

Epidemiologic Assessment

Doctor Shopping Reveals Geographical Variations in Opioid Abuse

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Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: None.

Manuscript received: 06-13-2012
Revised manuscript received:
08-13-2012
Accepted for publication: 09-11-2012

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www.painphysicianjournal.com

Background: Prescription opioid abuse is not homogeneous due to varying patterns of use and different geographic preferences. Because doctor shopping is one of the main sources of diversion, it has previously been used to estimate drug abuse.

Objectives: The aim of this study was to describe and compare opioid abuse in 2008 using doctor shopping to estimate abuse in 3 French regions.

Setting: Data for this study came from the General Health Insurance (GHI) reimbursement database, which covers 77% of the French population. All individuals living in Provence-Alpes-Côte d'Azur-Corse (PACA), Rhône-Alpes (RA), or Midi-Pyrénées (MP) that received at least one reimbursement for oral opioids from the GHI in 2008 were included.

Methods: Oral opioids under study were opioids for mild to moderate pain (dextropropoxyphene, codeine, tramadol, dihydrocodeine), opioids for moderately severe to severe pain (oral morphine, oxycodone, buprenorphine painkiller, hydromorphone), and opioid maintenance treatments (buprenorphine maintenance, methadone). For a given opioid, the Doctor Shopping Quantity (DSQ) is the quantity obtained by overlapping prescriptions from several prescribers. It is used to estimate the magnitude of abuse. The Doctor Shopping Indicator (DSI) is the DSQ divided by the total dispensed quantity. It is used to estimate the abuse corrected for use.

Results: The total DSQ for opioids in PACA (213.3 DDD/1,000 inhabitants) was twofold superior to that in RA (115.1 DDD/1,000) and in MP (106.2 DDD/1,000). The DSQ of opioids for mild to moderate pain was 75.5DDD/1000 (DSI=1.1%), 19.7DDD/1,000 (DSI=5.0%) for opioids for moderately severe to severe pain, and 55.3DDD/1,000 (DSI=6.2%) for opioid maintenance treatments. Emergent signals of abuse have been observed at a regional level for oxycodone in MP and dihydrocodeine in RA and MP.

Limitations: The main limitation of this study is that the GHI reimbursement database provides information about dispensed and reimbursed prescription drugs, and not necessarily the actual quantity used.

Conclusion: These results confirm important variations in the 3 French regions despite them being geographically close. Besides, they highlight different rates of opioid abuse between opioids for mild to moderate pain, opioids for moderately severe to severe pain, and opioid maintenance treatments, as well as differences within these groups.

Key words: Prescription drug abuse, Opioid abuse, Prescription opioid analgesics, opioids for mild to moderate pain, Opioids for moderately severe to severe pain, Opioid maintenance treatments, Prescription drug database, Doctor shopping

Pain Physician 2013; 16:89-100

Over the past 10 years the therapeutic use of opioids has escalated as has their abuse and non-medical use (1). However the public health impact of non-medical use and abuse of prescription opioids is not homogeneous due to varying patterns of use and different geographic preferences (2-8). Evaluating opioid abuse at a regional level may facilitate the detection of an emergent medication abuse problem that is restricted to one area before it spreads to other areas. Such an approach may optimize the local intervention strategies due to a better knowledge of determinants involved in abuse and non-medical use such as population characteristics or product availability (3,9).

In order to identify product availability, some studies have focused on the key diversion routes of prescription opioids and shown that the 2 main sources were friends or family and prescription or doctor shopping (10-13). Doctor shopping is when a patient consults several prescribers over the same period of time and thus obtains overlapping prescriptions (14-16). This behavior has been linked to substance abuse-related deaths in Australia (17) and in Ontario (18). Since the establishment of prescription drug monitoring programs in the US, this behavior can be identified (19-22). It has thus become a focus for clinical practice and authorities (23,24). Some years ago, a method that quantifies doctor shopping using the General Health Insurance (GHI) reimbursement database was developed to give the doctor shopping indicator (14,25,26). This quantitative assessment was used to estimate the magnitude of buprenorphine diversion (25) and to assess the impact of a national prescription drug monitoring program for buprenorphine (14). Recently, 2 other studies assessed the relative abuse potential of benzodiazepines in real-life settings using the doctor shopping indicator (26,27).

Even if some studies concerning doctor shopping have been published (15,16,27,28), few involved geographic information which may give a better comprehension of doctor shopping behavior (15).

Product availability is an important determinant of opioid misuse (4,9). The consumption of opioids has increased in France (29) as in other European countries (30,31) raising concerns about their misuse. Therefore this work focused on opioids including opioid analgesics and opiate maintenance treatments.

In this context, we performed a study based on 3 regions in the south of France: Provence-Alpes-Côte d'Azur-Corse (PACA), Rhône-Alpes (RA), and Midi-Pyrénées (MP) which represented a total of 14 million people in 2008.

The main objective of this study was to describe and compare opioid use and abuse using doctor shopping to estimate the abuse over a one year period (2008) in 3 French regions.

METHODS

Settings

Data for this study came from the GHI reimbursement database. The GHI is a public insurance system, which covers 77% of the French population. The remaining part of the French population is insured by other public insurance systems (32). It should be noted that in France, medication is dispensed in a pharmacy and then reimbursed by the GHI, either to the patient or directly to the pharmacist.

Everyone covered by the GHI in 2008 in the PACA (4,054,669), RA (4,732,936), and MP (1,980,913) regions was included. In PACA, RA, and MP, there were respectively 47, 36, and 27 care centers dedicated to drug users. This study analyzed, for every insured inhabitant of these regions, all oral and sublingual forms of prescription opioids dispensed and sent for reimbursement between January 1, 2008 and December 31, 2008. Medications dispensed in hospitals were not included in the GHI reimbursement database. Included medications were oral opioids for mild to moderate pain (codeine combinations [N02AA59], dextropropoxyphene combinations [N02AC54], dihydrocodeine [N02AA08], tramadol as a single-ingredient drug [N02AX02] or combination [N02AX52]), oral opioids for moderately severe to severe pain (buprenorphine painkiller [N02AE01], hydromorphone [N02AA03], immediate and sustained release oral morphine and morphine syrup [N02AA01], immediate and sustained release oxycodone [N02AA05]), and oral opioid maintenance treatments (methadone syrup, methadone tablets [N07BC02] and buprenorphine used as maintenance treatment [N07BC01]). Fentanyl was not included because no oral form was available in 2008 in France. Five variables were extracted: the date of dispensing, the CIP code (drug box identification code, which is a French equivalent to the national drug code in the USA), the patient's anonymous number, the prescriber's anonymous number, and the quantity of reimbursed medication given as defined daily doses (DDD).

