

Pharmacoepidemiological characterization of psychotropic drugs consumption using a latent class analysis

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France has one of the highest recorded rates of psychotropic use of drugs compared with other European countries, especially for anxiolytics, hypnotics and antidepressants. The aim of this study was to characterize the use of three psychotropic drugs among the most prescribed in France (bromazepam, paroxetine, zolpidem) using reimbursement databases in real-life conditions. Individuals from a region affiliated to the French General Health Insurance Scheme, who had received at least two dispensings of bromazepam, paroxetine or zolpidem reimbursed between 1 January and 30 June 2008, were included. We used a latent class analysis to identify different subgroups of users for these three psychotropic drugs. A total of 40 644 patients were included for bromazepam, 36 264 for zolpidem and 31 235 for paroxetine. Using latent class analysis, four clinical subtypes of users of bromazepam and zolpidem were identified: nonproblematic users, at-risk users, users with a probable mental disorder and compulsive users. Three subgroups were identified for paroxetine that differed

rather by the prescription patterns. Users of anxiolytics and hypnotics with at-risk behaviours represented a significant proportion in the studied population. This original method could be extended to other prescription databases to identify populations at risk of abuse or dependence to psychotropic drugs. *Int Clin Psychopharmacol* 26:54–62 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

The extent of psychotropic drug consumption has become a major public health concern in most developed countries. France has one of the highest recorded rates of psychotropic use of drugs compared with other European countries, especially for anxiolytics, hypnotics and antidepressants (Ohayon and Lader, 2002; Kovess *et al.*, 2004; Gasquet *et al.*, 2005). Over the last two decades, the use of these psychotropic drugs has become commonplace in the French population (Zarifian, 1996; Gasquet *et al.*, 2005; Briot, 2006). Results of epidemiological surveys indicated that more than one in five of the French population used at least one psychotropic drug during the last 12 months and one in three has already used one psychotropic drug during his life. Moreover the use of psychotropic drugs increases with age (Lecadet *et al.*, 2003; Gasquet *et al.*, 2005; Beck *et al.*, 2006).

If used appropriately, psychotropic drugs are generally effective and safe in the management of many mental disorders. However, overconsumption can have serious economic, social and health consequences. The most serious risks, include drug abuse (defined as an excessive and intentional use of a psychoactive substance, which has harmful consequences on physical or mental health)

and drug dependence (defined as the behavioural, cognitive and physiological manifestations in which the use of a psychoactive substance is a high priority; the main features are the obsessive desire to obtain and take the substance and its continuing research) (American Psychiatric Association, 2000), which are monitored by a specific system of health surveillance in France. The drug misuse, defined as a use of a drug not in agreement with the French Drug Monograph, is also monitored in search of drug diversion. As a matter of fact, the observation and assessment of abuse, dependence and behaviours associated with psychoactive drugs like misuse, are based on the national network of 11 Centres for Evaluation and Information on Pharmacodependence (CEIP). The three main aims of the CEIP are to collect data and assess the potential for dependence of psychoactive drugs, to provide information on the risk of abuse or dependence of psychoactive substances and drugs and to develop corresponding research projects and methods.

However, the major problem with the use of psychotropic drugs not only concerns dependence, which affects a small minority of users. Other potential risks, such as side effects, drug interactions or a withdrawal syndrome, may be significant because a large proportion of patients

from the general population are exposed to psychotropic drugs (American Psychiatric Association, 1990; Rickels *et al.*, 1990; Lejoyeux and Ades, 1997; Haddad *et al.*, 1998). These adverse consequences are well documented, especially among elderly people. In this population, long-term use of psychotropic drugs, mainly benzodiazepines, may be associated with impairment of performance, cognitive effects (Dealberto *et al.*, 1997; Paterniti *et al.*, 2002; Barker *et al.*, 2004; Barker *et al.*, 2005), dementia (Lagnaoui *et al.*, 2002; Verdoux *et al.*, 2005), falls and hip fractures (Wysowski *et al.*, 1996; Leipzig *et al.*, 1999; Souchet *et al.*, 2005).

Despite evidence of these risks, very few pharmacoepidemiological studies, assessing the use of psychotropic drugs in real-life conditions and their impact on the general French population, have been carried out. The French authorities emphasized that the lack of pharmacoepidemiological studies was now an obstacle to the implementation of effective measures to reduce psychotropic drug consumption and associated risks (Briot, 2006).

