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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Prevalence and patterns of methylphenidate use in French children and adolescents

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Abstract
Objective The aim of the study was to describe the prevalence and utilization patterns of methylphenidate (MPH) in children and adolescents in France.
Methods This was a population-based retrospective study in which the cohort consisted of patients for whom data were extracted from the dispensation drug claims database of the national health insurance (NHI) fund for self-employed workers. Annual prevalence of MPH use was evaluated on patients aged 6–18 years who were reimbursed for at least one MPH prescription a year. Between January 2004 and June 2005, features of MPH medication and user profile were described for the "new starters" having a screening period of 1 year without receiving a MPH prescription and a follow-up ≥12 months. Time to interruption of MPH regular use was analysed by Kaplan-Meier survival analysis. Mean duration of exposure to MPH treatment was computed with the 95% confidence interval (CI).
Results Annual prevalence of MPH per 1000 persons was 1.1 in 2003, 1.5 in 2004 and 1.8 in 2005 (relative increase of 63.5%). New starters (n=447) received their first MPH prescription through the hospital (65.1%) or through private practitioners (34.9%). The user profiles were: short (16.6%), occasional (33.8%) and regular (49.6%). Among the new starters, the median time to interruption of MPH regular use was 10.2 months (95% CI: 7.9–12.4). The mean duration of exposure to MPH treatment was: occasional (4.9 months, 95% CI: 4.3–5.5) and regular (25.7 months, 95% CI: 24.6–26.8).
Conclusion Although there is a low prevalence of MPH use in France, this survey revealed a wide profile of users and heterogeneous use patterns.

Keywords Children · France · Methylphenidate · Therapeutic uses

Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
MPH	Methylphenidate
NHI	National health insurance
RSI	Régime social des indépendants
SPC	Summary of product characteristics

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Introduction

Since 2000 there has been a significant worldwide increase in the prescribing of psychoactive drugs to children and adolescents [1, 2]. In terms of stimulant medications, the prescriptions and conditions of dispensation vary from one country to another [3]. In France, methylphenidate (MPH) has been commercially available since 1995 for patients from 6 years of age affected by attention-deficit/ hyperactivity disorder (ADHD), with restrictive conditions of prescription and delivery. Methylphenidate is listed in the schedule II "narcotics"; as such, a prescription is limited to a 28-day period and is valid for 1 year. The treatment should be initiated in hospitals by neurologists, psychiatrists or paediatricians. During intermediate periods, the prescription can be refilled by any other physician for a maximum period of 1 year but without the possibility of modifying the initially prescribed dosage and quantity. Moreover, pharmacies dispense MPH only on presentation of the initial prescription and, if appropriate, accompanied by the refill of the prescription. In the UK, MPH should be initiated by child and adolescent psychiatrists or paediatricians with expertise in ADHD, but continued prescribing and monitoring may be performed by general practitioners (GP) under shared care arrangements with a specialist [4]. In the USA, paediatricians, family practitioners, psychiatrists and neurologists are legally authorized to prescribe stimulants. Most States in the USA grant prescribing privileges to nurse practitioners; in Maryland, this privilege extends to the right to prescribe controlled substances [5].

In terms of the prevalence of stimulant medication use, studies published since 2000 on community practice setting have generally been limited to only a few countries [5–12]. To our knowledge, few studies, none of which were carried out in France, have reported results on the patterns of prescription and duration of exposure to treatment [6, 7, 11–14].

The aim of our study was to assess the prevalence and the utilization patterns of MPH in children and adolescents living in France.

Material and methods

Setting

This was a retrospective observational cohort study based on data obtained from the drug claims database of one of the three main national health insurance (NHI) funds, the Régime Social des Indépendants (RSI). The RSI covers about 3 million people, that is 4.5% of the France NHI beneficiaries, all of whom are exclusively self-employed workers in non-agricultural occupations (salespeople, craftsmen, professionals, such as physicians, pharmacists, veterinarians, lawyers, artists, architects, among others) and their dependants. This database includes detailed information on drug claims –prescription and dispensation reimbursements in particular (date of the prescription, identification product code, tablet strength, amount dispensed, speciality of the prescribing physician) – as well as the socio-demographic characteristics of the patients, their parents' occupation, residence. The database contains primary care records from approximately 130,400 French physicians (51% GPs, 2% paediatricians, 5% neurologists and psychiatrists, 42% others). Drug prescription claims are recorded daily by the pharmacists through a coding-secured internet transmission system. Extracts of information contained in the database are submitted for legal authorization. Requests made to the database are tracked. Permanent internal validation and quality control of the database are performed according to RSI standard operating procedures. The database has already used previously for drug utilization studies [15–17].