The DDD is the assumed average maintenance dose per day for a drug used according to its main indication in adults; DDD are defined by the World Health Organization (WHO) Collaborating Centre for Drug Statistics

Methodology, according to the ATC (Anatomical Therapeutic Chemical-code) classification index. One purpose of the ATC/DDD system is to allow comparison of drug consumption statistics at an international level. We used the 2010 version of this index (WHO, 2010) (33).

Calculation of Doctor Shopping Quantity (DSQ)

The principle of DSQ calculation is based on the number of overlaps of different prescribers' prescriptions for a given patient. This is illustrated in the appendix with an example of a fictitious patient with 2 prescribers.

A prescription period is defined for each prescriber/patient couple as the period between the first and the last observed dispensing. This prescription period is not necessarily continuous and may be interrupted. For instance the patient may consult another prescriber if the regular prescriber is on holiday. So when the interval between 2 consecutive dispensings is superior to a threshold, the prescription period is declared interrupted. This threshold is defined as the eightieth percentile of the observed intervals between 2 consecutive dispensings for all prescriber/patient couples. The threshold is calculated separately for each region and for each medication.

In the doctor shopping method, it is assumed that within the quantity obtained by multiple prescribers during overlapping prescription periods, a certain proportion is medically legitimate. For instance, in the case of overlapping prescription periods from 3 different prescribers, it is assumed that one-third of the total quantity is medically legitimate and the remaining two-thirds are obtained using doctor shopping.

Therefore, the DSQ is computed for each patient using the formula:

$$DSQ = \sum \frac{n_i - 1}{n_i} Q_i$$

where n_i is the number of simultaneous prescription periods at the date of dispensing i and Q_i the quantity dispensed.

When there is no overlap between prescription periods of several prescribers for a patient (one or several prescribers with non overlapping prescriptions), $n_i=1$ for all dispensings and therefore DSQ is null.

For a population, the total DSQ is the sum of doc-

tor shopping quantities of all patients. It reflects the magnitude of abuse. It is given in DDD/1,000 inhabitants covered by the GHI per year (DDD/1000) to allow geographical comparison.

The Doctor Shopping Indicator (DSI) is the DSQ divided by total dispensed quantity and reflects the abuse corrected for use. The DSI is considered clinically significant over 1% (27,34). Below this value, we consider that there is no signal of abuse.

Separate analyses were conducted on each medication and each region. Results were computed using SPSS V13.0®.

RESULTS

Opioid User Population

The number of individuals that received at least one dispensing of oral opioids reimbursed by the GHI in 2008 was 885,941 in PACA (21.8% of the insured population), 945,102 in RA (20.0% of the insured population), and 386,834 in MP (19.5% of the insured population). The male/female ratio was 0.43 in PACA, 0.45 in RA, and 0.44 in MP. The proportion of individuals under 30 years old was 19% in PACA, 18% in RA, and 19% in MP. The proportion of individuals over 60 year -old was 30% in PACA, 31% in RA, and 29% in MP. Thus, in the 3 regions studied, there was very little difference observed in the general profile of opioid users.

Product-Specific Analysis

Dispensed Quantity

For the 3 regions taken together, opioids for mild to moderate pain represented 83.8% ($n = 70, 388, 614$ DDD) of the total dispensed quantity of opioids, opioids for moderately severe to severe pain represented 5.0% ($n = 4, 120, 808$ DDD) and opioid maintenance treatments represented 11.2% ($n = 9, 536, 221$ DDD). The total dispensed quantities in 2008 in PACA, RA, and MP are presented in Table 1.

2.2. Doctor Shopping Quantity

The total DSQ for all oral opioids represented 150.5 DDD/1,000. Opioids for mild to moderate pain represented 50.2% (75.5 DDD/1,000) of the total DSQ for oral opioids, opioids for moderately severe to severe pain represented 13.1% (19.7 DDD/1,000) and opioid maintenance treatments represented 36.7% (55.3 DDD/1,000) (Table 2).

Table 1. Total dispensed quantity of oral opioids dispensed Provence-Alpes Côte-d'Azur Corsica, Rhône-Alpes and Midi-Pyrénées in 2008.

	PACA		RA		MP	
	Dispensed quantity (DDD)	Number of users	Dispensed quantity (DDD)	Number of users	Dispensed quantity (DDD)	Number of users
Weak opioid analgesics						
Codeine combinations	3 976 731	88 529	5 785 583	123 540	2 532 913	75 964
Dextropropoxyphene combinations	14 931 528	652 785	15 771 840	656 949	4 789 028	238 685
Dihydrocodeine	41 920	375	40 448	319	70 336	252
Tramadol	8 999 318	32 0021	10 137 602	340 129	3 811 368	145 749
Tramadol alone	5 382 128	107 700	6 196 532	147 872	2 329 906	47 304
Tramadol combinations	3 617 190	212 321	3 941 070	229 868	1 481 462	98 445
Strong opioid analgesics						
Buprenorphine painkiller	33 290	861	28 403	723	10 850	291
Hydromorphone	38 878	330	37 719	267	20 622	138
Oral morphine	1 447 789	18 216	1 452 723	22 871	474 215	9339
Morphine SR	1 157 120	10 860	1 111 412	13 720	356 132	5616
Morphine IR	279 723	12 224	325 151	15 656	111 369	6124
Morphine Syrup	10 946	644	16 160	915	6 714	396
Oxycodone	254 651	2856	211 943	2289	109 725	1492
Oxycodone SR	191 358	2219	163 460	1745	85 557	1095
Oxycodone IR	63 293	1910	48 483	1631	24 168	1032
Opioid maintenance treatments						
Buprenorphine maintenance	2 885 892	8137	2 660 504	10 148	1 152 769	4117
Methadone	1 169 124	2421	1 064 538	2306	603 393	1260
Methadone syrup	1 058 762	2358	995 821	2280	550 754	1248
Methadone tablet	110 363	491	68 718	293	52 639	200

Doctor Shopping Indicator

Opioids with the highest DSI were buprenorphine maintenance (8.0%), oral morphine (5.5%), dihydrocodeine (3.7%), buprenorphine painkiller (2.9%), and oxycodone (2.7%) (Table 2).

