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Evaluation of Abuse and Dependence on Drugs Used for Self-Medication

A Pharmacoepidemiological Pilot Study Based on Community Pharmacies in France

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Abstract

Background: Drugs that can be obtained without a medical prescription in community pharmacies are used to treat minor pathologies that can easily be diagnosed by the patient. Some of these drugs contain psychoactive substances with a potential for abuse and dependence. However, there is a lack of data concerning their problematic use in a wide population.

Objective: To explore the feasibility of a pharmacoepidemiological method to investigate misuse, non-medical use, abuse and dependence on drugs used for self-medication.

Methods: This cross-sectional pilot study, conducted during a 2-month period (from 15 January to 15 March 2007), was based on the participation of community pharmacies in the Midi-Pyrénées region of France to collect patient data. Patients requesting one drug from a list of available drugs used for self-medication and containing psychoactive substances (codeine in analgesics, pseudoephedrine, dextromethorphan and histamine H_1 receptor antagonists [antihistamines]) were included in the study. A control group was set up that consisted of patients requesting antacid drugs. The pharmacy staff proposed to the patients that they filled in an anonymous questionnaire. The questionnaire was designed to investigate patterns of drug use and the harmful consequences of overuse (abuse). In addition, questions on lack of control over drug use were adapted from the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV) criteria for evaluation of dependence.

Results: Thirty-two percent (n = 74) of the solicited pharmacies participated in the survey. Only 4.8% of the solicited patients (n = 817) refused to complete the questionnaire distributed by the pharmacy staff. The questionnaire was completed inside the pharmacy by 53.3% of the patients. The other patients took the questionnaire away from the pharmacy and 31.7% of them returned it in a prepaid envelope. The patient participation rate was 64.9%, and was higher for the psychoactive substance groups than the control group.

Statistically significant differences on misuse (and/or non-medical use), abuse and dependence were obtained between the codeine and antacid groups. In the codeine group, among the patients having used the product in the previous month (n = 53), 15.1% misused the drug and/or used the drug for a non-medical reason, 7.5% were cases of abuse and 7.5% presented criteria of lack of control over drug use related to dependence on the substance for the psychoactive effects or for pain relief.

Conclusion: The results obtained in this pilot study indicate that using anonymous self-administered questionnaires offered to patients by pharmacy staff is a reliable method to obtain information on the problematic use of drugs containing psychoactive substances purchased in a pharmacy for self-medication.

Background

In France, until July 2008, all non-prescription drugs were issued by pharmacists at the community pharmacies. The drugs were recommended by the pharmacist or spontaneously requested by the patients. According to The French Pharmaceutical Companies Association and Intercontinental Marketing Services, self-medication (defined here as non-prescribed medicines) accounted for 13.6% of the market share by quantity in France in 2007 and the economical and political will is to expand this market.[1] While the proportion of self-medication varies between countries, expansion of this market is spreading worldwide, requiring vigilance for the consequences on health. Whereas drugs used for self-medication must meet some safety criteria, there is a lack of data concerning risks in a wide population and in 'real-life' use of these medicines. The differences between issues related to monitoring the safety of over-the-counter (OTC) drugs and those obtained on prescription have been discussed previously.[2] The development of pharmacoepidemiological methods aimed at assessing the problem of abuse of and dependence on drugs containing psychoactive substances used for self-medication represents a particular challenge.[3]

In France, a national system of pharmacodependence evaluation was established in 1990. This system relies on a network of Centres for Evaluation and Information on Pharmacodependence (CEIP).[4] Spontaneous reports from physicians and pharmacists, directly addressed to CEIP, indicate that several medicines that can be obtained without a medical prescription, in particular codeine-containing drugs, may be used for their psychoactive effects and/or can lead to abuse/dependence. However, these cases are under-reported. The centres have developed epidemiological tools to assess the potential for abuse and dependence on medicines. The Ordonnances Suspectes Indicateur d'Abus et de Pharmacodependance (OSIAP) survey, conducted twice a year in a community pharmacy network, provides qualitative and quantitative data about drugs diverted from their therapeutic use by the identification of forged prescriptions.[5] However abuse of and dependence on drugs obtained without a prescription cannot be detected by this method.

It has been well stated in the review of Zacny et al.[6] that there are two major definitions of drug abuse. Much of the data collected in this area refers to the non-medical use of prescription drugs.[7] However, this definition of abuse does not reflect the sense of physical, psychological and behavioural harm resulting from drug use. From a clinical perspective, drug abuse is defined according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV) criteria for a substance abuse disorder or according to the *International Classification of Diseases* (ICD-10) as a harmful use. For others, and particularly in the scientific, regulatory

and law enforcement communities, drug abuse focuses on the non-medical use of a substance. The intent of the review of Zacny et al.[6] was to describe the scope of the problem of non-medical use and abuse of prescription opioids. For 'non-medical use' of a prescription drug they referred to the definition chosen by the National Household Survey on Drug Abuse as using a psychotherapeutic drug "even once, that was not prescribed for you, or that you took only for the experience or feeling it caused".[8]

In 2000, two studies on the perception of pharmacists on the abuse (non-medical use) of OTC medicines were conducted in Great Britain, relying on a questionnaire sent to pharmacists.[9,10] Respectively, 66% and 68% of participating community pharmacies thought OTC medicines were frequently abused (non-medical use), particularly codeine and histamine H_1 receptor antagonist (antihistamine)-containing drugs. A study based on the responses to a structured interview revealed that in Northern Ireland, the abuse (non-medical use) potential of some drugs used for self-medication was known by 85% of the general population, in particular for analgesics, sedatives, cough mixtures and laxatives.[11] These surveys underline the need to quantify misuse, non-medical use, abuse and dependence on drugs that can be obtained without a prescription.

