7.1
ARSALE	Alprazolam	68.9	70.8	25.5	33.0	72.8	75.2	27.4	33.9	73.3	30.2	72.5	30.0
	Lorazepam	34.2	51.6	15.1	25.2	36.5	55.1	17.3	28.2	47.3	21.6	49.0	22.8
	Diazepam	26.2	24.5	13.8	14.0	27.3	24.1	14.7	14.2	22.9	12.8	24.5	13.7
	Ethyl Loflazepate	17.4	11.7	6.3	5.9	12.1	7.5	4.2	4.3	15.4	6.3	13.0	5.6
	Bromazepam	13.5	15.1	5.3	7.5	14.2	15.7	5.5	7.8	14.6	6.0	14.7	6.3
ARSALG	Alprazolam	47.2	48.0	23.6	25.1	51.2	49.8	25.8	28.3	48.1	23.5	48.7	24.8
	Lorazepam	24.5	40.1	13.0	20.3	25.7	40.5	14.9	20.0	33.6	15.7	33.3	16.4
	Diazepam	14.8	12.9	8.2	8.2	14.5	12.5	8.4	9.2	12.4	7.5	13.2	8.1
	Ethyl Loflazepate	15.5	11.7	5.5	4.9	11.0	7.7	4.5	3.6	13.9	5.0	12.3	4.8
	Bromazepam	12.2	15.2	5.5	8.0	13.2	15.8	6.3	8.5	13.8	6.1	14.1	6.6

* DID stratified by age was calculated only between 2019 and 2020 since official data for the older population in the year of 2021 are grouped only in “over 65 years”.

Figure S1 A-E: Distribution of ARS in relation to prescription (DID) of (A) Alprazolam, (B) Lorazepam, (C) Diazepam, (D) Ethyl Loflazepate and (E) Bromazepam.



D



E



Figure S2: Portugal's Continental National Map divided by ARS



Legend:

ARSN – North Regional Health Administration (*Administração Regional de Saúde do Norte*)

ARSC – Center Regional Health Administration (*Administração Regional de Saúde do Centro*)

ARSLVT – Lisbon and Tagus Valley Regional Health Administration (*Administração Regional de Saúde de Lisboa e Vale do Tejo*)

ARSALE – Alentejo Regional Health Administration (*Administração Regional de Saúde do Alentejo*)

ARSALG – Algarve Regional Health Administration (*Administração Regional de Saúde do Algarve*)