Region Specific Analysis

Dispensed Quantity

PACA was the region with the highest total dispensed quantity of opioids per 1,000 insured inhabitants (8331 DDD/1,000), followed by RA (8030 DDD/1,000) and MP (6853 DDD/1,000). As shown in Fig. 1, PACA was the region with the highest dispensed quantity for each medication except for codeine (for which RA had the highest dispensed quantity), methadone, dihydrocodeine, and hydromorphone (for which MP had the highest quantities).

Doctor Shopping Quantity

The total DSQ for opioids was 213.3 DDD/1,000 in PACA, 115.1 DDD/1,000 in RA, and 106.2 DDD/1,000 in MP. According to Fig. 2, the 5 medications with the highest DSQ were buprenorphine maintenance (first in all regions), dextropropoxyphene (second in PACA and RA, and fourth in MP), codeine (second in MP, third in RA, and fifth in PACA), tramadol (third in PACA and MP, and fourth in RA) and oral morphine (fourth in PACA and fifth in RA and MP). PACA was the region with the highest DSQ for all medications except for oxycodone and dihydrocodeine, for which MP had the highest DSQ.

Doctor Shopping Indicator

As shown in Fig. 3, PACA had the highest DSI for all opioids except oxycodone (for which MP had the high-

Geographical Variations of Opioid Abuse

Table 2. *Dispensed quantity, doctor shopping quantity and doctor shopping Indicator of oral opioids in Provence-Alpes Côte-d'Azur Corsica, Rhône-Alpes and Midi-Pyrénées in 2008.*

	Dispensed quantity (DDD/1000)	Doctor Shopping Quantity (DDD/1000)	Doctor Shopping Indicator (%)
Weak opioid analgesics	6640	75.5	1.1%
Dextropropoxyphene	1199	27.6	0.8%
Codeine	3296	24.1	2.0%
Tramadol	2131	23.3	1.1%
Dihydrocodeine	14	0.5	3.7%
Strong opioid analgesics	395	19.7	5.0%
Oral morphine	324	17.8	5.5%
Oxycodone	56	1.5	2.7%
Buprenorphine painkiller	7	0.2	2.9%
Hydromorphone	9	0.2	1.8%
Opioid maintenance treatments	891	55.3	6.2%
Buprenorphine maintenance	626	50.3	8.0%
Methadone	265	4.9	1.9%

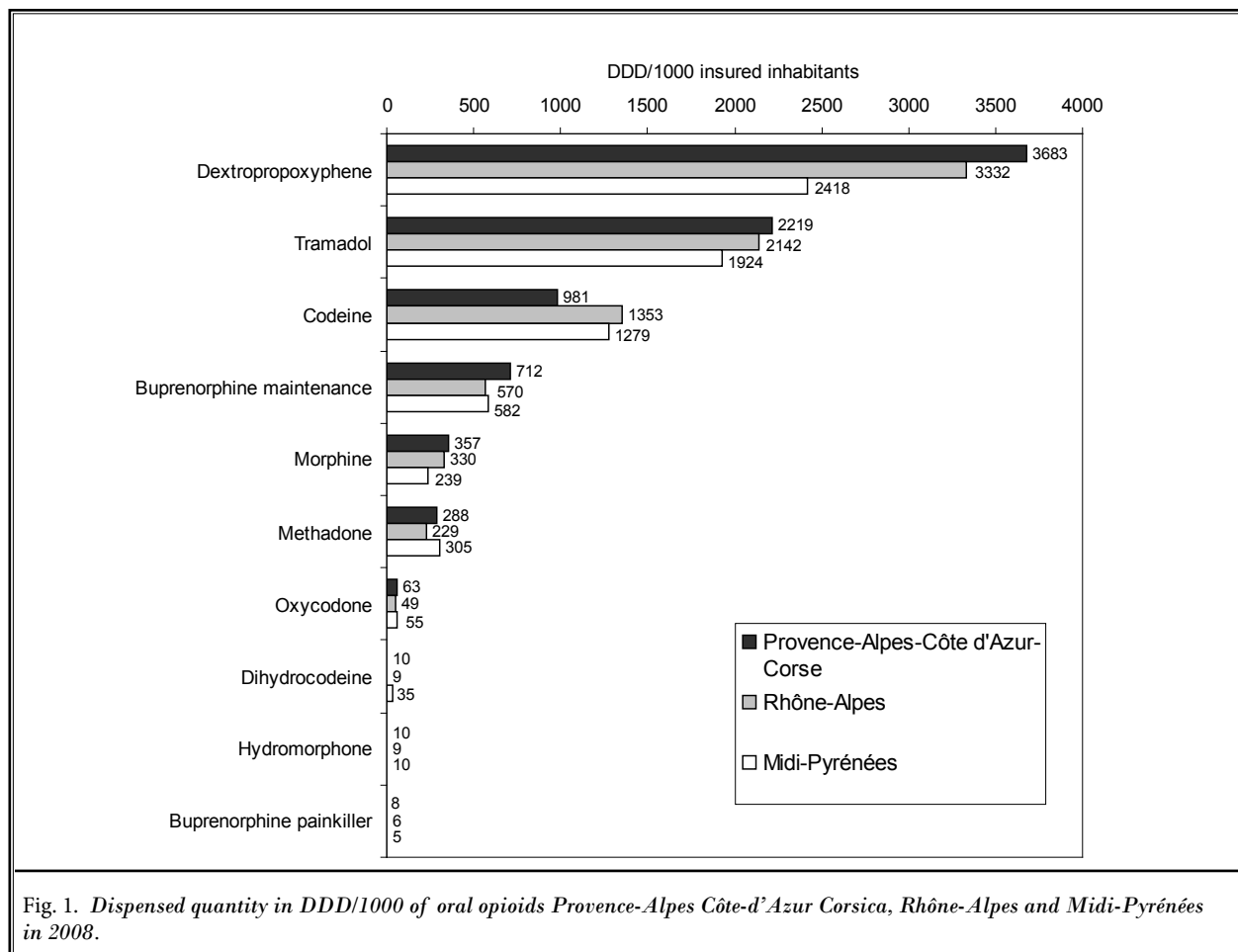


Fig. 1. *Dispensed quantity in DDD/1000 of oral opioids Provence-Alpes Côte-d'Azur Corsica, Rhône-Alpes and Midi-Pyrénées in 2008.*

