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Modelling the consumption of anxiolytics and its addictive behavior

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Abstract

Background: Population-based anxiolytics consumption (AX) is a widely debated subject because long-term AX may lead to tolerance and addiction. This study aims to obtain mathematical models that identify the various behaviours in AX prescription in accordance with gender, age and the continuous prescription of other drugs associated with chronic diseases.

Methods: Data were obtained from an electronic prescriptions database (n = 12,211,992) received by patients (n = 504,224) visiting the Primary Health Care Centres in the province of Castellón (East Spain) in 2009. A linear regression model was used to explain the number of defined daily doses (DDD) of AX prescribed in accordance with age, gender and more than 5 prescriptions of any drug associated with chronic diseases other than AX.

We used the logistic regression model to quantify the joint influence of the explanatory variables on the likelihood (L) of prescribing increasingly high DDD of AX.

Results: The mean annual DDD per patient was 133.13, and the DDD prescribed was 38.06 day/1000 inhabitants. Few differences, although significant, in prescriptions per gender were observed; males received fewer prescriptions than females. Conversely, differences in age groups were substantial; the older subjects become, the higher the prescribed DDD, although these differences disappeared after the age of 65. AX use was also positively associated with the presence of comorbidity: depression, psychosis and epilepsy. Sporadic AX prescriptions were not associated with any factor, except continuous use.

Conclusions: The prevalence of prescribing AX in the general population visiting the primary health centres in Castellón is over 16%. Prescriptions and the DDD of AX are barely higher for females than for males, and age is the most influential factor; the older the patient, the higher the number of prescribed DDD. The likelihood of potentially addictive behaviours is higher among the elderly and patients with comorbidity, mainly those patients with other chronic psychiatric conditions.

1. Introduction

Psychotropic drugs (antidepressants, antipsychotics, anxiolytics, hypnotic drugs and analgesics in the opiates group) are used as a long-term symptomatic treatment in several patient types; for such patients, uncontrolled, long-term use may lead to tolerance and addiction. Thus, there is considerable ongoing debate between suppliers and the Health Authorities on suitable use.

Of all the above drugs, the most widely used are anxiolytics (AX) belonging to the benzodiazepine group (BZN) [1] defined by the ATC N05B code (Anatomical, Therapeutic Chemical Classification System) [2]. The main reasons for prescribing AX are anxiety and insomnia [3]. Some studies report that 23% of patients who receive AX treatment for the first time present addiction after three months of treatment [4].

In Spain, BZN use has considerably increased since the 1990's. Specifically between 1995 and 2002 [5], a mean increase from 39.71 to 62.02 DDD (defined daily doses) has been observed per 1000 inhabitants in the prescriptions doctors prescribed in primary health care centres. Besides, the use of such drugs is potentially chronic for periods longer than 2 years [6]. Prolonged use may lead to tolerance and addiction [4,7], withdrawal symptoms if discontinued [8], possible osteoporosis-related fractures [9] and to other adverse reactions, most of which are never notified [10].

Several studies have demonstrated a higher number of prescriptions for female subjects and at more advanced ages [3, 6, 11]. AX use is also associated with comorbidity [12, 13, 14], presence of chronic conditions [15] and with other social, economic and demographic variables [16].

The identification of patients' chronic conditions initially began from their use of drugs [17] through the CDS (Chronic Disease Score) to assess the degree of patients' severity. The first step was to identify which chronic diseases could be associated with the prescribed drugs, and then score according to the number of therapeutic groups prescribed for each disease. Finally [18], we perfected and validated the CDS for clinical management purposes.

The next advance in this line consisted [19] in developing the CDI (Chronic Disease Index) based on former studies [17]. The index obtained was used to estimate the number of diseases that patients had based on the data available about the drugs prescribed. It was possible to determine the type of drugs which could indicate the chronic disease and to verify their effectiveness with real medical records to show that the CDI correlates well with the real number of chronic conditions among patients.

This study aims to obtain mathematical models to identify different behaviours in AX prescriptions according to age, gender and the continuous prescription of other drugs associated with chronic conditions to specifically define the exact factors that determine their level of prescription and the likelihood of them occurring at different DDD levels.

