BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12239

Usage patterns of 'over-the-counter' *vs.* prescription-strength nonsteroidal anti-inflammatory drugs in France

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Keywords
drug-related risks, over-the-counter nonsteroidal anti-inflammatory drugs, prescription nonsteroidal anti-inflammatory drugs, usage patterns

Received
21 March 2013

Accepted
28 August 2013

Accepted Article Published Online
16 September 2013

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Most nonsteroidal anti-inflammatory drug (NSAID)-related risks are pharmacological, dose and duration dependent.
- Although low-dose 'over-the-counter (OTC)' NSAIDs generate much speculation about their putative risks, little is known of their usage patterns, which could impact risks.
- The same is mostly true also of prescription NSAIDs.

WHAT THIS STUDY ADDS

- Only a small number (<20%) of prescription NSAIDs users buy enough drug to cover the use described in the clinical trials from which risks have been derived or modelled.
- For OTC NSAIDs, the numbers are even lower, and only a few per cent buy more than a few days' worth over a 2 year span.
- Risk models derived from clinical trials or from observational studies not including OTC-type usage may not be applicable to the real-life use of these drugs.

AIMS

Most risks of nonsteroidal anti-inflammatory drugs (NSAIDs) are pharmacological, dose and duration dependent. Usage patterns of prescription-only (POM) or 'over-the-counter (OTC)' NSAIDs may influence risks, but are not commonly described.

METHODS

The Echantillon Généraliste de Bénéficiaires database, the permanent 1/97 representative sample from the French national healthcare insurance systems, was queried over 2009–2010 to identify usage patterns, concomitant chronic diseases and cardiovascular medication in OTC and POM NSAID users.

RESULTS

Over 2 years, 229 477 of 526 108 patients had at least one NSAID dispensation; 44 484 patients (19%) were dispensed only OTC NSAIDs (93% ibuprofen) and 121 208 (53%) only POM NSAIDs. The OTC users were younger (39.9 *vs.* 47.4 years old) and more often female (57 *vs.* 53%); 69% of OTC users and 49% of POM users had only one dispensation. A mean of 14.6 defined daily doses (DDD) were dispensed over 2 years for OTC *vs.* 53 for POM; 93% OTC *vs.* 60% POM patients bought ≤ 30 DDD over 2 years, and 1.5 *vs.* 12% bought ≥ 90 DDD. Chronic comorbidities were found in 19% of OTC users *vs.* 28% of POM users; 24 *vs.* 37% had at least one dispensation of a cardiovascular drug over the 2 years.

CONCLUSIONS

Most of the use of NSAIDs appears to be short term, especially for OTC-type NSAIDs, such as ibuprofen. The validity of risk estimates for NSAIDs extrapolated from clinical trials or from observational studies not including OTC-type usage may need to be revised.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs), as inhibitors of cyclo-oxygenase (COX) are called, which also includes the so-called 'coxibs', are used over a very wide range of indications and patterns, from very short-term, intermittent use of low doses in common painful conditions, such as cold and influenza, headache or menstrual pain, to long-term continuous use of high doses in chronic inflammatory diseases, such as rheumatoid arthritis. Although the range of therapeutic and adverse effects of NSAIDs is very wide, in line with the ubiquitous distribution of prostaglandins, the adverse reactions of greatest concern for NSAIDs in recent years have been gastrointestinal and cardiovascular; for both of these, the dose and duration dependence of the risk has been demonstrated, in addition to other parameters such as drug half-life and selectivity for the COX isoforms [1–11]. The NSAIDs exist as prescription-only medicines (POMs) and as 'over-the-counter (OTC)' preparations, sometimes at the same dosage but with different names and pack sizes, promoted for different indications. Although NSAIDs are very common drugs, little is known of how they are really used. The real-life use of POM NSAIDs is probably more intermittent and shorter term, even for chronic diseases [12], than in the randomized clinical trials from which event rates or risks are often computed [13–15]. This would explain the lower than expected real-life event rates [16, 17]. Over-the-counter NSAIDs are probably used in younger people, at lower doses, for shorter times and for different indications than POM NSAIDs [18, 19].