In the area of pharmacoepidemiological research, CEIP has developed a number of new tools aimed at providing information on medications marketed in France (Frauger *et al.*, 2003; Lapeyre-Mestre *et al.*, 2003; Pradel *et al.*, 2004). In the last few years, they have been able to analyze the databases from the French General Health Insurance Scheme (GHIS) to achieve this goal (Micallef *et al.*, 2004).

Latent class analysis (LCA) is a statistical method used to identify groups of individuals with similar patterns of responses (McCutcheon, 1987). As factor analysis may be used to classify individuals based on data from continuous measures, LCA uses categorical data to classify individuals into groups. A growing number of epidemiological studies have applied this method to determine subtypes of users of different psychoactive drugs (Agrawal *et al.*, 2006; Reboussin *et al.*, 2006; Moss *et al.*, 2007; Ghandour *et al.*, 2008).

In our study, we have used LCA to assess the consumption of psychotropic drugs in the general population. We hypothesized that heterogeneity in psychotropic drugs consumption exists and could be explained by distinct patterns using several indicators of psychotropic drugs-related consumption behaviours. LCA allows the identification of groups of psychotropic drugs users based on the associations among a set of observed behaviours they have displayed.

Given the lack of pharmacoepidemiological research on the nature and patterns of psychotropic drugs users in France, this study was primarily exploratory. The aim of this study was to identify and characterize groups of users of three psychotropic drugs among the most prescribed in France in their respective therapeutic classes (bromazepam, paroxetine and zolpidem) using a LCA.

Methods

Studied psychotropic drugs

Bromazepam

Bromazepam is a benzodiazepine reported for its abuse and dependence potential. Bromazepam is one of the most prescribed benzodiazepines and a major psychotropic drug used by illicit drug users in France (Cadet-Taïrou *et al.*, 2008). Maximum recommended dose is 18 mg per day in France.

Paroxetine

Paroxetine is an antidepressant drug, serotonin reuptake inhibitor prescribed for depressive and anxiety disorders, and for which there is no report of abuse or dependence. Maximum recommended dose is 40 mg per day in France, whatever indication.

Zolpidem

Zolpidem is a nonbenzodiazepine hypnotic drug flagged for its abuse and dependence potential. Over the last few years, numerous cases of zolpidem abuse or dependence have been reported in various European countries and in the USA (Victorri-Vigneau *et al.*, 2007). Maximum recommended dose is 10 mg per day in France.

Population

Most French residents are affiliated to GHIS, which partly reimburses consultation fees and pharmaceutical expenses to the patients. Since 1997, all benefits reimbursed to patients affiliated to the GHIS are registered with the exact identification of drugs. This constitutes extensive databases of all drug prescriptions in France. Each drug has its own database, which comprises all the corresponding reimbursements. All these databases are anonymous.

This study used data from bromazepam, paroxetine and zolpidem reimbursements, extracted from the regional databases of the Pays de la Loire, and covered the first half of 2008. Thus, there were three populations, one for each studied drug similarly selected. From the population affiliated to the GHIS in the Pays de Loire region (in which there were 3.4 million residents in 2008), we have selected the patients who were aged over 18 years and who had received at least two dispensings of bromazepam, paroxetine or zolpidem between 1 January and 30 June 2008 at two different times. Patients who received two dispensings the same day were excluded from the study.

Assessment of psychotropic drugs consumption

Databases were made up of variables providing information on the patients, the prescribing physicians, the pharmacies which delivered the studied drugs, the number of dispensings and the dosage of each studied drug and finally the associated psychotropic drugs during the study period. The variables were the same for each drug's database.

Some categorical variables have been created from the original ones to identify several indicators of consumption behaviours. Transformations were performed to create the six following binary variables which have been included in the LCA:

Consumption factor

The consumption factor (CF) was defined by the estimate of the average daily consumption of a psychotropic drug divided by the maximum recommended daily dose as specified in the French Drug Monograph. The threshold for over consumption was defined by a value of the CF greater than 1.

Kind of prescribing physicians

Psychotropics drugs could be prescribed during a follow-up by a general practitioner or by a specialist.

'Doctor shopping' behaviour

Patients may develop a behaviour known as 'doctor shopping', which means that the same patient consults several physicians in the same time frame. The threshold for 'doctor shopping' was defined by a number of prescribing physicians greater than three during the 6-month study period.