To be as accurate as possible, studies about consumption behaviour of drugs used for self-medication must directly involve the patient. In 1999, Sinclair et al.[12] tested different methods for the recruitment of patients in community pharmacies. The aim was to collect pharmacovigilance data about ibuprofen-containing products available without a prescription. The patient participation rate was higher (52%) when the principle of the study was explained by the pharmacy staff, showing the importance of the participation of community pharmacies in pharmacoepidemiological surveys on drugs used for self-medication. Pharmacy-based observational studies have demonstrated their validity to obtain pharmacovigilance data on self-medication drugs.[2,12-17]

The aim of the present study was to develop a method based on the responses to a self-administered questionnaire given to the patients by the pharmacist to investigate misuse, non-medical use, abuse and pharmacodependence on drugs used for self-medication.

In the literature, the term 'misuse of medicine' is generally taken to mean that the drug is used incorrectly, usually in terms of dosage or duration. This is also the sense given by the French Health Products Safety Agency (Afssaps), i.e. the use not corresponding to the licensed conditions of use.[18] This definition relies on the conditions of use but not on the reasons for use. According to Afssaps, misuse relies on the change of the modality of administration of the drug (for example, intravenous administration instead of oral). Moreover, this definition includes the use of the drug in excessive doses (above the maximal dose recommended by the Summary of Product Characteristics [SPC]) and/or a too-long duration of use.

The present study was not designed to clinically evaluate patients. However, in accordance with the objectives of Zacny et al.[6] for prescription opioids, our questionnaire was designed to investigate drug abuse, if the consequences of the use of the drug in excess and for a longer period would be perceived by the patients as deleterious for themselves, whatever the reasons for the use. Moreover, we wanted to investigate the use of non-prescription drugs for non-medical reasons.

For these reasons, to evaluate drug abuse, we have used the French definition of the Public Health Law,[19] based on the criteria of diagnosis of abuse of psychoactive drugs of ICD-10, i.e. the recurrent and excessive use of a drug leading to clinically significant impairment or distress.[20] We also asked the patients for the negative consequences of this consumption on their social or professional life.

To investigate pharmacodependence on these medicines, we have used accurate behavioural items among the diagnostic criteria of dependence to psychoactive drugs of the DSM-IV.[21] We did not take into account the criteria of physical dependence and tolerance, as these criteria are normal physiological responses that often occur with the persistent use of several medications. Therefore, physical dependence and tolerance do not constitute sufficient evidence of pharmacodependence.[22]

The misuse and non-medical use of drugs in the context of self-medication have been recognized as an important issue within the community pharmacy setting, with opioids, antihistamines, sympathomimetics and laxatives being particularly problematic.[9,10,23-25] In the present pilot study, misuse, non-medical use, abuse and dependence on codeine in analgesics (combined with paracetamol [acetaminophen] or aspirin [acetylsalicylic acid]), dextromethorphan, pseudoephedrine and antihistamines (with well known sedative effects) have been investigated. These substances were chosen as they have psychoactive properties and have a suspected or proven potential for abuse and dependence. In order to test a method to evaluate drug misuse, non-medical use, abuse and dependence in the context of self-medication, we designed a pharmacy-based, cross-sectional study relying on the responses to a questionnaire given to the patients requesting one of the products containing the substances tested in the context of self-medication. The results were compared with those obtained for antacid drugs with no known psychoactive effect.

Methods

A cross-sectional study was conducted during a 2-month period (from 15 January to 15 March 2007), relying on a questionnaire given to patients in community pharmacies, after the agreement of the Council of the Pharmaceutical Order of Midi-Pyrénées region.

Research Network

The community pharmacies solicited to participate were the pharmacies belonging to the French Midi-Pyrénées area network involved in the survey of forged prescriptions (n = 167) and the community pharmacies of Midi-Pyrénées receiving pharmacy students for a 6-month placement (n = 61). An information sheet was sent to the pharmacies belonging to the network. The information sheet was given by the students to their training supervisors, who were the pharmacists receiving students for their 6 months of training in their community pharmacy. When the community pharmacies did not send back the invitation to join the study, they were asked to give their response via a telephone call from the study coordinator.

Questionnaire and Data Collection

We studied four categories of substances having psychoactive effects and having a suspected or proven potential for abuse and dependence: codeine in analgesics, dextromethorphan, pseudoephedrine and sedative antihistamines. The antihistamine drugs included in this study were doxylamine, alimemazine, chlorphenamine, promethazine, dimenhydrinate and oxomemazine. A fifth category was composed of antacid drugs, which are not known to have any psychotropic effect (control group). One of these groups of substances, as well as a list of products containing these substances, was attributed randomly to each participating pharmacy. Therefore, each pharmacy had to distribute a questionnaire about only one category.

The pharmacist was not required to ask the patient about the patterns of use of the studied drugs. The pharmacist only had to offer the questionnaire to each patient spontaneously requesting the studied drug that had been assigned to his/her pharmacy.

The anonymous questionnaire recorded demographic information, patterns of drug use, and criteria of misuse, abuse and dependence. The pharmacy staff were asked to obtain verbal consent. The study did not need any ethical approval, since the patients remained anonymous.

Misuse of the medicines containing codeine, dextromethorphan, antihistamine or antacid was determined when the medicine was used in excessive doses (above the maximum dose recommended by the SPC) and when the use was regular (more than 10 days during the last month). For pseudoephedrine, the SPC specifies that treatment must not exceed 5 days. For this reason, misuse of the medicines containing pseudoephedrine was determined as soon as the patients declared that they used a product containing pseudoephedrine for longer than 5 days even when they did not use it in excessive doses.

Non-medical use of the medicine was established when the reasons for use declared by the patients were to obtain a psychoactive effect that is not an indication of use in the SPC.

Abuse was considered to be the case when the patient used the drug in excess, permanently or intermittently, with this consumption having detrimental consequences on his or her health or social or professional life.

Pharmacodependence was determined according to responses to questions adapted from the DSM-IV criteria for problematic drug use.[21] The patient was considered pharmacodependent when he or she met the three relevant behaviour criteria for established dependence concerning the harmful consequences of consumption:

- negative effects of the drug use on health and social, familial or professional life;
- continued drug use despite these negative effects;
- a lot of time spent obtaining the medicine.

