Amyotrophic Lateral Sclerosis Incidence and Previous Prescriptions of Drugs for the Nervous System

Amyotrophic Lateral Sclerosis incidence and previous prescriptions of drugs for the nervous system

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Abstract

Background: An increased frequency of psychotic disorders in Amyotrophic Lateral Sclerosis (ALS) families compared to controls has been reported. Aim of our study was to assess the relationship between nervous system drugs (NSD) prescriptions and subsequent onset of ALS in a large Italian population.

Methods: The study population consisted of all subjects over 15 years old at the 2001 Italian census, resident in Turin since 1996 (n=687,324), followed up for ALS occurrence from 2002 to 2014. Exposure to NSD was measured until 2012, or until one year before ALS onset. The association of ALS with NSD was estimated for ever and cumulative exposure. Analyses were conducted through Cox proportional Hazards models adjusted for sex, age, education, marital status and drug co-exposure.

Results: In the analysis for ever exposure, Opioids were significantly inversely associated with ALS risk (HR=0.59), while Antiepileptics (HR=1.35) showed a marginally significantly positive association. Examining cumulative exposure, the protective role of Opiods associated with more than four prescriptions and the risk effect of Antiepileptics for over six prescriptions were confirmed.

Conclusions: The present study revealed associations of ALS onset with previous exposure to Opioids and Antiepileptics, which are novel findings, to our knowledge, and should be further investigated.

Keywords

Amyotrophic lateral sclerosis, nervous system drugs, antidepressant drugs, opioid drugs, antiepileptic drugs, survival analysis

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder of the motor system, characterized by muscular atrophy leading to death due to respiratory failure. During the trajectory of the disease, ALS patients experience progressive immobility and inability to speak, swallow and breathe. The median survival of ALS is 2-4 years from symptoms onset, while a period of 9-12 months usually occurs from first symptoms to diagnosis [1].

The mean annual incidence of ALS in Europe is estimated to be 2.08 (IQR 1.47-2.43) per 100,000 population [2]. ALS incidence increases with age, with a peak in the seventh decade [2], slightly lower for familial than for sporadic ALS [3].

ALS is familial in about 10% cases and sporadic in the remaining 90% [4]. The findings in ALS genetics in the last years have had a significant impact in improving our knowledge on the molecular mechanisms of motor neuron degeneration, although the etiology of most sporadic ALS cases remains unknown [5]. The research on environmental exposure for ALS produced a large number of contributes, although findings were mixed and not consistent [1].

A few recent studies, which focused on the potential role of the consumption of some drugs in ALS onset, have identified significant associations with centrally acting muscle relaxants (CAMRs), non-steroidal anti-inflammatory drugs (NSAIDs) and anti-hypertensive drugs. In particular, the risk of ALS was found to be reduced among subjects with previous consumption of CAMRs [6] and of NSAID [7,8,9], and of Angiotensin-Converting Enzyme (ACE) inhibitors drugs [10].

Additionally, Antipsychotic and Antidepressant drugs have been hypothesized to be protective toward ALS onset [11], while some studies have shown an increased risk of psychotic manifestations and other neurodegenerative disorders associated in ALS patients and their family aggregates [12,13,14,15]. However, no longitudinal studies have been conducted on the association between ALS onset and previous nervous system drugs (NSD) consumption.

The aim of the present study was to assess whether drugs acting on nervous system could have an effect on the development of ALS. For this purpose, we analyzed the association between prescriptions of NSD and subsequent risk of developing ALS in a large Italian urban population.

Materials and Methods

Data collection

The study population included all people older than 15 years, identified at 2001 Italian census and resident in the town of Turin (Italy) from January 1st 1996 (n=687,324). Baseline information on demographics, marital status and educational level was obtained from 2001 census data, which were linked, by means of a unique identification number, with the Municipality Registry, the ATC Drug Prescription Registry, and the Piedmont and Valle d'Aosta ALS Register (PARALS). The PARALS, established in 1995, is a prospective epidemiological register of ALS in two Italian regions (total population, 4,500,000 inhabitants) and has a very good level of completeness [16].

