

ORIGINAL ARTICLE

Prescription opioid analgesic use in France: Trends and impact on morbidity–mortality

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Conflicts of interest

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Abstract

Background: While data from USA and Canada demonstrate an opioid overdose epidemic, very little nation-wide European studies have been published on this topical subject.

Methods: Using a nationally representative sample of the French Claims database (>700,000 patients), the exhaustive nationwide hospital discharge database, and national mortality registry, all patients dispensed at least one prescription opioid (PO) in 2004–2017 were identified, to describe trends in PO analgesic use, shopping behaviour, opioid-related hospitalizations and deaths. Annual prevalence of PO use and shopping behaviour (≥ 1 day of overlapping prescriptions from ≥ 2 prescribers, dispensed by ≥ 3 pharmacies) was estimated.

Results: In 2004–2017, the annual prevalence of weak opioid use codeine, tramadol and opium rose by 150%, 123%, and 244%, respectively ($p < 0.05$). Strong opioid use increased from 0.54% to 1.1% (+104%, $p < 0.05$), significantly for oxycodone (+1950%). Strong opioid use in chronic noncancer pain rose by 88% ($p < 0.05$) and 1180% for oxycodone. Opioid shopping increased from 0.50% to 0.67% (+34%, $p < 0.05$), associated with higher mortality risk HR = 2.8 [95% confidence interval (CI): 1.2–6.4]. Opioid-related hospitalizations increased from 15 to 40 per 1,000,000 population (+167%, 2000–2017), and opioid-related deaths from 1.3 to 3.2 per 1,000,000 population (+146%, 2000–2015).

Conclusions: This study provided a first European approach to a nationwide estimation with complete access to several national registries. In 2004–2017 in France, PO use excluding dextropropoxyphene more than doubled. The increase in oxycodone and fentanyl use, and nontrivial increasing trend in opioid-related morbidity–mortality should prompt authorities to closely monitor PO consumption in order to prevent alarming increases in opioid-related morbidity–mortality.

Significance: In 2004–2017, prescription opioid use in France at least doubled and oxycodone use increased particularly, associated with a nontrivial increase in opioid-related morbidity–mortality. Although giving no indication for an ‘opioid epidemic,’ these findings call for proper monitoring of opioid use.

1. Introduction

Prescription opioid (PO) analgesic use, abuse, and related mortality have increased over the last decades in developed countries (Joranson et al., 2000; Kuehn, 2007; Manchikanti et al., 2010, 2012; Atluri et al., 2014; Dart et al., 2015). Worldwide, PO analgesic use more than doubled from 2001 to 2013, most significantly in North America, and in Western and Central Europe (Berterame et al., 2016). Considering the situation in Europe, data are still scarce (van Amsterdam and van den Brink, 2015), but there is a growing trend in the prescription of opioids with evidence of an increasing prescription of strong opioids (Helmerhorst et al., 2017), especially in the United Kingdom (Giraudon et al., 2013; Jani and Dixon, 2017). In UK, the number of strong opioid users each year increased by 466% in 2000–2010 (Zin et al., 2014). In Germany, the percentage of insured collecting at least one PO rose by 37% in 2000–2010 (Schubert et al., 2013). Overall although PO use is about four times lower in Europe than in USA or Canada, vigilance should be warranted. Still, there are major differences between the actual situation across Europe and in Canada or the USA. In the USA, PO analgesic sales quadrupled (Frenk et al., 2015) from 1999 to 2012 (Atluri et al., 2014) and despite significant decrease in 2012–2015, the amount of PO in 2015 remained three times as high as in 1999 (Guy et al., 2017). In Canada, strong opioid dispensing increased by 43% in 2005–2011 (Fischer et al., 2014). These increases were the result of campaigns against undertreated pain, but increasing the medical use of PO also increases the possibility of nonmedical use (McDonald and Carlson, 2014; van Amsterdam and van den Brink, 2015). In the USA from 2000 to 2014, deaths from PO overdose nearly quadrupled, from 1.5 to 5.9 deaths per 100,000 persons (Compton et al., 2016) and in 2016 more than 42,000 opioid-related deaths were reported while in Europe 9138 overdose deaths (related to opioids in 78% including heroin) were registered (European Monitoring Centre for Drugs and Drug Addiction, 2018). In response to these alarming trends, a variety of policies and programs aimed at curbing inappropriate prescription are now being implemented in the USA. Similarly, recent European guidelines for appropriate opioid prescribing in chronic pain management were released (O'Brien et al., 2017).

From a European perspective, we still need more data on trends in PO use, abuse, and mortality, in order to add on to the pattern of global trend. One recent article described the sales trends of PO in

2006–2015 in France compared to six European countries (Hider-Mlynarz et al., 2018), revealing different patterns across Europe and a clear higher use of PO in UK. However, patient-focused data are needed to assess the impact of current legislation and regulation. This study aimed to assess the trends in PO analgesic use, shopping behaviour, and opioid-related morbidity–mortality to bring some perspective to the field, both for France and in a larger picture for Europe.

2. Materials and methods

2.1 Data sources

This study was a repeated cross-sectional analysis of PO analgesics reimbursed between 1 January 2004, and 31 December 2017, reported in the General Scheme of the French Health Insurance claims database.

