Drug Saf (2013) 36:1159–1168
DOI 10.1007/s40264-013-0114-y

SHORT COMMUNICATION

Frequency and Severity of Adverse Drug Reactions Due to Self-Medication: A Cross-Sectional Multicentre Survey in Emergency Departments

Nathalie Asseray · Françoise Ballereau · Béatrice Trombert-Paviot · Jacques Bouget · Nadine Foucher · Bertrand Renaud · Lucien Roulet · Gerald Kierzek · Aurore Armand-Perroux · Gilles Potel · Jeannot Schmidt · Françoise Carpentier · Patrice Queneau

Published online: 26 October 2013

Abstract
Background Little is known about the relation of adverse drug reactions (ADRs) to self-use of medications.
Objective The aim of this study was to determine the frequency and severity of ADRs related to self-medication (ADR-SM) among emergency department (ED) patients and to describe their main characteristics.
Methods A prospective, cross-sectional, observational study was conducted over a period of 8 weeks (1 March to 20 April 2010), in the ED of 11 French academic hospitals. Adult patients presenting to the ED during randomization periods were included, with the exception of cases of self-drug poisoning, inability to complete self-medication questionnaire, or refusal. Clinical outcomes were assessed as well as history of self-medication behaviours and all drugs taken. All doubtful files and those related to ADR-SM were systematically reviewed by an expert committee.
Results A total of 3,027 of 4,661 patients presenting to the ED met the inclusion criteria. Of these, 84.4 % declared a self-medication behaviour, 63.7 % took at least one non-prescribed drug during the previous 2 weeks and 59.9 % took a prescribed medication. A total of 296 patients experienced an ADR (9.78 %), of which 52 (1.72 %) were related to self-medication. Those ADRs related to self-medication included prescribed drugs ($n = 19$), non-prescribed drugs ($n = 17$), treatment discontinuation ($n = 14$), and interactions between non-prescribed and prescribed drugs ($n = 2$). The ADRs attributed

Electronic supplementary material The online version of this article (doi:10.1007/s40264-013-0114-y) contains supplementary material, which is available to authorized users.

N. Asseray (✉)
Service des Maladies Infectieuses,
CHU de Nantes, Nantes, France
e-mail: nathalie.asseray@chu-nantes.fr

N. Asseray · F. Ballereau
EA 3826, Faculté de Médecine, 1 rue Gaston Veil, 44035 Nantes, France

F. Ballereau
e-mail: francoise.ballereau@univ-nantes.fr;
francoise.ballereau@chu-nantes.fr

F. Ballereau · N. Foucher
MEDQUAL Hôpital Saint Jacques, 44093 Nantes, France

N. Foucher
e-mail: nfoucher.billard@groupe-vitalia.com

B. Trombert-Paviot
EA 4607, Faculté de Médecine, 42023 Saint Etienne, France
e-mail: trombert@univ-st-etienne.fr

J. Bouget
Service des Urgences, CHU, 35033 Rennes, France
e-mail: jacques.bouget@chu-rennes.fr

B. Renaud
Service des Urgences, Hôpital Henri Mondor (APHP), 94000 Créteil, France
e-mail: bertrand.renaud@hmn.aphp.fr

L. Roulet
Pharmacie Hospitalière, Hôpital du Valais, 1651 Sion, Switzerland
e-mail: lucien.roulet@hopitalvs.ch

G. Kierzek
Service des Urgences, Hôtel-dieu (APHP), 75004 Paris, France
e-mail: gerald.kierzek@htd.aphp.fr

A. Armand-Perroux
Service des Urgences, CHU, 49100 Angers, France
e-mail: AuArmand@chu-angers.fr

to non-prescribed drugs represented 1 % of all patients taking non-prescribed drugs ($n = 1{,}927$). ADR severity was significantly lower for those related to self-medication ($p = .032$).
Conclusion Self-medication is frequent; its potential toxicity should not be neglected, taking into account the rate of adverse drug reactions in about 1 % of ED patient.

1 Background

Drug-related problems are an important cause of morbidity and mortality and a significant burden on healthcare resources. A high rate of adverse drug reactions (ADRs) has been demonstrated in hospitalized patients [1–4], potentially leading to death. As patients with severe or acute unexpected symptoms frequently present to emergency departments (EDs), some epidemiological studies of ADRs have been successfully conducted in this setting, showing that approximately 10–17 % of ED visits were related to an ADR [5, 6].

The definition of self-medication is still debated. According to the National Library of Medicines' MeSH (Medical Subject Headings) database, self-medication refers to self-administration of a medication not prescribed by a physician, or in a manner not directed by a physician. Furthermore, the WHO defines self-medication as the selection and use of medicines by individuals to treat self-recognized illnesses or symptoms [7], and cites self-medication as a common problem leading to incorrect use of medicine [8]. Therefore, a patient-based approach of self-medication should include all modalities of self-use of drugs, whether previously prescribed or not. This study was based on such a patient-based approach.

Despite numerous studies on ADRs, there are no available data informing us about the rate of ADRs directly related to self-medication (ADR-SM). As such, the risk related to current self-medication behaviours is under-investigated. In the ED-specific context, previously published studies [5, 6] have not focused on the link between self-medication and ADRs. No data on the rate and severity of ADRs related to self-medication in this setting are available.

To determine the prevalence ratio and severity of ADR-SM in the ED population, we designed a multicentre, ED-based, cross-sectional survey in 11 French hospitals. We also attempted to identify the characteristics of ED patients and their drugs associated with ADRs and ADR-SM.

2 Methods

2.1 Study Design

During the 8-week period from 1 March until 20 April 2010, a prospective, cross-sectional, observational study was conducted in the ED of 11 French academic hospitals distributed throughout the country.