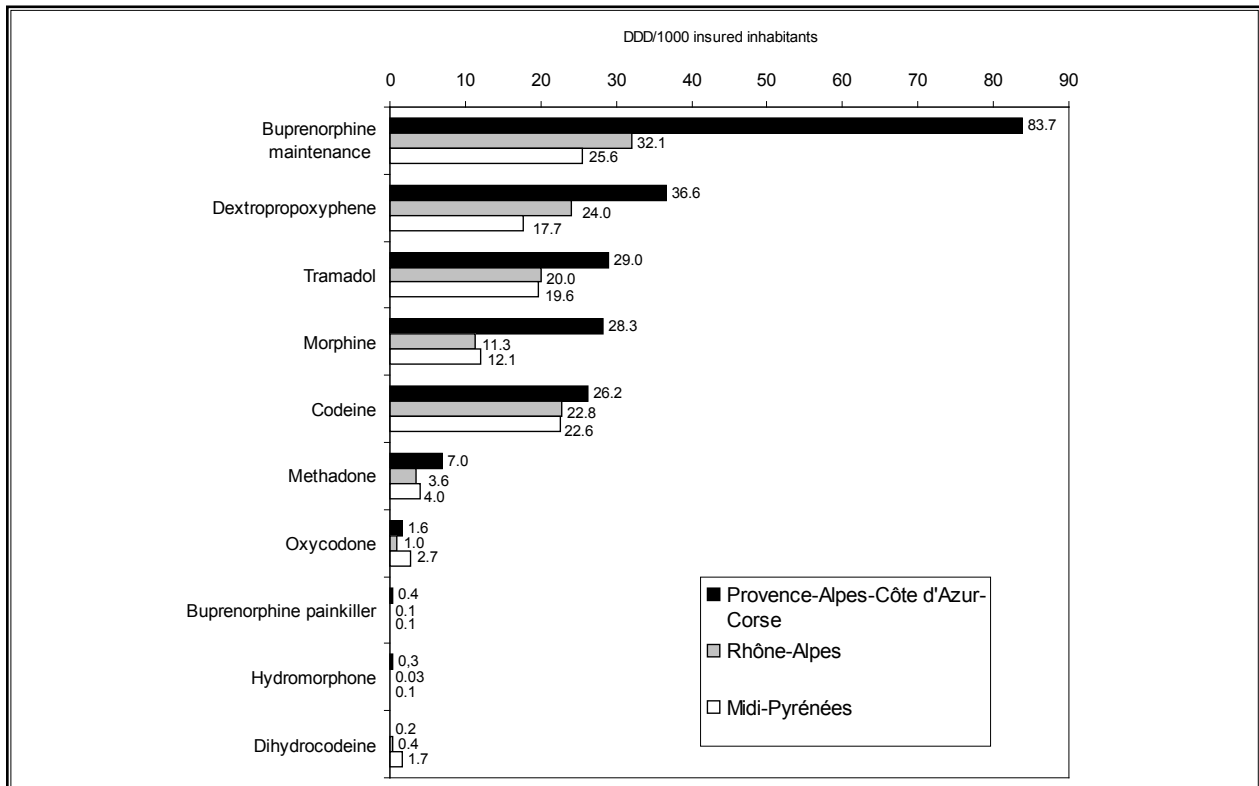


Fig. 2. Doctor shopping quantity of oral opioids in DDD/1000 Provence-Alpes Côte-d'Azur Corsica, Rhône-Alpes and Midi-Pyrénées in 2008.

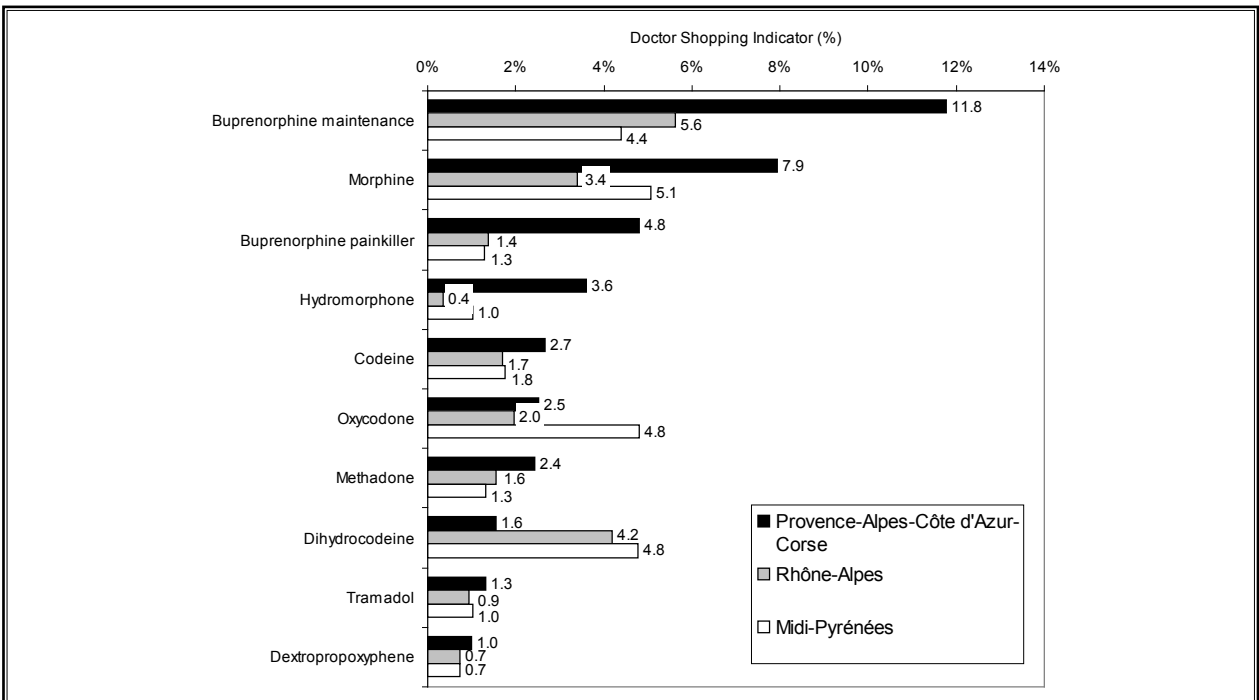


Fig. 3. Doctor shopping indicator of oral opioids Provence-Alpes Côte-d'Azur Corsica, Rhône-Alpes and Midi-Pyrénées in 2008.

est DSI) and dihydrocodeine (for which RA and MP had higher DSI).

