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ORIGINAL REPORT

Anxiolytics, hypnotics, and antidepressants dispensed to adolescents in a French region in 2002†

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SUMMARY

Purpose This study proposes to complete declarative studies by describing the prescriptions of anxiolytics, hypnotics, and antidepressants dispensed to adolescents in a French region in 2002.

Methods This cross-sectional study analyzes all the hypnotic, anxiolytic, and antidepressant prescriptions (ATC codes beginning with N05B, N05C, and N06A, respectively) sent by adolescents (aged 13–17 years) to the French Health Insurance system of the study region for reimbursement during one year (2002). It was performed in a southern France area with 120 908 adolescents covered by this insurance scheme. Adverse drug reactions (ADRs) recorded in the Pharmacovigilance database were also studied.

Results Three thousand two hundred and eighty-six adolescents (2.7% of adolescent population) had at least one prescription of the studied drugs. This prevalence increased with age and female sex, leading to a maximum of 6.3% for the 17-year-old girls. Two thousand four hundred and thirty-one of adolescents were dispensed anxiolytics, 935 antidepressants, and 548 hypnotics. The most dispensed drugs were zolpidem, zopiclone, and niaprazine for hypnotics; hydroxyzine, etifoxine, and bromazepam for anxiolytics; and paroxetine, sertraline, and fluoxetine for antidepressants. Zolpidem, hydroxyzine, and paroxetine accounted, respectively, for 82.9%, 57.1%, and 59.8% of the prescriptions. 75.5% of hypnotics users had only one prescription, 77.4% for anxiolytics, and 57.4% for antidepressants. Three ADRs were reported.

Conclusions This study confirms the large use of psychotropics in French adolescents and the influence of age and sex. Also, the results underline treatment for most adolescents is short, which may be beneficial for hypnotics and anxiolytics but not for antidepressants. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS — adolescents; psychotropic drugs; hypnotics; anxiolytics; antidepressants; pharmacoepidemiology; prescriptions databases

INTRODUCTION

Several studies have shown worrisome psychotropics consumption declared by French adolescents, especially girls.[1–3] French legal drug use is one of the largest in the world and it was the greatest in the European

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Union in 1997.[4] Among all the drugs, psychotropics were the second most consumed after analgesics in France in 2001–2002.[5] This consumption was characterized by its regularity (11% consumed a psychotropic on a regular basis) and by its increase with age and female sex (30% of women more than 60 years consumed a psychotropic).[6] During the last decade (1990–2000), consumption was stable for anxiolytics and hypnotics and increasing for antidepressants.[7] One explanation for this increase is the marketing of new antidepressants, such as selective serotonin reuptake inhibitors, and their licensing for other indications than depression (panic disorder, social phobia...).

In adolescents, psychotropic use has been studied many times through general questionnaires about health and consumption. From 1990, the declared consumption of psychotropics seemed to increase.[8] In 1993, the first important study in France found that 17% of 11- to 19-year olds declared consuming a psychotropic during the past year (22% for girls, 12% for boys).[3] In 1997–1998, another national study showed that 7.1% of 12- to 19-year olds took drugs for anxiety or nervousness, and 3.5% had hypnotics, especially girls.[2] In 2002, the latest results of ESCAPAD (national annual study in 17- to 19-year-old conscripts) showed similar levels of use; 2.6% of adolescents declared regular use (10 times or more in a month; 4.1% for girls, 1.1% for boys).[1] However, there is a lack of specific data about psychotropic medications in adolescence, [9] suggesting that more studies are warranted, in particular to describe the characteristics of this consumption: drug name, quantity and frequency of drugs prescribed, and origin of prescriptions (general physicians, specialized physicians...). Such information may be provided by databases of drugs reimbursed by the French health system.[10–12] These data are used to assess drug prescriptions dispensed in several countries.[5,13,14]

The aim of this study was to describe the prescriptions of anxiolytics, hypnotics, and antidepressants dispensed to adolescents in terms of patients' characteristics (age and gender variations) and the characteristics of prescriptions (drug name, prescribers) in a French region in 2002, using the French health system database.

METHODS

Study settings

This study was performed in southern France (Bouches du Rhône), an area with 1.8 million inhabitants, 2400 general practitioners, and a high prevalence of prescriptions of hypnotics, anxiolytics, and antidepressants.[15]

Study design, data management, and statistical methods

Based on European Agency for the Evaluation of Medicinal Products (EMEA) recommendations,[16] the definition of adolescence chosen was 13–17 years old (minor teenagers). This cross-sectional study analyzes all the hypnotic, anxiolytic, and antidepressant prescriptions sent to the health insurance system of the study region for reimbursement during one year (2002) for adolescents born between 1985 and 1989. More than 90% of the population of the same age in this geographic area was affiliated to this reimbursement system, that is, 120 908 adolescents. During this period, more than 99% of the dispensed prescriptions were coded and electronically sent to the system of health insurance.