2. Material and methods

2.1. Information sources

The study population in this work is made up of subjects who have received a prescription of any N05B group AX in the Primary Health Care Centres in the province of Castellón (Spain) during the period between November 2008 and October 2009. The drug use measuring unit employed was the total number of DDD prescribed to subjects. This province was selected because information about electronic prescriptions was available.

In 2009, 726,199 inhabitants were registered in the SIP[1] (Population-based Information System) in the province of Castellón, which represents 13.79% of the total number of inhabitants registered in the Valencian Community (Valencia, Alicante and Castellón). These inhabitants are covered by 4 health districts and 29 health centres.

Information about the prescription received was provided by the DGF (the Regional Valencian Government's General Pharmacy Management) and includes for each patient the drug type prescribed and the number of DDD prescribed.

In addition, the DGF also offers the following information for each patient in the province of Castellón: the health district, the basic health area, the patient's age and gender, whether drugs are freely prescribed or subsidised[2], and the price and date of each prescription.

With these two information sources, a data matrix was created which includes 504,224 rows corresponding to all the inhabitants registered with a number who had received a prescription of any drug type in the primary health care system during the study period.

In line with other studies [20], only those drugs that indicate chronic disease were considered, therefore we excluded any drugs commonly used to treat non-chronic conditions from this study. Moreover, we considered a continuous prescription form [1] of these drugs to consider the patient's genuine chronic condition; the continuous prescription form was established as more than 5 prescriptions per year.

The methodology employed to select chronic diseases was based on former [21] studies, which used those chronic conditions identified in the ATC (Anatomical Therapeutic Chemical) groups of prescribed medicines [18]**.** These authors assessed the relationship between the medicine and those diagnosed for the 28 chronic conditions established in the revised CDS version to finally obtain 25 chronic diseases relating with the ATC codes. This study identified 24 chronic diseases because prescriptions for HIV/AIDS are hospital managed, so we excluded them.

Consequently of the 504,224 registered inhabitants who were initially considered, approximately half (254,722) were prescribed drugs associated with the 24 chronic diseases determined. Of these, 84,394 (33.13%) had been prescribed some N05B group drug.

Furthermore for the purpose of analysing only the stable population in the studied province, we eliminated 8,616 registered inhabitants who did not correspond to the 4 health districts in the province under study. Thus the number of the analysed registered inhabitants was 75,778.

The database to be analyzed therefore consisted in 75,778 rows and 55 columns as follows: district, basic health area, primary health centre, a number for each patient, patient's gender, patient's age, free or subsidised prescriptions, and all 24 chronic diseases: the total DDD prescribed and the months between the first and last prescription received. The DDD for each medication included in the group were previously homogenised to the same measurement unit.

2.2. Analysis unit

The analysed study population is made up of 75,778 inhabitants who had received some form of AX prescription during the study period. Four groups were considered in accordance with the number of prescribed DDD: group 1 consisted in those inhabitants with less than 31 prescribed DDD (n=31,913); group 2 included those with prescriptions of between 31 and 90 DDD (n=14,852); group 3 received prescriptions of between 91 and 180 DDD (n=15,197); group 4 were prescribed more than 181 DDD (n=13,816).

We considered that a prescription of less than 31 DDD, the equivalent to 1 month or 1 prescription, does not produce tolerance. As the number of prescribed DDD increased, the risk of addiction became greater, to such an extent that those patients in group 4, who receive 6 prescriptions or more per year, could be considered to display a continuous drug use behaviour ([1] Bouquier, 2008). The division into intervals was based on clinical criteria[3].

2.3. Explanatory variables

The explanatory variables for AX prescriptions were: age, gender, freely prescribed drugs and being prescribed more than 5 drugs per year other than AX which are associated with any of the chronic diseases determined. Each drug was coded according to the ATC system to discover the population's morbidity with the list of prescribed drugs.

The information held of a medical and socio-economic nature belongs to the corresponding health district and the basic primary health care area. This information was not used in this study because it was not available.

2.4. Mathematical models

We firstly did a descriptive study into AX use with the aforementioned explanatory variables. Then we obtained the mathematical models by firstly using the multivariate linear regression model [1], and then the logistic regression model [11, 12, 15, 16, 22].

With the linear regression model, we attempted to explain the number of prescribed DDD for AX (dependent or regressor variables, Y) in terms of each considered explanatory variable (independent, regressor or covariables, Xi).