Definition of self-medication in the study protocol:

- To take drugs without relevant prescription (sold without prescription, rest of an ancient prescription or prescribed for another person)
- A self-modification of treatment
- A self-discontinuation of treatment

2.2 Approvals

The study protocol and patient informed consent procedures were approved by the Ethics Committee (St. Etienne CHU on 10 February 2008), and the Committee on Information in Health Research (CCTIRS/CNIL), according to French rules in clinical research.

2.3 Sampling and Randomization

A high volume of visits in participating EDs precluded uninterrupted prospective screening for inclusion throughout the study period. Additionally, as rates of hourly ED visits varied markedly within each day and from one day to another, we defined 13 time slots a priori covering the 24-h day as follows: 10 time slots of 1 h (from 10:00 am to 2:00 pm and from 5:00 pm to 11:00 pm), one time slot of 8 hours (from 11:00 pm to 7:00 am) and two time slots of 3 h (from 7:00 am to 10:00 am and from 2:00 pm to 5:00 pm). Subsequently, we randomly allocated these 13 predefined time slots throughout the 8 weeks of the study period for each participating ED. Randomization was done with computer-generated codes prior to the study enrolment period by our clinical research unit, which was not involved in data collection or patient care. Allocations were disclosed to research staff in every participating ED

G. Potel
Service des Urgences, Hôtel Dieu, 44092 Nantes, France
e-mail: gilles.potel@chu-nantes.fr

J. Schmidt
Service des Urgences, CHU, 63000 Clermont Ferrand, France
e-mail: jschmidt@chu-clermontferrand.fr

F. Carpentier
Service des Urgences, CHU, 38043 Grenoble, France
e-mail: FCarpentier@chu-grenoble.fr

P. Queneau
Académie Nationale de Médecine, 75006 Paris, France
e-mail: patrice.queneau@orange.fr

P. Queneau
CHU, Saint Etienne, France
e-mail: patrice.queneau@chu-st-etienne.fr

just prior to the study enrolment period. This method was designed to limit the potential for sampling bias. Additionally, patient demographics (age, gender and acute severity triage score) [9] were collected from administrative data of each participating centre over the same 8-week enrolment period. These data were compared with the overall study population to verify the representativeness of the ED population studied.

2.4 Patient Enrolment

All adult patients presenting to participating EDs during one of the predefined time slots were eligible for study enrolment. On entry, they were informed with a specific form about the study and the opportunity to participate. Medical or pharmacy students (hereafter designated as research staff) in every participating ED were specifically trained to screen candidates for study enrolment, using standardized screening forms. Consenting patients were subsequently included in the absence of exclusion criteria.

2.5 Exclusion Criteria

The following were precluded because we aimed to describe self-medication behaviour and unintentional related ADRs: (i) patients unable to participate because of cognitive impairment, neuropsychiatric disorders, language barriers or having presented with an unstable medical illness in the absence of a near relative who could answer for them; (ii) patients presenting for attempting suicide; and (iii) declining study participate (a written information form was submitted to patients and/or their relatives at the time of their admission to the ED). In each instance, the reason for exclusion was systematically recorded.

2.6 Variables and Data Collection

Self-medication behaviours were explored by a standardized questionnaire that had been previously built, implemented and tested in one centre [10] (see electronic supplementary material). This questionnaire is divided into two parts. The first part consists of a set of 20 closed-ended questions exploring all indications and dimensions of self-medication. The second part collects the characteristics of each medication cited by the patient during the first part (dosage, time between last dose and the ED visit, origin).

The method of data collection during the ED evaluation was then tested in three voluntary centres, which included standardized interviews of patients and/or their surrogates, as well as review of the medical record (i.e. physician notes and orders, laboratory reports, nursing notes, discharge instructions and ongoing prescriptions). Special attention was paid to all medications taken within 2 weeks prior to patient enrolment, including prescribed and non-prescribed drugs. All data were entered using online electronic case report forms (e-CRF), which allowed for real-time assessment of data completeness and patient follow-up. Data collection was performed by the local research staff, which was monitored by a clinical research pharmacist and supervised by the investigators.

2.7 Adverse Drug Reaction (ADR) Identification Process

The primary outcome was the diagnosis of ADR-SM and the identification of clinical and biological findings related to the effect of the drug(s). The investigators reviewed all cases to identify ADRs in each study centre, based on VIDAL dictionary (French book summarizing the characteristics of all medications, including pharmacology, adverse effects and drug-drug interactions). The local investigators were helped by the Naranjo scale [11] for drug causality assessment. Nevertheless, whatever could be the result of this score, they were asked to transmit all clinically relevant cases. The severity of the ADRs was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) [12], as (A) spontaneous regression; (B) regression after symptomatic treatment; (C) hospitalization with no life-threat; (D) life-threatening risk; and (E) death. The diagnosis of ADR and the drug causality assessment were then documented in the e-CRF. If necessary, notification of cases of drug toxicity was provided to the pharmacovigilance regional centre at the discretion of the local investigator.

All contentious issues transmitted by local investigators, every ADR-SM case (whether contentious or not), and some randomly assigned files were reviewed by an expert committee comprised of therapeutics professors, clinical pharmacists and emergency physicians, whose meetings and minutes were managed by the clinical research pharmacist. Furthermore, the entire database was scrutinized by the clinical research pharmacist in order to detect each case potentially related to an ADR; the expert committee was asked to assess such cases and to confirm drug causality (in order to validate the main outcome). Every local investigator was also asked to verify each subject file and to transmit all useful information regarding the possibility of an ADR to the expert committee. This committee was finally able to resolve each contentious case, and to validate the entire database. Last, the expert committee determined, for each ADR-SM case, the type of self-medication leading to the adverse event: self-modification of a prescribed treatment, discontinuation of treatment, non-prescribed drugs, or a drug interaction with non-prescribed drugs (i.e. self-prescription).