The prescriptions analyzed were extracted using ATC classification (developed by WHO's Collaborating Centre for Drug Statistics Methodology)[17]. All prescriptions with an ATC code beginning with N05B (anxiolytics), N05C (hypnotics), or N06A (antidepressants) were included.

Studied variables were ATC code, date and quantity of the dispensed prescriptions, age and sex of the patient, and practitioner identification. Means of individual doses were estimated if adolescents had at least two dispensed prescriptions. Prevalence of dispensed prescriptions was calculated with the adolescent population of the database as denominator.

Adverse drug reactions (ADRs) recorded in the French regional Pharmacovigilance database during 2002 were also studied.

To conform to French law concerning protection of patient anonymity, all names were kept confidential by doctors within the Social Security System. Statistical analysis was performed on a nameless file.

Usual statistical tests were used to compare the groups (Student *t*-test, Chi^2 test). All significance levels were set at 0.05. Analyses were carried out using the SPSS 11.5 statistical analysis program. The results are presented as means (with standard deviation in brackets).

RESULTS

Population: adolescents, practitioners

There were 3286 adolescents with at least one dispensed prescription of hypnotics, anxiolytics, or

Table 1. Distribution of adolescents, with at least one prescription of hypnotics, anxiolytics, or antidepressants dispensed in 2002, by sex and age

	Male			Female			Total	
	n	% by sex	% by age	*n*	% by sex	% by age	*n*	% by age
13	188	50.0	15.8	188	50.0	9.0	376	11.4
14	182	42.7	15.3	244	57.3	11.7	426	13.0
15	197	33.1	16.5	398	66.9	19.0	595	18.1
16	278	34.5	23.3	528	65.5	25.2	806	24.5
17	348	32.1	29.2	735	67.9	35.1	1083	33.0
Total	1193	36.3	100	2093	63.7	100	3286	100

antidepressants, corresponding to a 1-year period prevalence of 2.72% (3.6% for girls, 1.9% for boys). A total of 6900 prescriptions were dispensed by 1679 practitioners. Patient mean age was 15.5 (1.4) years. The number of adolescents increased with age (33% were 17 years old, Table 1). There were more girls (63.7%) and this percentage increased with age (from 50% at 13 years to 67.9% at 17 years, Table 1). Maximum prevalence of prescription (6.28%) was for the 17-year-old girls. This pattern is equivalent for each drug (Figure 1). Figure 2 shows the distribution of prescriptions during each month for the three drug classes for boys and girls.

Physicians prescribed 92.2% of the dispensed prescriptions, care centers 6.5%, and dentists 1.3%. The mean age of the physicians who prescribed at least one studied drug was 48 (7.7) years. During 2002, they prescribed such drugs to a mean of 2.1 (1.8) adolescents with a mean number of prescriptions per adolescent of 3.6 (4.7). Eighty per cent of physicians were general practitioners, 9.4% psychiatrists, and 2.1% pediatricians. Among the physicians who prescribed psychotropic drugs to adolescent during 2002, 41% prescribed at least one antidepressant, but prescription rate differed with specialties (79.5% for psychiatrists, 38.4% for GPs, and 15.2% for pediatricians).

Hypnotic prescriptions

During 2002, 548 adolescents (60.6% were girls) had at least one hypnotic prescription, for a total of 911 dispensed prescriptions. These adolescents represented 16.7% of our sample and 4.5‰ of the database. Prevalence of hypnotic prescriptions ranged from 1.7‰ for 13-year-old girls to 12.2‰ for 17-year-old girls (Figure 1a). For 75.5% of adolescents, only one prescription of hypnotic was dispensed (Table 2). The mean number of prescriptions was 1.66 (1.6), without significant difference between girls and boys.

Among the 10 different hypnotics dispensed during the year, 3 were found in 82.9% of prescriptions: zolpidem, zopiclone, and niaprazine (Table 3). The first benzodiazepine (nitrazepam) was in fourth rank.

Anxiolytic prescriptions

During 2002, 2431 adolescents (64.6% were girls) had at least one anxiolytic prescription, for a total of 3752 dispensed prescriptions. These adolescents represented 74% of our sample and 20.1‰ of the database. Prevalence of anxiolytic prescriptions ranged from 10.9‰ for 13-year-old boys to 46.8‰ for 17-year-old girls (Figure 1b). For 77.4% of adolescents, only one prescription of anxyolytic was dispensed (Table 2). The mean number of prescriptions was 1.66 (1.9) for boys and 1.48 (1.4) for girls ($p = 0.013$).