In each region, the opioids with the highest DSI were buprenorphine maintenance in PACA (11.8%) and RA (5.6%) and oral morphine in MP (5.1%). Oral morphine had the second highest DSI in PACA (7.9%) and the third in RA (3.4%). Oxycodone was second in MP (4.8%), fourth in RA (2.0%) and sixth in PACA (2.5%). Dihydrocodeine was eighth in PACA (1.6%), second in RA (4.2%), and second in MP (4.8%).

Discussion

The purpose of this study was to assess the geographical variations of opioid use and abuse in 3 French regions using doctor shopping to estimate abuse. Opioid abuse is a major public health issue, as one fifth of the population received at least one opioid in our study. The key findings of this study were that the total opioid DSQ per inhabitant of PACA (213.3 DDD/1,000) was twofold superior to that in RA (115.1 DDD/1,000) and in MP (106.2 DDD/1,000). The DSQ of opioids for mild to moderate pain was 75.5 DDD/ 1000 (DSI = 1.1%), 19.7

DDD/1,000 (DSI = 5.0%) for opioids for moderately severe to severe pain, and 55.3 DDD/1000 (DSI = 6.2%) for opioid maintenance treatments. Regional specificities were observed, such as the emergence of oxycodone abuse in MP and dihydrocodeine abuse in RA and MP.

Geographically-specific Analysis

Despite a comparable global level of opioid use across the 3 regions (approximately 8000 DDD/1,000 in PACA and RA, 7,000 DDD/1,000 in MP), the total opioid DSQ per inhabitant of PACA (213.3 DDD/1,000) was twofold superior to that in RA (115.1 DDD/1000) and in MP (106.2 DDD/1000). Moreover, PACA was the region with the highest DSI for all opioids except oxycodone (higher in MP) and dihydrocodeine (higher in RA and MP). A parallel could be drawn with socio-demographic and economic data presented in Table 3 (35). Indeed, several indicators, such as the number of crimes and offences/1,000 inhabitants, the proportion of the population living in difficult urban areas, the poverty rate, the unemployment rate, and the proportion of individuals covered by the universal complementary health insur-

Table 3. Socio-demographic and economic characteristics of the general population living in 2008 in Provence-Alpes Côte-d'Azur Corsica, Rhône-Alpes and Midi-Pyrénées

	PACA	RA	MP
Demographic characteristics			
Population	5 185 879	6 117 200	2 838 228
Gender (% of women)	52	51	51
Age>20 (%)	23	26	23
Age<60 (%)	25	21	25
Demographic and economical characteristics			
Density (inhabitants/km ²)	157	141	63
Urbanization indicator (%)*	59	35	36
Proportion of the population living in difficult urban areas (%)	8	6	2
Poverty rate† (%)	16	12	14
Median income per year (€)	17 147	18 143	17 157
Unemployment rate (%)	11	9	9
People covered by the universal complementary health insurance‡ (%)	7	5	6
Number of crimes and offences per 10 000 inhabitants	81	58	49
Health characteristics			
Obesity (%)	12	12	14
Tobacco consumption over 1 cigarette/day (%)	29	27	31
Alcohol consumption over 10 times per month (%)	8	9	9
Drunkness over 3 times/year (%)	24	28	27
Cannabis consumption over 10 times per month (%)	10	7	7

Sources: CNAMTS, RSI, CCMAS, INSEE

*Proportion of the population living in the 3 principal cities

†Proportion of individuals under the poverty threshold (60% of the median standing of living)

‡The universal complementary health insurance is a free complementary health insurance for poor people

ance (a GHI program dedicated to people with little or no income) showed that the economic and social situation was more unfavorable in PACA than in RA and in MP in 2008 (Table 3). Many factors could influence drug abuse and traffic, one of them is the proximity of trade areas such as ports (like Marseille and Nice in PACA) and the borders with Italy for PACA and RA and Spain for MP.

Results found in this study cannot be extrapolated to the whole of France even though areas under study are 3 nearby regions representing 14 million inhabitants and 22% of the French population. However, a future study could apply the doctor shopping method to the entire French territory in order to confirm that this method is efficient in detecting emergent abuse signal in regions. In such a study, geographical variations observed in this study are likely to be amplified and specific cases such as those observed with dihydrocodeine and oxycodone would be multiplied.

Product-Specific Analysis

Opioids for Mild to Moderate Pain

The most used oral prescription opioids were dextropropoxyphene and tramadol. They were respectively second and fourth of all oral opioids regarding their DSQ. However, the DSI for dextropropoxyphene and tramadol was relatively low (respectively 0.8% and 1.1%). In fact, the threshold value of DSI is estimated at 1% with the doctor shopping method, therefore below this value, there is no signal of abuse (27,34). Dextropropoxyphene and tramadol DSI are close to this threshold. Further studies using other abuse indicators are needed in order to confirm or exclude a signal of abuse.

In our study, dihydrocodeine has the second highest DSI in RA and MP. In a study by Pauly et al (36), using several drug abuse-related indicators, dihydrocodeine was first regarding the number of forged prescriptions per million reimbursed DDD in 2008. However, it was seventh regarding the rate of illegal acquisition by OPPIDUM users and fifth regarding the abuse/dependence suspicion rate by OPPIDUM users (36). It was only eighth regarding the DSI. However, first DSI was calculated based on data from PACA only, second the doctor shopping methods used in the 2 studies were not exactly the same. In fact, in the study by Pauly et al (31), a fixed interruption period threshold was used (35 days), while we used a threshold which varied according to the observed period between 2 dispensings.

Opioids for Moderately Severe to Severe Pain

Our study showed that opioids for moderately severe to severe pain represented 5.0% of all opioids dispensed; contrary to the US, where 84.9% of the prescriptions of opioid analgesics are for hydrocodone and oxycodone-containing products (37).