Given that OTC NSAIDs are usually not recorded in most healthcare databases, there are very few usage studies of these drugs, their usage patterns, quantities bought and concomitant risk factors, all of which could impact their risk profile [19–25]. In France, OTC NSAIDs may be reimbursed and recorded in the healthcare system databases if prescribed. This may represent up to 70% of all ibuprofen sales [26]. Many patients with recurrent or expected pain, such as osteoarthritis, migraine or dysmenorrhoea, will ask their physician for a prescription for these painkillers, for present or future use. In the same way, those who consult for influenza or trauma will also receive prescribed low-dose NSAIDs. Using a representative sample of the French healthcare system database [27, 28], our objective was to describe the characteristics of patients prescribed OTC and POM NSAIDs.

Methods

Data were extracted from the Echantillon Généraliste de Bénéficiaires (EGB) database, a permanent representative 1/97 sample of SNIIR-AM, the full population database of the persons covered by the French National Health Insurance Systems for salaried workers (75% of the French population in 2010). It contains anonymized demographic and some medical characteristics and records of healthcare reimbursements, as well as dispensing data for all prescribed and reimbursed medicines, including POM and OTC NSAIDs [27, 28]. Nonprescribed self-medication OTC NSAIDs are not registered. In a previous study, we found that 84% of paracetamol sales and 70% of ibuprofen sales were reimbursed by the healthcare systems and could be identified in this database [26].

The study cohort included all patients in EGB aged ≥15 years with at least one dispensation of any oral NSAID between 1 January 2009 and 31 December 2010. OTC and POM NSAIDs were identified by their Anatomical Therapeutic Chemical class (ATC, http://www.whocc.no/atc_ddd_index/) and European Pharmaceutical Market Research Association (EphMRA) codes, both of which are included in the EGB database. The ATC code M01A includes all NSAIDs. In EphRMA, low-dose NSAIDs that are used for the treatment of painful conditions and mostly approved for OTC use are identified with code N02B (analgesics), which also includes paracetamol and other analgesics (also coded N02B in ATC). The POM NSAIDs with indications for chronic inflammatory diseases have the EphRMA code M01A (anti-inflammatory drugs). The combination of ATC code M01A and EphRMA code N02B therefore identifies low-dose 'OTC' NSAIDs used for analgesia, whereas those with both ATC and EphMRA codes M01A (anti-inflammatory drugs) are the POM NSAIDs. Drugs with ATC and EphMRA codes M01A that are not NSAIDS, such as diacerein, chondroitin sulfate or glucosamine, were excluded from the study. The NSAIDs users were divided into exclusive OTC users, exclusive POM users, and mixed OTC and POM users. Exclusive OTC users were dispensed only OTC NSAIDs during the study period, whereas exclusive POM users were dispensed only POM NSAIDs. Patients who were dispensed both POM and OTC NSAIDs were not studied beyond basic demographics.

Demographic characteristics included age at the first NSAID dispensation, sex, and registration for long-term illnesses (affections de longue durée, ALD). The ALD are diagnoses that result in full coverage of all medical expenses concerning the disease. The ALD were categorized into prevalent, when patients had been registered with an ALD before inclusion, or incident, when patients had a new ALD registered after inclusion. All-type ALD was registered, and any of the five following cardiovascular ALD: stroke; chronic lower-limb arterial disease with ischaemic events; severe heart failure, severe arrhythmias, severe heart valve disease or severe congenital heart defects; severe arterial hypertension; and coronary heart disease. Cardiovascular drugs dispensed after inclusion were identified from ATC first-level code C, stratified on second-level code.