It was judged that the patients were spending a lot of time to obtain the medicine when they replied that if the drug was not available, they would not accept another drug proposed by the pharmacist and would go to another pharmacy to obtain the medicine.

The following data were also collected: age and sex of the patient, the reason for taking the medicine, the first time they took the medicine (on the advice of a pharmacist, physician or close family; after having seen an advertisement), whether they informed their general practitioner about this consumption, use of the medicine for other purposes than the one recommended, other medicines regularly used. The questionnaire was tested on a sample of five community pharmacies solicited to test the acceptability and comprehension of the questionnaire by the patients. The pharmacist evaluated with the patients the problems of filling in the questionnaire and reported them to the study centre. Minor amendments were made. Patients were able to choose to complete the questionnaire in the pharmacy or to take it away, as prepaid envelopes were provided. The pharmacy staff were asked to record information about the number of questionnaires offered to patients and the number of questionnaires refused, the reason(s) why patients did not agree to participate, and the place of completion.

Data Analysis

Data capture was performed using EpiInfo® 3.3.2 software (CDC, Atlanta, GA, USA). Statistical analysis was conducted using Stata® 9.0 software (STATA Corporation, College Station, Texas, TX, USA). Descriptive statistics of the study population were calculated. Only the patients who had used one of the studied substances during the previous month had to respond to the questions on the patterns of this use. We determined whether there were differences between each group of psychoactive substances and the control group only. For continuous variables, differences were assessed using Student's t-test or a nonparametric test. Categorical data were described as percentages and compared using a chi-squared test or Fisher's exact test.

Results

Recruitment Rates

A total of 228 pharmacies were solicited: 167 from the network and 61 training course supervisors. The 228 solicited pharmacies represented 20.8% of the 1097 community pharmacies in the Midi-Pyrénées area. The main reasons for refusal to participate were as follows: constraint of staff time, some did not want to solicit their patients, and several pharmacies stated that they were not concerned by the problem of pharmacodependence. Whereas 100 pharmacies originally agreed to participate, only 74 of them actively participated in the survey (32.5% of the pharmacies solicited initially). The number of pharmacies that actively participated in the study (n = 74) represented 6.7% of the total number of community pharmacies in the Midi-Pyrénées area. The active participation of pharmacies that are members of a research network or receiving a pharmacy student for a 6-month training period is shown in figure 1. Among the 74 pharmacies that participated in the study, 15 did not have the opportunity to include any patient according to the study protocol. Fifty-nine pharmacies distributed at least one

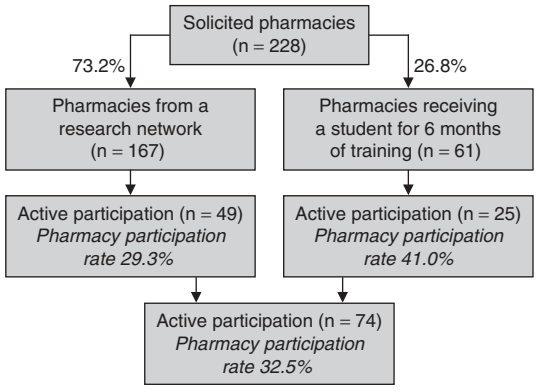

Fig. 1. Differences in pharmacy participation rates according to whether pharmacies were in a research network or receiving a student for a 6-month training period.

questionnaire. During the 2-month study period, 817 questionnaires were offered to patients. The results of patient participation rates are shown in figure 2. Thirty-nine patients told the pharmacist that they refused to respond to the questionnaire (4.8%). The number of refusals was lower in the psychoactive-substance groups (2.1%) than in the control group (11%). The reasons for refusal are indicated in figure 2. In the codeine group, one subject was aware of his dependence and did not want to fill in the questionnaire.

Among the 778 distributed questionnaires, 415 (53.3%) were completed inside the pharmacy; 363 (46.7%) patients chose to fill in the questionnaire outside the pharmacy; and 115 (31.7%) were returned by prepaid envelope. A total of 530 questionnaires were completed, of which 21.7% were returned using the prepaid envelopes. The participation rate, i.e. the number of patients having completed the offered questionnaire, was 64.9%. This rate was higher for medicines containing psychoactive substances than for the antacid control group (figure 2). Analysis of 491 questionnaires was performed; the remainder did not concern studied substances or the patients were under the age of 18 years. The rate of returned questionnaires that could be analysed according to the studied substances is shown in figure 2.

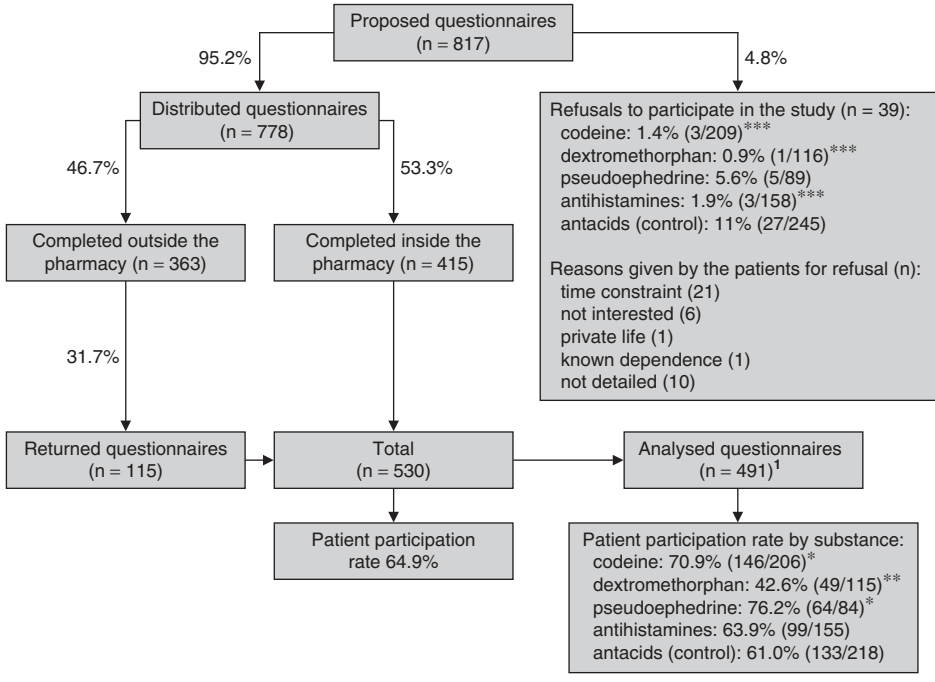

Fig. 2. Patient participation rate according to the modalities of completing the questionnaire inside or outside the pharmacy and according to the substances. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs control. **1** The remaining questionnaires (n = 39) were not analysed because they did not concern studied substances, or the patients were under 18 years of age.