Data were collected from the EGB (*Échantillon Généraliste des Bénéficiaires*) database, a representative 1/97th random sample of the population covered by the French national health insurance system (Martin-Latry and Bégaud, 2010; Tuppin et al., 2010; Moulis et al., 2015). The EGB database comprises almost 700,000 insured, with over 10 years of follow-up for some, and has been widely used for pharmaco-epidemiological purposes (Martin-Latry and Bégaud, 2010; Tuppin et al., 2010; Moulis et al., 2015; Vorilhon et al., 2015; Chenaf et al., 2016; Delorme et al., 2016).

This database contains administrative, medical and pharmaceutical data. Administrative data include birth date, gender, income status and date of death. Patients with mental health disorders were identified by International Classification of Disease, Tenth Revision, (ICD-10) codes ranging from F00 to F99 and opioid use disorders (encompassing desire to use, increased tolerance and withdrawal syndrome) by ICD-10 code F11. Painful conditions such as osteoarthritis (ICD-10 codes M15-M19), back pain (ICD-10 codes M40-M54) and neuropathic pain (ICD-10 code R5210) were identified. A history of surgery in the preceding 3 months before a PO dispensation was also collected. A single PO dispensation in the year was considered as a proxy for the indication of acute pain. Pharmaceutical data comprise all claims for reimbursed drugs dispensed in retail pharmacies (including dates of dispensing and supplied quantities, pharmacy and prescriber ID). Prescribers specialties were collected and medications were identified by their Anatomical Therapeutic Chemical class (ATC) codes. Buprenorphine painkillers (ATC code: N02AE01), fentanyl (N02AB03),

hydromorphone (N02AA03), morphine (N02AA01), oxycodone (N02AA05) and pethidine (N02AB02) were classed as strong opioids; codeine (N02AA59), dextropropoxyphene (N02AC04, N02AC54), dihydrocodeine (N02AA08), opium (N02BE71) and tramadol (N02AX02, N02AX52) as weak opioids. Of note, the marketing authorization for dextropropoxyphene was suspended in 2009–2010 by the European Medicines Agency; the first introduction of oxycodone on the French market was on April 2002.

The study was conducted using a fully anonymized database, and using EGB for medical research was approved by the French Data Protection Authority (CNIL, 1946535).

The exhaustive French nationwide hospital discharge database was employed to assess trends in opioid-related hospital admissions between 2000 and 2017. Opioid-related hospitalizations were identified using the following ICD-10 codes: T400, T401, T402, T403, T404 and T406. Drug-overdose deaths were identified using the ICD-10 underlying cause-of-death codes X40–X44, and opioid-related deaths using underlying cause-of-death codes X42 (unintentional) and F11 (opioid-related disorders), using exhaustive data from 2000 to 2015 from the French epidemiological centre on the medical causes of death (CépiDc–Inserm; France).

2.2 Measures

The prevalence of PO analgesic use and shopping behaviour was estimated for each year from 2004 to 2017. The prevalence of PO use was defined as the ratio of the number of patients of the main health insurance scheme (>80%) collecting at least one PO analgesic in the calendar year by the number of insured subjects comprised in the database. Chronic PO users were classified as chronic pain patients, defined as those receiving continuous PO dispensation for at least 3 consecutive months. A nonmalignant pain origin was defined by the absence of cancer ascertained by a cancer-related ICD-10 code (C00–D48). The quantity dispensed per patient was expressed as World Health Organization defined daily dose (DDD) (WHO, 2016) and oral morphine equivalent dose (OMED) (Pereira et al., 2001; Knotkova et al., 2009).

The prevalence of shopping behaviour was defined as the ratio of patients conducting at least one opioid shopping episode by the number of patients with opioid dispensation in the calendar year. Shopping behaviour was defined as at least one day of overlapping prescriptions written by at least two different prescribers and dispensed by at least three different

pharmacies. This definition was developed by Cepeda and has been applied in several previously conducted studies (Cepeda et al., 2012, 2013a,b, 2014; Delorme et al., 2016).

Mortality rates were assessed according to shopping behaviour or PO high-dose use (>150 mg daily OMED), and the Charlson Comorbidity Index (CCI) (Charlson et al., 1987; Quan et al., 2005) was calculated in order to account for the confounding influence of comorbidities. The CCI has been extensively applied in clinical research and is considered a valid prognostic indicator for mortality.

2.3 Statistical analyses

Descriptive analyses were performed in order to assess the 1-year prevalence of PO users and shopping behaviour for each year, with Poisson's models (significance level: 0.05) applied to test the differences between trends from 2004 to 2017. Linear regression models were created to test trends for mean DDD and mean OMED. Risk factors for shopping behaviour were identified using a logistic model so as to assess unadjusted and adjusted odds ratios, with their corresponding 95% confidence intervals (95% CI). Multicollinearity and potential interaction effects between examined factors were additionally evaluated. Mortality risk was assessed for opioid shoppers versus nonshoppers, as well as for PO high-dose versus low-dose users. After one-by-one matching using propensity score, calculated by logistic regressions for age, gender, cancer condition, mental health disorders and CCI, Cox proportional hazards models were applied with resulting hazard ratios [HR (95% CI)].

The design, analysis, and reporting of the research were carried out according to the STROBE guidelines (Supporting Information Data S1) (von Elm et al., 2007). All statistical analyses were performed using Stata 12.0 software for Windows (Stata Corp LP, College Station, Texas, USA).

