



## Full length article

# Doctor shopping of opioid analgesics relative to benzodiazepines: A pharmacoepidemiological study among 11.7 million inhabitants in the French countries

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## ABSTRACT

**Background:** The abuse of prescription opioids and its subsequent consequences is an important public concern particularly in the USA. The literature on opioid analgesic abuse is scarce.

**Objective:** We assess the extent and risk of opioid analgesics abuse relative to benzodiazepines (BZD) using the doctor shopping method, taken into account the pharmacological characteristics (dosage, route of administration, extended or immediate release).

**Methods:** We used SNIIRAM database covering 11.7 million inhabitants. All individuals with at least one reimbursement for non-injectable opioid analgesic or BZD in 2013 were included. Opioids for mild to moderate pain and for moderately severe to severe pain were studied. The Doctor Shopping Quantity (DSQ) is the quantity obtained by overlapping prescriptions from several prescribers. The Doctor Shopping Indicator (DSI) is the DSQ divided by the total dispensed quantity.

**Results:** The strong opioid analgesics have the highest DSI (2.79%) versus 2.06% for BZD hypnotics. Flunitrazepam ranked first according to its DSI (13.2%), followed by morphine (4%), and zolpidem (2.2%). The three-strong opioids having the highest DSI were morphine, oxycodone and fentanyl (respectively 4%, 1.7% and 1.5%). The highest DSI was observed for the highest dosages of morphine (DSI = 8.4% for 200 mg) and oxycodone (DSI = 2.8% for 80 mg). The highest DSI for fentanyl was described with nasal and transmucosal forms (4.1% and 3.3% respectively). The highest DSI for morphine was described for extended-release (4.1%).

**Conclusion:** There is a need to reinforce surveillance systems to track opioid misuse and to increase awareness of healthcare professionals.

## 1. Introduction

Prescription drug abuse has increased in recent years and is a topic of major concern throughout developed countries. The United Nation's International Narcotics Control Board forecasted in 2007 that worldwide misuse of medications would soon exceed illicit drug use (International Narcotics Control Board, 2008). This alarming prediction has been found to be an increasing reality in countries like the United States, where prescription drug abuse is second only to marijuana use across all age groups (Häuser et al., 2017; Hernandez and Nelson,

2010). Similar alarming figures have been found in some European countries where seizures reached record levels and treatment demand for abuse of opioids other than heroin increased (Casati et al., 2012; INCB, 2015). A survey by the European Monitoring Centre for Drugs and Drug Addiction has pointed out an increasing trend of pharmaceutical product abuse across European countries, highlighting the need to accurately monitor prescription drug diversion (Griffiths et al., 2012). To face this increasing problem, it is necessary to implement systems specifically dedicated to prescription drug abuse monitoring (Dart, 2009; Dart et al., 2015; Jouanjan et al., 2015; Schifano et al.,

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2016). Doctor shopping behavior is thought to be one of the principal means of diversion for prescriptions medications and has also been linked to death related to substance disorders in different countries (Baumblatt et al., 2014; Dhalla et al., 2009; McDonald and Carlson, 2013; McDonald and Carlson, 2014; Peirce et al., 2012; Hall et al., 2008; Martyres et al., 2004). With the development of prescription drug monitoring programs and reimbursement databases, this behavior is now identified more easily as reported in the literature (Cepeda et al., 2012; Chilcoat et al., 2016; Lu et al., 2015; Martyres et al., 2004; Simeone, 2017). Using data from the French Health Insurance database, we have validated a method that quantifies precisely the doctor shopping (calling Doctor Shopping Indicator, DSI) allowing identify the relative abuse liability of several psychoactive drugs in real-life setting (Frauger et al., 2011; Frauger et al., 2016; Micallef et al., 2015; Pradel et al., 2004, 2009; Rouby et al., 2012). We used the first-time doctor shopping method to assess the extent of doctor shopping for buprenorphine maintenance therapy between September 1999 and December 2000 (Pradel et al., 2004). Then we have tested its change over time (sensitivity) in a study assessing the impact of the prescription monitoring program for maintenance treatment on doctor shopping (Pradel et al., 2009). We have also identified different groups of benzodiazepines according to their abuse potential assessed by DSI (Pradel et al., 2010), corroborating data obtained from national survey among patients from drug dependence centers (Thirion et al., 2002) and from national survey related to falsified prescriptions by pharmacies (Boeuf et al., 2007). We have also shown the emergent place of clonazepam among benzodiazepines in 2005, with the second most important DSI after flunitrazepam. The clonazepam DSI was different according to the formulations (6.2% for tablets and 0.7% for oral solutions) in agreement with other surveys showing that only its solid formulation was abused (Frauger et al., 2011).