2.8 Grouping of Data

The diagnosis of the chief complaint and that of the ADR were first encoded to the International Classification of Diseases, 10th revision (ICD-10). To further improve grouping, data were re-coded using a standardized classification designed by the Société Française de Médecine d'Urgence (SFMU: French Society of Emergency Medicine) [13]. All drugs cited by patients, whether prescribed or not, were encoded to the Anatomical Therapeutic Chemical (ATC) classification system [14]. Medications not covered by the ATC were encoded as 'Z' (herbal medicines, vitamins, food supplements, calcium, magnesium, diosmine, anti-nausea or anti-diarrhoea pills, some medicines for constipation, balms and topical emollients, topical medicines for common cold, some anti-tussive syrups, omega 3 …).

2.9 Statistical Analysis of Data

Sample size: considering a rate of ADR-SM possibly not over 1 % of ED patients (personal data), we targeted the enrolment of approximately 5,000 patients (in order to observe a minimum of 30 cases, alpha risk 0.05, power >0.80).

Patient characteristics are presented as the mean and frequency with 95 % confidence intervals (CIs) using Jeffreys confidence limits for the binomial proportion. Chi-square tests for qualitative variables or Student *t* tests for quantitative variables were computed to determine if an association exists between patients admitted with ADRs and self-medication. A *p*-value of less than 0.05 was considered to be significant. In a second step, a multivariate logistic regression analysis was used to predict whether or not a patient had an ADR-SM based on significant characteristics of the patients as determined by univariate analysis. Analyses were carried out with SAS version 9.2 (SAS Institute Inc, Cary, NC, USA).

3 Results

3.1 Characteristics of the Study Population

During the randomization periods, 4,661 patients were admitted to the ED. Among these, 35.1 % were not included (Fig. 1), which was most often due to inability to answer the self-medication standardized questionnaire. Table 1 shows the comparison of the study population with the total ED population during the study period. The demographic data appeared relatively equivalent. Nevertheless, there was a significant difference in terms of gender between the groups. Likewise, the acute severity

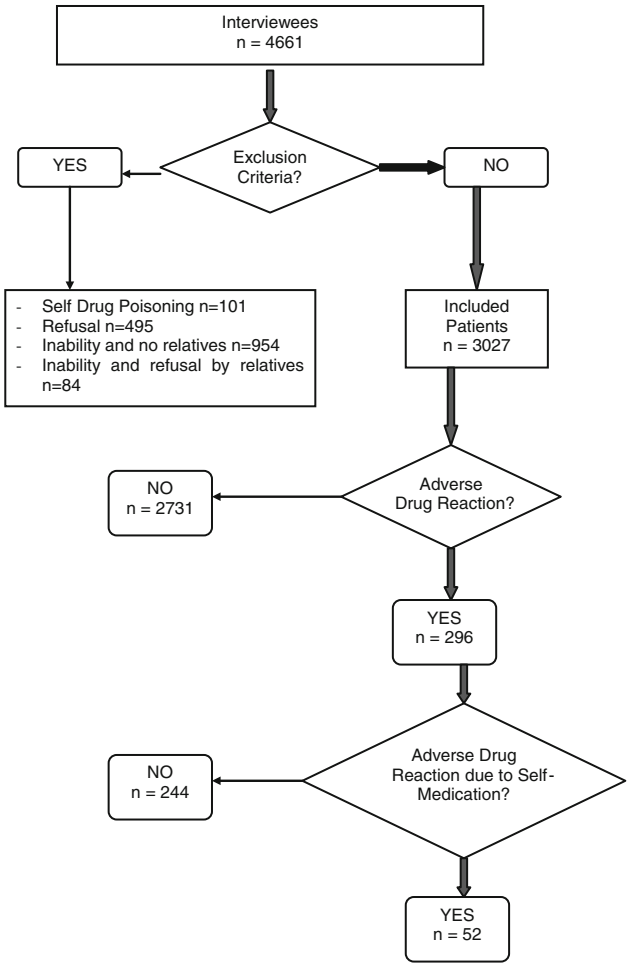

Fig. 1 Flowchart

triage score was also different, whereby level 1 was underrepresented and level 5 was overrepresented among the study patients. The 3,027 study patients were 53.5 % female (including 16 pregnant women) and had a median age of 43 years (range 18–99). The chief complaint was trauma in about one-third of the patients, with the other most frequent complaints being abdominal pain, weakness and cardiovascular diseases (Table 2).

3.2 Pharmaceutical Data

Of the patients included, 59.9 % took at least one prescribed medication, and 63.7 % self-medicated during the previous 2 weeks. Additionally, 84.1 % declared a self-medication behaviour (Table 2). Of the 11,724 drugs taken by the study population, 32.5 % were in a self-medication manner, and the most frequent were analgesics ($n = 2,184$, 75 % self-medication). Among the 3,848 drugs used in self-medication, origin was most frequently a non-prescribed medication purchased over the counter (OTC) at

Table 1 comparison of the study population with total emergency department (ED) population during the study period

	Study patients (%)	ED population (%)[a]	
Age (years)	$n = 3,027$	$n = 86,757$	
18–29	27.7	27.9	
30–39	17.4	17.0	
40–49	12.9	14.3	
50–59	11.8	12.1	
60–69	9.4	8.2	
70–79	8.4	7.9	
80–89	10.2	9.7	
>89	2.1	2.8	
Gender	$n = 3,027$	$n = 88,531$	$p = 0.01$
Male	46.4	44.6	
Female	53.5	55.3	
CCMU[b]	$n = 2,104$	$n = 58,268$	$p < 0.0001$
Level 1	8.7	14.4	
Level 2	59.4	59.4	
Level 3	27.1	21.7	
Level 4	4.1	2.7	
Level 5	0.7	1.8	