Description of Patient Characteristics

The mean age of the patients was 45.8 ± 15.1 years and the majority (64.8%) were women. In the control group, the patients were significantly older than in the other groups, except the antihistamine group. The results are shown in table I.

Analysis of Patients Having Used the Medicine in the Previous Month

Approximately half of the patients (48.9%; n = 240) had used the medicine during the previous month (table I). The mean age was 48.1 ± 15.0 years and the majority (58.3%) were women. In the control group, patients were significantly older than in the codeine, dextromethorphan and pseudoephedrine groups. The patients had informed their general practitioner about their use of the studied medicine in only 49.2% of cases. Sixty-six percent of regular users had started consumption on medical (38.8%) or pharmacist (27.5%) advice, 21.3% had first purchased the drug following family advice and 5% after seeing an advertisement.

Quantitative values of misuse and abuse and dependence on codeine, dextromethorphan, pseudoephedrine or antihistamines were compared with the values obtained for antacid drugs. The results are summarized in table II.

Codeine

Among the 53 patients having used codeine in association with paracetamol in analgesics used for self-medication in the previous month, eight (15.1%) misused and/or had a non-medical use of this medicine, four (7.5%) abused and four (7.5%) presented behavioural criteria of dependence (table II). As presented in detail in table III, misuse (and/or non-medical use) and abuse or dependence can be observed for the same patient. One patient refused to complete the questionnaire distributed by the pharmacist and told him that he was aware of his dependence and did not want to talk about it. The description of the cases according to sex, age, dose and return of the questionnaire with a prepaid envelope is presented in table III.

Table I. Description of patient characteristics of the sample surveyed and of the subset of users in the previous month

Patient characteristics	Codeine	Dextromethorphan	Pseudoephedrine	Antihistamines	Control	Total
No. of subjects (total sample)	146	49	64	99	133	491
age (y) [mean ± SD (range)]	43.8 ± 13.9 (20–82)***	39.5 ± 11.9 (20–75)***	42.3 ± 14.0 (19–85)**	49.0 ± 16.0 (19–83)	49.9 ± 15.8 (20–85)	45.8 ± 15.1 (19–85)
no. of women (%)	87 (59.6)	30 (61.2)	45 (70.3)	76 (76.8)**	80 (60.2)	318 (64.8)
No. of subjects (users in the previous month)	53	17	32	60	78	240
age (y) [mean ± SD (range)]	45.7* ± 13.7 (20–82)	38*** ± 9.1 (21–50)	41.1*** ± 12.7 (19–74)	52.1 ± 15.9 (19–82)	51.8 ± 15.0 (20–85)	48.1 ± 15.0 (19–85)
no. of women (%)	31 (58.5)	14 (82.4)*	10 (31.2)	46 (76.7)***	39 (50)	140 (58.3)
First-time use of the medicine [n (%)]						
On physician advice	20 (37.7)	10 (58.8)*	16 (50)*	24 (40)	23 (29.5)	93 (38.8)
On pharmacist advice	13 (24.5)	2 (11.8)	8 (25)	20 (33.3)	23 (29.5)	66 (27.5)
On close family advice	12 (22.6)	3 (17.6)	4 (12.5)	13 (21.7)	19 (24.4)	51 (21.3)
On advertisement	0 (0)*	0 (0)	2 (6.3)	1 (1.7)*	9 (11.5)	12 (5)
Other	4 (7.5)	2 (11.8)	1 (3.1)	2 (3.3)	3 (3.8)	12 (5)
General practitioner aware of the use	27 (50.9)	7 (41.2)	17 (53.1)	33 (55)	34 (43.6)	118 (49.2)

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs control group.

Table II. Misuse and/or non-medical use, abuse and dependence[a] on codeine, dextromethorphan, pseudoephedrine, antihistamines and antacids (control) among the patients having used these drugs for self-medication during the previous month

Use [n (%)]	Codeine (n = 53)	Dextromethorphan (n = 17)	Pseudoephedrine (n = 32)	H_1 antihistamines (n = 60)	Control (n = 78)
Misuse and/or non-medical use	8 (15.1)**	2 (11.8)	5 (15.6)**	1 (1.7)	1 (1.3)
Abuse	4 (7.5)*	0 (0)	1 (3.1)	0 (0)	0 (0)
Dependence	4 (7.5)*	1 (5.9)	0 (0)	0 (0)	0 (0)

a As presented in the details in table III, misuse (and/or non-medical use) and abuse or dependence can be observed for the same patient.

* $p < 0.05$, ** $p < 0.01$ vs control group.

Six patients declared codeine use for a goal other than pain relief (cases 1, 3, 4, 7, 8 and 9; table III). For two patients (cases 3 and 4), the drug was used against stress, as a tranquillizer. Two other patients (cases 1 and 9) declared they needed it as an illicit drug. Five patients had a higher consumption of the medicine than the maximum dose recommended in the SPC; the highest daily consumption was 2.7-fold higher than the maximum dose recommended (case no. 1; table III). Daily consumption of the product by this patient meant that he used 6.4 g/day of paracetamol. This corresponds to an overdose, since the maximum recommended dose of paracetamol is 4 g/day. This patient said he used this medicine because he needed it. He first purchased the drug on the advice of a friend. Three of the five patients misusing codeine with higher doses than recommended are also considered as abusers since they declared that they suffered deleterious consequences from their codeine consumption on their physical health or social or professional life (cases 1, 2 and 5; table III). These three patients were also dependent on codeine, since they said they continued drug use despite these negative effects and also that they would not accept another drug proposed by the pharmacist and would go to another pharmacy to obtain it. Finally, one patient did not misuse codeine but sometimes used the drug in excess with deleterious consequences. Moreover, this patient was dependent on the drug (case no. 6; table III). Only one of the six patients declaring codeine use for a goal other than pain relief was also judged as dependent on this drug and abusing it (case no. 1; table III). The other three patients judged as dependent showed behavioural signs of dependence in a context of self-medication for headaches (two patients, cases 2 and 6; table III) and for chronic back pain (case no. 5; table III).