Among the 16 different anxiolytics dispensed, 6 represented 85.7% of the prescriptions (Table 3). The first, hydroxyzine, was dispensed in 31.8% of cases. The first benzodiazepine (bromazepam) was in third rank.

Antidepressant prescriptions

During 2002, 935 adolescents (65.6% were girls) had at least one antidepressant prescription, for a total of 2237 dispensed prescriptions. These adolescents represented 28.5% of our sample and 7.7‰ of the database. Prevalence of antidepressant prescriptions ranged from 3.2‰ for 13-year-old boys and girls to 20.9‰ for 17-year-old girls (Figure 1a). For 57.4% of adolescents, only one prescription of antidepressant was dispensed (Table 2). The mean number of prescriptions was 2.39 (2.5) without significant difference between girls and boys.

Among the 19 antidepressant medications, 4 represented 71.4% of prescriptions; the first (paroxetine) represented 29.9% of prescriptions (Table 3).

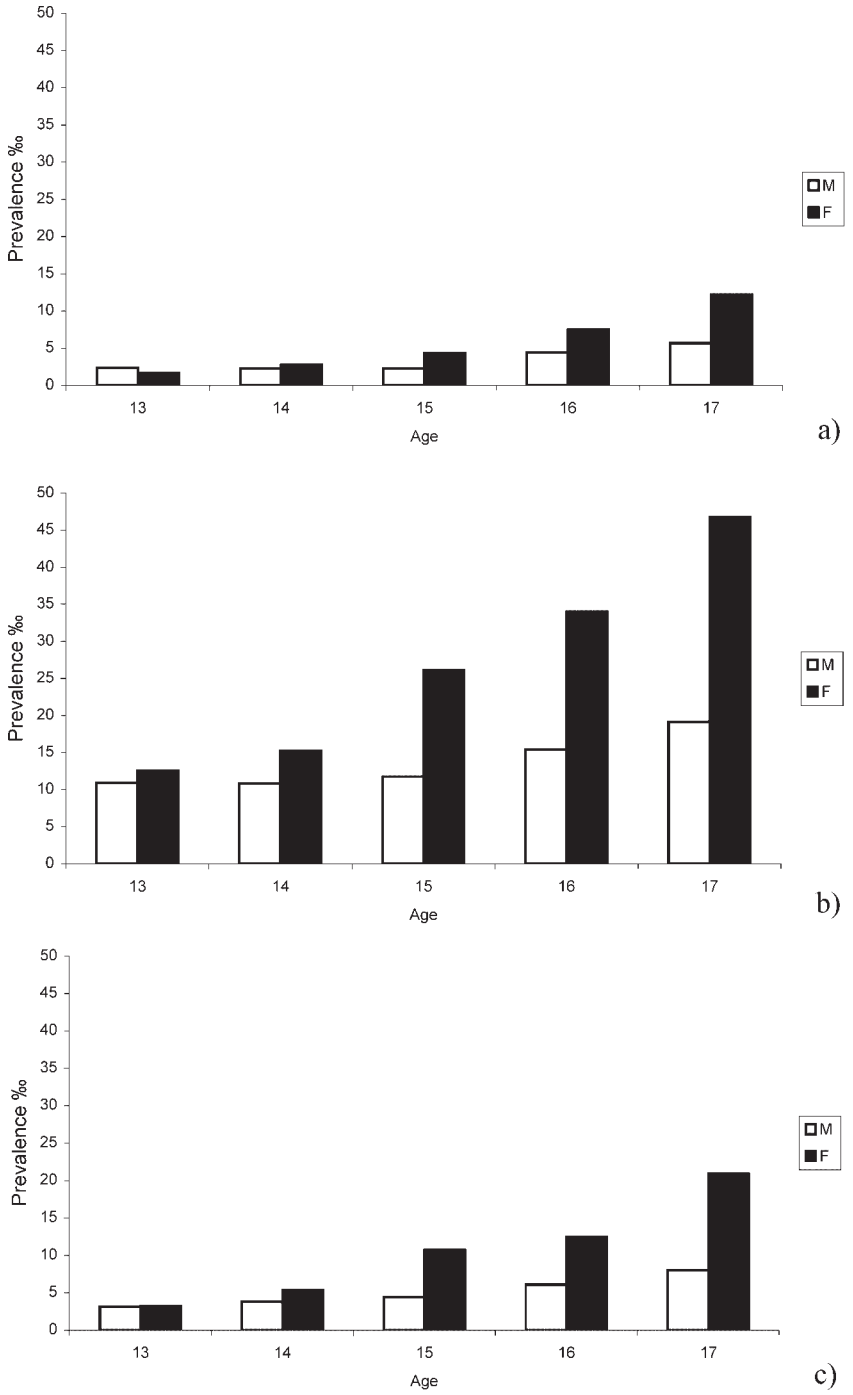

Figure 1. Prevalence (‰) by sex (M, male; F, female) of psychotropic prescriptions to adolescents of a French region dispensed in 2002: (**a**) hypnotics; (**b**) anxiolytics; (**c**) antidepressants