The estimated mathematical expression was:

$$Y = \propto + \beta 1 * x1 + \cdots \ldots + \beta n * Xn \quad (1)$$

[1] Each inhabitant is provided a SIP number to be identified within the National Health System.
[2] Pensioners obtain drugs free of charge, most are retired; the remaining inhabitants pay 40% of the cost.
[3] The optimal prescription should not exceed 2-4 weeks (equivalent to approximately 1 month), as recommended by the therapeutic prescription guide developed by the National Institute for Health and Clinical Excellence (NICE), for such period there is no risk of developing dependence, etc. Also, there are studied [4] that shows the 23% of patients developed addiction after the third month of treatment. Any longer period it is not appropriate and produces dependency. The longer the time of consumption is, the greater the dependence is. Also it is assumed that anything more than 180 days it is an excessive consumption and dependence is clearly evident in periods exceeding 6 months.

The goodness of fit was determined by the corrected R^2 and the Snedecor's F test, while the student's t-test values were obtained for each coefficient to determine its level of significance.

The logistic regression model quantified the joint influence of the explanatory variables (independent variables, regressors or covariables), which were considered predictive, on the likelihood (l) of prescribing a certain number of DDD of AX (dependent variable or regressor).

The mathematical expression of the binomial logistic regression for the 4 levels of prescribed DDD, as determined in the analysis unit section, is:

$$Ln\left\{\frac{P(y=1/x_1,x_2,....x_n)}{P(y=0/x_1,x_2,...x_n)}\right\}=\alpha+\beta_1*x_1+\beta_2*x_2+.....+\beta_n*x_n \quad (2)$$

where Y is now a binary variable. It takes the value of 1 when a certain number of DDD is prescribed, and 0 otherwise.

The multiple binomial logistic regression [22] allows the direct calculation of the likelihood of the binomial process for the different independent variables values, this being a logistic distribution function, by means of the following expression:

$$P(y=1/x_1,x_2,.....x_n)=\frac{e^{\alpha+\beta_1*x_1+\beta_2*x_2+.....+\beta_n*x_n}}{1+e^{\alpha+\beta_1*x_1+\beta_2*x_2+.....+\beta_n*x_n}}=\frac{1}{1+e^{-(\alpha+\beta_1*x_1+\beta_2*x_2+....\beta_n*x_n)}} \quad \textbf{(3)}$$

The odds coefficient indicates how many times more likely it is for an AX drug to be prescribed at the indicated DDD level in relation to it not being prescribed (likelihood of success versus failure). This ratio is defined as follows:

$$Odds=\frac{P(y=1/x_1,x_2,.....x_n)}{P(y=0/x_1,x_2,....x_n)}=\frac{P(y=1/x_1,x_2,...x_n)}{1-P(y=1/x_1,x_2,.....x_n)}=e^{\alpha+\beta_1*x_1+\beta_2*x_2+....+\beta_n*x_n} \quad (4)$$

The odds ratio (OR) will provide the measurement of the association between the prescribed AX drug and the presence or absence of the independent variables. This is the quotient between the odds with the presence of independent variables and the odds with the absence of independent variables:

$$OR=\frac{\left(\frac{1}{1+e^{-(\alpha+\beta_1X_1+.....+\beta_nX_n)}}\right)/\left(1-\frac{1}{1+e^{-(\alpha+\beta_1X_1+.....+\beta_nX_n)}}\right)}{\left(\frac{1}{1+e^{-\alpha}}\right)/\left(1-\frac{1}{1+e^{-\alpha}}\right)} \quad (5)$$

The OR indicates how much the risk of using the drug is multiplied in relation to the presence or absence of independent variables.

When all the independent variables are X_i=0, or are absent, the Odds is equal to:

$$Odds=e^{\alpha} \qquad \alpha=LnOdds$$

When the independent variable X_i is present, the OR is equal to:

$$OR=e^{\beta_i} \qquad \beta_i=LnOR$$

Y quantifies the magnitude of the association between the response (prescribed drug) and the factor of interest (age, gender, etc.). This is the OR used to increase a unit in variable Xi, while the rest remain constant.

The estimators are estimated by maximum likelihood calculation, and Wald ($\chi 2$) contrasts and the associated p-value are obtained for each one.