Among the nine patients who misused and/or had a non-medical use, abused or were dependent on the analgesic products containing codeine, seven (77.8%) filled in the questionnaire outside the pharmacy and returned it to the study centre with a prepaid envelope. This rate was significantly higher ($p < 0.01$) than for the 44 patients who did not have a problematic use of codeine, since only 11 of them (25%) filled in the questionnaire outside the pharmacy and returned it in the prepaid envelope.

Dextromethorphan

Two patients (11.8%) misused dextromethorphan as they declared they used this medicine with an aim other than the recommended one. One of them said he used it by habit. Whereas it is recommended not to use dextromethorphan for more than 5 consecutive days, these two patients took it at the normal dosage but daily. One of the two patients presented behavioural signs of dependence, as he continued to use dextromethorphan despite negative consequences on his health, social or professional life and he did not want to take any medicine other than this one (table IV).

Pseudoephedrine

Five patients (15.6%) misused drug products containing pseudoephedrine. One of them used it with an aim other than the recommended one but did not give the reason. Whereas it is indicated in the SPC that the maximum duration of treatment

Table III. Cases of misuse, non-medical use, abuse or dependence on over-the-counter medicines containing codeine and paracetamol purchased at the community pharmacy

Case no.	Sex, age (y)	Dose of codeine base (mg)	Dose of paracetamol [acetaminophen] (g)	Misuse (excessive dose and duration)	Non-medical use declared by patient	Reason for use	Abuse	Dependence	Questionnaire returned in prepaid envelope	Substances contained in medicine
1	M 34	250 daily	6.4 daily	Yes	Yes	Need	Yes	Yes	Yes	Codeine, paracetamol
2	F 53	156 daily	4 daily	Yes	No	Migraine	Yes	Yes	Yes	Codeine, paracetamol, caffeine
3	M 36	125 daily	3.2 daily	Yes	Yes	Relaxant, well-being	No	No	Yes	Codeine, paracetamol
4	M 35	125 (4 days out of 7)	3.2 (4 days out of 7)	Yes	Yes	Against stress	No	No	Yes	Codeine, paracetamol
5	F 41	94 (daily)	2.4 daily	Yes	No	Back pain	Yes	Yes	No	Codeine, paracetamol
6	F 26	94 (2 days out of 7)	2.4 (2 days out of 7)	No	No	Headache	Yes	Yes	Yes	Codeine, paracetamol
7	F 42	94 (3 days out of 7)	2.4 (3 days out of 7)	Yes	Yes		No	No	Yes	Codeine, paracetamol
8	M 40	62.5 daily	1.6 daily	Yes	Yes		No	No	Yes	Codeine, paracetamol, caffeine
9	M 32	31 daily	0.8 daily	Yes	Yes	Illicit drug addict	No	No	No	Codeine, paracetamol

F = female; **M** = male.

Table IV. Cases of misuse, non-medical use, abuse or dependence on medicines containing dextromethorphan, pseudoephedrine, antihistamines and antacids purchased at the community pharmacy for self-medication

Case no.	Sex, age (y)	Dose of studied drug (mg)	Dose of associated drug	Misuse (excessive dose and duration)	Non-medical use declared by patient	Reason for use	Abuse	Dependence	Questionnaire returned in prepaid envelope	Substances contained in medicine
Dextromethorphan										
1	F 30	66 daily	NA	No	Yes		No	Yes	No	
2	M 36	66 daily	NA	No	Yes	Habit	No		No	
Pseudoephedrine										
1	F 28	49 daily	Paracetamol (acetaminophen) 1 g daily	Yes	No	Headache and cough	No	No	Yes	Pseudoephedrine, paracetamol
2	F 54	25 daily	Ibuprofen 200 mg daily	Yes	No	Nasal congestion	No	No	No	Pseudoephedrine, ibuprofen
3	F 74	25 daily	Ibuprofen 200 mg daily	Yes	No	Nasal congestion	No	No	No	Pseudoephedrine, ibuprofen
4	F 26	148 (2 days out of 30)	Ibuprofen 1.2 g (2 days out of 30)	No	Yes		No	No	No	Pseudoephedrine, ibuprofen
5	M 24	147 (3 days out of 7)	NA	Yes	No	Nasal congestion	Yes	No	No	
Antihistamines										
1	F 54	3.3 daily	NA	No	Yes	To sleep	No	No	No	Oxomemazine
Antacids										
1	M 34	Calcium carbonate 4.08 g daily	Magnesium carbonate 0.48 g daily	Yes	No	Stomach burn	No	No	No	Calcium carbonate, magnesium carbonate

F = female; **M** = male; **NA** = not applicable.

with pseudoephedrine is 5 days, four patients used it for longer than 5 consecutive days and three of them used it daily during the previous month. One of the patients who had used a brand medicine containing pseudoephedrine in excess during the previous month declared it to have deleterious consequence on his health, social or professional life. This man was therefore classified as an abuser. He used it to treat nasal congestion (table IV).

Antihistamines

Only one patient – among 60 who had used an antihistamine sedating drug during the previous month – used oxomemazine to sleep, whereas this medicine should be used to treat a cough (table IV).

Antacid Drugs

Only one patient – among 78 who had used an antacid drug during the precedent month – took carbonates of calcium and magnesium daily, whereas it is recommended in the SPC that consumption of the medicine is stopped after 10 days (table IV).