During the period of the study, MPH, whose active ingredient is methylphenidate hydrochloride, was the only stimulant medication marketed in France (also registered for the treatment of ADHD and of narcolepsy in patients 6 years of age and older). Methylphenidate is available as immediate release tablets (10 mg), prolonged release tablets (18, 36, 54 mg) and prolonged release capsules (20, 30, 40 mg). The dosage and schedule of administration recommended in the French summary of product characteristics (SPC) are: start with low doses (½ tablet of 10 mg twice daily); increase gradually the dosage (5–10 mg a week); stop the treatment if there is no improvement after 1 month. Stopping the treatment during the week-end and holidays was also recommended. The French laws limits the duration of each prescription to a 28-day period refilled for a maximum of 1 year.

Study population

Population for annual prevalence of MPH

For each year of the study (2003, 2004 and 2005), children and adolescents aged 6–18 years reimbursed at least one Euro for any kind of care or service (overall reimbursed patients) were extracted from the RSI data base. Among this population, those having at least one MPH prescription (MPH reimbursed patients) were eligible for MPH annual prevalence evaluation.

Population selection for the retrospective cohort

Between January 1, 2004 and June 30, 2005 children and adolescents aged 6–18 years having a previous screening period of at least 1 year in which they did not receive a

MPH prescription were enrolled in the cohort and named "new starters" [18]. As data on drug claims were not available before January 1, 2003, the number of new starters in 2003 could not be determined. All new starters were followed for at least 1 year and were classified according to the frequency of the prescriptions: (1) *short term users,* if they had only one prescription whatever the number of unit pack reimbursed (2) *regular users,* if they received prescriptions on a regular and continuous basis for at least 9 months; at most, one interval a year (no longer than 4 months in line with a planned wash-out summer holidays' period) was accepted between the recommended end date of the prescription and the prescription refill; [6]; (3) *occasional users* (neither short nor regular users).

Data analysis

The overall prevalence of children and adolescents receiving MPH prescriptions by calendar year (annual prevalence of MPH) was calculated. From the RSI database, we could extract data for each calendar year on (1) the age-class distribution of overall reimbursed patients, (2) the age-class distribution of MPH reimbursed patients, (3) the distribution by year of birth of the RSI-insured individuals. As the distribution of RSI-insured individuals was based on a criterion different from that used for MPH-reimbursed patients, we did not use RSI-insured individuals in the calculation of the prevalence as reference population. Therefore, in a preliminary step, we attempted to infer whether the number of overall reimbursed patients did actually approximate the number of RSI-insured individuals in each age-class between 6–18 years by computing the proportion of overall reimbursed patients in the corresponding French population in each age class from 6 to 18 years [19]. We observed that the proportion was similar across age classes (4.4%, range 3.9–4.7%) and approximated the proportion of RSI-insured individuals on the overall France NHI beneficiaries (4.5%). These results suggested that (1) the numbers of RSI-insured individuals and the RSI overall reimbursed individuals are similar, and (2) major biases can be excluded in considering the age-class distribution of RSI overall reimbursed patients as a proxy of the age-class distribution of RSI insured individuals. Thus, we estimated the annual prevalence of MPH (per 1000 persons for each year) as the proportion of patients reimbursed for MPH aged 6–18 years against the overall reimbursed patients in the same age-class. The amount of each MPH form (normal or prolonged release) by calendar year was calculated for each child and adolescent. In the new starter population, the following patient characteristics were described according to the user profile (short, occasional and regular users): age (6–11 years, 12–18 years), gender, geographic region of residence (six regions were identified), parents' occupation (salespeople, craftsmen, professionals) and features of medication for first and refill prescriptions (practice setting for MPH prescriptions). Proportions were compared using a chi-squared (χ^2) test and means were compared using the Kruskal–Wallis test. *P* values were two-sided and considered significant if less than 0.05. In order to assess the regular users, we assigned to each prescription a theoretical end date of 28 days (1 month) that corresponded to the recommended prescription duration. Duration of MPH regular use was estimated for all new starters and by user subgroup using the Kaplan-Meier survival analysis [20]. The cumulative proportions of individuals still in regular use of MPH at different times since the first prescription were estimated together with the 95% confidence interval (CI). The mean and median durations of exposure to MPH treatment with 95% CI were computed in the overall population and by subgroup of users. STATA software, version 8.0 was used for all statistical analyses (Stata Corp, College Station, TX).