[a] The ED population data are the administrative data obtained for the total ED population during the study period

[b] The French clinical classification of emergency patients, usually used for care prioritization (9): Level 1: Clinical condition considered as stable and decision of no further procedure in the emergency room; Level 2: Level 1 and decision of further procedure in the emergency room; Level 3: Clinical condition likely to worsen; Level 4: Life-threatening risk and no decision of starting resuscitation procedures; Level 5: Level 4 and decision of starting resuscitation procedures in the emergency room

the pharmacy (50.5 %), followed by the rest of a previous prescription (19.9 %) and the use of a conditional prescription (14.5 %). Less frequent sources of self-medication were drugs supplied by relatives (5.3 %), the use of a prescribed drug with self-modification of the dose or duration (2.1 %), drugs purchased by mail or internet (1.2 %) and other unspecified sources (6.5 %).

3.3 Frequency of ADRs Related to Self-Medication (ADR-SM)

Of the entire cohort, 9.8 % (296/3,027) of patients experienced an ADR that was related to self-medication in 52 cases (Fig. 1). Depending on the population considered for the denominator, the rate of ADR-SM could be expressed as 17.6 % of patients experiencing an ADR (52/296), 1.7 % of the study population (52/3,027) or 2 % of patients reporting a self-medicating behaviour (52/2,556).

– *ADR-SM related to prescribed drugs (self-medication behaviour):* The type of self-medication leading to an ADR was most frequently associated with prescribed drugs, as a self-modification of a prescribed treatment in 21 cases or discontinuation of treatment in 14 cases. Finally, about two-thirds of ADR-SM are subsequent to the patients' own decision on prescribed treatment.
– *ADR-SM related to non-prescribed drugs:* The use of non-prescribed drugs occurred in 16 cases of ADR-SM, and drug interaction with non-prescribed drugs in 1 case (so non-prescribed drugs led to a total of 17 cases of ADR-SM). The rate of ADRs related to non-prescribed drugs was 32.7 % of ADR-SM, 5.7 % of ADRs, and approximately 0.9 % among patients taking non-prescribed drugs during the previous 2 weeks (17/1,927).

3.4 Characteristics of ADR-SM in Comparison With Other ADRs

Bleeding was the most frequent ADR diagnosed, but for ADRs related to self-medication the diagnoses were most frequently neurologic and psychiatric. The drugs most frequently causative of ADRs were antithrombotics (class B). For ADR-SM, drugs belonging to the nervous system drugs (class N) accounted for more than half of the causative agents, of which analgesics (class N02) were significantly associated with ADR-SM. The severity of ADR-SM was lower than that of other ADRs (Table 3). From the multivariate analysis, young age and ATC class N could both be considered as independent factors associated with ADR-SM (Table 4).

4 Discussion

This epidemiological study showed that self-medication could result in ADRs, representing about 1–2 % of ED patients, depending on the type of self-medication and the denominator considered. In comparison with ADRs related to a medical prescription, ADR-SM more frequently resulted in neurologic or psychiatrics side effects, and were more frequently related to nervous system drugs (ATC class N). The frequency and severity of ADRs seem to be weaker when related to self-medication. Nevertheless, these results should be carefully interpreted. The importance of the risk demonstrated here in the ED population should be weighed against the potential benefit, which has to be important enough to make the risk acceptable.

Several studies have confirmed that antithrombotic agents, especially vitamin K inhibitors, are a common cause of ADRs [2–4]. These data are confirmed in our results; however, we have not observed ADR-SM related to this class in the study population. We have observed that

Table 2 Characteristics of the study population, whether or not experiencing an ADR-SM