Discussion

The aim of this cross-sectional study was to explore the feasibility of a pharmacoepidemiological approach based on the participation of community pharmacies to investigate misuse, non-medical use, abuse and dependence on drugs used for self-medication. Monitoring the safety of medicines used for self-medication presents several methodological issues. One of the major difficulties is to conduct studies large enough to reach sufficient statistical power and to detect associations. According to this pilot study, the prevalence of the misuse, non-medical use, abuse or dependence on codeine seems higher than with any of the other drugs studied. The participation rates of pharmacies and patients and the results obtained with dextromethorphan, pseudoephedrine and antihistamines used for self-medication enable the number of participating pharmacies required to investigate the problematic use of these substances to be calculated.

The rate of effective participation of community pharmacies in this study was 32.4%, whereas 43.9% had agreed to participate at the beginning of the study. A participation rate of just under 50% has been obtained in a study to evaluate the feasibility of setting up a method for the pharmacovigilance of OTC medicines in the UK.[26] However, the level of participation of community pharmacies in the present study could have been biased by the mode of selection of the pharmacies. The pharmacies were solicited when they received a pharmacy student for a 6-month training period or when they were a member of a network regularly involved in pharmacoepidemiological studies on drug abuse and dependence. The participation rate was better among training course supervisors (41.0%) compared with the pharmacies from the network (29.3%). The organization of a meeting with the pharmacy students was an effective way to recruit participants. Moreover, the student was totally in charge of the study in the pharmacy, resulting in rigorous participation, since this was considered as part of his/her training. Involving pharmacy students in pharmacoepidemiological surveys is a way to make them aware of their future role as pharmacists.[27] The other pharmacies take part in a network on a voluntary basis and they regularly participate in the OSIAP survey in the French Midi-Pyrénées area.

A selection bias in the recruitment of patients cannot be excluded depending on the pharmacies with or without a student trainee. However, no data supported this hypothesis. Moreover, there is no argument to support the idea that the acceptability of the questionnaire by the patients should have been different between the two groups of pharmacies. Other patient selection bias could exist whatever the pharmacy.[26] For example, periods of high workload in the pharmacy may have led to patients being missed.

The patient participation rate was 64.9%. This is a high rate considering that the questions about misuse, non-medical use, abuse and dependence could have been an obstacle to patients' response. One patient refused to participate because he was

aware of his dependence to codeine and was not included in the study. Therefore quantification of the number of patients misusing, abusing or dependent on codeine in analgesics in the context of self-medication may have been underestimated. However, the number of refusals in the psychoactive substances groups (2.1%) was lower than in the control group (11%). In the case of codeine, the rate of refusal of the questionnaire was only 1.4%. Furthermore, the number of patients using codeine who returned the questionnaire was important; significantly higher than in the antacid control group (70.9% vs 61%; $p<0.05$). Several factors have probably contributed to the high response rate of the patients. First, our questionnaire was designed keeping in mind that the length influences the response rate, as has been previously discussed.[28] The version of our questionnaire was short (two pages). Furthermore, it was essential, in the context of the survey, to give the patient the opportunity to fill in the questionnaire outside the pharmacy, particularly for patients who misused, had a non-medical use, abused or were dependent on a medicine. Questionnaires returned in prepaid envelopes represented 21.7% of the completed questionnaires. Whereas 75% of the patients who did not have a problem with the use of codeine filled the questionnaire inside the pharmacy, 77.8% of the patients misusing, abusing or dependent on the analgesics containing codeine completed the questionnaire outside the pharmacy and returned it to the study centre with a prepaid envelope. These results suggest that patients did not want the pharmacist to be aware of their pattern of use of codeine-containing medicines.

An important strength of our study is to have used a control group to get a comparative evaluation of the extent of the problem with different drugs. One of the major difficulties is related to the choice of an appropriate control group. To assess abuse and dependence, we chose a therapeutic class known to have no psychotropic effects. The antacid drugs represent a therapeutic class used to treat dyspepsia, heartburn and other gastrointestinal problems. The drugs of this class chosen were mineral salts (magnesium, aluminium and calcium). Although we did not find any case of abuse or dependence with antacid drugs, one patient misused carbonate of calcium and magnesium, as he used it daily whereas it is recommended to stop consumption after 10 days. The finding of misuse in the control group gives a background of misusing with no intention of obtaining mind-altering effects but instead for ignoring the recommendations on the duration of use. We observed a statistically significantly higher rate of patients misusing pseudoephedrine than antacid drugs. Four of the five such patients used this nasal decongestant for a longer period than recommended. One patient using pseudoephedrine in excess reported deleterious consequences and was therefore classified as an abuser. No patient said they used pseudoephedrine for the stimulant effect caused by this sympathomimetic. It should be noted that among the psychoactive drugs being studied, the number of refusals of the questionnaire by the patients was the highest for drugs containing pseudoephedrine (5.6%). A study in Northern Ireland in 1999 showed that community pharmacists were aware that pseudoephedrine in OTC drugs was used for non-medical purposes, but at a lower frequency than opioids, antihistamines and laxatives.[23] The reason to use this drug could be for its stimulant effects for performance enhancement in sport.[29] Furthermore, concerns about the illicit conversion of pseudoephedrine into methamphetamine have obliged pharmaceutical companies in the US to switch from pseudoephedrine to phenylephrine in nasal decongestant products.[30]

Concerning abuse and dependence, the comparison of the results obtained with pseudoephedrine, dextromethorphan and antihistamines with the control group did not show statistically significant differences. This may be due to the insufficient number of questionnaires that could be analysed in the present pilot study. However, two cases of misuse and one of dependence on dextromethorphan were identified, suggesting that a greater number of questionnaires would reveal significant differences with the control group. Recreational abuse of dextromethorphan has been reported in several countries and can lead to intoxications, particularly in adolescents.[31] However, the extent of abuse of

dextromethorphan in products used for self-medication is unknown.[32]

The present study has identified misuse, abuse and dependence with codeine combined with paracetamol in drugs used for self-medication. It is well known that Néocodion®, a codeine-containing cough suppressant (codeine camphosulfonate + grindelia + sulfogaiacol), is sometimes used as a diversion drug or to treat withdrawal symptoms by opiate addicts in France.[33,34] Given this potential for abuse, the sale of Néocodion® in community pharmacies is limited to one packet of 20 tablets per purchaser in France. However, in addition to Néocodion®, 15 analgesic formulations that can be obtained without a medical prescription at a pharmacy in France also contain codeine and can be sold without limit. In these products, codeine is combined with paracetamol, or, less frequently, with aspirin. The extent of the problematic use of codeine in analgesics used for self-medication is unknown.