3. Results

3.1 Patient characteristics

From 2004 to 2017, a minimum of 88,649 and maximum of 101,872 PO analgesic users were included each year, comprising 2755 to 5900 strong opioid users and 87,171 to 100,972 weak opioid users. In 2017, the mean age of PO analgesic users was 51.5 ± 19.4 years, 57.0% were women, and 10.2% had low income.

3.2 Medical data

Among PO analgesics users, a number of painful conditions have been identified and presented in Table 1. Acute pain was the most frequent painful condition (70%).

Moreover, regarding main comorbidities, PO analgesics users had cancer (8.9%), diabetes (8.8%), mental health disorders (8.5%) and opioid use disorders (0.4%) (Table 1).

3.3 PO analgesic use

Between 2004 and 2017, despite the 16% increase (from 55.9% to 64.6%) in the annual prevalence of overall analgesic use, that of PO analgesic use in the general population decreased by 8.9%, from 19.2%

to 17.5% ($p < 0.05$) (Fig. 1A). Strong opioid use increased by 104%, from 0.54% to 1.1%, ($p < 0.05$) (Fig. 1B), while weak opioid use decreased by 10.5%, from 19.1% to 17.1%, ($p < 0.05$) (Fig. 1C). Among PO analgesic users, the proportion of strong opioid users doubled, from 2.8% in 2004 to 6.0% in 2017, while the proportion of weak opioid users decreased from 97.2% to 94.0%.

Focusing on individual PO analgesic use in the general population (Fig. 1B and C), the prevalence of use increased for morphine (+25%), fentanyl (+74%), tramadol (+105%), codeine (+127%), opium (+212%) and oxycodone (+1950%) from 2004 to 2017. Among strong opioid users (Fig. 2A), the 2004–2017 prevalence remained steady for fentanyl (35–32%, $p > 0.05$), decreased from 74% to

Table 1 Characteristics of prescription opioid analgesic users in 2017.

	No. (%) ^a		<i>p</i> value*	No. (%)		<i>p</i> Value [†]
	Nonopioid analgesic users <i>n</i> = 264,176	Opioid analgesic users <i>n</i> = 98,122		Strong opioid users <i>n</i> = 5900	Weak opioid users <i>n</i> = 92,222	
Age (years)						
Mean ± SD	36.8 ± 25.3	51.5 ± 19.4	<0.001	63.6 ± 19.0	50.8 ± 19.2	<0.001
Age group (years)						
<15	70,461 (26.7)	1178 (1.2)		17 (0.3)	1161 (1.3)	
15–25	27,117 (10.3)	7489 (7.6)		108 (1.8)	7381 (8.0)	
25–45	62,279 (23.6)	27,902 (28.4)	<0.001	857 (14.5)	27,045 (29.3)	<0.001
45–65	59,113 (22.4)	34,754 (35.4)		1993 (33.8)	32,761 (35.5)	
≥65	45,206 (17.1)	26,799 (27.3)		2925 (49.6)	23,874 (25.9)	
Gender						
Female	146,823 (55.6)	55,973 (57.0)		3497 (59.3)	52,476 (56.9)	<0.001
Male	117,353 (44.4)	42,149 (43.0)	<0.001	2403 (40.7)	39,746 (43.1)	
Low-income status	31,337 (11.9)	10,029 (10.2)	<0.001	386 (6.5)	9643 (10.5)	<0.001
CCI mean ± SD	0.22 ± 0.87	0.56 ± 1.51	<0.001	2.1 ± 3.0	0.47 ± 1.31	<0.001
Mental health disorders	13,261 (5.0)	8316 (8.5)	<0.001	964 (16.3)	7352 (8.0)	<0.001
Opioid use disorders	729 (0.3)	402 (0.4)	<0.001	58 (1.0)	344 (0.4)	<0.001
Diabetes	12,330 (4.7)	8641 (8.8)	<0.001	784 (13.3)	7857 (8.5)	<0.001
Cancer condition	11,319 (4.3)	8773 (8.9)	<0.001	1539 (26.1)	7234 (7.8)	<0.001
Acute pain	–	68,654 (70.0)	–	2955 (50.1)	65,699 (71.2)	<0.001
Chronic pain	10,178 (3.9)	14,904 (15.2)	<0.001	2530 (42.9)	12,374 (13.4)	<0.001
Neuropathic pain	14 (0.01)	117 (0.12)	<0.001	54 (1.0)	63 (0.07)	<0.001
Osteoarthritis	1503 (0.6)	2765 (2.9)	<0.001	389 (7.0)	2376 (2.6)	<0.001
Back pain	6636 (2.5)	8566 (8.9)	<0.001	1198 (21.6)	7368 (8.1)	<0.001
Prescribers, %						
GP	–	88.1	–	88.7	–	86.3
Dentist	–	3.1	–	0.3	–	2.8
Rheumatologist	–	0.7	–	1.7	–	2.2
Orthopaedist	–	0.3	<0.001	1.3	–	1.9
History of surgery (in the preceding 3 months)	7570 (2.8)	10,345 (10.7)	<0.001	1195 (21.5)	9150 (10.0)	<0.001

CCI, Charlson Comorbidity Index; GP, general practitioner; No. (%), number of patients (percentage).