'Pharmacy shopping' behaviour

Patients may also develop a behaviour known as 'pharmacy shopping', which means that the same patient goes to several pharmacies in the same time frame. The threshold for 'pharmacy shopping' was defined by a number of pharmacies who delivered the drug greater than three times during the 6-month study period.

French practice guidelines on the suitable use of psychotropic drugs help physicians prescribing psychotropic drugs and their associations. From the first-line guidelines on the use of psychotropic drugs, two binary variables have been created:

- (1) Prescription in agreement with practice guidelines relating to the therapeutic class of the studied psychotropic drug
- (2) Prescription in agreement with practice guidelines relating to other classes of associated psychotropic drugs

In this study, a patient was not in compliance with the guidelines if he had received two anxiolytic-hypnotic drugs or more, and/or two antidepressant drugs and/or two antipsychotic drugs and/or two opioid maintenance therapies (methadone or buprenorphine).

Statistical analysis

The same statistical analysis strategy was used for the study of each psychotropic drug. LCA used the six following indicators of consumption behaviours: CF, kind of prescribing physicians, 'doctor shopping' behaviour,

'pharmacy shopping' behaviour, prescription in agreement with practice guidelines relating to (i) the therapeutic class of the studied psychotropic drug and (ii) other classes of associated psychotropic drugs.

LCA is characterized by two parameters: (i) the probability of being in each class, which provides an estimate of the prevalence of each latent class, (ii) the conditional response probability, corresponding to the probability that an individual in a given class will show particular consumption behaviour.

LCA is based on the assumption of local independence meaning that observed variables are conditionally independent within each latent class. As a consequence, it is hypothesized that the associations between consumption behaviours (observed variables) should be explained by the class membership (individuals belong to different latent classes). Using this model, we obtained for each individual a posterior probability of belonging to each latent class.

The number of latent classes was determined by the LCA models. We fitted 1-class to 6-class latent class models for each studied psychotropic drug and statistically assessed the fit of each one to the data. The best-fitting models were chosen based on the Bayesian Information Criterion (BIC). The models with the lowest BIC value were selected (Magidson and Vermunt, 2004; Nylund *et al.*, 2007). The software Latent Gold (version 4.0) was used for model fitting. With this software, the local independence assumption was evaluated and taken into account when appropriate (Vermunt and Magidson, 2005).

One limitation of LCA is the problem of local maxima and convergence, which are related to the complexity of the model. To guard against local maxima solutions, we ran the estimation algorithm several times with different parameter start values and we chose the best solution using the BIC. Using the Latent Gold software, we implemented options for automatic testing of numerous starting values (Vermunt and Magidson, 2005; Uebersax, 2009).

The profiles of bromazepam, paroxetine and zolpidem users have been described by latent class prevalence and conditional probabilities. Sociodemographic characteristics (sex and age) and other terms related to the consumption of psychotropic drugs, which included original quantitative variables (duration of treatment, daily dose, number of dispensings, number of pharmacies who delivered the drug, number of prescribing physicians, CF), were covariates in the model. Therefore they were not involved in the construction of the model but allowed, once LCA model was fitted, for a better description and characterization of classes of psychotropic drugs users. Means (with standard deviations) and proportions (with a confidence interval) weighed on posterior probability were calculated for continuous and

categorical covariates, respectively in each latent class. Analysis of variance and χ^2 tests were used to compare means and proportions, respectively.

Results

Description of populations

Databases were all complete; there was no missing data.

Bromazepam

A total of 40 644 patients who received at least two dispensings of bromazepam during the first half of 2008 were included in the study. The population included 74% women whose average age was 62 years. More than four out of five times, the prescription was made by a general practitioner. Only 1.1% of patients displayed a CF greater than 1 and a very small proportion of patients consulted many prescribing physicians (0.4%) or many pharmacies (1.2%). Nearly 40% of prescriptions were not in agreement with practices guidelines related to the therapeutic class of bromazepam and 7% were not in agreement with practices guidelines related to other classes of associated psychotropic drugs.

Zolpidem

A total of 36 264 patients who received at least two dispensings of zolpidem during the first half of 2008 were included in the study. This population had similar characteristics as bromazepam users. However larger overconsumption behaviour was observed: 17.8% of patients had a CF greater than 1. In over half of the cases, the prescription of zolpidem was not in agreement with practices guidelines related to its therapeutic class.