Subjects were followed up for ALS occurrence from January 1st 2002 to December 31st 2014, or until the date of emigration out of Turin, death or ALS onset, defined as the time of motor symptoms onset. The outcome was represented by ALS onset, ascertained through the PARALS and recorded up to December 31st, 2014. Subjects diagnosed with ALS before the start of follow-up were excluded from the study (N= 92).

NSD were extracted from the Piedmont Regional Drugs Registry, in which all drugs prescribed by medical doctors of the National Health Service (NHS) were registered since January 1st 1997. All drugs bought without NHS general practitioners' prescriptions (e.g. over the counter drugs) are not included in the regional Drug Prescription Registry. NSD were identified through the presence of the macro-code "N" of the Anatomical Therapeutic Chemical (ATC) classification, a system developed by

the World Health Organization which classifies all drugs into definite groups, based on their therapeutic, pharmacological and chemical properties [17]. Some families of NSD were not considered because of the small numbers of subjects who were prescribed drugs belonging to these families, and because the Piedmont Regional Drug Registry does not include certain classes of drugs which cannot be prescribed through the Italian NHS, the most important being anxiolytics, hypnotics and sedatives.

The association between ALS and drug prescriptions was explored for the following ATC families of NSD, up to the third level of classification: Opioids (N02A); Antiepileptic drugs (N03A); Antiparkinsonian drugs (N04); Antipsychotics (N05A); Antidepressants (N06A).

The study was conducted using Italian administrative data under the frame of the National Plan of Statistics [18]. The record-linkage between administrative data (census, drug prescriptions and mortality data) and PARALS was performed in accordance with Italian regulations on the privacy and with the approval of the local ethical committee.

Statistical analysis

Exposure to NSD was measured from 1997 January 1st until December 31st 2012 or, for ALS cases, until one year before the onset of the disease. Exposure to each drug family considered was treated as time-dependent variable, which changed at the date of every new prescription. A time-span dataset was then constructed in order to perform survival analysis: the first observation covered the time span from the entry into the study until the time of a new prescription, the second observation spans from the last prescription to the time of a second new prescription, and so on.

The association between NSD consumption and ALS onset was assessed using Cox proportional Hazards models with robust standard errors. A first model was adjusted for age class (15-29, 30-44, 45-59, 60-74, over 75 years), sex and prescription of NSD families other than the one examined. A second model was built adjusting also for educational level (primary, secondary, higher and graduate education) and marital status (married, unmarried and previously married).

The association of ALS with each class of NSD was estimated for both ever and cumulative exposure, using subjects without prescriptions as the reference category of the corresponding class of drugs. Ever exposure was defined as having at least one prescription of the corresponding drug family, while cumulative exposure as the number of prescriptions for each drug family, classified in three ordinal categories, built on the basis of the distribution of the exposed cases (unexposed, low and middle-high exposed, where low exposed corresponded to the first tertile of cumulative dose and middle-high to the second and the third tertiles).

Furthermore, in order to explore whether the association of a certain drug family was attributable to specific drugs within this family, the relationship between ALS and ever exposure to specific active pharmaceutical ingredients with five or more ALS exposed cases was examined in a model controlled for age, sex, education and marital status.

Last, a sensitivity analysis was performed, in which exposure to drugs was truncated two years before ALS onset, instead of one year, in order to limit the possibility that the association observed with ALS was actually attributable to their use as therapeutic agents for ALS at start of symptoms, although before its diagnosis (e.g. drugs consumption for pain therapy).

Results

Descriptive results

During the follow-up period, 300 subjects resident in the town of Turin were diagnosed with ALS (165 men and 135 women). Descriptive statistics of the study population are presented in Table 1: distributions by sex, age, educational level and marital status are referred to the start of follow-up. Distributions of NSD prescriptions (Table 2) are instead referred to the whole follow-up period.

The mean ALS annual incidence in the study population over 15 years was 4.0 per 100,000 inhabitants (4.8 among men and 3.4 among women). As expected, an increasing trend of ALS rates with increasing age was observed until 75 years, with a strong increase above 45 years and only 6.4% of subjects with ALS onset below 45 years.