Results

The total number of reimbursed patients aged 6–18 years were 374,221 in 2003; 389,247 in 2004; 430,150 in 2005. The number of patients aged 6–18 years reimbursed for MPH was 421 in 2003, 596 in 2004 and 791 in 2005. The annual prevalence of MPH was, therefore, 1.1, 1.5 and 1.8 per 1000 persons in 2003, 2004 and 2005, respectively (relative increase of 63.5% between 2003 and 2005). A total of 17,088 prescriptions of MPH (12,279 normal release and 4809 prolonged release) were filled in the 2003–2004–2005 period. The use of the normal release form of MPH started to decline at the beginning of 2004, while the use of the prolonged release form started to increase during this same period; 41% normal release and 59% prolonged release forms were prescribed in 2005. The following results were obtained on the 447 new starters enrolled in the cohort between January 1, 2004 and June 30, 2005. The characteristics of the 447 new starters at enrolment according to their MPH user profiles (short, occasional and regular) are described in Table 1. Parents of new starters were predominantly salespeople or craftsmen and lived in the South-East of France: these data did not differ from the profiles of the overall reimbursed patients aged 6–18 years. As expected, boys were more likely to be prescribed MPH than girls (85 vs. 15%). The proportion of MPH users was higher in the 6- to 11-year age group (61.5%) than in the 12- to 18-year age groups (38.5%). For 65.1% of the new starters, the first MPH prescription was written in a hospital, while 34.9% of new starters obtained it from private practitioners. The user profiles were: short (16.6%), occasional (33.8%), regular users (49.6%). Regular users were younger than short users (10.1 vs. 11.2;

Table 1 User profile description at enrolment in the overall studied population treated by methylphenidate (MPH) (n=447) and in subgroups of users

	Total, n=447 (100%)	Short, n=74 (16.6%)	Occasional, n=151 (33.8%)	Regular, n=222 (49.6%)	P values
Age, years [mean (SD)]	10.5 (3.0)	11.2 (3.0)	10.7 (3.2)	10.1 (2.8)	0.018[a]
Age category, n (%)					0.122[b]
6–11 years	275 (61.5)	41 (14.9)	87 (31.6)	147 (53.5)	
12–18 years	172 (38.5)	33 (19.2)	64 (37.2)	75 (43.6)	
Sex, n (%)					0.095[b]
Male	380 (85.0)	57 (15.0)	129 (33.9)	194 (51.1)	
Female	67 (15.0)	17 (25.4)	22 (32.8)	28 (41.8)	
Parent profession, n (%)					0.331[b]
Sales people	186 (41.6)	35 (18.8)	62 (33.3)	89 (47.9)	
Craftsmen	145 (32.4)	18 (12.4)	46 (31.7)	81 (55.9)	
Professionals	116 (26.0)	21 (18.1)	43 (37.1)	52 (44.8)	
Geographic origin, n (%)					0.231[b]
South-East	146 (32.7)	24 (16.4)	50 (34.3)	72 (49.3)	
North-West	107 (23.9)	20 (18.7)	34 (31.8)	53 (49.5)	
South-West	81 (18.1)	13 (16.1)	24 (29.6)	44 (54.3)	
Paris suburban	74 (16.6)	10 (13.5)	28 (37.8)	36 (48.7)	
North-East	29 (6.5)	4 (13.8)	8 (27.6)	17 (58.6)	
Overseas	10 (2.2)	3 (30.0)	7 (70.0)	0	
First prescription, n (%)					0.537[b]
Hospital	291 (65.1)	44 (15.1)	100 (34.4)	147 (50.5)	
Private practice	156 (34.9)	30 (19.2)	51 (32.7)	75 (48.1)	

[a] $P < 0.05$ according to the Kruskal–Wallis test, [b] $P< 0.05$ according to the χ^2 test.