Paroxetine

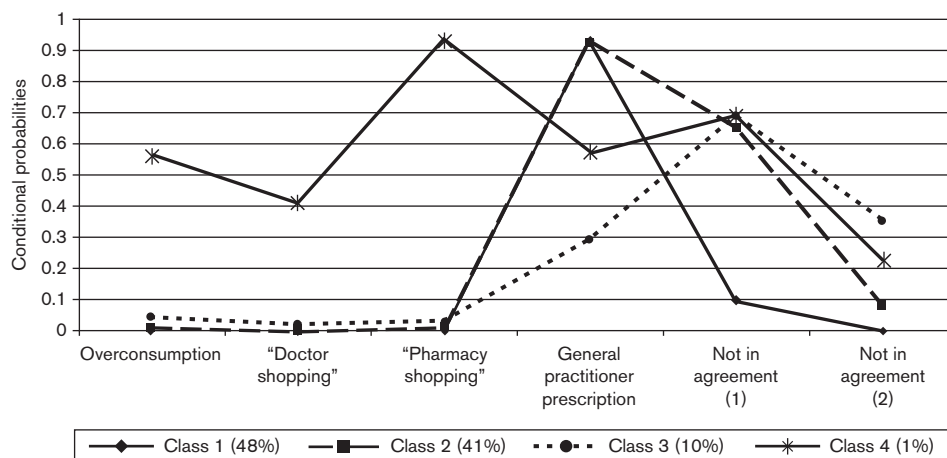
A total of 31 235 patients who received at least two dispensings of paroxetine during the first half of 2008 were included in the study. This population was younger than the populations described earlier (average age: 57 years) and 72% were women. Overconsumption was rarely observed (0.3%). Nonagreement with practices guidelines related to classes of associated psychotropic drugs (26%) was greater than the one related to paroxetine's therapeutic class (13%).

Latent class analysis

Bromazepam

A 4-class model was selected using the BIC. The class prevalences and conditional probabilities estimated by the latent class model are shown in Fig. 1. The characteristics of each latent class are presented in Table 1. We identified four clinical subtypes of users of bromazepam. Class 1 was the most prevalent subtype (48%) with individuals older than in the other classes. This group was characterized by an absence of 'doctor shopping' or 'pharmacy shopping' behaviours and an absence of overconsumption behaviour. The prescriptions of psychotropic drugs came mostly from general practitioners (93%) and were generally in agreement with the practice guidelines (90% or more). Class 2 was also a prevalent group (41%) with a larger proportion of women as compared with other classes. Prescriptions stemmed essentially from a general practitioner (92%) and were most often not in agreement with practice guidelines related to anxiolytics and hypnotics (65%). Class 3 (10%) comprised individuals receiving psychotropic drugs associations with the highest rate of nonagreement of the

Fig. 1



(1) Prescription not in agreement with practice guidelines relating to the therapeutic class of the studied psychotropic drug
 (2) Prescription not in agreement with practice guidelines relating to other classes of associated psychotropic drugs

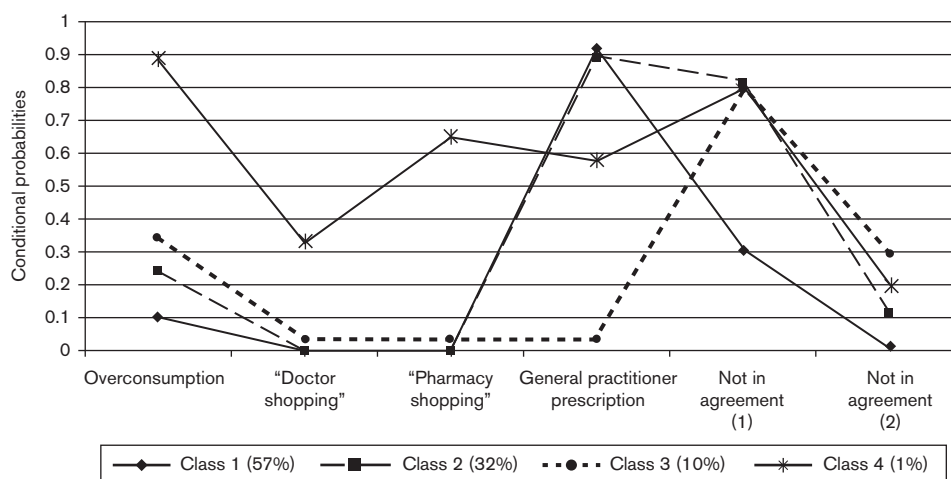
Estimated class probabilities and conditional probabilities for the four latent class models of bromazepam users.