Oral morphine was the opioid for moderately severe to severe pain with the highest dispensed quantity, DSQ, and DSI (Table 2). This is consistent with results of a survey among patients seen in care centers, where 56% of the oral morphine was illegally obtained (38). This is also consistent with the multi-indicator study where morphine was the only opioid to obtain the highest values for several drug abuse-related indicators (36).

The second opioid for moderately severe to severe pain according to its DSQ and the third according to its DSI was oxycodone. In MP it had the highest DSI of all oral opioids. It has been on the market in France since 2001. Its use increased fourfold from 2004 to 2008 (29). To our knowledge, no abuse signal has ever been detected regarding oxycodone in France. In 2008, oxycodone was fifth of all opioid analgesics regarding the number of forged prescriptions per million reimbursed DDD and its use was not declared by any patients seen in centers dedicated to drug users in the OPPIDUM survey (36).

If our results are validated by further analyses on oxycodone and dihydrocodeine abuse, they could suggest that the doctor shopping method allowed the detection of an emerging signal of abuse at a geographically specific level. Moreover, further research could assess whether the signals of abuse are transient or not using data from 2009 and 2010.

Opioid Maintenance Treatments

Concerning opioid maintenance treatments, buprenorphine maintenance had the highest magnitude of abuse (DSQ=50.3DDD/1,000) and abuse corrected for use (DSI=8.0%) of all opioids. In France, abuse of buprenorphine is acknowledged and has been extensively studied (39,40). Several reasons could explain the higher DSQ and DSI of buprenorphine compared to methadone. Firstly, methadone is registered as a narcotic whereas buprenorphine is not. Secondly, buprenorphine maintenance can be prescribed by every physician without any training. On the contrary, the initiation of methadone treatment is only authorized in specialized care centers for substance abuse or in hospitals. Third, the buprenorphine maintenance formula-

tion is a tablet (which can be crushed, snorted, or injected) whereas methadone was only available as syrup until April 2008, when a tablet form was introduced. As a consequence, methadone is less used in France than buprenorphine.

Strengths and Limitations

The GHI reimbursement database is a large database that includes 77% of the French population (32). We cannot exclude the risk of underestimation of doctor shopping if doctor shoppers do not ask for opioid reimbursement to avoid checks by the GHI fraud department. Moreover, it is probable that poor people could not afford to pay the entire cost of their medication. So, people living in a lower socio-economic area may request reimbursement more frequently than those living in a higher socio-economic area, leading to a risk of selection bias. However, the general health insurance and other public health insurances cover every French inhabitant, whatever the socio-economic status. Consequently, to pay for medication in cash and not ask for reimbursement would be highly suspect for a pharmacist, particularly in the case of opioid dispensing. Therefore, we assumed that selection bias has a negligible impact on our results.

Additional validity regarding dispensed quantities is provided by a study that assessed the trend in opioid use from 2004 to 2008 using data from the national GHI database. In this study, the total reimbursed opioid quantity was 8712 DDD/1,000 in 2008 (29), whereas in our study it was 7851 DDD/1000. The difference corresponds to the non-oral reimbursed opioids quantity.

The doctor shopping method has been slightly modified in this study. In the previous studies using the doctor shopping method, the main assumption was the threshold defining prescription interruption, fixed at 35 days (27). In a study where the doctor shopping method was applied to benzodiazepines, sensitive analyses using different threshold values showed no major variations (27). However, we consider that this threshold value should not be applied to all opioids. Indeed their indications are very different, which suggests that the modalities of use could vary between opioids. Moreover, the maximal dispensing duration for opioids is limited to 28 days except for methadone (14 days) and buprenorphine painkiller (30 days). Thus, in this study,

the threshold value was a function of the observed periods between 2 consecutive dispensings (and therefore less arbitrary).

A limitation of doctor shopping to estimate abuse is that part of the DSQ may have been received by individuals for legitimate reasons, such as loss of prescription or the patient or physician being on vacation for instance. In addition, doctor shopping is not the only source for prescription drug diversion, although most studies suggested that it is one of the principal means (12,13,41). Moreover, federal agencies in the US considered that diverted drugs enter the illegal market primarily through "doctor shoppers", inappropriate prescribing practices by physicians, and improper dispensing by pharmacists (1).