	ADR-SM $n = 52$	ADR-no SM $n = 244$	p-value (ADR-SM /ADR-noSM)	Total no. of ADRs $n = 296$	No ADR $n = 2,731$	p-value (ADR/no ADR)	Study population $n = 3,027$
Age (years)	45.4 [40.0–50.8]	67.5 [64.9–70.0]	<0.0001	63.6 [61.1–66.1]	45.6 [44.8–46.4]	<0.0001	47.4 [46.6–48.1]
Gender (% female)	48.1 [34.0–61.5]	57.4 [51.1–63.5]	NS	55.7 [50.1–61.3]	45.4 [43.6–47.3]	0.0007	46.5 [44.7–48.2]
Self-medication habit (%)	–	–	–	77.0 [72.2–81.8]	84.8 [83.5–86.2]	0.0005	84.1 [82.8–85.4]
Chief complaint (%)							
Neurologic diseases	32.7 [21.1–46.1]	11.9 [8.3–16.4]		15.5 [11.8–20.0]	5.9 [5.1–6.9]	<0.0001	6.9 [6.0–7.8]
Mental illness	15.4 [7.6–26.9]	1.2 [0.35–3.2]		3.7 [2.0–06.3]	3.0 [2.4–3.7]		3.1 [2.5–3.7]
Weakness	13.5 [6.2–24.6]	16.4 [12.2–21.4]		15.9 [12.1–20.4]	6.5 [5.6–7.5]		7.4 [6.5–8.4]
Trauma	11.5 [5.0–22.2]	13.5 [9.7–18.2]		13.2 [9.7–17.4]	39.3 [37.5–41.17]		36.8 [35.1–38.5]
Cardiovascular diseases	7.7 [2.7–17. 3]	7.0 [4.3–10.7]		7.1 [4.6–10.4]	7.4 [6.5–8.5]		7.4 [6.5–8.4]
Abdominal pain	5.8 [1.7–14.6]	7.4 [4.6–11.2]		7.1 [4.6–10.4]	10.2 [9.1–11.36]		9.9 [8.9–11.0]
Endocrine and metabolic diseases	5.8 [1.7–14.6]	4.9 [2.7–8.2]		5.1 [3.0–08.0]	0.66 [0.41–1.0]		1.1 [0.8–1.5]
Musculoskeletal diseases	3.9 [0.81–11.8]	3.7 [1.8–6.6]	[a]	3.7 [2.0–06.3]	6.1 [5.2–7.0]		5.9 [5.1–6.7]
Skin and soft tissues diseases	1.9 [0.21–08.6]	2.5 [1.0–5.0]		2.4 [1.1–04.6]	1.7 [1.3–2.3]		1.8 [1.4–2.3]
Respiratory diseases	1.9 [0.21–08.6]	6.2 [3.6–9.7]		5.4 [3.3–08.4]	5.8 [5.0–6.8]		5.8 [5.0–6.7]
Infections	0.0 [0]	7.0 [4.3–10.7]		5.7 [3.5–08.8]	4.5 [3.7–5.3]		4.6 [3.9–5.4]
Hepato-gastrointestinal diseases	0.0 [0]	3.7 [1.8–6.6]		3.0 [1.5–05.5]	2.7 [2.1–3.3]		2.7 [2.2–3.3]
Bleeding	0.0 [0]	12.7 [8.97–17.3]		10.5 [7.4–14.3]	1.5 [1.1–2.0]		2.4 [1.9–3.0]
Genitourinary diseases	0.0 [0]	1.2 [0.35–3.2]		1.0 [0.3–02.7]	1.7 [1.3–2.3]		1.7 [1.2–2.2]
Continuity of care	0.0 [0]	0.82 [0.17–2.6]		0.7 [0.1–02.2]	1.2 [0.8–1.6]		1.1 [0.8–1.6]
Other diseases	0.0 [0]	0.0 [0]		0.0 [0]	1.8 [1.4–2.3]		1.6 [1.2–2.1]
Medications' characteristics							
Average number of drugs taken	5.9 [4.8–6.9]	7.6 [7.2–8.0]	0.0017	7.3 [6.9–7.7]	3.6 [3.5–3.8]	<0.0001	4.0 [3.8–4.1]
>5 drugs taken (%)	57.7 [44.2–70.4]	79.1 [73.7–83.8]	0.0011	75.3 [70.2–80.0]	31.1 [29.4–32.8]	<0.0001	35.4 [33.7–37.1]
ATC class of drugs taken (%)							
C, Cardiovascular system drugs	26.9 [16.4–40.0]	72.1 [66.3–77.5]	0.0644	64.2 [58.6–69.5]	24.8 [23.2–26.4]	<0.0001	28.6 [27.1–30.3]
B, Blood drugs—antithrombotics and platelet aggregation inhibitors	0.0 [0]	10.7 [7.3–15.0]	0.0119	8.8 [6.0–12.4]	2.7 [2.1–3.3]	<0.0001	3.3 [2.7–4.0]
N, Nervous system drugs (N02–analgesics excluded)	67.3 [53.9–78.9]	53.3 [47.0–59.5]	<0.0001	55.7 [50.1–61.3]	25.6 [24.0–27.3]	<0.0001	28.6 [27.0–30.2]
Average number of prescribed drugs	3.7 [2.8–4.8]	6.6 [6.1–7.0]	<0.0001	6.1 [5.7–6.5]	2.3 [2.2–2.5]	<0.0001	2.7 [2.6–2.8]
Average number of SM drugs	2.2 [1.7–2.7]	1.0 [0.86–1.2]	<0.0001	1.2 [1.1–1.4]	1.3 [1.2–1.3]	NS	1.3 [1.2–1.3]
At least one SM drug (%)	–	–	–	60.5 [54.8–65.9]	64.0 [62.2–65.8]	NS	63.7 [61.9–65.4]

[a] Test not performed because the conditions of application were not met

ADRs adverse drug reactions, *ADR-SM* ADR related to self-medication, *ADR-no SM* ADR not related to self-medication, *ATC* Anatomical Therapeutic Chemical, *NS* not significant

Table 3 Characteristics of ADR-SM (% [95 % CI])