With respect to the distribution of drugs prescriptions, ever exposure was most common for Antidepressant drugs (ALS cases: 25.3%, non-cases: 28.2%), followed by Opioids (ALS cases: 5.8%, non-cases: 18.5%) and Antiepileptics (ALS cases: 10.3%, non-cases: 11.1%), whereas for Antiparkinsonians and Antipsychotics the proportion of subjects with at least one prescription did not exceed 10%.

TAB. 1

TAB. 2

In ALS cases, most common active ingredients in the Opioids family were Tramadol (61.0%) and Codeine and combinations (27.0%), while among Antiepileptics the most common was Gabapentin (49%) (Table 5, Online Resource).

Among ALS cases, average latency between first drug prescription and clinical onset of ALS was 2.8 years for Opioids, 5.6 years for Antiepileptics, 4.7 years for Antiparkinsonians, 7.2 years for Antipsychotics, and 5.7 years for Antidepressants.

Association between NSD and ALS onset

The associations of ALS with ever and cumulative exposure to the different drug families are shown in Tables 2 and 3. In both tables, Model 1 shows results adjusted for age, sex and drug co-exposure, and

Model 2 reports the results adjusted also for education and marital status. Since the results of Model 1 and 2 were very similar, only the latter will be presented and commented in the text.

In the fully adjusted model for ever exposure (Table 2), only Opioids were significantly associated with ALS risk and showed a protective effect (HR=0.59; 95% CI=0.35-0.97). A non-significant decrease of ALS risk was also observed for the exposure to Antiparkinsonian drugs (HR=0.62, 95% CI=0.27-1.40). Conversely, the prescription of Antiepileptics was associated with a non-significant increase of ALS risk (HR=1.35; 95% CI=0.92-2.00). For Antipsychotics and Antidepressants, Hazard Ratios were close to one and non-significant.

When examining cumulative exposure (Table 3), in the fully adjusted model (Model 2) Opiods showed a significant decreasing trend in ALS risk across ordered increasing levels of cumulative exposure (test for trend: p=0.014), although only the highest exposure category was marginally significantly associated with ALS (HR=0.25; 95% CI=0.06-1.01). Cumulative exposure to Antiepileptics also showed a significant trend with increasing ALS risk (test for trend: p=0.040), but in the opposite direction: in this case, too, only the highest exposure category was marginally significantly associated with ALS (HR=1.84; 95% CI=0.99-3.42). Antidepressant drugs in the lower cumulative exposure category were also significantly associated with an increased ALS risk (HR=1.39, 95% CI: 1.02-1.90), although the risk was below one and non-significant for the highest one. No trend in risk or association with ALS was instead observed for any category of cumulative exposure to Antiparkinsonian or Antipsychotic drugs.

TAB. 3

TAB. 4

When examining the associations with specific active ingredients, for none of the drugs examined a significant association with ALS was found, although the direction remained the same as for drug families. Among Opioids, HR for Tramadol was 0.60 (95% CI: 0.32-1.14) and for Codeine and

combinations was 0.52 (95% CI: 0.21-1.30). Regarding Antiepileptic drugs, the relative risk associated with Gabapentin was 1.52 (95% CI: 0.93-2.47).

The results of the sensitivity analysis, in which drugs exposure was truncated two years before ALS onset, were similar to the previous ones, except for the loss of significance of the association observed between the risk of ALS and low cumulative exposure to Antidepressants (HR=1.28; 95% CI=0.94-1.76).

Discussion

The present study found a protective effect of Opioids and a detrimental effect of Antiepileptics on the onset of ALS. The dose-response effect observed between ALS risk and cumulative exposure to these NSD families indicates that these associations may reflect a causal relationship. It is however uncertain whether these associations are actually attributable to the diseases for which these drugs were prescribed, rather than to detrimental or protective effects of the drugs themselves.

In our cohort we found an increased exposure to Antiepileptics well before ALS onset (5.6 years on average). This observation may indicate that epilepsy is an antecedent phenomenon laying in the developing trajectory of the disease, in according with a previous observation that in a cohort of ALS patients the incidence of epilepsy was higher than in the general population [19]. A possible direct detrimental effect of Antiepileptic drugs on ALS onset cannot be excluded, although neuroprotective effects of Gabapentin and Valproic acid have been found in ALS mouse models [20,21], which were confirmed in clinical trials on humans [22,23].