Whereas diversion of opioid analgesics from their therapeutic use has been described worldwide, very few studies have addressed the problem with codeine-containing medicines. It seems, however, that patients misusing or dependent on codeine-containing analgesics require specialized care.[35] Furthermore, numerous websites exist where patients having a problematic use of codeine through analgesics explain their problems. According to websites from the UK, most patients started codeine use for appropriate analgesic indications, but became dependent on this opioid analgesic and now ask for help through websites.[3] In the present study, except for one patient who needed high daily doses of codeine combined with paracetamol, three of the four patients who presented three behavioural criteria of dependence to codeine combined with paracetamol said they used it for a medical purpose (headache or back pain). These patients can be qualified as having 'pseudo-addiction' which should stop when the pain is correctly treated.[36] Ferrari et al.[37] used the Leeds Dependence Questionnaire in order to compare the need for analgesics between headache patients and addicts using illicit drugs. They concluded that in contrast to the primary dependence of drug addicts, the need for the analgesic drug to treat headaches results from its ability to help patients to cope with life.

Several methodological approaches have been used previously to study the problematic use of drugs used for self-medication. Most of the studies have been based on the perception of the pharmacists,[9,10,23,38] and therefore are much too subjective to obtain reliable qualitative and quantitative data on misuse and abuse and dependence on drugs used for self-medication. Interviews with 1000 people in the general population in Northern Ireland revealed that one-third of them had personally encountered cases of inappropriate use of medicines used for self-medication.[11] Visits to emergency departments related to non-medical use of prescription and OTC drugs increased by 21% from 2004 to 2005 in the US.[39] Whereas the non-medical use of medicines is well recognized as a growing phenomenon, the extent of the problem with drugs obtained without a prescription is unknown.

Another possibility to get information on drug misuse is based on the registration by the pharmacist of the quantities of the drug sold to a patient. However, quantification is complicated by the fact that patients can obtain the drug from several pharmacies. In the near future, an electronic pharmaceutical file will be available in community pharmacies in France. It will be possible for the pharmacists to register and to consult all the medicines sold to a patient throughout France during the previous 4 months. However, registration of the medicines supplied to a patient will be possible only with the patient's consent. Furthermore, mere quantitative data will not inform on the negative consequences of excessive use on patient health or social or professional life. Therefore abuse, as well as behavioural signs of dependence, cannot be assessed. In order to evaluate misuse, non-medical use, abuse or dependence on a drug obtained at the pharmacy without a prescription, the pharmacist will have to approach the patient. However, the results of an interview with the patient by the pharmacist would be biased, since the patients can deny their problematic use of the drug, as has already been observed in a study aimed to identify and prevent or treat the harmful consequences of non-rational use of OTC drugs.[24]

Conclusion

The present study was based on patients' answers to a self-questionnaire provided in community pharmacies to address misuse, non-medical use, deleterious consequences of overuse and lack of control over drug use related to dependence on drugs containing psychoactive substances used for self-medication and purchased in a pharmacy. The results obtained in this pilot pharmacoepidemiological study indicate that this method is reliable to obtain valuable information on the problematic use of a drug obtained in a pharmacy for self-medication. Prevalence data should help to define more accurately the roles of the pharmacist in counselling or referring these patients to a physician. On the basis of the participation rates obtained in the present study according to the different therapeutic classes of drugs, work is now ongoing to apply this method to a greater number of pharmacies to discover the extent of the problem concerning misuse, non-medical use, abuse or dependence in the context of self-medication.

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References

1. Le marché de l'automédication en France [online]. Available from URL: http://www.leem.org/htm/themes/article.asp?id_article=437 [Accessed 2008 Dec 18]
2. Bond C, Hannaford P. Issues related to monitoring the safety of over-the-counter (OTC) medicines. Drug Saf 2003; 26 (15): 1065-74
3. Ford C, Good B. Over the counter drugs can be highly addictive. BMJ 2007 May 5; 334 (7600): 917-8
4. Micaleff J, Jolliet P, Victorri-Vigneau C, et al. First meeting of the French CEIP (centres d'évaluation et d'information sur la pharmacodépendance): assessment of the abuse and pharmacodependence potential during drug development. Therapie 2008 Jan-Feb; 63 (1): 55-65
5. Boeuf O, Lapeyre-Mestre M, and French Network of Centers for Evaluation and Information Pharmacodependence (CEIP). Survey of forged prescriptions to investigate risk of psychoactive medications abuse in France: results of OSIAP survey. Drug Saf 2007; 30 (3): 265-76
6. Zacny J, Bigelow G, Compton P, et al. College on Problems of Drug Dependence taskforce on prescription opioid non-medical use and abuse: position statement. Drug Alcohol Depend 2003 Apr 1;69 (3): 215-32
7. NIDA. NIDA InfoFacts: prescription and over-the-counter medications [online]. Available from URL: http://www.nida.nih.gov/infofacts/PainMed.html [Accessed 2008 Dec 18]
8. Substance Abuse and Mental Health Services Administration (SAMHSA), Office of Applied Studies. Results from the 2001 National Household Survey on Drug Abuse. Vol. II. Technical appendices and selected data tables. Rockville (MD): NHSDA series H-18, DHHS publication no. SMA 02-3759
9. Matheson C, Bond C, Pitcairn J. Misuse of over-the counter medicines from community pharmacies: a population survey of Scottish pharmacies. Pharm J 2002 Jul 13; 269: 66-8
10. Pates R, McBride AJ, Li S, et al. Misuse of over-the counter medicines: a survey of community pharmacies in a South Wales health authority. Pharm J 2002 Feb; 268: 179-82
11. Wazaify M, Shields E, Hughes CM, et al. Societal perspectives on over-the-counter (OTC) medicines. Fam Pract 2005 Apr; 22 (2): 170-6
12. Sinclair HK, Bond CM, Hannaford PC. Pharmacovigilance of over-the-counter products based in community pharmacy: a feasible option? Grampian Pharmacy Network. Pharmacoepidemiol Drug Saf 1999 Dec; 8 (7): 479-91
13. Hasford J, Fagerstrom KO, Haustein KO. A naturalistic cohort study on effectiveness, safety and usage pattern of an over-the-counter nicotine patch: cohort study on smoking cessation. Eur J Clin Pharmacol 2003 Sep; 59 (5-6): 443-7
14. Hasford J, Moore N, Hoye K. Safety and usage pattern of low-dose diclofenac when used as an over-the-counter medication: results of an observational cohort study in a community-based pharmacy setting. Int J Clin Pharmacol Ther 2004 Aug; 42 (8): 415-22
15. Stewart D, Helms P, McCaig D, et al. Monitoring adverse drug reactions in children using community pharmacies: a pilot study. Br J Clin Pharmacol 2005 Jun; 59 (6): 677-83
16. Schulz M, Hämmerlein A, Hinkel U, et al. Safety and usage pattern of an over-the-counter ambroxol cough syrup: a community pharmacy-based cohort study. Int J Clin Pharmacol Ther 2006 Sep; 44 (9): 409-21
17. Hinkel U, Schuijt C, Erckenbrecht JF. OTC laxative use of sodium picosulfate: results of a pharmacy-based patient survey (cohort study). Int J Clin Pharmaco Ther 2008 Feb; 46 (2): 89-95
18. Glossaire des vigilances [online]. Available from URL: http://afssaps.sante.fr/pdf/5/glossaire_vigilances.pdf [Accessed 2008 Dec 18]