	ADR-SM $n = 52$	ADR-no SM $n = 244$	p-value (ADR-SM/ADR-noSM)	Total no. of ADRs $n = 296$
Diagnosis of ADR			[a]	
Neurologic diseases	34.6 [22.8–48.1]	8.6 [5.6–12.6]		13.2 [9.7–17.4]
Mental status change	17.3 [8.9–29.2]	2.1 [0.79–4.4]		4.7 [2.7–7.6]
Cardiovascular diseases	9.6 [3.8–19.8]	14.8 [10.7–19.6]		13.9 [10.3–18.1]
Weakness	7.7 [2.7–17.3]	4.9 [2.7–8.2]		5.4 [3.3–8.4]
Fall	7.7 [2.7–17.3]	7.8 [4.9–11.7]		7.8 [5.1–11.2]
Endocrine and metabolic diseases	5.8 [1.7–14.6]	11.9 [8.3–16.4]		10.8 [7.7–14.7]
Skin and soft tissues diseases	5.8 [1.7–14.6]	5.7 [3.3–9.2]		5.7 [3.5–8.8]
Hepato-gastrointestinal diseases	5.8 [1.7–14.6]	12.7 [9.0–17.3]		11.5 [8.2–15.5]
Bleeding	1.9 [0.21–8.6]	18.9 [14.3–24.1]		15.9 [12.1–20.4]
Infections	1.9 [0.21–8.6]	4.1 [2.1–7.2]		3.7 [2.0–6.3]
Others diseases	1.9 [0.21–8.6]	2.5 [1.0–5.0]		2.4 [1.1–4.6]
Coagulopathy	0	2.9 [1.3–5.6]		2.4 [1.1–4.6]
Haematological diseases	0	2.9 [1.3–5.6]		2.4 [1.1–4.6]
Respiratory diseases	0	0.4 [0.04–1.9]		0.3 [0.04–1.6]
ADR severity			0.032	
A: Spontaneous regression	34.6 [22.8–48.1]	18.9 [14.3–24.1]		21.6 [17.2–26.6]
B: Regression after symptomatic treatment	28.9 [17.9–42.1]	30.3 [24.8–36.3]		30.1 [25.1–35.5]
C: Hospitalization with no life-threat	36.5 [24.5–50.1]	44.7 [38.5–50.9]		43.2 [37.7–48.9]
D: Life-threatening risk	0	6.2 [3.6–9.7]		5.1 [3.0–8.0]
E: Death	0	0		0
ATC of causative drugs	$n = 68$	$n = 404$		$n = 472$
C, Cardiovascular system drugs	8.8 [3.8–17.3]	27.5 [23.3–32.0]	0.001	24.8 [21.1–28.8]
B, Blood drugs—antithrombotics and platelet aggregation inhibitors	0	19.3 [7.3–15.0]	<0.0001	16.5 [13.4–20.1]
N, Nervous sytem drugs (N02–analgesics excluded)	55.9 [44.0–67.2]	20.1 [16.4–24.2]	<0.0001	25.2 [21.5–29.3]
N02–analgesics	19.1 [11.2–29.6]	5.7 [3.7–8.3]	0.0001	7.6 [5.5–10.3]

[a] Test not performed because the conditions of application were not met

ADRs adverse drug reactions, *ADR-SM* ADRs related to self-medication, *ADR-no SM* ADRs not related to self-medication, *ATC* Anatomical Therapeutic Chemical

Table 4 Characteristics explicating adverse drug reactions related to self-medication

Characteristics	Odds ratio	95 % CI
Age (≥65 years vs. 18–64 years)	0.12	0.05–0.30
Gender	0.75	0.38–1.51
Nervous system drugs	4.07	1.74–9.47
Number of drugs taken (≥5 vs. 0–4)	0.65	0.31–1.36

the most common class associated with ADR-SM was psycholeptic and analgesic drugs. The increasing consumption of analgesic self-medication highlights the need for information and prevention regarding the risks of OTC medications [15], particularly as patients commonly underrate the risks of ADR-SM [16]. Moreover, the high frequency of ADR-SM associated with self-modification or self-discontinuation of treatment advocates strongly for patient education, especially for the use of psycholeptic and antiepileptic drugs. Tracks for the analysis of ADR-SM were proposed 2 decades ago to understand how they arise [17], whereby the most commonly explored are factors dependent on doctors, healthcare professionals and institutions. On the other hand, factors that appear linked to the patient and to the doctor-patient relationship are lesser studied. As a consequence, the patients' therapeutic behaviours and self-medication with non-prescribed drugs must be examined to explore actual causes of ADRs. Indeed, the individual's assessment of illness and their subsequent response to it are not so spontaneous, as these result from learning (not only with professionals) that is based on the representation of illness and medications [18].

This sociopsychological approach considers the patient as greater in importance than the drug or the

professional. Therefore, the definition of self-medication should not be restricted to OTC drugs. In a national French report [19], self-medication was recognized as a behaviour rather than as a class of medications (specifically OTC, as it is recognized in the UK). This approach allows for the inclusion of all therapeutic choices decided by the patient in the definition of self-medication and self-medicating behaviour. However, scientific data regarding self-medication are, to date, rare in the medical literature, and they mostly concern OTC drugs and focus on pharmaceutical aspects of self-medication [20, 21]. Moreover, data that are available tend to be quantitative consumption data issued from industry and pharmacist surveys regarding only OTC medicines [ISM Health, AESGP (Association Européenne des Spécialités Pharamaceutiques Grand Public) for the European self-medication industry [19]] or they are declarative data from patients themselves revealed by some opinion surveys. In France, the use of drugs available without medical order is lower than in other countries, being about 8 % of revenue and 17 % of sale units [19]. Additionally, the frequency of declared self-medication is about 80 % among people interviewed by opinion survey promoted by pharmaceutical manufacturers [22], which is in line with our results. Several risks are related to self-medication, of which ADRs are a part. Self-medication is also associated with diagnostic risks, because the treatment of symptoms could be delayed before visiting a physician or the clinical setting could be modified enough to lead the physician to a medical error. Other risks should also be considered in the overall management of self-medication, such as exacerbation of psychiatric diseases [23, 24] and addiction to drugs [25]. Strategies to control and to minimize the risk of self-medication should involve monitoring systems, the promotion of education and information, and a partnership between patients, physicians and pharmacists [26, 27].

The context and objectives of this study have generated some bias that requires discussion. Because of the focus of this study, the self-medication behaviours are explored by self-report, restricting those enrolled to patients able to answer the standardized questionnaire. Therefore, the sample of included patients could not exactly represent the entire ED population, particularly along the lines of the severity of illness. Moreover, the collection of declarative data could lead to recall and reporting bias. The known discrepancies in self-medication access, depending on local rules and on the financial ability of patients to pay for their drugs, could also have influenced our results. Despite these recognized limits, the overall quality of this survey renders our results strong enough to be considered as quantitative of the frequency of ADR-SM in patients admitted to the ED.