Concerning Opioids, it could well be that ALS patients experience pain during the onset period and be treated with these drugs in order to reduce it, but in this case Opioids consumption should be positively associated with ALS, in contrast with our findings.

The low risk associated with the high cumulative exposure category of Antidepressants suggests that the excess risk observed for the low cumulative exposure category is probably a fortuitous finding, considering that a great proportion of subjects in this category (40%) were prescribed Antidepressants only for a short period or even once, and it does not seem biologically plausible that such a low cumulative exposure could have had an influence on ALS development. Nonetheless, this finding appears consistent with the results of a recent study on ALS patients, which observed, more than one year before ALS diagnosis, a two-fold prevalence ratio of antidepressant use, compared to the general population [24]. A narrative review on the relationship between exposure to Antipsychotics and Antidepressants, and ALS onset has hypothesized that these drugs may reduce the risk of developing ALS [11].

In this longitudinal study, prevalent cases have been excluded before start of follow-up allowing therefore to take into account the temporal sequence between drug exposure and ALS occurrence and to minimize the possibility of selection bias due to the short duration of the disease and. Several studies found associations of neurodegenerative and psychiatric disorders with ALS, but were not able to examine the temporal relation with ALS onset [12,13,14,15,19]. The type of analysis performed, i.e. survival analysis, which considers the exposure to drugs as time-dependent variables, has allowed to classify correctly exposed and non-exposed periods at the individual level and to compute appropriately exposed and non-exposed person-years.

This study has some weakness. First, the exposure to the drugs was assessed for a relatively limited period, since data on lifetime exposure were not available. However, incomplete reconstruction of the history of the exposure to drugs might cause non-differential exposure misclassification, leading to an attenuation bias, which may explain null results for some drug families (such as Antiparkinsonian, Antipsychotic and Antidepressant drugs), but not the significant associations identified. Second, we could not include in the analysis as covariates life style habits, such as tobacco smoking, alcohol consumption, obesity or physical activity, although among these only smoking has been consistently associated with ALS [25]. However, adjustment for educational level should have at least partly controlled for differences in smoking habits between exposed and non-exposed groups.

Conclusion

The present study was performed in order to evaluate the association between previous consumption of NSD and ALS onset in a large Italian population. Opioids and Antiepileptics played a significant role on the onset of ALS: the former played a protective role on developing ALS disease, while the latter showed a detrimental effect. No significant effects were found for Antiparkinsonian, Antipsychotic and Antidepressant drugs. These associations between the drugs of nervous system and the onset of ALS represent a novel finding, which should be further investigated.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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TABLES

Table 1. Frequency distribution of sex, age, educational level and marital status at start of follow-up in ALS cases, non-cases and total populations.

	Non-ALS population		ALS Population		Total population	
	N	**%**	**N**	**%**	**N**	**%**
Sex						
male	319,911	46.6	165	55.0	320,076	46.6
female	367,113	53.4	135	45.0	367,248	53.4
Age						
15-29 years	114,640	16.7	2	0.7	114,642	16.7
30-44 years	165,873	24.1	17	5.7	165,890	24.1
45-59 years	164,951	24.0	101	33.6	165,052	24.0
60-74 years	165,743	24.2	153	51.0	165,896	24.2
over 75 years	75,817	11.0	27	9.0	75,844	11.0
educational level						
no school or elementary school	181,430	26.4	92	30.7	181,522	26.4
middle school	231,910	33.8	92	30.7	232,002	33.7
high school	196,168	28.5	79	26.3	196,247	28.6
graduation	77,516	11.3	37	12.3	77,553	11.3
marital status						
married	380,305	55.4	210	70.0	380,515	55.4
unmarried	188,650	27.4	31	10.3	188,681	27.4
previously married	118,069	17.2	59	19.7	118,128	17.2
Total	**687,024**	**100.0**	**300**	**100.0**	**687,324**	**100.0**

Table 2. Frequency distribution of nervous system drugs prescriptions (categorical cumulative dose classified in tertiles) at end of follow-up in ALS cases, non-cases and total populations.