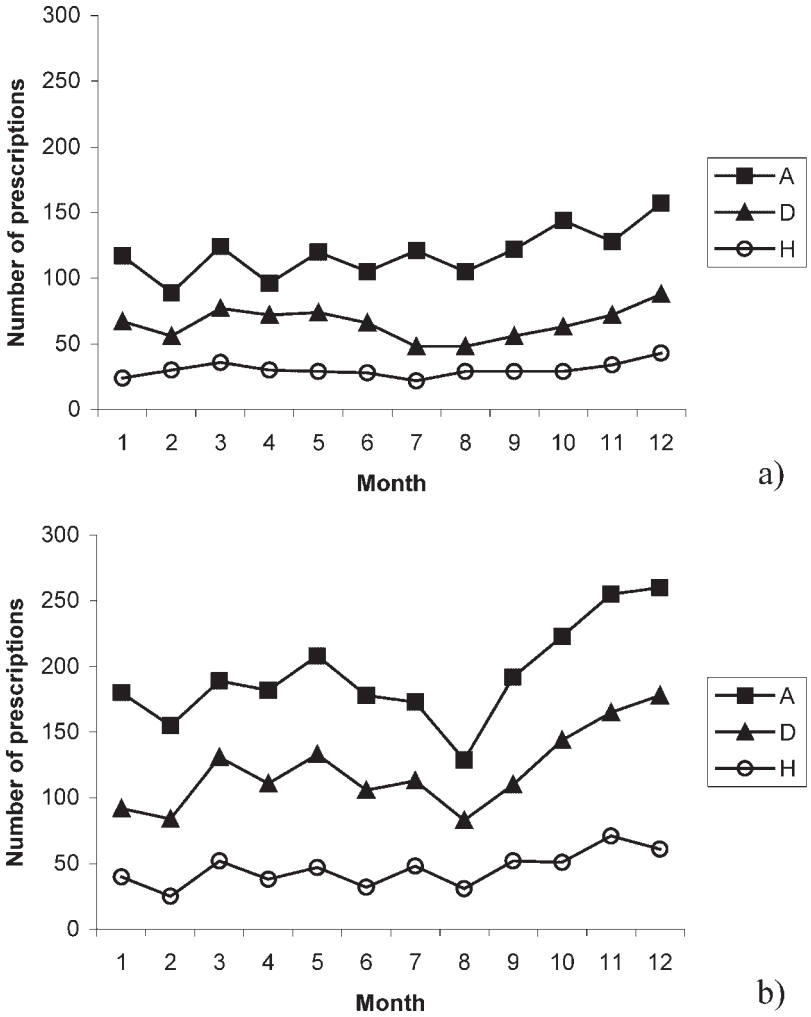

Figure 2. Seasonal variation of hypnotic (H), anxiolytic (A), or antidepressant (D) prescriptions dispensed to adolescents of a French region in 2002: (**a**) boys; (**b**) girls

Associations

During the year, 535 adolescents (16.3%) had dispensed prescriptions of at least two types of psychotropic medication. The most frequent association was anxiolytics and hypnotics. Figure 3 shows the frequency of these multiple psychotropic prescriptions.

Adverse drug reactions

During the year, 18 477 ADRs were recorded in the French Pharmacovigilance Database. Of these, 1422 were collected by our Regional Center of Pharmacovigilance (PACA-Corse); 51 adverse events concerned adolescents. In the area of our study (department 13, Bouches-du Rhône), three ADRs with the studied drugs were reported among adolescents: two cutaneous reactions (urticaria) with etifoxine and adverse reactions related to citalopram overdose (headache, nausea, tremor, visual disturbance, chest pain).

DISCUSSION

Prevalence

The main finding of this study is that the 1-year prevalence of dispensed prescriptions of hypnotics, anxiolytics, or antidepressants in a 13- to 17-year-old population was 2.7% (1.9% for boys, 3.6% for girls).