The contrast over the overall model is performed with the likelihood ratio logarithm calculation (*log. Likelihood ratio*) and the Hosmer-Lemeshow tests.

3. Results

3.1. Descriptive analysis.

We firstly analysed the prescribed drugs associated with the 24 chronic diseases. Of all these prescriptions, 37.8% were free of charge while 62.1% were subsidised. As the second column in Table 1 indicates, a total of 254,722 inhabitants were prescribed at least one drug associated with chronic

diseases, of which 46% were male and 54% were female. Regarding age groups, the number of people prescribed these drugs increased with age until the 45-64 age group after which the number of patients dropped, which may be possibly due to a lower number of patients in these older age groups.

When we analysed only those patients with a continuous form of prescriptions of more than 5 prescriptions per year, the most frequently prescribed drugs were those that treat chronic conditions like peptic acid disease, hypertension, hyperlipidaemia, pain and inflammation, anxiety and depression, and in this order.

When we focussed exclusively on the N05B group drugs, the total number of AX prescriptions in the 4 health districts in Castellón came to 579,224 and were prescribed to a total of 75,778 inhabitants, which represents a prevalence of 16.73%. This result is lower than that found in other studies [6], and represents 11.6% of the whole study population. These figures reveal and justify the importance of their isolated study as part of this work.

A total of 10,088,935 DDD of AX have been prescribed in the province of Castellón between November 2008 and October 2009. This is the equivalent of an annual mean DDD per patient of 133.13, and 38.06 DDD prescribed day/1000 inhabitants on average.

Of the active principles within the NO5B drugs group, the most frequently consumed were: Alparzolam (32.00%), Lorazepam (20.45%) and Diazepam (12.70%).

The way the AX prescriptions were distributed according to gender, age and the continuous prescription of drugs for chronic diseases is seen in column 3 of Table 1, while column 4 depicts their relationship with column 2. Practically twice as many females than males received an AX prescription during the study period, and 36% of the female patients and 22% of the male patients who take medicines associated with chronic conditions also received AX prescriptions.
The number of people who were prescribed AX increased with age until the 65-79 age group, and thereafter dropped, as did the use of the group of drugs associated with chronic diseases. Nonetheless, the percentage of people who were prescribed AX versus the group of drugs increased with age, going from 6.85% for the youngest age group to 34.57% for the group aged over 79 years.

When we examined the relationship between AX prescriptions and the continuous prescription form of other drugs, we found there were more patients with the chronic condition of depression as 64.20% of the patients who received more than five prescriptions for antidepressants were also prescribed some form of AX. This was followed by pain, psychotic illness (including bipolar disorders) and epilepsy.

Finally, columns 5 and 6 present the number of patients having received AX prescriptions of more than 180 DDD and their percentage in relation to all the patients who had received some prescribed AX, respectively. Once more, we found that female patients used higher DDD of AX than males; 19.42% of female patients consumed more than 180 DDD versus 15.89% of male patients. This use increased with age in such a way that 23.06% of those aged 65-79 years received an AX prescription of over 180 DDD.

The study of the association between the three factors: age, gender and drug consumption related to the presence of other chronic diseases is shown in Table 2. The first row contains the total number of consumers of AX by gender and age. As age increases, there is a higher consumption in women than in men and, increasingly, becoming more than tripled in the older group. Although this could be due to a larger population of women than men. The association between age and gender is shown through Pearson Chi-square test ($p<0.001$).

Each cell of the remaining rows of Table 2, indicates the percentage of consumers of AX on the population of consumers of other drugs associated with chronic diseases. The results show as at a young age (0-14 years) the prescription of AX is not associated with any disease or any gender, except, even when very slightly in relation to the group of drugs to treat epilepsy and respiratory system diseases.

However, the percentage consumption of AX in the presence of other chronic diseases mildy increases with age in most cases, but more pronounced in patients with drug consumption related to cardiovascular disease, hyperlipidemia, hypertension, and depression, as well as with other drugs less specific to a disease such as those of inflammatory pain due to multiple causes and stomach protectors presciption.

3.2. Regression model

We obtained a multivariate logarithm regression model (Table 3) to explain the number of DDD of prescribed AX. The model coefficients are presented in column 2 and the coefficient exponents are provided in column 3.