	Non-ALS	ALS	Total

	Population		Population		population	
	N	%	N	%	N	%
Opioids– N02A						
no prescriptions	560,112	81.5	282	94.0	560,394	81.5
I tertile (up to 3)	46,776	6.8	10	3.3	46,786	6.8
II tertile (4 – 14)	39,428	5.8	4	1.3	39,432	5.8
III tertile (over 15)	40,708	5.9	4	1.4	40,712	5.9
Antiepileptics – N03A						
no prescriptions	610,613	88.9	269	89.7	610,882	88.9
I tertile (up to 6)	25,672	3.7	16	5.3	25,688	3.7
II tertile (7 – 35)	25,556	3.7	8	2.7	25,564	3.7
III tertile (over 36)	25,183	3.7	7	2.3	25,190	3.7
Antiparkinsons – N04						
no prescriptions	661,470	96.3	294	98.0	661,764	96.3
I tertile (up to 14)	8,676	1.3	2	0.7	8,678	1.3
II tertile (15 – 65)	8,378	1.2	3	1.0	8,381	1.2
III tertile (over 66)	8,500	1.2	1	0.3	8,501	1.2
Antipsychotics – N05A						
no prescriptions	624,432	90.9	275	91.7	624,707	90.9
I tertile (up to 8)	22,085	3.2	10	3.3	22,095	3.2
II tertile (9 – 41)	19,918	2.9	9	3.0	19,927	2.9
III tertile (over 42)	20,589	3.0	6	2.0	20,595	3.0
Antidepressants – N06A						
no prescriptions	493,221	71.8	224	74.7	493,445	71.8
I tertile (up to 4)	68,777	10.0	41	13.7	68,818	10.0
II tertile (5 – 21)	61,641	9.0	16	5.3	61,657	9.0
III tertile (over 22)	63,385	9.2	19	6.3	63,404	9.2
Total	**687,024**	**100.0**	**300**	**100.0**	**687,324**	**100.0**

Table 3. Hazard Ratios (HR) of ALS onset associated with nervous system drugs prescriptions distinguished by drug family (ATC) and ever exposure – Cox proportional Hazards models adjusted for age[a], sex, drug co-exposure *(Model 1), and also education[b] and marital status[c] (Model 2). Robust standard errors.*

	Model 1		Model 2	
	HR	**95% CI**	**HR**	**95% CI**
no prescriptions	1	-	1	-
Opioids (N02A)	**0.56**	**0.34-0.93**	**0.59**	**0.35-0.97**
Antiepileptics (N03A)	1.33	0.91-1.96	1.35	0.92-2.00
Antiparkinsons (N04)	0.61	0.28-1.39	0.62	0.27-1.40
Antipsychotics (N05A)	0.98	0.64-1.52	0.99	0.64-1.54
Antidepressants (N06A)	1.15	0.86-1.54	1.14	0.85-1.53

[a] age in 5 classes: 15-29, 30-44, 45-59, 60-74, over 75;

[b] education in 4 classes: no school or elementary school, middle school, high school and graduation;

[c] marital status in 3 classes: married, unmarried and previously married;

Table 4. Hazard Ratios (HR) of ALS onset associated with nervous system drugs prescriptions distinguished by drug family (ATC) and categorical cumulative dose – Cox proportional Hazards models adjusted for age[a], sex, drug co-exposure *(Model 1), and also education[b] and marital status[c] (Model 2). Robust standard errors.*

	Model 1		Model 2	
	HR	**95% CI**	**IRR**	**95% CI**
Opioids (N02A)				
no prescriptions	1	-	1	-
I tertile (up to 3)	0.68	0.40-1.16	0.71	0.42-1.21
II & III tertiles (over 4)	**0.24**	**0.06-0.96**	**0.25**	**0.06-1.01**
Antiepileptics (N03A)				
no prescriptions	1	-	1	-
I tertile (up to 6)	1.25	0.80-1.96	1.27	0.81-1.99