5 Conclusion

Self-medication could lead to the alteration of individual's health status in about 1 % of the population reporting self-medication behaviours, as shown here in the ED population. This first result of frequency and severity of ADRs related to self-medication should lead to further studies beyond the ED population. The misuse of self-medication in the general population and its potential impact on the occurrence of ADRs has to be further explored. Before considering self-medication as a safe and economic method of care, the reality of the risk related to self-medication should be taken into account by healthcare professionals and institutions. In addition, prevention strategies should include all aspects of self-medication (including self-use of prescribed drugs), which must be re-configured to make self-medication a valuable way of care involving all concerned, including patients and healthcare professionals.

Acknowledgments The authors thank the MEDQUAL office for its logistic and technical support, Bioscience Writers, LLC, for editing support and Dr Hervé Maisonneuve for his contribution to the manuscript. We are also grateful to the National Medicine Academy and the French Society for Clinical Pharmacy for their support, to the French Association of Therapeutics' Professors (APNET) for promoting this study, and to all members of the collaborative study group.

This article was published in a supplement sponsored by the Foundation for the National Institutes of Health (FNIH). The supplement was guest edited by Stephen J.W. Evans. It was peer reviewed by Olaf H. Klungel who received a small honorarium to cover out-of-pocket expenses. S.J.W.E has received travel funding from the FNIH to travel to the OMOP symposium and received a fee from FNIH for the review of a protocol for OMOP. O.H.K has received funding for the IMI-PROTECT project from the Innovative Medicines Initiative Joint Undertaking (http://www.imi.europa.eu) under Grant Agreement no 115004, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

Role of the funding sources National Medicine Academy: approving the study design; funding.

French Society for Clinical Pharmacy (SFPC): approving the protocol, supporting enrolment and training of pharmacy students; funding.

French Association of Pharmaceutical Manufacturers for a responsible self-medication (AFIPA): approving the protocol and conduct of the study; funding.

Sanofi Aventis: approving the protocol and conduct of the study; funding.

None of these funding sources have intervened in the collection, management, analysis and interpretation of the data; and preparation, review, or approval of the manuscript.

Contribution of authors Conception and design of the study: Nathalie Asseray, Françoise Ballereau, Jacques Bouget, Béatrice Trombert-Paviot, Lucien Roulet, Gerald Kierzek, Aurore Armand-Perroux, Gilles Potel, Jeannot Schmidt, Françoise Carpentier, Patrice Queneau.

Collection and validation of data: Nathalie Asseray, Françoise Ballereau, Jacques Bouget, Nadine Foucher, Bertrand Renaud, Lucien

Roulet, Gerald Kierzek, Aurore Armand-Perroux, Jeannot Schmidt, Françoise Carpentier.

Analysis of data: Nathalie Asseray, Jacques Bouget, Nadine Foucher, Béatrice Trombert-Pavior.

Interpretation of results: Nathalie Asseray, Françoise Ballereau, Jacques Bouget, Béatrice Trombert-Paviot, Nadine Foucher, Bertrand Renaud, Lucien Roulet, Gerald Kierzek, Aurore Armand-Perroux, Gilles Potel, Jeannot Schmidt, Françoise Carpentier, Patrice Queneau.

Drafting the paper: Nathalie Asseray.

Critical revising and approval: Françoise Ballereau, Jacques Bouget, Béatrice Trombert-Paviot, Bertrand Renaud, Gerald Kierzek, Aurore Armand-Perroux, Jeannot Schmidt, Françoise Carpentier, Patrice Queneau.

Funding research: Gilles Potel, Patrice Queneau.

Conflicts of interest statement All authors have declared no potential conflicts of interest regarding this study.

Appendix: Collaborators (collaborative study group)

Supported by the French Society of Therapeutics' Professors (APNET – promoting the study), the following collaborators have contributed to the work: Stéphanie Allorent (PharmD, MEDQUAL, Nantes; stéphanie.allorent@chu-nantes.fr); Anne Chiffoleau (MD, Pharmacology, Nantes; anne.chiffoleau@chu-nantes.fr); Philippe Cestac (PharmD, PhD, Pharmacy, Toulouse; cestac.p@chu-toulouse.fr); Dominique Pateron (MD, PhD, Emergency, Paris Saint Antoine; dominique.pateron@sat.aphp.fr); Pierre Emmanuel Gancel (MD, Emergency, Caen; gancel-pe@chu-caen.fr); Tanguy Roman (Data manager, Nantes; tanguy.roman@chu-nantes.fr); Carl Ogereau (MD, Emergency, Paris Hotel Dieu; carl.ogereau@htd.aphp.fr); Rui Batista (MD, Emergency, Paris Hotel Dieu; rui.batista@htd.aphp.fr); Aline Santin (MD, Emergency, Créteil Henri Mondor; aline.santin@hmn.aphp.fr); Céline Lejeune (MD, Emergency, Paris Saint Antoine; celine.lejeune@sat.aphp.fr); Stéphanie Gestin (MD, Emergency, Paris Cochin ; stephanie.gestin@cch.aphp.fr); Dominique Lauque (MD, PhD, Emergency, Toulouse; lauque.d@chu-toulouse.fr); Emilie Degris (PharmD, Pharmacy, Toulouse; degris.e@chu-toulouse.fr); Marie-Dominique Touze (MD, Emergency, Nantes; mdtouze@chu-nantes.fr); Alain Durocher (MD, PhD, Intensive care, Lille, Pdt APNET ; alain.durocher@chru-lille.fr). Written permission has been obtained from all persons named here.