CONCLUSION

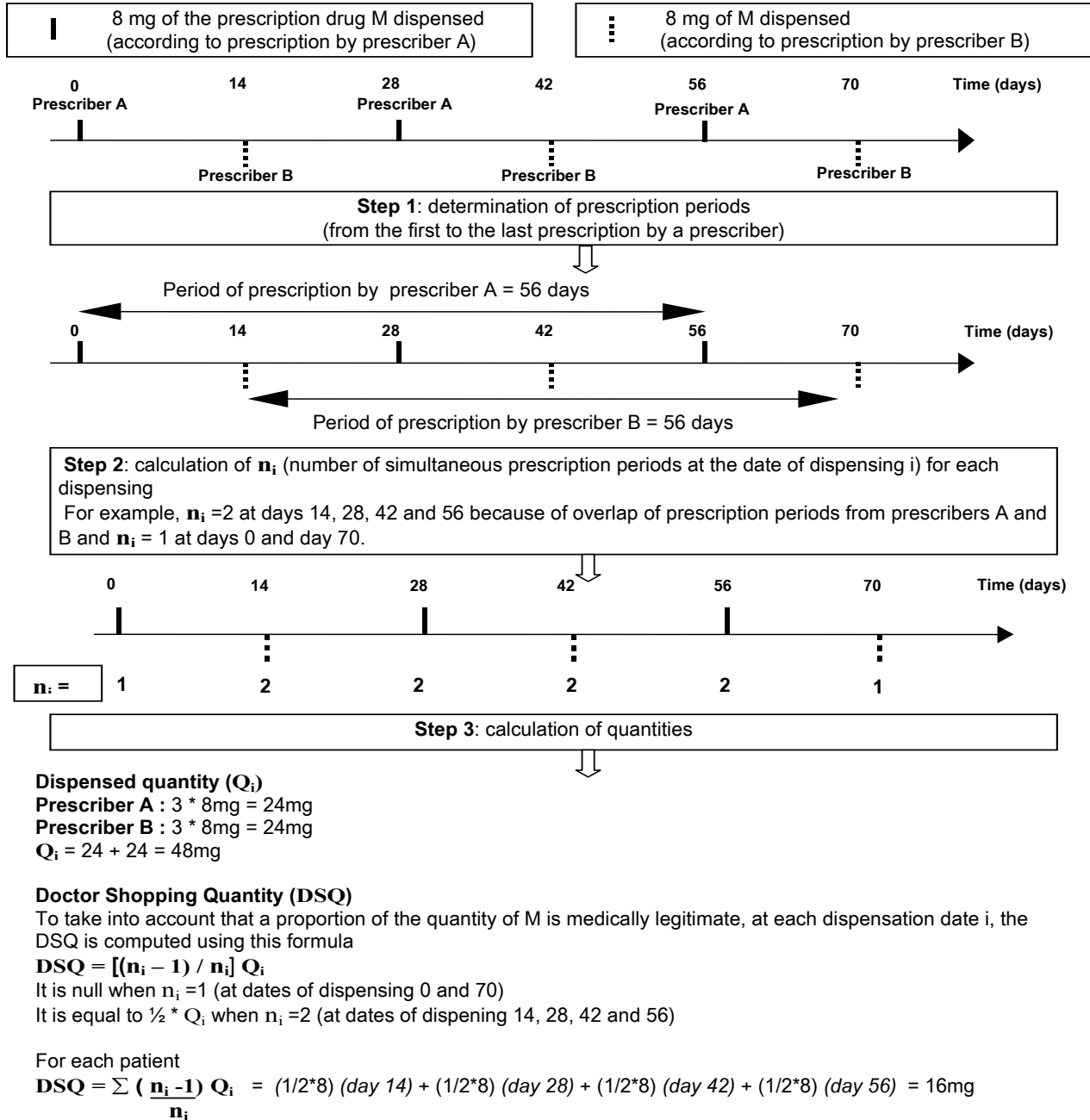
Magnitude of abuse and abuse corrected for use (estimated respectively by DSQ and DSI) provide different and complementary information. First, these results confirm important variations among the 3 French regions although they are geographically close. Next, they highlight different rates of opioid abuse between opioids for mild to moderate pain, opioids for moderately severe to severe pain, and opioid maintenance treatments, as well as differences within these groups. This methodology should be extended to a wider geographical area including the northern half of France, and even overseas territories, to assess these variations between all French regions. Should oxycodone and dihydrocodeine abuse be confirmed by these analyses, it would confirm that the doctor shopping method is efficient in detecting regional emergent abuse signals.

ACKNOWLEDGEMENTS

The authors would like to thank Dr Vincent Sciertino (Head of the PACA CNAM-TS medical office), Dr Gérard Dubial (Head of the Midi-Pyrénées CNAM-TS office), Dr Gilbert Weill (Head of the Rhône-Alpes CNAM-TS office), and their respective teams (Dr Véronique Allaria Lapierre and Dr François Natali from the PACA CNAM-TS office; Dr Robert Bourrel and Carole Suarez from the Midi-Pyrénées CNAM-TS office; Valérie Tainturier and Philippe Dufour from the Rhône-Alpes CNAM-TS office)