**p*-value for characteristic comparisons between nonopioid analgesic users and opioid analgesic users.

[†]*p*-value for characteristic comparisons between strong opioid users and weak opioid users.

^aData are expressed as No. (%) unless otherwise indicated.

47% ($p < 0.05$) for morphine, and increased from 3.2% to 39% ($p < 0.05$) for oxycodone. Among weak opioid users (Fig. 2B), there were 7.4% dextropropoxyphene users in 2011 compared to 76% in 2004 (the marketing authorization for dextropropoxyphene was suspended in 2009–2010 by the European Medicines Agency), while the proportion of codeine users increased from 16% to 40% (+150%), that of opium users from 9% to 31% (+244%), and that of tramadol users from 22% to 49% (+123%) (p for trends < 0.05).

In 2017, PO analgesics were primarily prescribed in community medicine (84%), in public hospitals (14%) and in private hospitals (4%). Accordingly, general practitioners accounted for a 87% of PO analgesics dispensed (Table 1), followed by dentists (2.4%), rheumatologists (2.1%) and orthopaedists (1.8%). The proportion of strong and weak opioids prescribed was balanced for GPs, rheumatologists and orthopaedists, usually confronted with patients with pain of moderate to strong intensity while the prescription of weak opioids dominated among dentists confronted with pain most often acute and of moderate intensity.

3.4 Prescription opioid quantity

In 2004–2017, the DDD/1000 inhabitants/day for weak opioid analgesics (Fig. 1D) decreased by 6.8%

(from 16.2 to 15.1). In contrast, that of strong opioids increased by 59% (from 1.7 to 2.7).

In 2017, the mean annual DDD per user for fentanyl was 101 (−1% vs. 2004), for morphine 84 (−12%), for oxycodone 81 (−13%), for codeine 25 (−14%), for opium 15 (+7%) and for tramadol 35 (−3%). The mean annual OMED per user was 11,521 mg for fentanyl (−6%), 8345 mg for morphine (−12%), 9163 mg for oxycodone (−12%), 637 mg for codeine (−11%), 153 mg for opium (−30%) and 2083 mg for tramadol (−3%). Trends were statistically significant for opium.

3.5 Prescription opioid analgesic use according to pain and cancer status

Irrespective of the year, PO analgesics were typically used for noncancer pain (88% of all PO analgesic users in 2004, 91% in 2017). In the general population in 2017, the 17.5% of PO analgesic users were distributed as follows: 13.7% were treated for non-chronic noncancer pain, 2.2% for chronic non cancer pain (CNCP), 1.2% for nonchronic pain and cancer, and 0.4% for chronic pain and cancer. Considering weak opioid users, this period demonstrated no significant variation in the pattern of prescription according to chronic pain or cancer. As for strong opioid users, the absolute number of CNCP-related

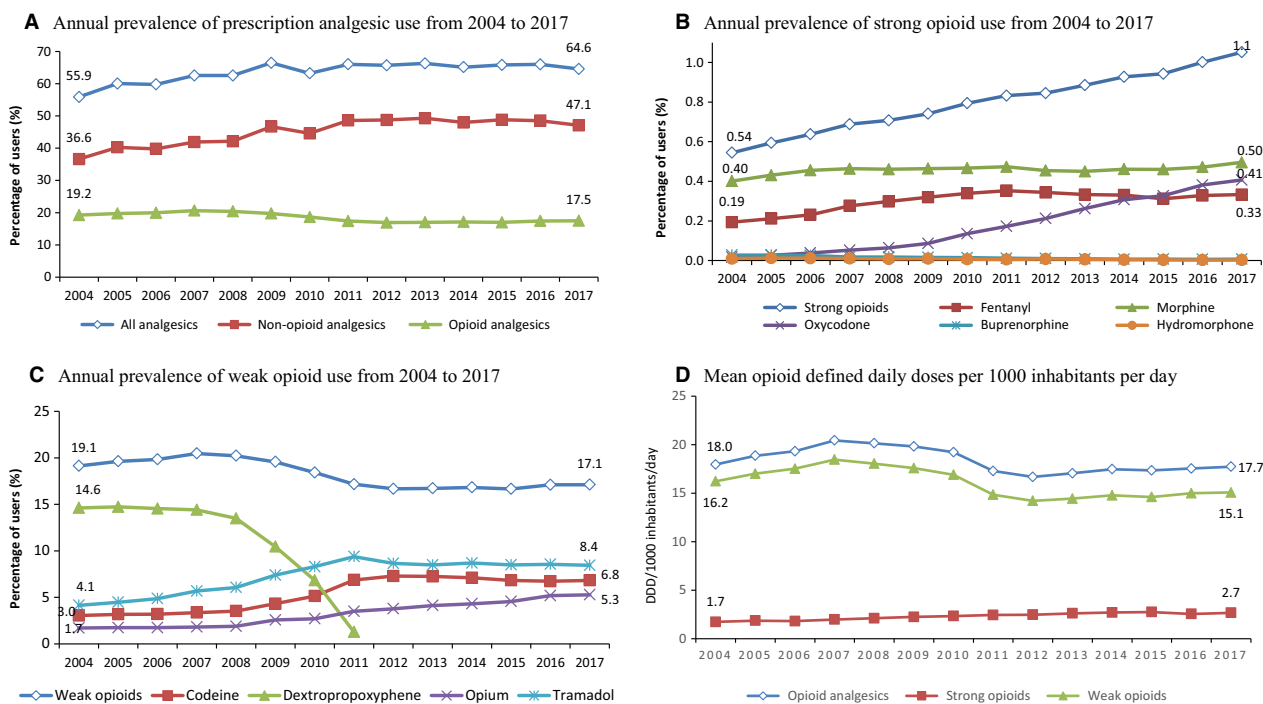


Figure 1 Trends in prescription opioid analgesic use in the general population from 2004 to 2017 in France. p for trends < 0.05 for all.