All the explanatory variables are qualitative and they take a value of 1 when they possess the characteristic and 0 otherwise. Specifically, the gender variable takes the value of 1 for male subjects and 0 for female subjects.

All the coefficients were significant at 99.9%, and the R^2 and the Snedecor's F test showed goodness of fit. Few differences, although significant, in prescriptions were observed in relation to gender; thus male subjects received fewer prescriptions than female subjects, as indicated by the negative coefficient of the variable. On the other hand, the differences between age groups found were notable; the older the patient, the higher the number of prescribed DDD. However, these differences disappeared as from the age of 65.

The continuous use of 10 of the 24 drugs associated with chronic diseases also contributed to the increased number of DDD prescribed for AX, basically in relation to depression, psychotic illnesses and epilepsy.

The free-of-charge prescription condition did not appear in the model as it correlates highly with age.

3.3. Logistic model

The results obtained with the logistic regression analyses for the 4 prescribed DDD groups (< 30, 31-90, 91-180 and >181) are presented in columns 4, 5, 6 and 7 of Table 3. All the coefficients were significant at 99% and the likelihood logarithm methods and the Hosmer-Lemeshow tests showed goodness of fit in the 4 models.

We can see how the effect of age, gender and the continuous use of the drugs associated with chronic diseases on the likelihood of prescribing AX of a DDD under 30 was virtually null. This suggests that sporadic AX use is not determined by definite patterns as far as these variables are concerned.

The prescription of higher DDD was virtually not due to gender differences. Male patients showed a slightly higher risk (1.094 times) of receiving prescriptions of below 30 DDD, and a slightly lower risk (0.929 times) of receiving prescriptions of 91-180 DDD. No significant gender differences were found for the other dose levels.

Conversely, patients' age proved to be a key factor. For instance, the risk of receiving prescriptions of between 31-90 DDD for the 15-29 age group was 15 times greater than for the under 14-year-old age group, and was almost 29 times greater for the over 79-year-old age group. A similar situation was noted in the other two DDD prescription groups as the risk of receiving prescriptions of 91-180 DDD was 50 times greater for the over 79-year-old age group than for the under 14-year-old age group.

Nonetheless, the risk of prescriptions of 91-180 DDD was lower for the under 44 year-old age group than the risk of receiving prescriptions of 31-90 DDD, while the exact opposite was observed for the age group of over 45 years.

We may state that the continuous use of other drugs associated with chronic diseases was associated with an increased risk of receiving AX prescriptions of high DDD, but not low DDD. The greatest effect was seen for depression as its effect became greater the higher the DDD of the prescribed AX. Indeed, the likelihood of being prescribed AX of a DDD over 180 was almost 4 times higher, and was followed by patients with psychotic illnesses and epilepsy.

4. Discussion

The results of this study coincide with the findings reported by other authors in Spain [6] and in other countries [1, 10, 15].

When we compare this work with other similar studies, the limitations of our results lie in the lack of socio-economic and clinical data that link to AX prescriptions. However, the strong point of this study lies in its large study sample size as it includes the whole population of a given geographical area.

The original contribution of this work is that it combines linear regression and logistic regression models, and that the logistic regression model also considers the different prescription levels which have allowed us to distinguish the factors associated with the different levels of prescribed DDD.

The mean daily AX dose prescribed per 1000 inhabitants (38.06 DDD) in the province of Castellón is lower than that obtained in other studies performed in Spain [5] which not only report between 39.71 DDD in 1995 and 62.02 DDD in 2002 prescribed in primary health care centres, but also the influence of socio-cultural factors on the demand of such medications.

In our population study, AX are prescribed significantly more frequently for female patients and at more advanced ages, which is in agreement with several other previous studies [3, 6, 15].

Gender differences in AX use and prolonged use have also been reported by other authors [11, 15]; nonetheless, no clear consensus has been reached. Our descriptive results reveal that this higher prescription frequency in females is more noticeable as from the age of 45. However, the mathematical models obtained indicate that the number of DDD prescribed to females scarcely increases; indeed, the probability of higher DDD being prescribed is practically null for the medium and high DDD.

What this and other similar studies highlight is the importance of acting on medical decision making in an attempt to improve education and training in the side effects of BZN use and the existing alternative therapies in order to reduce the volume of this type of prescribed treatments.