The abuse of prescription opioids and its subsequent consequent are an important public concern (especially in the USA) (Atluri et al., 2014; Simeone, 2017; Volkow and McLellan, 2016; Weisberg and Stannard, 2013), which increased alongside with the therapeutic use of opioids for pain management. In France, the consumption of opioids has increased as in other European countries (Berterame et al., 2016; Giraudon et al., 2013; Palmaro et al., 2016; Palmaro and Lapeyre-Mestre, 2017; Pauly et al., 2011) raising concerns about their misuse. To our knowledge, the literature on opioid analgesic abuse in Europe is scarce (Casati et al., 2012; Kotecha and Sites, 2013; van Amsterdam and van den Brink, 2015). For the first time, we propose to assess, according to the doctor shopping method, the extent and risk of abuse of opioid analgesics, among 11.7 million inhabitants from France. Opioid analgesics were compared to benzodiazepines (including BZD like) which in France and elsewhere cause concerns because of misuse, massive utilization and doctor shopping (Micallef et al., 2016; Pradel et al., 2010; Okumura et al., 2016; Wilsey et al., 2010; Moore et al. (2015); Olfson et al. (2015); Paterno et al., 2017). For medications with a signal of abuse on doctor shopping method, complementary analysis has been performed taking into account the pharmacological characteristics (dosage, route of administration, extended or immediate release).

## 2. Materials and methods

### 2.1. Data source and study settings

Data were extracted from the Global Health Insurance (GHI) reimbursement database, called SNIIRAM, which collects medical-administrative information of 77% of the French population (including unemployed). Other public insurance systems insure the remaining part of the French population (farmers, independent professions...) is insured by other public insurance systems. Regarding medications' details, only those reimbursed in pharmacies are available excluding those dispensed in hospitals (Moulis et al., 2015; Palmaro et al., 2016; Nordmann et al., 2013).

This study analyzed medications reimbursed by the GHI between January 1st and December 31st, 2013 to insured inhabitant from South-East of France (11.7 million insured subjects for 14.4 million of inhabitants).

### 2.2. Medications under study

Medications were selected from the SNIIRAM database and classified in the therapeutic class according to the ATC/DDD index. Only Opioids and BZD with intended to be used by oral, transmucosal or transdermal route were considered in this study (excluding injectable forms).

The 30 medications studied were:

- Opioids for mild to moderate pain ("weak" opioid analgesic): codeine in association, dihydrocodeine, tramadol, tramadol in association
- Opioids for moderately severe to severe pain (strong opioid analgesic): buprenorphine painkiller (0.2 mg tablet), fentanyl, hydromorphone, morphine, oxycodone
- BZD anxiolytics: alprazolam, bromazepam, clobazam, potassium clorazepate, clonazepam, diazepam, ethyl loflazepate, lorazepam, nordazepam, oxazepam, prazepam,
- BZD hypnotics and BZD-like hypnotics: estazolam, flunitrazepam, loprazolam, lormetazepam, nitrazepam, temazepam, zolpidem, zopiclone
- BZD antiepileptics: clonazepam, midazolam

Only molecules with at least 1000 dispenses during the study period were kept for analysis, leaving 29 medications (excluding temazepam with only 210 dispenses during the study)

### 2.3. Extracted variables

Five variables were extracted: date of dispensing, drug box identification code, patient's anonymous number, prescriber's anonymous number and quantity of medication reimbursed.

### 2.4. Calculation of doctor shopping parameters

The principle of calculation is based on the number of overlaps of prescriptions of a given medication (or class of medication) from different prescribers for a given patient (illustrated with an example from a fictitious patient with two prescribers in the Annex).

A prescription period is defined for each prescriber/patient couple as the period between their first and their last observed dispensing. This prescription period is not necessarily continuous and can be interrupted (for instance, the patient may consult another prescriber if the regular prescriber is on holiday). So, when the interval between two consecutive dispensing is superior to a given threshold for a prescriber/patient couple, the prescription period is interrupted. This threshold is defined as 35 days in this study (28 days, the maximum duration of prescription for most medications in France, plus a delay of 7 days).

In the doctor shopping method, a certain proportion of medication obtained by overlapping prescription from different prescribers is considered medically legitimate. For instance, if 3 prescription periods (from 3 different prescribers to the same patient) are overlapping, it is assumed that one-third of the total quantity is medically legitimate and the remained two-thirds are considered diverted by doctor shopping.

Therefore, the Doctor Shopping Quantity (DSQ) is computed for each dispensing period using the formula:

$$DSQi = \frac{n_i - 1}{n_i} Q_i$$

Where  $n_i$  is the number of prescription periods overlapping at the date of dispensing  $i$  and  $Q_i$  the quantity dispensed. It is straightforward that

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