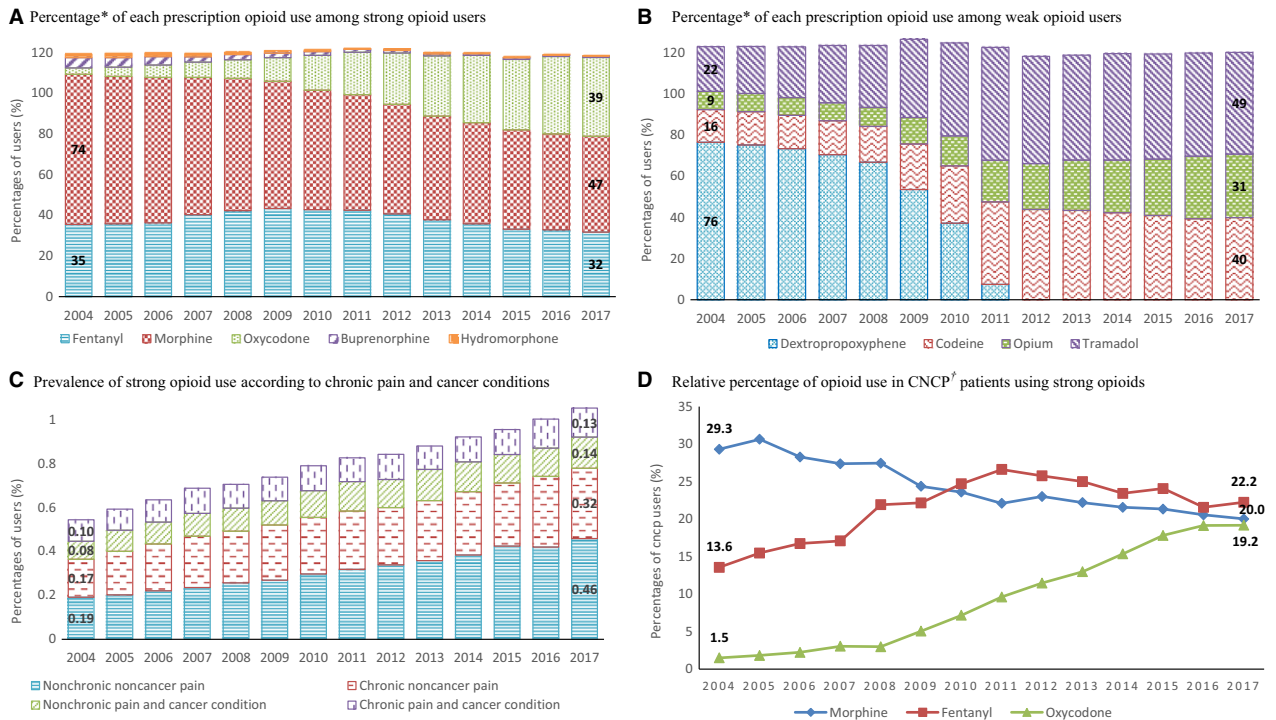


Figure 2 Prescription opioid use according to opioid potency and chronic pain and cancer conditions. *The total of percentages could exceed 100% because one patient may use different opioid analgesics. †CNCP, chronic non-cancer pain.

users increased by 88% from 0.17% to 0.32% over the same period (Fig. 2C). This was primarily due to a steep increase in the proportion of chronic oxycodone users (Fig. 2D), from 1.5% to 19.2% of CNCP patients (+1180%), while the proportion of fentanyl users remained steady from 2010 onwards, and the proportion of morphine users decreased from 29.3% to 20% (-32%).

3.6 Prescription opioid shopping behaviour

Considering all PO analgesics, shopping behaviour increased by 34%, from 0.50% (95% CI: 0.43–0.52) in 2004 to 0.67% (95% CI: 0.61–0.72, *p* < 0.05) in 2017. Shopping behaviour for weak opioids increased from 0.16% (95% CI: 0.13–0.18) in 2004 to 0.56% (95% CI: 0.51–0.61, *p* < 0.05) in 2017, while a downward trend was observed for strong opioids from 0.76% (95% CI: 0.44–1.08) in 2004 to 0.59% (95% CI: 0.40–0.79) in 2017. On multivariate analysis (Fig. 3), risk factors associated with PO shopping behaviour were younger age (≤65 years) [Odds Ratio (OR) = 2.1; 95% CI: 1.8–2.5], male gender (OR = 1.2; 95% CI: 1.1–1.4), low-income status (OR = 2.6; 95% CI: 2.3–3.1), cancer (OR = 2.3; 95% CI: 2.0–2.8), mental health disorder (OR = 2.6; 95% CI: 2.2–3.1),

opioid use disorder (OR = 5.1; 95% CI: 3.6–7.2), and benzodiazepine use (OR = 6.2; 95% CI: 5.4–7.1).