II & III tertiles (over 7)	1.80	0.97-3.34	**1.84**	**0.99-3.42**
Antiparkinsons (N04)				
no prescriptions	1	-	1	-
I tertile (up to 14)	0.62	0.22-1.72	0.63	0.23-1.73
II & III tertiles (over 15)	0.72	0.18-2.88	0.72	0.18-2.87
Antipsychotics (N05A)				
no prescriptions	1	-	1	-
I tertile (up to 8)	1.10	0.69-1.76	1.12	0.70-1.78
II & III tertiles (over 9)	0.93	0.38-2.31	0.95	0.38-2.35
Antidepressants (N06A)				
no prescriptions	1	-	1	-
I tertile (up to 4)	**1.40**	**1.03-1.91**	**1.39**	**1.02-1.90**
II &III tertiles (over 5)	0.78	0.49-1.24	0.76	0.48-1.21

[a] age in 5 classes: 15-29, 30-44, 45-59, 60-74, over 75;

[b] education in 4 classes: no school or elementary school, middle school, high school and graduation;

[c] marital status in 3 classes: married, unmarried and previously married;

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Table 5. Frequency distribution of ATC drugs prescriptions codes and active ingredients in ALS cases, non-cases and total populations.

ATC code	Active ingredient	Non-ALS population		ALS population		Total population	
		N	%	N	%	N	%
N02AA01	Morphine	5,041	4.0%	1	5.6%	5,042	4.0%
N02AA03	Hydromorphone	329	0.3%	0	0.0%	329	0.3%
N02AA05	Oxycodone	1,297	1.0%	0	0.0%	1,297	1.0%
N02AA55	Oxycodone, combinations	1,147	0.9%	0	0.0%	1,147	0.9%
N02AA59	Codeine, combinations excl.	51,167	40.3%	5	27.8%	51,172	40.3%

	psycholeptics						
N02AA99	Various associations	5,277	4.2%	0	0.0%	5,277	4.2%
N02AB03	Fentanyl	5,735	4.5%	1	5.6%	5,736	4.5%
N02AC02	Methadone	4	0.0%	0	0.0%	4	0.0%
N02AD01	Pentazocine	35	0.0%	0	0.0%	35	0.0%
N02AE01	Buprenorphine	2,063	1.6%	0	0.0%	2,063	1.6%
N02AG01	Morphine and antispasmodics	6	0.0%	0	0.0%	6	0.0%
N02AX02	Tramadol	54,405	42.9%	11	61.1%	54,416	42.9%
N02AX06	Tapentadol	389	0.3%	0	0.0%	389	0.3%
N02AX52	Tramadol, combinations	17	0,0%	0	0,0%	17	0,0%
	Total N02A – Opioids	**126,912**	**100.0%**	**18**	**100.0%**	**126,930**	**100.0%**
N03AA02	Phenobarbital	4,943	6.5%	2	6.5%	4,945	9.0%
N03AA03	Primidone	503	0.7%	0	0.0%	503	0.9%
N03AA04	Barbexaclone	485	0.6%	2	6.5%	487	0.9%
N03AB02	Phenytoin	655	0.9%	0	0.0%	655	1.2%
N03AB52	Phenytoin, combinations	1	0.0%	0	0.0%	1	0.0%
N03AD01	Ethosuximide	30	0.0%	0	0.0%	30	0.1%
N03AE01	Clonazepam	3,045	4.0%	1	3.2%	3,046	5.5%
N03AF01	Carbamazepine	10,165	13.3%	3	9.7%	10,168	18.4%
N03AF02	Oxcarbazepine	1,803	2.4%	3	9.7%	1,806	3.3%
N03AF03	Rufinamide	1	0.0%	0	0.0%	1	0.0%
N03AG01	Valproic acid	8,004	10.5%	1	3.2%	8,005	14.5%
N03AG02	Valpromide	241	0.3%	0	0.0%	241	0.4%
N03AG04	Vigabatrin	169	0.2%	0	0.0%	169	0.3%
N03AG06	Tiagabine	9	0.0%	0	0.0%	9	0.0%
N03AG99	Various associations	1	0.0%	0	0.0%	1	0.0%
N03AX09	Lamotrigine	1,083	1.4%	0	0.0%	1,083	2.0%
N03AX10	Felbamate	5	0.0%	0	0.0%	5	0.0%
N03AX11	Topiramate	1,323	1.7%	0	0.0%	1,323	2.4%