19. Article R 5132-99 du Code de la santé Publique [online]. Available from URL: http://agmed.sante.gouv.fr/htm/10/pharma/indpharm.htm [Accessed 2008 Dec 18]
20. World Health Organization. International statistical classification of diseases and related health problems. 10th rev. Geneva: World Health Organization, 2007
21. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed, text revision. Washington, DC: American Psychiatric Association, 2000
22. Højsted J, Sjøgren P. Addiction to opioids in chronic pain patients: a literature review. Eur J Pain 2007 Jul; 11 (5): 490-518
23. Hughes GF, McElnay JC, Hughes CM, et al. Abuse/misuse of non-prescription drugs. Pharm World Sci 1999 Dec; 21 (6): 251-5
24. Fleming GF, McElnay JC, Hughes CM. Development of a community pharmacy-based model to identify and treat OTC drug abuse/misuse: a pilot study. Pharm World Sci 2004 Oct; 26 (5): 282-8
25. Wazaify M, Hughes CM, McElnay JC. The implementation of a harm minimisation model for the identification and treatment of over-the counter drug misuse and abuse in community pharmacies in Northern Ireland. Patient Educ Couns 2006 Dec; 64 (1-3): 136-41
26. Layton D, Sinclair HK, Bond CM, et al. Pharmacovigilance of over-the-counter products based in community pharmacy: methodological issues from pilot work conducted in Hampshire and Grampian, UK. Pharmacoepidemiol Drug Saf 2002 Sep; 11 (6): 503-13
27. Llau ME, Lapeyre-Mestre M, Plas L, et al. Forged medical prescriptions in a community pharmacy network in Midi-Pyrénées area: assessment of a falsification ratio. Eur J Clin Pharmacol 2002 Feb; 57 (12): 911-2
28. Kalantar JS, Talley NJ. The effects of lottery incentive and length of questionnaire on health survey response rates: a randomized study. J Clin Epidemiol 1999 Nov; 52 (11): 1117-22
29. Bents RT, Marsh E. Patterns of ephedra and other stimulant use in collegiate hockey athletes. Int J Sport Nutr Exerc Metab 2006 Dec; 16 (6): 636-43
30. Eccles R. Substitution of phenylephrine for pseudoephedrine as a nasal decongestant: an illogical way to control methamphetamine abuse. Br J Clin Pharmacol 2007 Jan; 63 (1): 10-4
31. Schwartz RH. Adolescent abuse of dextromethorphan. Clin Pediatr (Phila) 2005 Sep; 44 (7): 565-8
32. Cranston JW, Yoast R. Abuse of dextromethorphan. Arch Fam Med 1999 Mar-Apr; 8 (2): 99-100
33. Olivier P, Maréchal K, Llau ME, et al. Use of codeine and non-codeine cough suppressants. Clin Drug Investig 2002; 22 (6): 399-402
34. Armand C, Thirion X, Saillard C, et al. Neocodion misuse: evolution between 1992 and 2002. Therapie 2004 Sep-Oct; 59 (5): 547-53
35. Myers B, Siegfried N, Parry CD. Over-the-counter and prescription medicine misuse in Cape Town: findings from specialist treatment centres. S Afr Med J 2003 May; 93 (5): 367-70
36. Elander J, Lusher J, Bevan D, et al. Understanding the causes of problematic pain management in sickle cell disease: evidence that pseudoaddiction plays a more important role than genuine analgesic dependence. J Pain Symptom Manage 2004 Feb; 27 (2): 156-69
37. Ferrari A, Cicero AF, Bertolini A, et al. Need for analgesics/drugs of abuse: a comparison between headache patients and addicts by the Leeds Dependence Questionnaire (LDQ). Cephalalgia 2006 Feb; 26 (2): 187-93
38. MacFadyen L, Eadie D, McGowan T. Community pharmacists' experience of over-the-counter medicine misuse in Scotland. J R Soc Health 2001 Sep; 121 (3): 185-92
39. McCarthy M. Prescription drug abuse up sharply in the USA. Lancet 2007 May 5; 369 (9572): 1505-6

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