Exposure to NSAIDs was described by the name and number of NSAIDs dispensed, number and frequency of dispensations, number of defined daily doses (DDD) per

dispensation, and total number of DDD dispensed over the 2 year study period. The DDD was obtained from the WHO Collaborating Centre for drug statistics methodology (http://www.whocc.no/atc_ddd_index/). If the DDD was not available, the recommended daily dose in the 2012 French national drug formulary (VIDAL® dictionary, Paris) was used. For individual drugs, DDD, strength and numbers of DDD dispensed per pack are indicated in Tables S1 and S2.

The statistical analyses were conducted with SAS® 9.2 (SAS Institute, Cary, NC, USA), and were limited to descriptive analyses. There was no prior hypothesis to test, and no formal statistical comparisons were made. Considering the number of subjects in the samples, any descriptive difference >0.1% would be statistically significant, and 95% confidence intervals would be <1% of the point estimates.

Results

In the EGB, 229 477 patients aged ≥15 years had at least one dispensation of any NSAID in 2009–2010 (43.6% of the total database population of 526 108). Of these, 44 484 (19.4%) patients used only OTC NSAIDs, 121 208 (52.8%) used only POM NSAIDs, and 63 785 patients (27.8%) were dispensed both OTC and POM NSAIDs. There were six OTC NSAIDs, namely ibuprofen, diclofenac, ketoprofen, naproxen, fenoprofen and mefenamic acid, and 20 POM NSAIDs (Tables S1 and S2). Four NSAIDs (ibuprofen, ketoprofen, diclofenac and naproxen) were available as both OTC and POM preparations. Other NSAIDs had either only OTC preparations (1924 patients, 4.3% of exclusive OTC NSAIDs users) or only POM preparations (78 423 patients, 64.7% of exclusive POM NSAIDs users).

Table 1 shows the demographic characteristics of exclusive OTC and POM NSAID users, for all drugs combined, including those with no POM or OTC counterpart, respectively. The OTC users were younger than POM users (39.9 *vs*. 47.4 years old) and more often female (56.7 *vs*. 53.0%). Those who used both OTC and POM NSAIDs were on average 41 years old and 62.7% female. The OTC users had fewer prevalent ALD than POM users (18.9 *vs*. 27.6%) and fewer cardiovascular ALD. Severe arterial hypertension was the most common of the cardiovascular ALD present at inclusion, reported in 1.4% OTC *vs*. 2.5% POM users. New ALD reported during follow-up were more common in POM users (4.3 *vs*. 2.5%). There were <1% of any individual incident cardiovascular ALD over the 2 years of observation. During follow-up, 23.7% of OTC users had at least one dispensation of a cardiovascular drug, *vs*. 36.7% of POM users; these were mostly β-blockers, agents acting on the renin–angiotensin system and lipid-lowering agents.

Over 2 years, OTC users bought 14.6 DDD on average, POM users 53.0 DDD (Table 2) and the users of both OTC and POM NSAIDs 68 DDD (not shown). Two-thirds of OTC users had only one NSAID dispensation over 2 years, compared with half of POM users. Among patients having at least two dispensations, the average interval between dispensations was about 5 months.

Half the OTC users bought fewer than seven DDD (e.g. a total of 21 400 mg or 42 200 mg ibuprofen tablets) over 2 years, and >90% of OTC users bought fewer than 30 DDD. Only 1.5% bought 90 days or more (Table 2). Among POM users, 60% bought fewer than 30 DDD, 34% bought

Table 1

Demographic characteristics of exclusive OTC dosage or prescription-strength (POM) NSAID users