Appendix

Example of calculation of the Doctor Shopping Quantity



REFERENCES

1. Manchikanti L, Helm S II, Fellows B, Janata J, Pampati V, Grider JS, Boswell MV. Opioid epidemic in the United States. *Pain Physician* 2012; 15:ES9-ES38.
2. Maxwell JC. The prescription drug epidemic in the United States: A perfect storm. *Drug Alcohol Rev* 2011; 30:264-270.
3. Brownstein JS, Green TC, Cassidy TA, Butler SF. Geographic information systems and pharmacoepidemiology: Using spatial cluster detection to monitor local patterns of prescription opioid abuse. *Pharmacoepidemiol Drug Saf* 2010; 19:627-637.
4. Cicero TJ, Surratt H, Inciardi JA, Munoz A. Relationship between therapeutic use and abuse of opioid analgesics in rural, suburban, and urban locations in the United States. *Pharmacoepidemiol Drug Saf* 2007; 16:827-840.
5. Butler S, Budman S, Licari A, Cassidy T, Lioy K, Dickinson J, Brownstein J, Benneyan JC, Craig Green T, Katz N. National addictions vigilance intervention and prevention program (NAVIPPRO): a real-time, product-specific, public health surveillance system for monitoring prescription drug abuse. *Pharmacoepidemiol Drug Saf* 2008; 17:1142-1154.
6. Curtis LH, Stoddard J, Radeva JL, Hutchison S, Dans PE, Wright A, Woosley RL, Schulman KA. Geographic variation in the prescription of schedule II opioid analgesics among outpatients in the United States. *Health Serv Res* 2006; 41:837-855.
7. Paulozzi LJ, Ryan GW. Opioid analgesics and rates of fatal drug poisoning in the United States. *Am J Prev Med* 2006; 31:506-1051.
8. Smith MY, Irish W, Wang J, Haddox JD, Dart RC. Detecting signals of opioid analgesic abuse: Application of a spatial mixed effect poisson regression model using data from a network of poison control centers. *Pharmacoepidemiol Drug Saf* 2008; 17:1050-1059.
9. Gerada C, Ashworth M. ABC of mental health. Addiction and dependence--I: Illicit drugs. *BMJ* 1997; 315:297-300
10. Cicero TJ, Kurtz SP, Surratt HL, Ibanez GE, Ellis MS, Levi-Minzi MA, Inciardi JA. Multiple determinants of specific modes of prescription opioid diversion. *J Drug Issues* 2011; 41:283-304.
11. Fischer B, Bibby M, Bouchard M. The global diversion of pharmaceutical drugs non-medical use and diversion of psychotropic prescription drugs in North America: A review of sourcing routes and control measures. *Addiction* 2010; 105:2062-2070.
12. Inciardi JA, Surratt HL, Cicero TJ, Beard RA. Prescription opioid abuse and diversion in an urban community: The results of an ultrarapid assessment. *Pain Med* 2009; 10:537-548.
13. Inciardi JA, Surratt HL, Kurtz SP, Cicero TJ. Mechanisms of prescription drug diversion among drug-involved club- and street-based populations. *Pain Med* 2007; 8:171-183.
14. Pradel V, Frauger E, Thirion X, Ronfle E, Lapiere V, Masut A, Coudert C, Blin O, Micallef J. Impact of a prescription monitoring program on doctor-shopping for high dosage buprenorphine. *Pharmacoepidemiol Drug Saf* 2009; 18:36-43.
15. Cepeda MS, Fife D, Chow W, Mastrogianni G, Henderson SC. Opioid shopping behavior: How often, how soon, which drugs, and what payment method. *J Clin Pharmacol* 2012; In Press.
16. Cepeda MS, Fife D, Chow W, Mastrogianni G, Henderson SC. Assessing opioid shopping behaviour: A large cohort study from a medication dispensing database in the US. *Drug Saf* 2012; 35:325-334.
17. Martyres RF, Clode D, Burns JM. Seeking drugs or seeking help? Escalating "doctor shopping" by young heroin users before fatal overdose. *Med J Aust* 2004; 180:211-214.
18. Dhalla IA, Mamdani MM, Sivilotti ML, Kopp A, Qureshi O, Juurlink DN. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. *CMAJ* 2009; 181:891-896.
19. Simeone R, Holland L. An evaluation of prescription drug monitoring programs. 2006. Retrieved from http://pmpexcellence.org/pdfs/simeone_pdpmp_eval2006.pdf.
20. Reisman, RM, Shenoy PJ, Atherly AJ, Flowers CR. Prescription opioid usage and abuse relationships: An evaluation of state prescription drug monitoring program efficiency. *Substance Abuse: Research and Treatment* 2009; 3:41-51.
21. Paulozzi LJ, Kilbourne EM, Desai HA. Prescription drug monitoring programs and death rates from drug overdose. *Pain Medicine* 2011; 12:747-754.
22. Baehren DF, Marco CA, Droz DE, Sinha SS, Callan EM, Akpunonu BS. A statewide prescription monitoring program affects emergency department prescribing behaviors. *Ann Emerg Med* 2010; 56:19-23.
23. Perrone J, Nelson LS. Medication reconciliation for controlled substances - an "ideal" prescription-drug monitoring program. *N Engl J Med* 2012; 366:2341-2343.
24. Worley J. Prescription drug monitoring programs, a response to doctor shopping: Purpose, effectiveness, and directions for future research. *Issues Ment Health Nurs* 2012; 33:319-328.
25. Pradel V, Thirion X, Ronfle E, Masut A, Micallef J, Bégaud B. Assessment of doctor-shopping for high dosage buprenorphine maintenance treatment in a French region: Development of a new method for prescription database. *Pharmacoepidemiol Drug Saf* 2004; 13:473-481.
26. Pauly V, Frauger E, Pradel V, Nordmann S, Pourcel L, Natali F, Sciortino V, Lapeyre-Mestre M, Micallef J, Thirion X. Monitoring of benzodiazepine diversion using a multi-indicator approach. *Int Clin Psychopharmacol* 2011; 26:268-277.
27. Pradel V, Delga C, Rouby F, Micallef J, Lapeyre-Mestre M. Assessment of abuse potential of benzodiazepines from a prescription database using "doctor shopping" as an indicator. *CNS Drugs* 2010; 24:611-620.
28. Wilsey BL, Fishman SM, Gilson AM, Casamaluapa C, Baxi H, Lin TC, Li CS. An analysis of the number of multiple prescribers for opioids utilizing data from the California Prescription Monitoring Program. *Pharmacoepidemiol Drug Saf* 2011; 20:1262-1268.
29. Pauly V, Pradel V, Frauger E, Micallef J, Thirion X. Evolution of opioids reimbursement since 2004 from the National Database of the General Health Insurance System. *Therapie* 2011; 66:369-372.
30. De Conno F, Ripamonti C, Brunelli C. Opioid purchases and expenditure in nine western European countries: "Are we killing off morphine?". *Palliat Med* 2005; 19:179-184.
31. Fredheim OM, Skurtveit S, Breivik H, Borchgrevink PC. Increasing use of opioids from 2004 to 2007 - pharmacoepidemiological data from a complete national prescription database in Norway.

- Eur J Pain* 2010; 14:289-294.
32. Tuppin P, de Roquefeuil L, Weill A, Ricordeau P, Merlière Y. French national health insurance information system and the permanent beneficiaries sample. *Rev Epidemiol Sante Publique* 2010; 58:286-290.
 33. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment, 2010. Oslo, 2009.
 34. Rouby F, Pradel V, Frauger E, Pauly V, Natali F, Reggio P, Thirion X, Micallef J. Assessment of abuse of tianeptine from a reimbursement database using "doctor-shopping" as an indicator. *Fundam Clin Pharmacol* 2012; 26:286-294.
 35. Ministère des Affaires sociales et de la Santé. Regional indicators collection. 2010. www.drees.sante.gouv.fr/recueil-d-indicateurs-regionaux-2010,1739.html. (Last accessed on May, 21, 2012).
 36. Pauly V, Pradel V, Pourcel L, Nordmann S, Frauger E, Lapeyre-Mestre M, Micallef J, Thirion X. Estimated magnitude of diversion and abuse of opioids relative to benzodiazepines in France. *Drug Alcohol Depend* 2012; 126:13-20.
 37. Volkow ND, McLellan TA. Curtailing diversion and abuse of opioid analgesics without jeopardizing pain treatment. *JAMA* 2011; 305:1346-1347.
 38. Frauger E, Nordmann S, Orleans V, Pradel V, Pauly V, Thirion X, Micallef J. Which psychoactive prescription drugs are illegally obtained and through which ways of acquisition? About OPPIDUM survey. *Fundam Clin Pharmacol*. 2012; 26:549-556.
 39. Nordmann S, Frauger E, Pauly V, Orléans V, Pradel V, Mallaret M, Thirion X, Micallef J. Misuse of buprenorphine maintenance treatment since introduction of its generic forms: OPPIDUM survey. *Pharmacoepidemiol Drug Saf* 2012; 21:184-190.
 40. Carrieri MP, Amass L, Lucas GM, Vlahov D, Wodak A, Woody GE. Buprenorphine use : the international experience. *Clin Infect Dis* 2006; 43:S197-S215.
 41. McLellan AT, Turner B. Prescription opioids, overdose deaths, and physician responsibility. *JAMA* 2008; 300:2672-2673.