Table 2. Number of hypnotic, anxiolytic, and antidepressant prescriptions dispensed to adolescents of a French region during 2002

Number of prescriptions	Adolescents with at least one hypnotic prescription		Adolescents with at least one anxiolytic prescription		Adolescents with at least one antidepressant prescription	
	n	%	*n*	%	*n*	%
1	414	75.5	1881	77.4	537	57.4
2–5	109	19.9	481	19.8	299	32.0
>5	25	4.6	69	2.8	99	10.6
Total	548	100	2431	100	935	100

This result concurs with an article published in France showing, respectively, for boys and girls (10- to 19-year-old), prescription prevalences of 2.1% and 3.9% for anxiolytics, 0.9% and 1.6% for antidepressants, and 0.5% and 0.8% for hypnotics during 2000.[18] As mentioned earlier, declarative studies[1–3] have found a higher prevalence, leading to several hypotheses. First, the lack of precise questionnaires (e.g., 'During the past year, did you use drugs for nerves?')[2]. This may refer to other compounds such as alternative medicines (herbal medicines and homeopathy). Besides, a recent study has shown large consumption of these compounds by French adolescents.[19] In addition, a study on secondary schools showed that nearly 40% of students were not able to give the name of the drug used and 15% of the others were mistaken.[20] A second hypothesis is related to self-medication, defined as obtaining and consuming a drug without the advice of a physician and without a diagnosis, prescription, or surveillance of the treatment. For adolescents, a study has shown that the last psychotropic use was medically prescribed only for 48% for occasional use[1] and another study found that 13% of adolescents had used psychotropics without medical prescription.[21] Finally, other factors may explain the differences with previous estimations of use, for example, age of included adolescents and year of the study.

Sex and age variation

As reported by others,[22] the prevalence of use differed with gender: girls used more psychotropic medications than boys did. Contrary to an Oslo declarative study showing no differences in psychotropic drug use between male and female 15- to 16-year-old adolescents,[23] our study shows significant gender difference among adolescents 14 years old and more. Besides, the girl and boy ratios per age increased for all three psychotropic medications (Figure 1), as reported by a recent study.[24] This increase may be explained by the difference of attitudes between girls and boys toward the use of medications. Girls seem to use less self-medication than boys[1] but more often consult physicians and consume more medications.[2] This gender variation increases further in the adult population for all types of psychotropic medication.[18]

Dispensed prescriptions of different psychotropics

Among the psychotropic agents studied, anxiolytics were the most widely dispensed among the 13- to 17-year olds (20.1‰), followed by antidepressants (7.7‰) and hypnotics (4.5‰).

For each psychotropic class, only a few drugs are the majority of prescriptions. Hydroxyzine is the most dispensed anxiolytic, followed by etifoxine and bromazepam. Nevertheless, because of its other indications such as allergy, we cannot confirm that it was prescribed only for its anxiolytic properties. Among these three products, only etifoxine was used 'off label' in adolescents. Among hypnotics, zolpidem is the most prescribed, followed by zopiclone and niaprizine; only niaprizine was licensed for pediatric use. Among the first five antidepressants prescribed (paroxetine, sertraline, fluoxetine, citalopram, amitryptiline), only two (sertraline and amitryptiline) were licensed for pediatric use. Sertraline is marketed only for obsessive-compulsive disorder and not for depression. In fact, it was impossible to know from the data what indication the product was used for (obsessive-compulsive disorders or depression). For paroxetine, the French drug agency has recalled that this product was not licensed for use under the age of 15,[25] following reports of an increased risk of suicidal thinking and suicide attempts related to the use of this drug in children and adolescents with major depressive disorder.[26,27] In our study, among 669 prescriptions of paroxetine, only 28 concerned adolescents under the age of 15. Recently, EMEA concluded

Table 3. Description of hypnotic, anxiolytic, and antidepressant prescriptions to adolescents of a French region during 2002