We must also take into account that age has a significant influence not only on the number of DDD prescribed, but also on the likelihood of the number of DDD being prescribed.

Other studies have also demonstrated the chronic use of these drugs [6], reveal that these treatments do not match recommendations, and indicate that they lead to multiple adverse reactions which are never notified [10].

Evidently, the use of group N05B drugs to treat anxiety is associated with the use of those drugs to treat other mental pathologies, a scenario which has also been reflected by other authors [8].

5. Conclusions

This study demonstrates that the prevalence of AX use in the general population who go to the primary health care centres in the province of Castellón is over 16%. AX use is barely higher among females than among males, and age is the most influential factor; the older the patient, the higher the number of prescribed DDD.

The likelihood of potentially addictive behaviours is greater among the elderly and in patients with comorbidity, mainly among those with other chronic psychiatric conditions.

These results provide very relevant information for Health Authorities' policy making in relation to the rational use of AX drugs and for preventing the risk of addiction and adverse effects. These measures may help inform the population and primary health care professionals about the alternatives to AX treatment so that chronic use lowers.

Future studies will be necessary to establish geographic, socio-demographic and medical practice variations.

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Table 1
Descriptive analysis of the prescription of anxiolytics.

Characteristics	No. of patients with prescriptions for drugs associated with chronic diseases (*a*)	No. of patients with a prescription for anxiolytics (*b*)	Percentage (%) (*b*/*a*)	No. of patients with over 180 DDD of anxiolytics (*c*)	Percentage (%) (*c*/*b*)
Constants					
Gender					
– Female	139,383	50,349	36.12	9778	19.42
– Male	115,339	25,419	22.04	4038	15.89
Age (years)					
– 0–14	42,065	2881	6.85	14	0.49
– 15–29	37,646	4909	13.04	320	6.52
– 30–44	66,059	14,223	21.52	2085	14.62
– 45–64	89,594	24,363	27.19	4930	20.23
– 65–79	61,443	19,349	31.49	4462	23.06
– >79	29,072	10,050	34.57	2012	20.02
Other chronic conditions[a]					
– Depression	24,962	16.025	64.20	6412	40.01
– Psychotic disorders	6,797	3.335	49.07	1575	47.23
– Epilepsy	8,206	3.702	45.11	1520	41.06
– Pain due to inflammation	32,405	12.798	39.49	3444	26.91
– Hypertension	52,263	17.077	32.68	4100	24.01
– Hyperlipidaemia	51,222	16,394	32.01	4068	24.81
– Pain	8,506	4348	51.12	1397	32.13
– Thyroid irregularities	3,106	1217	39.18	351	28.84
Peptic	55,623	22,658	40.73	6313	27.86
Respiratory	15,303	4284	27.99	989	23.08
Cardiac	22,922	11,451	49.95	2166	18.91
Parkinson	1,546	677	43.79	234	34.56
Diabetes	24,832	6766	27.24	1630	24.09
Glaucoma	12,025	3417	28.41	941	27.53
Rheumatism	3,541	1269	35.83	274	21.59
Transplant	757	206	27.21	43	20.87
Coronary disease	33,758	11,451	33.92	2633	22.99
Anxiolytics	32,301				

[a] More than 5 prescriptions.

Table 2
Distribution of the AX consumers by sex, age, and consumption of drugs associated to other chronic diseases.