Table 1 Description of the characteristics of the four latent classes of bromazepam users

	Class 1	Class 2	Class 3	Class 4	P value
Class probability (prevalence)	0.48	0.41	0.1	0.01	
Sex, female (%)	73.0 (72.4–73.6)	74.9 (74.2–75.6)	72.1 (70.7–73.5)	66.3 (61.7–70.9)	<0.001
Age (years)	63.1 (10.3)	62.1 (9.8)	57.4 (5.0)	45.3 (0.8)	<0.001
Number of prescribing physicians	1.1 (0.3)	1.2 (0.3)	1.6 (0.2)	3.2 (0.2)	<0.001
Number of pharmacies who delivered the medication	1.2 (0.3)	1.3 (0.4)	1.4 (0.2)	5.3 (0.2)	<0.001
Duration of treatment (days)	112.8 (31.7)	112.9 (30.5)	115.4 (15.6)	152.7 (2.2)	<0.001
Number of dispensings	3.7 (1.2)	3.9 (1.2)	4.4 (0.7)	11.6 (0.6)	<0.001
Daily dose (mg/day)	4.5 (1.6)	5.2 (2.0)	6.6 (1.5)	21.2 (1.1)	<0.001
Consumption factor	0.2 (0.1)	0.3 (0.1)	0.4 (0.1)	1.2 (0.1)	<0.001

Data were weighted means (standard deviation) for quantitative variables and weighted proportions for categorical variables (confidence interval). Analysis of variance tests were performed for quantitative variables and χ^2 tests were performed for categorical variables.

Fig. 2



(1) Prescription not in agreement with practice guidelines relating to the therapeutic class of the studied psychotropic drug
 (2) Prescription not in agreement with practice guidelines relating to other classes of associated psychotropic drugs

Estimated class probabilities and conditional probabilities for the four latent class models of zolpidem users.

prescription with the practice guidelines (69%). However this prescription more often stemmed from a specialist (71%). Finally, class 4 was a minority subtype (1%). A substantial proportion of these individuals displayed 'doctor shopping' behaviour (41%), 'pharmacy shopping' behaviour (93%) and overconsumption behaviour (56%). This class was younger and the daily dosage was two to three times higher than in the other classes.

Zolpidem

A 4-class model was selected using the BIC. This 4-class model seemed to have similarities with the one obtained for bromazepam and the classes could be interpreted the same way. Nevertheless prevalence of class 1 was more important (57%) and less important for class 2 (32%). Moreover, the rates of overconsumption and nonagreement of prescriptions with practice guidelines related to the therapeutic class of zolpidem were higher among all the classes than for the respective classes of bromazepam users (Fig. 2). The characteristics of each latent class

for zolpidem seemed to be fairly similar to those observed with bromazepam (Table 2). Furthermore, we observed that the average duration of treatment is well above the recommended maximum time in the French Drug Monograph (4 weeks), whatever the class.

Paroxetine

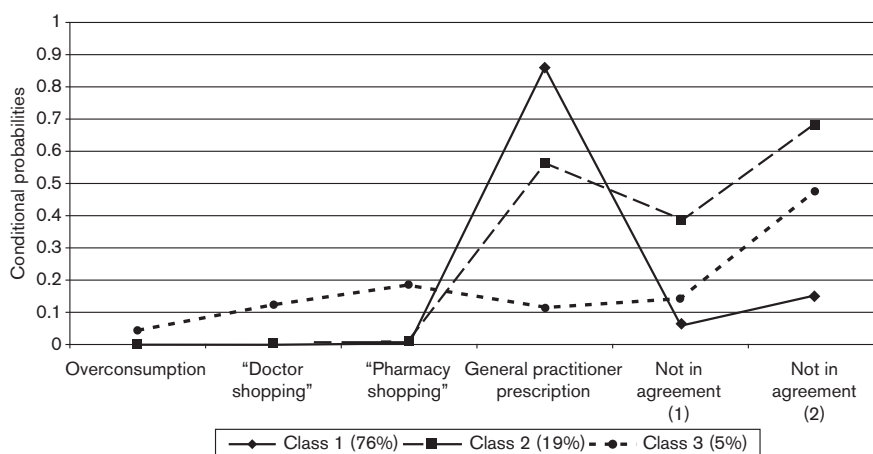
Using the BIC, a 3-class model was selected. The resulting model is shown in Fig. 3. The characteristics of each latent class are presented in Table 3. Class 1, the most prevalent subtype (76%), comprised users whose prescription stemmed from a general practitioner (86%), with a low rate of nonagreement with practices guidelines, and whose consumption was not associated with an overconsumption, a 'doctor shopping' or a 'pharmacy shopping' behaviour. Class 2 was a group of users with the highest proportion of nonagreement with practice guidelines mostly unrelated to the antidepressant, but rather related to associated psychotropic drugs. These prescriptions were made by a general practitioner in over half the