3.7 Mortality and opioid-related hospitalizations and deaths

Prescription opioid shoppers were found to have almost threefold higher adjusted-risk of all-cause mortality [HR = 2.8 (95% CI: 1.2–6.4), *p* = 0.017], compared to nonshoppers (Fig. 4A). Similarly, the risk of death was also higher for high-dose PO users compared to low-dose users [HR = 2.7 (95% CI: 2.0–3.8), *p* < 0.001] (Fig. 4B).

From 2000 to 2017, rates of prescribed opioid-related hospital admissions increased by 167% from 15 (*n* = 881) to 40 (*n* = 2586) per 1,000,000 population (Fig. 4C). In comparison, rates of methadone (from 1.0 to 5.4 per 1,000,000 population) or heroin-related hospitalizations (from 1.6 to 1.5 per 1,000,000 population) were much lower over the same period.

Opioid-related deaths significantly increased by 146% from 1.3 (*n* = 76) per 1,000,000 population in 2000 to 3.2 (*n* = 204) in 2015 (Fig. 4D). The number of unintentional overdose deaths involving opioids nearly tripled in 2000–2015, accounting for 8.5% of

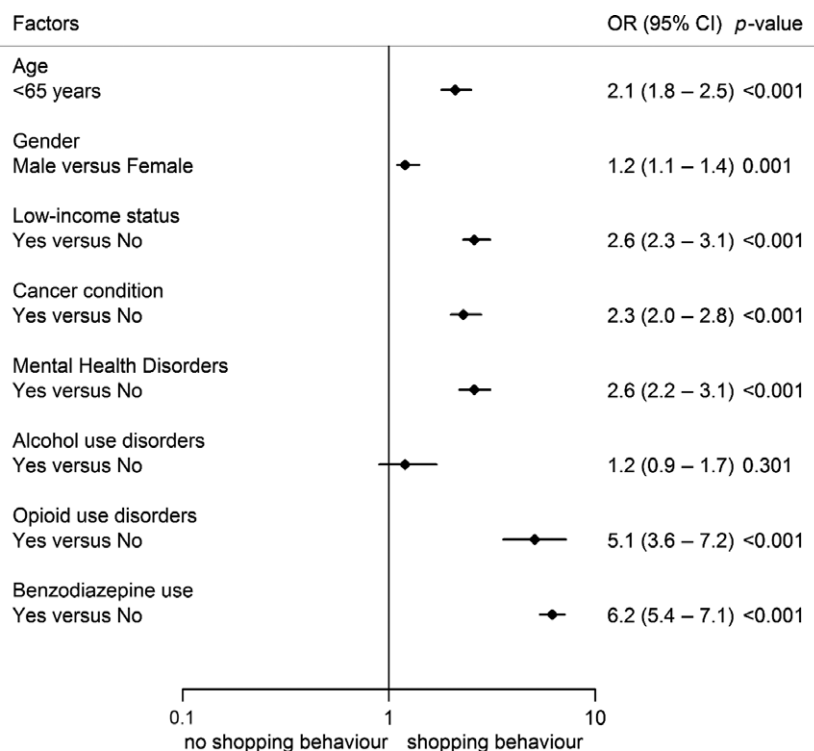


Figure 3 Risk factors associated with opioid shopping behaviour. OR (95% CI): odds ratio (95% confidence interval).

unintentional drug overdose deaths in 2000 and 15% in 2015.

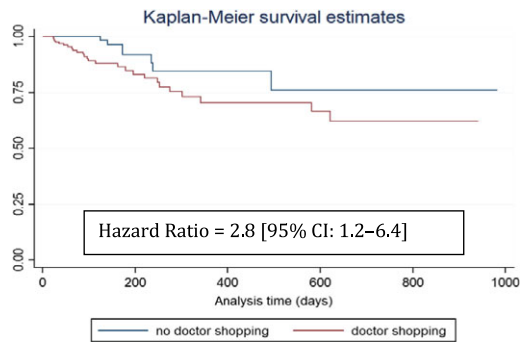
4. Discussion

From a European perspective, this study provides a first comprehensive approach to a nationwide estimation with complete access to national registries. In 2004–2017 in France, PO analgesic use, mainly due to GPs’ prescription, decreased owing to dextro-propoxyphene market withdrawal in March 2011 (Afsaps, 2010; EMEA, 2010), while strong opioid (+104%) and weak opioid (other than dextro-propoxyphene) (+123–244%) use increased, yet not sufficiently to offset the fall due to dextro-propoxyphene withdrawal. Of note was the dramatic rise in oxycodone use, especially in CNCP patients. Shopping behaviour (+34%) increased yet remained low, while opioid-related hospitalizations (+167%) and deaths (+146%) increased significantly, although not to the same alarming rate as in the USA. However, besides indicating the absolute number of events, these estimates serve principally to indicate trends.