P=0.018) and male are more frequently regular users than female; they did not differ from other users in terms of first MPH prescription practice. There was no difference in the practice setting for the prescription renewal among regular and occasional users (data not shown). In the overall new starters, the median time to interruption of the regular use of MPH was 10.2 months (95% CI: 7.9–12.4). The cumulative proportions of regular users at 12 and 18 months since the first prescription were 92.3% (95% CI: 87.9–95.1) and 76.1% (95% CI: 69.2–81.6), respectively (Fig. 1). The mean duration of exposure to MPH treatment was: occasional (4.9 months, 95% CI: 4.3–5.5) and regular (25.7 months, 95% CI: 24.6–26.8).

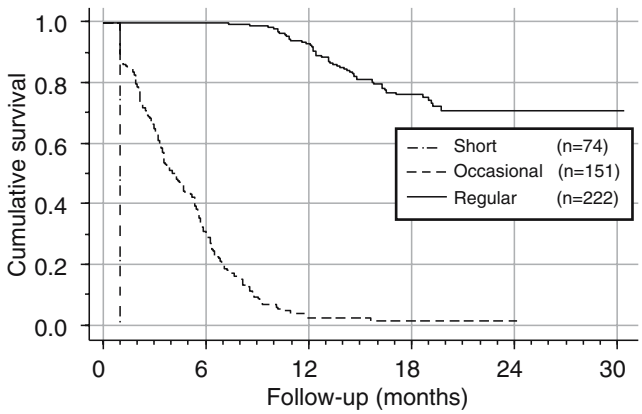

Fig. 1 Kaplan-Meier analysis on methylphenidate (MPH) use among new starters by subgroup of users

Discussion

In 2005, 1.8 per 1000 (0.18%) RSI patients aged 6–18 years were exposed to MPH medication. The large increase in MPH prescription rates observed from 2003 to 2005 corresponds to the launch of the prolonged release form of MPH in 2004 onto the French market. Based on a comparison of data from previous years, it appears that the prevalence of MPH use in France increased eightfold between 1997 and 2005 [21, 22] (Fig. 2). Our results are consistent with the increase in the value of the reimbursements associated with MPH medication paid to salaried workers affiliated with the French NHI fund [23]. We can also assume the number of patients given MPH in France in 2005 to be around 17,500 out of a total population of 9,745,022 children and adolescents aged 6–18 years [19]. This means that less than 10% of the French children and adolescents affected by ADHD (Table 2) are under MPH treatment, which is in accordance with previous data (unpublished data from the French Medicines Agency, communicated to the National Institute of Health during a meeting in Rome in 2004). However, our study reveals some surprising data. One particularly noticeable finding is that for one third of the patients, the first prescription was written outside the hospital, which is contrary to French regulations governing MPH drug use. A study involving prescribers and pharmacists needs to be carried out to determine why the regulations governing the first prescription were not always

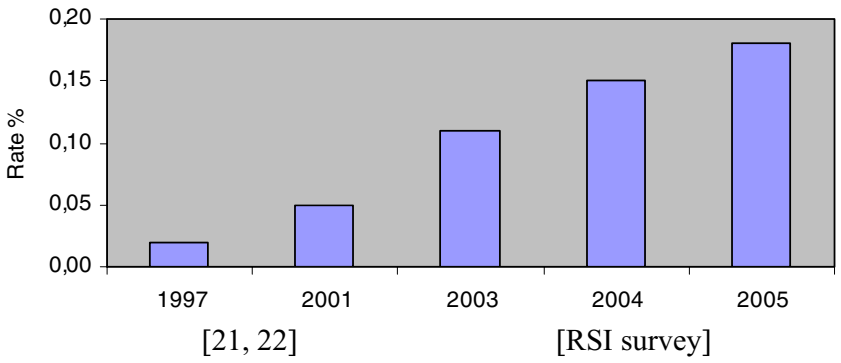

Fig. 2 Prevalence of MPH use in children and adolescents aged 6–18 years in France between 1997 and 2005

respected and why the pharmacists allowed the initial dispensation of MPH prescribed outside the hospital. Another unexpected result is that 50% of the patients beginning MPH treatment tend to be occasional or short-term users despite ADHD being a chronic condition that requires long-term intervention [24, 25]. This could be explained by (1) a wrong initial diagnosis performed by a physician without expertise in ADHD; (2) a premature treatment interruption due to a bad tolerance to MPH or no improvement in the patient's condition, as recommended in the French SPC; (3) poor compliance; (4) a doubtful effectiveness. Eventually, despite a good initial response to the pharmacological treatment, a certain pressure from close family on parents to stop MPH may have been occurred, followed by a symptom relapse which entailed restarting the treatment. It should be noticed that most of the regular users remain regular for at least 2 years.