Table 2 Description of the characteristics of the four latent classes of zolpidem users

	Class 1	Class 2	Class 3	Class 4	P value
Class probability (prevalence)	0.57	0.32	0.1	0.01	
Sex, female (%)	69.1 (68.5–69.7)	71.2 (70.4–72.0)	65.5 (64.0–67.0)	69.5 (64.8–74.2)	<0.001
Age (years)	65.2 (11.6)	62.7 (9.1)	57.8 (5.3)	53.4 (1.7)	<0.001
Number of prescribing physicians	1.2 (0.3)	1.2 (0.3)	1.9 (0.2)	2.8 (0.3)	<0.001
Number of pharmacies who delivered the medication	1.2 (0.3)	1.3 (0.3)	1.5 (0.3)	4.0 (0.3)	<0.001
Duration of treatment (days)	113.3 (33.9)	112.6 (27.5)	113.1 (16.3)	143.1 (3.9)	<0.001
Number of dispensings	3.6 (1.3)	4.1 (1.1)	4.8 (0.7)	9.1 (0.7)	<0.001
Daily dose (mg/day)	6.3 (2.4)	7.6 (2.3)	8.8 (1.4)	17.2 (1.5)	<0.001
Consumption factor	0.6 (0.2)	0.8 (0.2)	0.9 (0.1)	1.7 (0.2)	<0.001

Data were weighted means (standard deviation) for quantitative variables and weighted proportions for categorical variables (confidence interval). Analysis of variance tests were performed for quantitative variables and χ^2 tests were performed for categorical variables.

Fig. 3



(1) Prescription not in agreement with practice guidelines relating to the therapeutic class of the studied psychotropic drug
 (2) Prescription not in agreement with practice guidelines relating to other classes of associated psychotropic drugs

Estimated class probabilities and conditional probabilities for the three class models of paroxetine users.

cases. Finally, class 3 was a minority subgroup (5%) with younger individuals. A specialist followed an important proportion of these individuals (89%). They were the only group to display ‘doctor shopping’ (12%) and ‘pharmacy shopping’ behaviour (18%). Absence of overconsumption was observed for paroxetine, whatever the class.

Discussion

This study has described the characteristics of consumption of three psychotropic drugs among the most used in the French general population in real-life conditions. We used the same statistical method to study the consumption of the three drugs, allowing observing specificities in consumption patterns according to the pharmacological class.

As supported in the literature in developed countries, the consumption of anxiolytics, hypnotics and antidepressants is widespread among adult population, particularly

among elderly people and women. The overrepresentation of women is shown in many studies at almost all ages (Mazza *et al.*, 1995; Paulose-Ram *et al.*, 2004; Beck *et al.*, 2005; Gasquet *et al.*, 2005; Paulose-Ram *et al.*, 2007).