	0–14		15–29		30–44		45–64		65–79		>79		Total	
	F	M	F	M	F	M	F	M	F	M	F	M	F	M
Total number of AX consumers	1370	1511	3161	1748	9054	5170	16,391	7973	13 163	6187	7216	2834	50,355	25,423
Percentage														
Cardiac diseases			0.2	0.1	0.6	0.7	5.0	5.8	20.2	20.8	35.0	36.8	12.0	11.1
Coronary disease			0.1	0.3	0.8	1.5	5.9	14.5	23.3	37.2	35.1	44.4	13.2	18.9
Depression	0.2	0.3	10.6	11.2	20.6	15.3	27.5	17.5	29.1	14.6	24.7	14.9	24.5	14.6
Diabetes	0.2	0.2	0.6	0.5	1.0	1.5	6.0	10.2	16.8	18.6	13.7	14.6	8.5	9.7
Epilepsy	4.2	4.1	3.1	6.5	4.8	6.2	5.6	5.1	5.2	4.4	3.6	3.2	4.9	5.0
Glaucoma			0.1	0.3	0.3	0.5	3.1	2.6	10.5	9.3	11.8	11.6	5.5	4.5
Hyperlipidaemia		0.1	0.2	0.3	2.0	4.6	19.8	24.6	41.0	38.5	31.1	25.9	22.0	20.9
Hypertension			0.3	1.1	2.2	4.1	16.1	22.6	39.7	42.6	42.9	43.3	22.2	23.2
Pain		0.1	0.5	0.3	1.6	1.5	5.7	4.2	10.7	6.7	11.5	6.6	6.6	4.0
Pain (inflammation)	1.2	1.1	2.7	2.2	7.6	5.0	21.4	11.8	31.8	18.8	21.3	12.7	19.9	10.9
Parkinson					0.0	0.0	0.2	0.3	1.4	1.8	2.8	3.8	0.8	1.0
Acid peptic disease	0.4	0.7	2.7	2.6	7.9	9.1	25.1	24.8	52.2	46.8	54.6	53.7	31.3	27.2
Psychosis	0.4	0.9	2.1	8.4	3.7	8.5	3.4	5.2	3.9	3.5	6.4	6.0	3.8	5.5
Respiratory diseases	5.3	6.9	1.6	1.8	2.0	1.8	3.3	4.5	6.3	14.3	8.4	18.2	4.6	7.8
Rheumatism	0.5	0.4	0.3	0.4	1.0	0.8	1.6	2.2	2.2	3.1	1.6	2.6	1.5	1.9
Thyroid irregularities	0.1		0.3		1.0	0.3	2.2	0.4	3.4	0.8	2.7	0.6	2.2	0.5
Transplant			0.3	0.2	0.3	0.4	0.3	0.5	0.2	0.4	0.1	0.0	0.2	0.4

Table 3
Linear logarithmic regression and logistic regression models.

	Linear logarithmic regression		Logistic regression			
Characteristics	Coefficients (α and β)	Exp(α and β)	OR (exp β) <30 DDD	OR (exp β) 31–90 DDD	OR (exp β) 91–180 DDD	OR (exp β) >180 DDD
Constants	1.348	3850	–	0.011	0.007	0.005
Gender (X_1)	−0.027	0.973	1.094	–	0.929	–
– Female						
– Male						
Age (years)						
– 0–14						
– 15–29 (X_2)	1.548	4702	0.080	15.171	9.226	10.130
– 30–44 (X_3)	1.991	7323	0.041	21.253	16.938	21.711
– 45–64 (X_4)	2.242	9412	0.025	25.458	27.576	27.960
– 65–79 (X_5)	2.386	10,870	0.017	26.181	41.098	29.406
– >79 (X_6)	2.396	10,903	0.014	28.863	49.410	24.404
Other drugs[a]						
– Depression (X_7)	0.908	2479	0.213	0.859	1.491	3.579
– Psychotic disorders (X_8)	0.777	2175	0.330	0.843	0.882	3.074
– Epilepsy (X_9)	0.420	1522	0.525	0.823		1.880
– Pain (inflammation) (X_{10})	0.136	1146	0.712		1.111	1.203
– Hypertension (X_{11})	0.176	1192	0.686		1.247	
– Hyperlipidaemia (X_{12})	0.099	1104	0.778	0.946	1.196	
– Pain (X_{13})	0.052	1053		0.880		1.116
– Parkinson's (X_{14})						1.270
– Thyroid irregularities (X_{15})	0.142	1.153		0.794		1.318
– Cardiac problems (X_{16})			0.754		1.105	
Peptic complaints (X_{17})	0.316	1372				1.559
Respiratory disorders (X_{18})	0.066	1068				
Diabetes (X_{19})			1.036	0.899		
Glaucoma (X_{20})				0.892		
Rheumatism (X_{21})				1.175		
Transplant (X_{22})				1.676		
Coronary disease (X_{23})					1.147	
R^2	31.4958					
R^2 adjusted	31.4813					
F	2176.92					
Likelihood coefficient logarithm. Likelihood ratio				*1389.391*	*5030.464*	*8904.912*
Hosmer–Lemeshow test				30.515	184.454	

Note: All the coefficients are significant at the 99% level of confidence.
[a] More than 5 prescriptions.