Main investigator: Pr Patrice Queneau

Mailing address: CHU, SLAT, 8 Rue Bossuet, 42055 Saint-Etienne Cedex 2

Tel: 04 77 12 77 73, Fax: 04 77 12 03 93

E-mail address: patrice.queneau@chu-st-etienne.fr

References

1. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998;279(15):1200–5.
2. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ. 2004;329(7456):15–9.
3. Mercier E, Giraudeau B, Ginie's G, et al. Iatrogenic events contributing to ICU admission: a prospective study. Intensive Care Med. 2010;36(6):1033–7.
4. Budnitz DS, Lovegrove MC, Shehab N, et al. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med. 2011;365:2002–12.
5. Queneau P, Bannwarth B, Carpentier F, Guliana JM, Bouget J, Trombert B, Leverve X, Lapostolle F, Borron SW. Adnet F; Association Pédagogique Nationale pour l'Enseignement de la Thérapeutique (APNET). Emergency department visits caused by adverse drug events: results of a French survey. Drug Saf. 2007;30(1):81–8.
6. Budnitz D, Shehab N, Kegler S, Richards C. Medication use leading to emergency department visits for adverse drug events in older adults. Ann Intern Med. 2007;147:755–65.
7. Medicines: Rational use of medicines. Geneva: World Health Organization, 2010. http://www.who.int/mediacentre/factsheets/fs338/en/. Accessed 28 March 2012.
8. Guidelines for the Regulatory Assessment of medicinal Products for use in Self-Medication. Geneva: World Health Organization, 2000. http://apps.who.int/medicinedocs/pdf/s2218e/s2218e.pdf. Accessed 28 March 2012, [cited in "The role of pharmacist in self-care and self-medication". http://apps.who.int/medicinedocs/pdf/whozip32e/whozip32e.pdf. Accessed 28 March 2012.
9. Fourestié V, Roussignol E, Elkharrat D, et al. [Clinical classification of emergency patients: definition and reproducibility.] Classification clinique des malades des urgences. Définition et reproductibilité. Réan Urg. 1994;3:573–8.
10. Roulet L, Asseray N, Foucher N, Potel G, Lapeyre-Mestre M, Ballereau F. A questionnaire to document self-medication history in adult patients visiting emergency departments. Pharmacoepidemiol Drug Saf. 2013;22(2):151–9. doi:10.1002/pds.3364.
11. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239–45.
12. Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol. 2003;13(3):176–81.
13. Thesaurus Médecine d'Urgence (Emergency Medicine Diagnosis Classification). Société Française de Médecine D'urgence (French Society of Emergency Medicine). http://www.sfmu.org/documents/ressources/referentiels/emploi_thes.pdf. Accessed 15 May 2012.
14. Anatomical Therapeutic Chemical (ATC) classification system. WHO Collaborating Center for Drug Statistics Methodology. http://www.whocc.no/atc/structure_and_principles. Accessed 11 May 2012.
15. Stosic R, Dunagan F, Palmer H, et al. Responsible self-medication: perceived risks and benefits of over-the-counter analgesic use. Int J Pharm Pract. 2011;19(4):236–45 Epub 2011 Mar 21.

16. Cullen G, Kelly E, Murray F. Patients' knowledge of adverse reactions to current medications. Br J Clin Pharmacol. 2006;62:232–6.
17. Queneau P, Chabot JM, Rajaona H, Boissier C, Grandmottet P. [Iatrogenic disease observed in a hospital setting. II: analysis of causes and suggestions for novel preventive measures.] Analyse des causes et propositions pour de nouvelles mesures préventives.. Bull Acad Natl Med 1992;176(5):651–67.
18. Steudler F. [Sociological approach of self-medication.] Aspects sociologiques de l'automedication. In: Queneau P, editor. [Self-medication, self-prescription, self-consumption.] Automedication Autoprescription Autoconsommation. John Libbey Eurotext, 2000;29–38.
19. Coulomb A, Baumelou A. [Situation of self-medication in France and outlook: market, behavior, players' positions.] Situation de l'auto-medication en France et perspectives d'évolution: marché, comportment et positions des acteurs. French Government report. http://www.ladocumentationfrancaise.fr/var/storage/rapports-publics/074000030/0000.pdf. Accessed 28 March 2012.
20. Indermitte J, Reber D, Beutler M, et al. Prevalence and patient awareness of selected potential drug interactions with self-medication. J Clin Pharm Ther. 2007;32(2):149–59.
21. Eickhoff C, Hämmerlein A, Griese N, et al. Nature and frequency of drug-related problems in self-medication (over-the-counter drugs) in daily community pharmacy practice in Germany. Pharmacoepidemiol Drug Saf. 2012;21(3):254–60.
22. [Information and Self-Medication.] Information et Auto-Medication. AFIPA (French Association of Pharmaceutical Manufacturers for a responsible self-medication) and SOFRES (French Society of samples surveys). http://www.afipa.org/fichiers/3949_etude1.pdf. Accessed 28 March 2012.
23. Robinson J, Sareen J, Cox BJ, et al. Role of self-medication in the development of comorbid anxiety and substance use disorders: a longitudinal investigation. Arch Gen Psychiatry. 2011;68(8):800–7.
24. Schepis TS, Hakes JK. Non-medical prescription use increases the risk for the onset and recurrence of psychopathology: results from the National Epidemiological Survey on Alcohol and Related Conditions. Addiction. 2011;106(12):2146–55.
25. Arria A, Dupont R. Non-medical prescription stimulant use among college students: why we need to do something and what we need to do. J Addict Dis. 2010;29(4):417–26.
26. Ruiz ME. Risks of self-medication practices. Curr Drug Saf. 2010;5(4):315–23.
27. Hughes C, McElnay J, Fleming G. Benefits and risk of self-medication. Drug Saf. 2001;24(14):1027–37.