Similar exponential increases in MPH use by children and adolescents are apparent in other European countries, with the exception of Italy where MPH was withdrawn from the market for a long period [26] and reintroduced only in 2007 together with atomoxetine. Between 1998 and 2004, the number of prescriptions for stimulant drugs (methylphenidate and dexamphetamine) almost doubled in the UK [4, 10]. In Germany, MPH prevalence doubled from 0.6 to 1.4% for children aged 5–15 years between 2000 and 2001 [8]. In the Netherlands, the prevalence of stimulant use increased from 0.6% in 1998 to 1.2% in 2002 for children aged 0–19 years [12]. In Switzerland, an exponential increase in the global quantity of MPH was observed from 1996 to 2000. As in France, most of the Swiss children and adolescents seem to be treated not on a continuous basis, suggesting that numerous prescriptions were given for short periods and that the administration of the drug was often interrupted during the year [7]. However, the prevalence of MPH use in France remains one of the lowest in Europe and is much lower than that of the USA: of ten children affected by ADHD, one is treated in France whereas five are treated in the USA [27]. This difference may be explained by the discrepancy between these countries in terms of the diagnostic method used to define populations eligible for MPH treatment [28, 29]. As a result, very large differences in the evaluation of the prevalence of the disorder are observed (Table 2).

Table 2 Prevalence of attention-deficit/hyperactivity disorder (ADHD) in the USA, UK, France, Italy

Country	USA	UK	France	Italy
Source	Centres for Disease Control and prevention CDC 2003 [27]	National Institute for Health and Clinical Excellence NICE 2006 [4]	Expertise collective INSERM Institut National de la Santé et de la Recherche Médicale 2002 [32]	Italian National Institute of Health Knellwolf et al. 2006 [23]
School-aged children (age range in years)	4–17	6–16	6–14	6–18
Number of school-aged children (in millions)	56.6	7.3	6.8	7.5
Number of school-aged children affected by ADHD	4,400,000	366,000	137,000	75,000
Prevalence of ADHD among school-aged children	8%	5%	2%	1%

Limitations

(1) Diagnosis-related data are not recorded in the RSI database. However, MPH can only be prescribed in France for ADHD and narcolepsy. As the prevalence of narcolepsy among children and adolescents is very low (0.0075%) compared to that of ADHD (2%), it can reasonably be assumed that treatment with MPH is related to a diagnosis of ADHD [30, 31].
(2) Any comparison with the rates of MPH use in other countries may have been inappropriate on occasion as the studies reporting rates from these countries covered a different period of time, studied different populations, measured exposure to MPH differently (amount of drug prescribed, number of prescriptions, number of patients treated) and included different pharmacological treatment categories.
(3) The RSI database provides data on the date of the prescription but not on its duration, which is a weakness of the database. A theoretical end date of 28 days (1 month) was assigned to each prescription in order to assess the regular users. This duration corresponds to the actual prescription duration recommended.

Conclusion

Despite an exponential increase in MPH use by children and adolescents in France during the past 10 years, the prevalence of MPH use seems to be lower here than in most of other western countries. This could be explained by the under-diagnosis of ADHD and/or the reluctance of the physicians to prescribe pharmacological treatment to affected patients. The patterns of MPH use show that regular users are long-term users. Much concern has been raised regarding the unusual and unexpected patterns of MPH use. Our data reveal that the strict regulations regarding the prescription of MPH are not always being applied. Our results question the appropriateness of MPH use in France and therefore contribute data that can be used for re-evaluating of MPH use guidelines. A prospective study among French physicians should be carried out in order to explain short prescriptions or irregular patterns of MPH use and also to determine whether MPH prescriptions are appropriate (i.e., have young patients had a diagnosis made with the right evaluation tools and justifying a MPH treatment?). It must not be forgotten that a first careful diagnosis using standardized instruments is needed before any effective intervention. Other important issues must be stressed for promoting optimum management of the disorder: disseminate useful information and appropriate training to professionals [32], improve the collaboration between primary and secondary care [11], implement a national registry to monitor the benefits and safety of long-term treatments [23, 26], follow the patients in hospital every 3–6 months once the patient is stable [33] and carry out studies on ADHD using a population-based approach [4, 34].

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