We identified four clinical subtypes of users of bromazepam and zolpidem, for which the patterns of consumption seem to be comparable according to latent class models. From a pharmacological perspective, individuals in class 1 represented nonproblematic users of psychotropic drugs and were the most prevalent group. In contrast, individuals in class 4 displayed behaviours, as ‘doctor shopping’ or ‘pharmacy shopping’ behaviours that are considered as fraudulent. The French Health system is not a gate-keeper system with referral practitioners, such as the National Health Service in the UK. This system makes possible a greater availability of psychotropic drugs in France. Indeed, patients can consult as many physicians as they want and be reimbursed for a part of their consultation fees and pharmaceutical expenses by GHIS. This system has led to some groups of patients developing

Table 3 Description of the characteristics of the three latent classes of paroxetine users

	Class 1	Class 2	Class 3	P value
Class probability (prevalence)	0.76	0.19	0.05	
Sex, female (%)	72.6 (72.0–73.2)	69.6 (68.4–70.8)	65.3 (62.9–67.7)	<0.001
Age (years)	57.9 (15.4)	56.1 (7.6)	51.1 (3.5)	<0.001
Number of prescribing physicians	1.2 (0.4)	1.4 (0.3)	2.0 (0.2)	<0.001
Number of pharmacies who delivered the medication	1.4 (0.6)	1.4 (0.3)	2.0 (0.3)	<0.001
Duration of treatment (days)	127.5 (41.6)	115.7 (23.2)	131.0 (9.5)	<0.001
Number of dispensings	5.1 (1.6)	4.9 (0.9)	5.7 (0.5)	<0.001
Daily dose (mg/day)	17.2 (7.0)	20.1 (4.5)	23.2 (3.0)	<0.001
Consumption factor	0.3 (0.11)	0.3 (0.1)	0.4 (0.0)	<0.001

Data were weighted means (standard deviation) for quantitative variables and weighted proportions for categorical variables (confidence interval). Analysis of variance tests were performed for quantitative variables and χ^2 tests were performed for categorical variables.

fraudulent behaviour. These characteristics of consumption suggest that the users in class 4 may have a compulsive use of psychotropic drugs, probably as a part of polysubstance abuse or dependence. The official enquiries conducted in France by CEIP showed that bromazepam and zolpidem are among the most commonly used psychotropic drugs among illicit drug users. Furthermore, among this group of users, the frequency of illicit obtaining of bromazepam and zolpidem seemed to have increased between 2005 and 2008 (Agence Française de Sécurité Sanitaire des Produits de Santé, 2005, 2006, 2007a, 2008; Beck *et al.*, 2006). In addition, in 2007, zolpidem was the first psychotropic drug on the forged prescriptions list (Agence Française de Sécurité Sanitaire des Produits de Santé, 2007b). The users belonging to class 3 may suffer from a resistant or severe mental disorder requiring a larger association of psychotropic drugs, not always in agreement with first-line guidelines. However, these prescriptions are most often monitored through a specialized follow-up. Finally, class 2 comprised users who could have developed a tolerance to anxiolytic or hypnotic effects after a chronic use and then require the addition of another anxiolytic–hypnotic drug to get the same effect. This consumption might become uncontrolled and could be at risk of abuse or dependence in the long term. This class represents a target population for which it is necessary to implement educative and preventive measures.

The abuse and dependence potential with anxiolytics and hypnotics is now well documented. Three types of drug addiction appeared in this study for these psychotropic drugs: (i) a drug addiction in multiple-dependent patients who developed fraudulent behaviours to obtain psychotropic drugs (class 4), (ii) an addiction secondary to a probable mental disorder requiring psychotropic drugs (class 3), (iii) a drug abuse and addiction under medical prescription related to a social and a cultural overconsumption of psychotropic drugs (class 2). Regarding zolpidem, the CEIP network recently conducted an official enquiry to reassess its dependence potential. Two population profiles have appeared in relation to the desired effect: the chronic users of high doses, but with a therapeutic use, relevant to our classes 2 and 3, and a population with a misuse in search of an effect other than hypnotic, corresponding to class 4 (Victorri-Vigneau *et al.*, 2007).

Paroxetine is an antidepressant drug whose dependence potential has not been described. The LCA revealed differences rather based on the prescription patterns. Class 1 comprised nonproblematic users. Two other groups have been identified. On the one hand, there was a group of consumers with a higher proportion of nonagreement with practice guidelines related to associated psychotropic drugs (class 2). We are faced with a medical prescription that seems not always controlled, as with bromazepam and zolpidem. In contrast, there was a minority subgroup of younger individuals followed by a specialist (class 3). They may be more likely to have a serious or resistant mental disorder requiring associations of psychotropic drugs. These patients may be equally more fragile. Consequently, they are more likely to become addicted and develop fraudulent behaviours as ‘doctor’ or ‘pharmacy shopping’. Thus, the findings showed the emergence of fraudulent behaviours in this group.