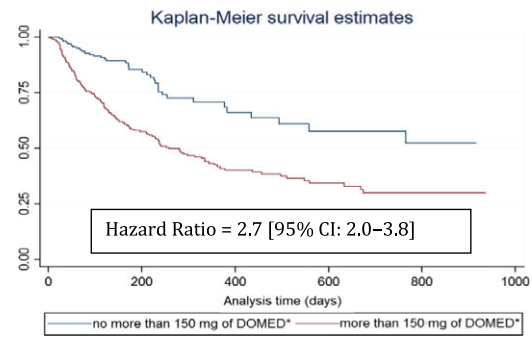
Except for dextropropoxyphene, PO use increased in France, as reported for the USA (Atluri et al.,

2014; Dart et al., 2015; Compton et al., 2016), Canada (Fischer et al., 2014), Australia (Karanges et al., 2016), as well for other European countries such as Germany (Schubert et al., 2013), Denmark (Ekholm et al., 2014), Nordic countries (Hamunen et al., 2009), and the UK (Weisberg et al., 2014; Zin et al., 2014). However, while France’s increasing PO use remained below levels reported in the USA and Canada, it approached the rates reported in European countries and Australia. Indeed, PO use in 2017 was similar to an Australian study’s findings of 17 DDD/1000pop/day (Karanges et al., 2016). The 1.9% prevalence of long-term PO therapy for CNCP patients was not different from that found in Germany (1.3%) (Marschall et al., 2016), and the prevalence of strong opioid use (1.1%) was similar to that of the UK in 2010 (0.92%) (Zin et al., 2014). Although the overall increase in PO use in France does not seem alarming, this has to be seen in the light of the unexpected progressive surge in both opioid-related hospitalizations and opioid-related deaths since 2000 in France, demonstrated in our study, although this surge is not nearly as dramatic as that seen in the USA or Canada. Moreover, considering that our study found oxycodone accounted for 39% of the strong opioid users in 2017 (vs. 3% in 2004),

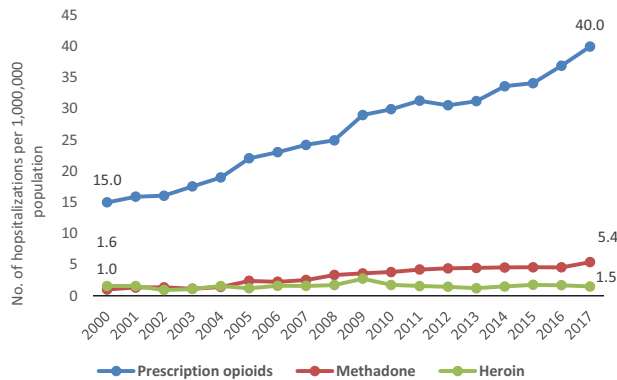
A Survival analysis according to opioid shopping behaviour



B Survival analysis according to daily oral morphine equivalent dose



C Opioid-related hospital admissions from 2000 to 2017 in France^a



D Opioid-related deaths from 2000 to 2015 in France^{a, b}

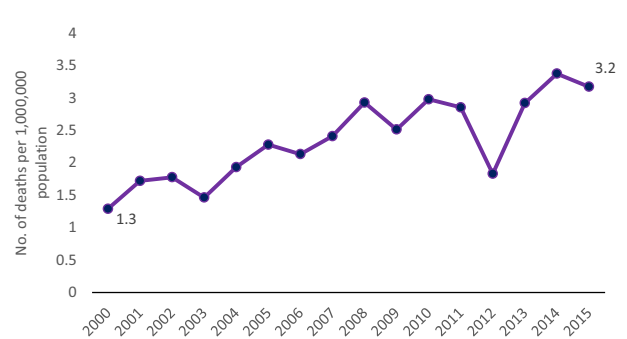


Figure 4 Mortality associated with opioid shopping behavior, high dose use (>150 mg DOMED), hospitalizations (2000–2017), and deaths (2000–2015). *DOMED, Daily Oral Morphine Equivalent dose; 95% CI: 95% Confidence Interval. ^a*p* for trend <0.05. ^bICD-10 coding practices temporarily changed in 2012 which resulted in this ‘artificial’ decrease in the number of deaths.

together with the 1950% increase in oxycodone use, authorities should be prompted to closely monitor this sharp rise, since oxycodone was one of the most common drugs involved in PO overdose deaths in the USA (Rudd et al., 2016). It is also worth noting that oxycodone was one of the leading causes of the ongoing opioid epidemic in the USA, marketed in the push for increased focus on pain management along with the erroneous claim that it is not dangerous (Van Zee, 2009). Our study also highlighted a 88% increase in strong opioid use in the context of CNCP, mainly driven by the steep increase in the proportion of chronic oxycodone users, which may be problematic since there is still much controversy about the long-term use of strong opioids for CNCP, where their risks and long-term benefits are much less clear (Kissin, 2013; Cheung et al., 2014; Dowell et al., 2016). However, this increase may correspond to an extension of oxycodone’s indications in France since September 2012 (chronic neuropathic pain and acute post-operative pain) and October 2014 (intense pain in the context of osteoarthritis of the knee or hip and

chronic lumbar pain). Synthetic opioids like fentanyl should also be looked at closely, since it is considered ‘the new centre of the opioid crisis’ in Canada (Fischer et al., 2015), and thought to herald the next wave of the US opioid crisis (Rudd et al., 2016) where fentanyl as well as illicit heroin are the drivers of the actual opioid epidemic, involved in most of the opioid-related deaths (Pergolizzi et al., 2018; Schnoll, 2018).