Product	Prescriptions			Adolescents with at least one prescription		
	n	%	Cumulative %	*n*	%	Cumulative %
Hypnotics						
Zolpidem	398	43.7	43.7	284	49.1	49.1
Zopiclone	184	20.2	63.9	137	23.7	72.8
Niaprazine	173	19	82.9	87	15.1	87.9
Nitrazepam	84	9.2	92.1	16	2.8	90.7
Lormetazepam	47	5.2	97.3	36	6.2	96.9
Loprazolam	13	1.4	98.7	10	1.7	98.6
Triazolam	6	0.7	99.4	3	0.5	99.1
Temazepam	3	0.3	99.7	3	0.5	99.6
Estazolam	2	0.2	99.9	1	0.2	99.8
Flunitrazepam	1	0.1	100	1	0.2	100
Total	911	100		578	100	
Anxiolytics						
Hydroxyzine	1192	31.8	31.8	950	35	35
Etifoxine	497	13.2	45.0	411	15.1	50.1
Bromazepam	453	12.1	57.1	393	14.5	64.6
Clobazam	411	11.0	68.0	120	4.4	69.0
Alprazolam	330	8.8	76.8	246	9.1	78.1
Prazepam	331	8.8	85.7	192	7.1	85.2
Diazepam	139	3.7	89.4	101	3.7	88.9
Captodiame	81	2.2	91.5	70	2.6	91.5
Buspirone	71	1.9	93.4	56	2.1	93.6
Clorazepate Potassique	73	1.9	95.4	43	1.6	95.2
Meprobamate	64	1.7	97.1	42	1.5	96.7
Clotiazepam	41	1.1	98.2	30	1.1	97.8
Lorazepam	22	0.6	98.7	22	0.8	98.6
Nordazepam	19	0.5	99.3	14	0.5	99.1
Ethyle Loflazepate	14	0.4	99.6	13	0.5	99.6
Oxazepam	14	0.4	100	12	0.4	100
Total	3752	100		2715	100	
Antidepressants						
Paroxetine	669	29.9	29.9	254	24.5	24.5
Sertraline	390	17.4	47.3	146	14.1	38.6
Fluoxetine	279	12.5	59.8	138	13.3	51.9
Citalopram	260	11.6	71.4	133	12.8	64.7
Amitriptyline	130	5.8	77.2	85	8.2	72.9
Tianeptine	130	5.8	83.1	84	8.1	81.0
Clomipramine	120	5.4	88.4	55	5.3	86.3
Venlafaxine	106	4.7	93.2	55	5.3	91.6
Imipramine	46	2.1	95.2	30	2.9	94.4
Fluvoxamine	34	1.5	96.7	11	1.1	95.5
Mianserine	31	1.4	98.1	17	1.6	97.1
Milnacipran	11	0.5	98.6	9	0.9	98.0
Dosulepine	10	0.4	99.1	6	0.6	98.6
Mirtazapine	7	0.3	99.4	6	0.6	99.2
Maprotiline	4	0.2	99.5	2	0.2	99.4
Toloxatone	4	0.2	99.7	1	0.1	99.5
Trimipramine	3	0.1	99.9	3	0.3	99.7
Doxepine	2	0.1	99.9	2	0.2	99.9
Desipramine	1	0.0	100	1	0.1	100
Total	2237	100		1038	100	

that the risk-benefit balance for paroxetine[28] and for serotonin-selective and serotonin-norepinephrine reuptake inhibitors in general[29] was not acceptable for children and adolescents.

Taken together, these results show that many drugs used to treat children and adolescents are either not licensed for use in children or are prescribed outside the terms of their product license (‘off label

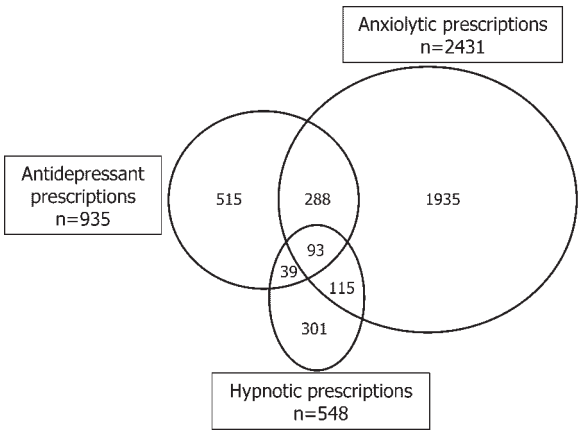

Figure 3. Association during the year of hypnotic, anxiolytic, and antidepressant prescriptions dispensed to adolescents of a French region during 2002

prescribing') as previously observed at hospitals and in general practice.[30–34] The three ADRs recorded are well known and are described in the Summary of Products Characteristics. Nevertheless, the number of ADRs is possibly underestimated because physicians may hesitate to declare such events after the prescription of an 'unlicensed' drug.

Health professionals concerned about the lack of information on the use of drugs in adolescents are in a difficult situation. To ensure that children and adolescents are not exposed to unnecessary risks, controlled clinical studies are required to determine the most appropriate dose in children and adolescents. In this way, the new European guideline on the clinical investigation of medicinal products encourages pharmaceutical companies to increase the availability of medicinal products that are appropriately evaluated and adapted to the needs of children and adolescents by incentives and obligatory measures.[16]

Association and seasonal variation

Associations during the year were not rare but the data were insufficient to perform a complete analysis. Antidepressants and hypnotics were in nearly half of the cases associated during the year with other psychotropic drugs (essentially anxiolytics).

The increased drug consumption during the year could be explained as a cohort effect: because only the year of birth was used to calculate age at prescription dispensation; the adolescents were 1 year older in December than in January. So, given the increased consumption with age, the frequency of prescriptions is expected to increase from January to December. Nevertheless, prescriptions of antidepressants and anxiolytics to girls decreased in summer holidays while those of hypnotics remained stable. Several hypotheses can explain these results: influence of the absence of prescribers during holidays (but prescriptions of hypnotics for girls and psychotropics for boys remain stable for the same period) or an improvement of anxio-depressive symptomatology for girls during summer holiday. Further studies are needed to confirm these results and to explain this seasonal variation.