N03AX12	Gabapentin	23,545	30.8%	15	48.4%	2,356	4.3%
N03AX14	Levetiracetam	1,012	1.3%	1	3.2%	1,013	1.8%
N03AX15	Zonisamide	3	0.0%	0	0.0%	3	0.0%
N03AX16	Pregabalin	19,383	25.4%	3	9.7%	19,386	35.1%
N03AX18	Lacosamide	2	0.0%	0	0.0%	2	0.0%
	Total N03A – Antiepileptics	**76,411**	**100.0%**	**31**	**100.0%**	**76,442**	**100.0%**
N04AA01	Trihexyphenidyl	179	1.3%	0	0.0%	179	0.8%
N04AA02	Biperiden	4,811	35.0%	0	0.0%	4,811	20.5%
N04AA03	Metixene	237	1.7%	0	0.0%	237	1.0%
N04AA04	Procyclidine	61	0.4%	0	0.0%	61	0.3%
N04AA11	Bornaprine	390	2.8%	0	0.0%	390	1.7%
N04AB02	Orphenadrine (chloride)	231	1.7%	0	0.0%	231	1.0%
N04BA01	Levodopa	3	0.0%	0	0.0%	3	0.0%
N04BA02	Levodopa and decarboxylase inhibitor	1,083	7.9%	2	33.3%	10832	46.1%
N04BA03	Levodopa, decarboxylase inhibitor and COMT inhibitor	14	0.1%	0	0.0%	14	0.1%
N04BA04	Melevodopa	1	0.0%	0	0.0%	1	0.0%
N04BA05	Melevodopa and decarboxylase inhibitor	390	2.8%	0	0.0%	390	1.7%
N04BB01	Amantadine	2	0.0%	0	0.0%	2	0.0%
N04BC00	Other dopamine agonists	231	1.7%	0	0.0%	231	1.0%
N04BC01	Bromocriptine	419	3.1%	0	0.0%	419	1.8%
N04BC02	Pergolide	251	1.8%	0	0.0%	251	1.1%
N04BC04	Ropinirole	508	3.7%	1	16.7%	509	2.2%
N04BC05	Pramipexole	3,954	28.8%	3	50.0%	3,957	16.9%
N04BC06	Cabergoline	436	3.2%	0	0.0%	436	1.9%
N04BC07	Apomorphine	6	0.0%	0	0.0%	6	0.0%
N04BC09	Rotigotine	83	0.6%	0	0.0%	83	0.4%

N04BC49	Various associations	150	1.1%	0	0.0%	150	0.6%
N04BD01	Selegiline	230	1.7%	0	0.0%	230	1.0%
N04BD02	Rasagiline	48	0.3%	0	0.0%	48	0.2%
N04BX01	Tolcapone	3	0.0%	0	0.0%	3	0.0%
N04BX02	Entacapone	7	0.1%	0	0.0%	7	0.0%
	Total N04 – Antiparkinsians	**25,554**	**100.0%**	**6**	**100.0%**	**25,560**	**100.0%**
N05AA01	Chlorpromazine	1,771	3.1%	1	4.0%	1,772	2.9%
N05AA02	Levomepromazine	314	0.5%	0	0.0%	314	0.5%
N05AA03	Promazine	40	0.1%	0	0.0%	40	0.1%
N05AB01	Dixyrazine	50	0.1%	0	0.0%	50	0.1%
N05AB02	Fluphenazine	199	0.3%	0	0.0%	199	0.3%
N05AB03	Perphenazine	23	0.0%	0	0.0%	23	0.0%
N05AB06	Trifluoperazine	54	0.1%	0	0.0%	54	0.1%
N05AC01	Periciazine	1,367	2.4%	0	0.0%	1,367	2.2%
N05AC02	Thioridazine	161	0.3%	0	0.0%	161	0.3%
N05AC99	Other Phenothiazines	2	0.0%	0	0.0%	2	0.0%
N05AD01	Haloperidol	9,402	16.3%	5	20.0%	9,407	15.4%
N05AD05	Pipamperone	15	0.0%	0	0.0%	15	0.0%
N05AD06	Bromperidol	275	0.5%	0	0.0%	275	0.4%
N05AE04	Ziprasidone	3	0.0%	0	0.0%	3	0.0%
N05AF02	Clopenthixol	9	0.0%	0	0.0%	9	0.0%
N05AF05	Zuclopenthixol	34	0.1%	0	0.0%	34	0.1%
N05AG02	Pimozide	259	0.4%	0	0.0%	259	0.4%
N05AH02	Clozapine	462	0.8%	0	0.0%	462	0.8%
N05AH03	Olanzapine	3,268	5.7%	0	0.0%	3,268	5.3%
N05AH04	Quetiapine	211	0.4%	2	8.0%	2,112	3.5%
N05AH06	Clotiapine	1,868	3.2%	1	4.0%	1,869	3.1%
N05AL00	Other benzamides	168	0.3%	1	4.0%	1,681	2.7%
N05AL01	Sulpiride	989	1.7%	0	0.0%	989	1.6%