Clearly, Europe must learn from the USA opioid epidemic as stated by Helmerhorst et al. (2017): ‘the general public and the medical and legal professions in Europe [...] need to be careful not to make the same mistakes made in the United States and Canada’. While the USA possesses probably one of the most efficient drug abuse surveillance systems in the world, France lacks a systematic method for identifying and monitoring trends in PO use over time, resulting in a lack of understanding of opioid-related potential harms. It is obvious that vigilance is needed now more than ever since the introduction and broad use of oxycodone in expanded

indications, especially for treating CNCP. These developments are reminiscent of the marketing techniques applied in the USA in order to positively impact prescribing (Maxwell, 2011), facilitated by marketing strategies that downplayed oxycodone's addictive potential (Van Zee, 2009).

Nevertheless, the USA opioid epidemic is far from hitting France and Europe more broadly, which contrast strongly with America in terms of legislation, practice, and drug consumption patterns (Weisberg et al., 2014; van Amsterdam and van den Brink, 2015; Heilig and Tägil, 2018). In France, PO analgesics can be obtained only through prescription (except for <20 mg doses of codeine). Strong opioids are on the list of narcotics with prescription limited to 28 days following a strict framework based on a secure prescription form. Also, a new clinical evaluation needs to be performed before any strong opioid refill. These regulation measures are also accompanied by guidelines and recommendations (Vergne-Salle et al., 2012; Moisset et al., 2016) from pain specialists defining the best practice of opioid prescribing in CNCP. The European Pain Federation (EFIC) also recently provided guidelines for appropriate opioid prescribing in chronic pain management (O'Brien et al., 2017). However, France can still benefit from the USA's resulting experience, such as the recent updated measures proposed by the Food and Drug Administration (Califf et al., 2016) and the Centers for Disease Control (Dowell et al., 2016) as a proactive response to growing opioid abuse and overdose, where implementing prescription drug monitoring programmes and enforcement of regulatory actions seem to be helping reduce abuse (Dart et al., 2015; Levy et al., 2015; Compton et al., 2016).

As reported in other studies, shopping behaviour (Peirce et al., 2012) and the use of high doses (Gomes et al., 2011; Dasgupta et al., 2016) were associated with higher risk of death, suggesting that efforts are still required so as to prevent fatalities and characterize at-risk populations, even when rates are low. The identified risk factors associated with shopping in our study were also reported by several other authors (Pergolizzi et al., 2012; Delorme et al., 2016) and are useful for identifying high-risk patients who must be offered regular reassessment of their opioid effectiveness to prevent potential abuse and overdose.

4.1 Limitations

This is the first comprehensive European study to assess the trends in PO analgesic use, shopping behaviour and opioid-related morbidity–mortality over

the last decade in France. Such findings are useful both for health authorities who should ensure better PO use surveillance and for care providers who should prescribe opioid analgesics properly and educate their patients to prevent misuse. Nonetheless, there were several limitations common to most studies using health insurance claims databases. The EGB database provides measures of PO utilization using reimbursed dispensations, and as a result does not provide a measure of actual PO consumption, nor an account of over the counter codeine use. However, strong correlation between consumption and drug dispensing has been demonstrated using the French Health Insurance System (Noize et al., 2009), and the proportion of reimbursed codeine sales assessed from IMS drugs data represented more than 90% of overall codeine sales.

Secondly, as clinical indication for the prescription is classically not available in these databases, it cannot be ruled out that the France's increasing PO use may simply reflect a population growth with severe chronic pain and legitimate clinical indication of opioid prescription, which will in any case not prevent the need to monitor or even prevent the potential associated risks.

Thirdly, PO abuse might have been underestimated in this study, since purchases made via doctors are not the sole means of PO analgesics abuse. Patients can, in fact, also obtain large quantities of opioids through friends, family, the Internet, or black markets (Manchikanti et al., 2012; Winstock et al., 2014; Markotic et al., 2018).

Finally, the potential for confounding by indication is another limitation to this study: The higher risk of death for high-dose users may result from indication bias, as the presence of other serious comorbidities besides cancer cannot be excluded. However, other studies (Ekholm et al., 2014; Ray et al., 2016) found similar higher risks of death associated with PO use in CNCP, suggesting that PO analgesics should be used cautiously in these cases.

5. Conclusion

Although we found no indication of a 'prescription opioid epidemic' occurring in France over the 2004–2017 period, these study findings call for vigilance considering both the sharp increase in oxycodone and other PO such as fentanyl, as well as the nontrivial increased trends in opioid-related morbidity–mortality. In this context, European authorities should closely monitor trends of PO analgesic use to further prevent an opioid epidemic and its potential risks.

Author contributions

All authors discussed the results and commented on the manuscript. Experiments were conceived and designed by C.C., J.L.K., J.D. and N.A. The experiments were performed by J.L.K. and C.C. The data were analysed by J.L.K., B.P. and A.M. The manuscript was written by C.C., J.L.K., J.D., A.E. and N.A. Critical revision of the manuscript was performed by M.Z., N.D., N.A., D.A. and A.E.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. STROBE Statement – checklist of items that should be included in reports of observational studies.