Characteristic	OTC (*n* = 44 484)	POM (*n* = 121 208)
Age at first dispensation		
Mean (years)	39.9	47.4
Median (years)	37.0	47.0
15–30	32.9%	18.7%
30–45	31.8%	26.6%
45–60	20.3%	28.4%
60–75	10.7%	18.1%
≥75	4.3%	8.1%
Sex		
Female	56.7%	53.0%
Users with at least one ALD [*n* (%)]		
Any prevalent ALD	8 407 (18.9)	33 393 (27.6)
Stroke	162 (0.4)	583 (0.5)
Lower-limb arterial disease with ischaemia	189 (0.4)	957 (0.8)
Severe heart failure, severe arrhythmias, severe heart valve diseases, severe congenital heart defects	302 (0.7)	1 099 (0.9)
Severe arterial hypertension	636 (1.4)	3 066 (2.5)
Coronary artery diseases	454 (1.0)	2 069 (1.7)
Any incident ALD	1 121 (2.5)	5 256 (4.3)
Stroke	38 (0.1)	153 (0.1)
Lower-limb arterial disease with ischaemia	28 (0.1)	201 (0.2)
Severe heart failure, severe arrhythmias, severe heart valve diseases, severe congenital heart defects	67 (0.2)	327 (0.3)
Severe arterial hypertension	113 (0.3)	588 (0.5)
Coronary artery diseases	76 (0.2)	332 (0.3)
Users with at least one dispensation of cardiovascular drugs during follow-up (ATC code)	23.7%	36.7%
C01-Cardiac therapies	4.9%	8.0%
C02-Antihypertensive agents	1.2%	2.0%
C03-Diuretics	4.3%	7.3%
C04-Peripheral vasodilators	1.3%	2.3%
C05-Vasoprotectors	4.4%	5.9%
C07-β-Blockers	7.2%	11.3%
C08-Calcium channel inhibitors	4.2%	7.4%
C09-Agents acting on the renin–angiotensin system	10.1%	17.4%
C10-Serum lipid-reducing agents	10.4%	18.3%

Abbreviations are as follows: ALD, chronic disease resulting in 100% coverage of medical expenses; NSAID, nonsteroidal anti-inflammatory drug; OTC, over-the-counter preparations; and POM, prescription-only preparations. Any difference of >0.1% can be considered significant ($P < 0.05$).

Table 2

Dispensing pattern for all exclusive OTC and POM NSAIDs

	OTC (*n* = 44 484)	POM (*n* = 121 208)
Number of different NSAIDs used within the study period		
Mean	1.0	1.5
1	97.6%	65.6%
2–3	2.4%	31.4%
≥4	0.0%	2.9%
Total number of dispensations		
Mean	1.7	2.6
1	68.7%	49.4%
2	18.5%	21.6%
3	6.2%	10.6%
≥4	6.6%	18.4%
Users with at least two dispensations of NSAIDs [*n* (%)]	13 919 (31.3)	61 282 (50.6)
Time interval between two dispensations (months)		
Mean	5.8	5.0
<1	11.4%	11.9%
1–2	13.1%	16.1%
2–3	11.4%	13.9%
3–6	26.9%	28.5%
6–12	25.5%	21.4%
≥12	11.6%	8.2%
Total number of DDD dispensed		
Mean	14.6	53.0
Median	6.7	22.5
Number of DDD per dispensation		
Mean	7.7	17.3
Numbers of DDD dispensed over 2 years (%)		
1–7	51.2	6.3
7–14	27	12.4
14–21	10.3	27.5
21–28	3.5	8
1–30	93.3	60.2
30–60	4.3	20.9
60–90	1	7.3
90–120	0.4	3.6
120–150	0.3	2
150–180	0.2	1.3
180–210	0.1	0.8
210–24	0.1	0.6
240–270	0.1	0.5
270–300	0.1	0.4
300–330	0.1	0.3
330–360	0	0.3
360–390	0	0.2
>390 DDD	0.1	1.7

Abbreviations are as follows: DDD, defined daily dose; NSAID, nonsteroidal anti-inflammatory drug; OTC, over-the-counter preparations; and POM, prescription-only preparations. Any difference of >0.1% can be considered significant ($P < 0.05$).

30–180 DDD, and ~2% of users were dispensed more than 180 DDD over 2 years.