N05AL03	Tiapride	1,916	3.3%	0	0.0%	1,916	3.1%
N05AL05	Amisulpride	27,542	47.7%	12	48.0%	27,554	45.0%
N05AL07	Levosulpiride	355	0.6%	0	0.0%	355	0.6%
N05AL49	Various associations	1,495	2.6%	1	4.0%	1,496	2.4%
N05AN01	Lithium	2,004	3.5%	1	4.0%	2,005	3.3%
N05AX08	Risperidone	3,281	5.7%	1	4.0%	3,282	5.4%
N05AX12	Aripiprazole	159	0.3%	0	0.0%	159	0.3%
N05AX13	Paliperidone	36	0.1%	0	0.0%	36	0.1%
	Total N05a – Antipsychotics	**62,592**	**100.0%**	**25**	**100.0%**	**62,617**	**100.0%**
N06AA01	Desipramine	120	0.1%	0	0.0%	120	0.1%
N06AA02	Imipramine	721	0.4%	0	0.0%	721	0.4%
N06AA04	Clomipramine	4,955	2.6%	5	6.6%	496	0.3%
N06AA05	Opipramol	25	0.0%	0	0.0%	25	0.0%
N06AA06	Trimipramine	152	0.1%	0	0.0%	152	0.1%
N06AA09	Amitriptyline	24,957	13.1%	9	11.8%	24,966	14.1%
N06AA10	Nortriptyline	536	0.3%	0	0.0%	536	0.3%
N06AA15	Butriptyline	3	0.0%	0	0.0%	3	0.0%
N06AA19	Amineptine	2,975	1.6%	1	1.3%	2,976	1.7%
N06AB03	Fluoxetine	12,487	6.6%	3	3.9%	1,249	0.7%
N06AB04	Citalopram	36,466	19.2%	12	15.8%	36,478	20.7%
N06AB05	Paroxetine	37,756	19.8%	18	23.7%	37,774	21.4%
N06AB06	Sertraline	24,016	12.6%	8	10.5%	24,024	13.6%
N06AB08	Fluvoxamine	2,137	1.1%	1	1.3%	2,138	1.2%
N06AB10	Escitalopram	14,107	7.4%	4	5.3%	14,111	8.0%
N06AX03	Mianserin	201	0.1%	1	1.3%	2,011	1.1%
N06AX05	Trazodone	14,283	7.5%	8	10.5%	14,291	8.1%
N06AX09	Viloxazine	44	0.0%	0	0.0%	44	0.0%
N06AX11	Mirtazapine	2,522	1.3%	1	1.3%	2,523	1.4%
N06AX12	Bupropion	239	0.1%	0	0.0%	239	0.1%

N06AX16	Venlafaxine	8,707	4.6%	4	5.3%	8,711	4.9%
N06AX18	Reboxetine	182	0.1%	0	0.0%	182	0.1%
N06AX21	Duloxetine	2,726	1.4%	1	1.3%	2,727	1.5%
N06AX22	Agomelatine	1	0.0%	0	0.0%	1	0.0%
N06AX49	Desipramine	38	0.0%	0	0.0%	38	0.0%
	Total N06a – Antidepressants	**193,803**	**100.0%**	**76**	**100.0%**	**193.879**	**100.0%**