Using LCA, we have provided estimates of the prevalence of psychotropic drug user profiles. This information is very valuable as it is often difficult to estimate the proportion of users developing a problematic use of psychotropic drugs. The strength of our approach is certainly not to have focused on a specific subgroup of the population, but to have studied for each psychotropic drug the entire population of users, which covers distinct clinical profiles. In France, the only data available are focused on specific populations and come from the specific system of health surveillance. Only psychotropic drugs abuse and dependence are systematically monitored, whereas a minority of patients displays these behaviours. However in our study, there were a significant proportion of patients who seemed to have a problematic use of zolpidem or bromazepam, 43 and 52% of the population, respectively (classes 2, 3 and 4).

Our findings should be interpreted in the light of several limitations, first of all inherent to GHIS databases. One limitation is that this study is based on data of drugs reimbursements, not on the actual consumption. Indeed the drug delivered may not be consumed, may be given or resold. Moreover, it is not possible to differentiate misuse from other consumption behaviours. However, these

behaviours are displayed only by a minority of the general population (Briot, 2006). Another limitation is because of available variables in the databases and their use in the LCA. To characterize the psychotropic drugs consumption, new variables related to consumer behaviours were created and dichotomized from the original variables. These transformations could have caused a loss of information. Nevertheless, they improved the pharmacological interpretation of the models. Finally, lack of clinical and sociodemographic data limited our ability to better describe the classes determined by the models.

Special attention should be given to the choice of the practice guidelines on which we relied in our study, especially for the use of antidepressants. To define the thresholds of agreement/nonagreement with guidelines, we actually based on first-line guidelines for the treatment of depressive and anxiety disorders. Two important points justified this choice. First, first-line treatment guidelines apply to the most frequent cases especially in outpatient care and are currently the best known. In France, resistant depressive and anxiety disorders are not yet the subject of specific guidelines, and the therapeutic strategies currently available remain unclear. In our study, some individuals may be classified as 'not in agreement with practice guidelines' although this is not true if we consider the resistant disorders, probably requiring a combination of two antidepressants. However, given the low prevalence of these resistant disorders and the few studies on this subject, we studied the majority population. In the second place, this decision corresponds to a methodological choice to reach a good potential of classes discrimination. If we have considered the association of two antidepressants as complying with the guidelines, virtually all the population could be 'in agreement with guidelines' and this variable could be not discriminating to determine the classes with LCA. In addition, we have clearly identified these resistant patients in class 3 for the three drugs studied, as having a severe mental disorder.

Despite these limitations, health insurance databases allowed us to assess psychotropic drugs consumption in real conditions of use in the French general population. One of the strengths of this study is that it included all the dispensing of the three psychotropic drugs in the population affiliated to the GHIS in the Pays de Loire region during the study period (i.e. 78% of the regional population). Another advantage of these databases is to provide data that are not exposed to bias related to self reporting, in which there may be an underestimate of actual rates of consumption. Applying LCA to these databases provides information on both psychotropic drugs consumption and on physician's prescription habits.

Conclusion and prospects

These findings provided an original overview of the patterns of psychotropic drugs use in a French region,

which have important implications for health policies and for prevention. Indeed, the challenges of this study are 2-fold.

On the one hand, it helped to improve knowledge about psychotropic drugs and met the regulatory requirements for evaluation and monitoring of drug abuse and dependence. LCA represents a new tool for identifying and quantifying problematic use of psychotropic drugs, which is complementary to the official enquiries of CEIP network.

In contrast, it could allow implementing concrete measures by the authorities and the prescribers to preserve the public health. First, it is necessary to maintain regulatory measures and to assess their efficacy to reduce the risk of psychotropic drugs abuse and dependence. Information and training of physicians are necessary to improve their prescribing practices. In this objective, information on the psychotropic drugs should be strengthened and communication activities must be implemented to the prescribing physicians by the French authorities. The elaboration of practice guidelines based on factual data should be improved in France to decrease the psychotropic drugs consumption and to facilitate the management of psychotropic drugs related disorders.

Pharmacoepidemiological research must remain a public health priority as it allows effective risk monitoring and helps health authorities to take such effective measures to protect towards public health. In this context, latent class models could be extended to other databases of drugs reimbursements to identify and quantify populations at risk of abuse or dependence to psychotropic drugs.

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