Among the drugs with both OTC and POM formulations (Table 3), ibuprofen users had the same OTC-type pattern for both OTC and POM NSAIDs, with >90% of users buying fewer than 30 DDD, and little or no long-term use. Ketoprofen showed distinct patterns for OTC and POM prescription, with frequent long-term use for the POM but not for the OTC forms. Diclofenac followed the OTC–POM divide, in that 87% of OTC diclofenac users bought fewer than 14 DDD over 2 years and only 3% of users bought more than 90 DDD, whereas POM users more often bought 14–35 DDD, and 10% bought more than 90 DDD. Naproxen users usually bought small amounts (mostly 14–21 DDD), but in contrast with other OTC NSAIDs, there seemed to be a more sizable long-term use for the OTC preparations

While the other drugs have only one strength available for OTC usage, ibuprofen has two main preparations, i.e. 200 and 400 mg tablets. Other strengths, such as 300 mg slow-release tablets, have marginal usage. Considering all exclusive users of ibuprofen, about 69% used exclusively 400 mg preparations (OTC or POM), and 24% used exclusively 200 mg preparations. The latter were dispensed a mean of 9.0 (SD 20.3) DDD over 2 years (median 5, interquartile range 5–8.3), and exclusive users of 400 mg preparations bought a mean of 14.7 (SD 27.2) DDD over 2 years (median 10, interquartile range 6.7–13.3).

The 1 year use of individual drugs, including those with only POM preparations, which were not the main focus of the present study, is shown in Table S3, from the SALT study.

Discussion

About 40% of a representative sample of persons registered in the French national healthcare insurance system had at least one reimbursed dispensation of an OTC or prescription NSAID over 2 years, i.e. ~20% per year, as in Denmark [29]. About half of these were exclusive users of POM NSAIDs, and 20% exclusive users of OTC NSAIDs. Whether POM or OTC, each patient received only a very small number of dispensations, and only a few days' worth of the drugs; for the OTC NSAIDs, the average number of DDD dispensed was 14 DDD over 2 years, and 50% of users had fewer than 7 DDD, enough for two treatment episodes (3.3 DDD per episode) over 2 years [19, 25]. Users of prescription NSAIDs bought an average of 53 DDD over 2 years, and half bought 23 or fewer DDD. Almost half had only one dispensation, and only 18% had four or more dispensations. These numbers are similar to a nationwide study of prescription NSAIDs in Denmark [29].

Similar results had been found in previous studies in France, whether from regional reimbursement databases [30] or from field or combination studies [12, 18, 31, 32]. In a randomized clinical trial of paracetamol, aspirin and ibuprofen for common pain, on average patients used 20 tablets (3.3 DDD) over 5 days of any of the three analgesics, even though they were provided with 7 DDD [19]. Similar

Table 3

Data for individual NSAIDs with OTC-dosage and prescription-strength (POM) formulations: data for exclusive users of OTC or POM formulations