Frequency

One particular finding of this study is that the vast majority of adolescents treated with psychotropic agents had only one prescription dispensed during the year. Even if the indication of prescription is not recorded in French database, the short duration of treatment for anxiolytics and hypnotics is in accordance with the recommendations. The short duration of treatment is more difficult to interpret for antidepressants. In major depression of adolescence, the maximal response rates are obtained after 10 weeks of treatment,[35] so the observed duration of treatment may be too short to be useful for these adolescents.

Limits

The use of dispensed prescriptions databases is limited by several factors. The results concern prescriptions and only give an estimation of the consumption. Some parameters lead to an underestimation of consumption because self-medication cannot be studied and some dispensed prescriptions were not included in this database (hospital dispensed prescriptions and adolescents affiliated to other reimbursement systems). Other parameters that lead to an overestimation are drugs dispensed but not used and other indications than psychotropic ones (antiallergenic, anticonvulsive). The French reimbursement system does not contain medical information, contrary to other European databases such as the General Practice Research Database.[14,36]

Means of individual doses were not calculated because most often only one prescription was dispensed. Defined Daily Doses (DDD) were not used for the same reason and because they were not adapted to the pediatric population. Because multiple medications were rare, the chronology of associations (simultaneity, overlapping, therapeutic escalation, distinct episodes, etc.) was not studied.

Conclusion, prospects

To our knowledge, this is the first French study to describe the prevalence of anxiolytic, hypnotic, and

KEY POINTS

- The study of reimbursement system databases confirms the large use of psychotropics in French adolescents and the influence of age and sex.
- Treatment for most adolescents is short, which may be beneficial for hypnotics and anxiolytics but not for antidepressants.

antidepressant agent consumption by adolescents with Health Insurance data. Besides, these results confirm an increase of girl versus boy ratios from the age of 13 to 17 years. Finally, the study outlines that use of unlicensed psychotropic medications to treat adolescents is widespread and that more controlled studies are warranted to assess quality, safety, and efficacy of psychotropic medications in adolescents.