	Ibuprofen		Ketoprofen		Diclofenac		Naproxen	
	OTC	POM	OTC	POM	OTC	POM	OTC	POM
n (% of all OTC or POM)	41 178 (93.0%)	3096 (7.0%)	805 (1.8%)	19 581 (16.2%)	244 (0.5%)	15 056 (12.4%)	333 (0.7%)	5052 (4.2%)
Age at first dispensation (years)	39.8	40.6	44.7	45.2	49.8	52.6	45.6	46.6
Gender female (%)	55.8	52.3	53.3%	44.5	62.7 %	50.6 %	62.8 %	49.6%
Prevalent ALD	18.8%	19.0 %	25.5%	27.2%	23.4%	30.4%	19.5%	25.3%
Incident ALD	2.5%	1.9%	2.4%	3.3%	2.0%	4.0%	3.3%	3.2%
Cardiovascular drugs	23.5%	23.3%	32.3%	30.0%	37.7%	48.2%	33.0%	32.6%
Number of dispensations	1.66	1.26	1.69	1.79	1.97	2.16	1.92	1.77
One dispensation (%)	70	87	79.3	73.5	79.5	70.3	78.4	77.9
Two or three dispensations (%)	23.9	10.9	13.8	19.7	11.2	19.1	12.3	16.4
Four or more dispensations (5)	6.1	2.1	7.0	6.8	8.6	10.7	9.3	6.7
Total number of DDD dispensed								
Mean	14.3	14.9	9.24	43.72	11.9	47.5	31.8	46.3
Median	6.67	10.0	3.33	20	3.75	22.5	8.8	17.6
Distribution of number of DDD dispensed over 2 years (%)								
1–7	52.1	0	81.9	0	67.6	0	0	0.5
7–14	26.9	79.9	8.3	9.8	19.7	2.7	66.1	0.2
14–21	10	13.4	3	58.6	4.1	36.1	17.4	63.8
21–28	3.3	0	1.2	1.3	2	28	3.9	3.4
1–30	93.6	96.4	94.9	69.8	93.9	74.3	87.4	69.1
30–60	4.1	2.2	2.7	20.9	2.5	12.6	4.5	20.2
60–90	0.9	0.5	1.1	2.7	1.6	4.7	2.1	4
90–120	0.4	0.4	0.4	2.2	0	1.7	0.6	1
120–150	0.3	0.1	0.1	0.6	0.8	1.2	0.6	1.3
150–180	0.2	0.1	0.1	0.8	0	1	1.5	0.8
180–210	0.1	0.1	0.4	0.4	0.4	0.6	0	0.4
210–240	0.1	0	0.2	0.4	0.4	0.5	0.9	0.2
240–270	0.1	0.1	0	0.2	0	0.5	0.3	0.4
270–300	0.1	0	0	0.2	0.4	0.3	0	0.2
300–330	0.1	0	0	0.2	0	0.2	0.3	0.1
330–360	0	0.1	0	0.2	0	0.3	0.3	0.1
360–390	0	0	0	0.1	0	0.3	0	0.2
>390 DDD	0.1	0.1	0	1.4	0	1.8	1.5	2

Abbreviations are as follows: ALD, chronic disease resulting in 100% coverage of medical expenses; DDD, defined daily dose; NSAID, nonsteroidal anti-inflammatory drug; OTC, over-the-counter preparations; and POM, prescription-only preparations.

results were found in an observational pharmacy-based study of OTC diclofenac [25]. Among 14 000 initial users of celecoxib [33], 30% had four or more dispensations, and only 7% had six dispensations or more, similar to the CLASS study [14]. The distribution of 60–70% short-term users of POM NSAIDs (<30 days' worth over 2 years), with 30% of users using between 30 and 120 DDD, and a few per cent using 180 DDD or more, is also consistent with the usage and indications distribution found in field studies, with ~60–70% of patients using NSAIDs for common pain, 30% for osteoarthritis, and 3% for rheumatoid arthritis [18, 30–32].

Users of NSAIDs, whether OTC or POM, were rather young, slightly <40 years old for the OTC users and ~47 years old for POM users, as found in previous studies [12, 18, 19, 21, 22, 25, 29, 31, 32]. Both OTC and prescription users had low rates of concomitant chronic diseases, as expected from their age. The younger OTC users had fewer concomitant diseases than the older POM users. Among the drugs used to treat or prevent cardiovascular disease, the most commonly dispensed were β-blockers, agents acting on the renin–angiotensin system and lipid-lowering agents. New-onset chronic disease during the study period was rare, between 0.3 and 0.5% for hypertension and 0.2–0.3% for ischaemic heart disease. Considering the very short exposure to NSAIDs for the vast majority of these low-risk patients, the probability of a significant impact on cardiovascular risk or interaction with cardiovascular drugs appears remote [34–43].

Most OTC users were dispensed fewer than 30 DDD over 2 years, whereas 40% of prescription NSAIDs users received more than 30 DDD, 12% more than 90 DDD, and ~2% more than 360 DDD. In the VIGOR study, patients received 1000 mg of naproxen daily (2 DDD), with a median follow-up of 9 months (i.e. a total of 540 DDD) [15]. In the CLASS study, patients were given 2400 mg ibuprofen (2 DDD) or 150 mg diclofenac (1.5 DDD), daily for 6 months, i.e. 360 and 270 DDD, respectively [14]. Tramer *et al*., reviewing the gastrointestinal risks associated with NSAIDs [13], included only clinical trials of at least 3

months (90 DDD), which in our study represents at most 12% of POM and 1.5% of OTC users. Longer usage patterns are found only in a very small number of patients. This probably explains, at least in part, why gastrointestinal risks predicted from clinical trials [13, 44] are not found at the same level in real life [16, 17]. The cardiovascular risks of NSAIDs were initially demonstrated in clinical trials of selective COX-2 inhibitors [45–47]. They seem mostly to be of concern beyond 30 days of treatment [11], which in our study is only 19% of POM users and 2.4% of OTC users. Although NSAIDs are very commonly used, only a small minority of users may be at increased risk. This is also true when the same drug exists as both OTC and POM preparations. Although OTC usage is overwhelmingly ibuprofen, other drugs, such as ketoprofen or diclofenac, also show distinct usage patterns for OTC *vs*. POM preparations, with less use in somewhat younger patients.

These considerations apply mostly to the pharmacologically induced adverse reactions, such as gastrointestinal bleeding and cardiovascular risk, which in both cases when this could be measured have shown a dose dependence in observational studies [2, 3, 10, 48]. For nondose-dependent reactions, such as acute liver failure, we found no difference between individual NSAIDs [26, 49].

One limit of this study may be that the OTC drugs we studied had to have been prescribed to be included in the database. The use of nonprescribed OTC NSAIDs may differ from that of those prescribed OTC. However, prescribed ibuprofen represents >70% of the overall sales of ibuprofen in the country [26] (IMS, http://www.afipa.org/fichiers/20110310133130_Presentation_IMS.pdf). In a country with essentially free healthcare, including medical consultations, ibuprofen can be prescribed because of an acute pain [19] or to anticipate an expected need in patients with repeated painful episodes, such as osteoarthritis, intermittent musculoskeletal pain, migraine or period pain, so that nonprescribed OTC NSAIDs would be used only for an unanticipated or first pain episode, before a visit to a physician. Nonprescribed OTC usage in France might concern patients who would not routinely consult a physician, maybe a different population from the one studied here, but probably with even fewer concomitant medications and illnesses. Another strong incentive for using prescribed OTC medication if possible is the cost; for nonreimbursed OTC medication, the pharmacist can charge freely. The cost of prescribed OTC ibuprofen is 2.46€ (3.28$) for 30 200 mg tablets [0.5€ (0.66$) per DDD], mostly paid by the healthcare insurance system, compared with 2.90€ (3.87$) for 20 200 mg tablets for the nonprescription OTC [0.9€ (1.20$) per DDD], paid out of pocket. This may seem trivial, but could represent a significant incentive to have analgesic NSAIDs prescribed. In a study of OTC diclofenac from Norwegian pharmacies [25], the reasons for the use and the usage pattern of individual OTC episodes were mostly the same as for prescribed OTC in the PAIN study in France [19]. However, these short-term, single-episode studies do not provide longitudinal information on possible repeated usage. In Scotland, about 30% of responders in a population survey had already used OTC analgesics (much the same as our repeat OTC dispensations), but the usage patterns were not described [21, 22].

Chronic concomitant diseases, which mainly concern the more severe chronic forms of these diseases, were rare. Severe hypertension concerned only 1.7–2.3% of the patients, and all cardiovascular ALD together concerned 4.8% of OTC and 7.8% of POM NSAIDs users; 23.7% of OTC and 36.7% of POM users had at least one cardiovascular drug (ATC class C) prescribed at any time during the study period. Of course, actual concomitance is uncertain; for OTC drugs, the average dispensation covered 2.0% of the 2 year study period, and 7.3% for prescription NSAIDs. Most NSAIDs are not taken regularly, and an NSAID used on a given day might have been bought long before [50], so it is difficult to say when any of the NSAIDs dispensed might have been taken, and whether that was within the period during which other drugs were used.