REFERENCES

1. Beck F, Legleye S. *Usages de drogues et contextes d'usage entre 17 et 19 ans, évolutions récentes—ESCAPAD 2002*. OFDT: Paris, 2003; 164.
2. Arwidson P, Gautier A, Guilbert P. Douleurs, consommation de soins et médicaments. In *Baromètre santé jeunes 97/98*, CFES (ed). CFES: Vanves, 1998; 267–281.
3. Choquet M, Ledoux S. *Adolescents. Enquête nationale*. INSERM: Paris, 1994; 346.
4. Chambaretaud S. La consommation de médicaments dans les principaux pays industrialisés. *Drees Etudes et résultats* 2000; **47**: 1–8.
5. Pigeon M, Criquilion B, Lancry PJ. *MEDIC'Assurance Maladie—Les médicaments remboursés par le Régime Général d'Assurance Maladie au cours des années 2001 et 2002*. CNAMTS: Paris, 2003; 114.
6. Zarifian E. *Le prix du bien-être. Psychotropes et société*. Odile Jacob: Paris, 1996; 285.
7. Costes JM, Bello PY, Palle C. Les addictions en France: Etat des lieux. *Rev Prat* 2003; **53**: 1299–1303.
8. Observatoire Français des Drogues et des Toxicomanies. *Drogues et Dépendances, indicateurs et tendances.* OFDT: Paris, 2002; 368.
9. Pommereau X. *Santé des jeunes. Orientations et actions à promouvoir en 2002.* Ministère de l'emploi et de la solidarité: Paris, 2002; 33.
10. Weill A, Ricordeau P, Vallier N, Bourrel R, Fender P, Allemand H. L'analyse des prestations remboursées par l'assurance maladie: matériel et méthodes. *Diabetes Metab* 2000; **26**(Suppl 6): 49–54.
11. Thirion X, Lapierre V, Micallef J, *et al*. Buprenorphine prescription by general practitioners in a French region. *Drug Alcohol Depend* 2002; **65**: 197–204. DOI: 10.1016/S0376-8716(01)00161-2.
12. Lapeyre-Mestre M, Llau ME, Gony M, *et al*. Opiate maintenance with buprenorphine in ambulatory care: a 24-week follow-up study of new users. *Drug Alcohol Depend* 2003; **72**: 297–303. DOI: 10.1016/j.drugalcdep.2003.08.005.
13. Madsen H, Andersen M, Hallas J. Drug prescribing among Danish children: a population-based study. *Eur J Clin Pharmacol* 2001; **57**: 159–165. DOI: 10.1007/s002280100279.
14. Strom BL. *Pharmacoepidemiology* (3rd edn). Wiley: Chichester, 2000; 800.
15. Lecadet J, Vidal P, Baris B, *et al*. Médicaments psychotropes: consommation et pratiques de prescription en France métropolitaine. II. Données et comparaisons régionales, 2000. *Revue Médicale de l'Assurance Maladie* 2003; **34**: 233–248.
16. The European Agency for the Evaluation of Medicinal Products. *Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population.* EMEA: London, 2000; 12.
17. World Health Organisation Collaborating Centre for Drug Statistics Methodology. *Anatomical Therapeutic Chemical classification System (ATC).* World Health Organisation: Oslo, 2002.
18. Lecadet J, Vidal P, Baris B, *et al*. Médicaments psychotropes: consommation et pratiques de prescription en France métropolitaine. I. Données nationales, 2000. *Revue Médicale de l'Assurance Maladie* 2003; **34**: 75–84.
19. Pommier J, Billot L, Mouchtouris A, Deschamps JP, Romero MI, Zubarew T. French adolescent attitudes towards informal care for physical and emotional or relational problems. *Acta Paediatr* 2002; **91**: 466–474. DOI: 10.1080/080352502317371733.
20. De Peretti C, Leselbaum N. *Les lycéens parisiens et les substances psychoactives: évolutions*. OFDT, INRP, Paris X: Paris, 1999; 163.
21. Choquet M, Ledoux S, Hassler C. *Alcool, cannabis et autres drogues illicites parmi les élèves de collège et de lycée: ESPAD 99 france, Tome I.* OFDT: Paris, 2002; 148.
22. Ledoux S, Choquet M. Usage de médicaments à but psychotrope à l'adolescence: pourquoi plus les filles ? Etude sur un échantillon des 12-20 ans scolarisés en Haute-Marne (France). *Rev Epidemiol Sante Publique* 1994; **42**: 216–223.
23. Skurtveit S, Rosvold EO, Furu K. Use of psychotropic drugs in an urban adolescent population: the impact of health-related variables, lifestyle and sociodemographic factors–The Oslo Health Study 2000-2001. *Pharmacoepidemiol Drug Safe* 2005; **14**: 277–283. DOI: 10.1002/pds.1078.
24. Hansen EH, Holstein BE, Due P, Currie CE. International survey of self-reported medicine use among adolescents. *Ann Pharmacother* 2003; **37**: 361–366. DOI: 10.1345/aph.1C111.
25. Deleau N. EFFEXOR® et EFFEXOR® LP (venlafaxine): confirmation de la contre-indication chez les patients de moins de 18 ans. *Vigilances* 2003; **17**: 2.
26. Waechter F. Paroxetine must not be given to patients under 18. *Br Med J*. 2003; **326**: 1282. DOI: 10.1136/bmj.326.7402. 1282-b.
27. Ryan ND. Treatment of depression in children and adolescents. *Lancet* 2005; **366**: 933–940. DOI: 10.1016/S0140-6736(05)67321-7.
28. European Medicines Agency Press office. *CHMP Meeting on Paroxetine and Other SSRIs.* EMEA: London, 2004; 4.
29. European Medicines Agency Press office. *European Medicines Agency Finalises Review of Antidepressants in Children and Adolescents.* EMEA: London, 2005; 4.
30. Conroy S, Choonara I, Impicciatore P, *et al*. Survey of unlicensed and off label drug use in paediatric wards in European countries. European Network for Drug Investigation in Children. *Br Med J* 2000; **320**: 79–82.

31. Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed and off label drug use in paediatric wards: prospective study. *Br Med J* 1998; **316**: 343–345.
32. Martin RM, Wilton LV, Mann RD, Steventon P, Hilton SR. Unlicensed and off label drug use for paediatric patients. General practitioners prescribe SSRIs to children off label. *Br Med J* 1998; **317**: 204.
33. Horen B, Montastruc JL, Lapeyre-Mestre M. Adverse drug reactions and off-label drug use in paediatric outpatients. *Br J Clin Pharmacol* 2002; **54**: 665–670. DOI: 10.1046/j.1365-2125.2002.t01-3-01689.x.
34. Chalumeau M, Treluyer JM, Salanave B, *et al*. Off label and unlicensed drug use among French office based paediatricians. *Arch Dis Child* 2000; **83**: 502–505.
35. Ambrosini PJ, Wagner KD, Biederman J, *et al*. Multicenter open-label sertraline study in adolescent outpatients with major depression. *J Am Acad Child Adolesc Psychiatry* 1999; **38**: 566–572.
36. Garcia Rodriguez LA, Perez GS. Use of the UK General Practice Research Database for pharmacoepidemiology. *Br J Clin Pharmacol*. 1998; **45**: 419–425. DOI: 10.1046/j.1365-2125.1998.00701.x.