Other limitations are common to most healthcare databases, i.e. the dearth of data concerning comorbidities, except long-term illnesses, the lack of information on drug indications and dose prescribed. This may be a major issue in countries where the amount dispensed depends on the prescription. In France, products are dispensed as boxes with a constant number of defined-strength tablets. The total quantity of drug dispensed is perfectly determined, and so the number of DDD. As a result of this, the general indications can be deduced; it is highly unlikely that the dispensation of only a few days' worth of treatment over 2 years would be for rheumatoid arthritis or osteoarthritis, but more probably for episodes of acute pain. However, because NSAIDs are symptom-relieving dugs, the time of use in relationship to the time of dispensation may be uncertain [50], whereas for chronically used drugs, such as antiepileptic, antihypertensive or lipid-lowering drugs, utilization will usually be consistent with dispensation [50, 51].

Conclusion

The usage patterns of OTC NSAIDs are consistent with the usual OTC or common pain indications [19, 25]. Users in this study bought much less NSAID, whether OTC or prescription, than participants are usually given in clinical trials. Very few patients bought the amount of drug dispensed in most clinical trials, from which many of the risks of NSAIDs are derived. Applying the results of clinical trials to real-life usage and risks of NSAIDs should take these usage patterns into account. Any extrapolation of risk from clinical trials to real use may be only at best extremely tentative. Clearly, further real-life studies are needed to specify better the real risks of prescription or low-dose OTC NSAIDs in practice.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; Mai Duong did the study as a master's thesis in Bordeaux, with a grant from the French Embassy in Hanoi; other authors had the following relationships with pharmaceutical companies and other entities that might have an interest in the results of this study. Abdelilah Abouelfath, Régis Lassalle, Cécile Droz and Patrick Blin are employed by ADERA, a nonprofit organization depending on Bordeaux University. Their salaries are covered by research contracts of Bordeaux University with public entities and private companies, some of which may market some of the NSAIDs cited in the study. Francesco Salvo is an employee of Bordeaux University, paid with funding from the European FP7 SOS project on NSAIDs, and other projects not related to NSAIDs. Antoine Pariente is an employee of Bordeaux University and Bordeaux University Hospitals, and participates in SOS and other European projects; he is not involved in industry-funded studies. Nicholas Moore is an employee of Bordeaux University and Bordeaux University Hospitals. He is Director of the INSERM Clinical Investigation Centre in Bordeaux, and has been or is the main investigator for many clinical trials and pharmacoepidemiological studies with public or private funding. The pharmaceutical companies funding research in the Centre include most or all manufacturers of NSAIDs, though the research may or may not concern NSAIDs. Current and recent studies can be found on http://www.pharmacoepi.eu. In addition, Nicholas Moore has given advice to Boots Healthcare, Aventis, Novartis, Reckitt Benciser, Helsinn Healthcare, Roche, Pfizer, Merck and others on the subject especially of low-dose and OTC NSAIDs, including ibuprofen, naproxen, diclofenac, ketoprofen and other NSAIDs, such as celecoxib, rofecoxib, aceclofenac, nimesulide, among others, related to efficacy or safety issues. The present study was generated internally to answer repeated interrogations on the usage patterns of these drugs at OTC or prescription dosages. It was not requested or suggested by any specific pharmaceutical company.

This study was not funded.

The authors would like to thank the French Embassy in Hanoi for financial support to Mai Duong.

Authorship/Contribution

MD constructed the study, assembled the data, analysed it and wrote the initial study draft paper.

AA and RS extracted the data from EGB, analysed the data, supervised and accompanied the whole study project.

AP, CS, CD and PB contributed to the study design, analysis and interpretation.

NM had the original idea, supervised the project and wrote the final version of the paper.

All authors saw and approved the final version of the paper.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1
Over-the-counter dosage preparations that can prescribed and reimbursed in France
Table S2
Prescription NSAIDs available in France
Table S3
Individual drug utilization in number of DDD dispensed in France over 1 year in the SALT study (26)