



Codeine Shopping Behavior in a Retrospective Cohort of Chronic Noncancer Pain Patients: Incidence and Risk Factors

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Abstract: Codeine is a widely used opioid analgesic but studies on its misuse in chronic noncancer pain (CNC) are still lacking. The aim of this study was to assess the incidence of codeine shopping behavior in CNC patients and to identify the associated risk factors. This was a population-based retrospective cohort study from the French health insurance claims database from 2004 to 2014. The main outcome was the one-year incidence of codeine shopping behavior defined as ≥ 1 day of overlapping prescriptions written by ≥ 2 different prescribers and filled in ≥ 3 different pharmacies. A total of 1,958 CNC patients treated with codeine were included, with a mean age of 62.7 ± 16.1 years, 36.8% men. The 1-year incidence rate of codeine shopping behavior was 4.03% (95% confidence interval [CI], 3.07–5.28). In multivariate analysis, risk factors associated with shopping behavior were younger age (≤ 40 years) (hazard ratio [HR] = 7.29; 95% CI, 4.28–12.42), mental health disorders (HR = 2.25; 95% CI, 1.08–4.67), concurrent use of anxiolytic benzodiazepines (HR = 3.12; 95% CI, 1.55–6.26), and previous use of strong opioids (HR = 2.94; 95% CI, 1.24–6.98). The incidence of codeine shopping behavior in CNC patients was 4% and risk factors identified were shared with those of opioid abuse.

Perspective: Shopping behavior for codeine was not infrequent in CNC patients. The risk factors identified in this study are similar to those identified for opioid abuse in other studies. Appropriate use of codeine from the perspectives of patients and healthcare providers should be encouraged.

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Key words: Chronic pain, codeine, opioid analgesics, doctor shopping, opioid misuse.

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Opioid analgesic use has increased in recent years in developed countries with an increase in misuse of prescription opioids and related fatalities.^{3,20,42} In the United States between 1990 and 2010, the use of prescription opioids increased 10-fold and the rate of death from prescription opioids overdose quadrupled.¹⁹ Although a similar problem is developing across the globe including in Canada,²⁶ Australia,³⁷ Germany,⁶² Denmark,²⁴ Nordic countries,³² and the United Kingdom⁶⁷; there are major differences between the current situation in the United States or Canada and across Europe.⁶⁷ Although prescription opioid consumption is approximately 4 times lower in Europe,

vigilance is warranted with regard to opioids misuse and related deaths.

The increase in use resulted from strategies for promoting opioid use for pain control particularly in chronic noncancer pain (CNCP).^{18,48} However, availability of strong scientific evidence supporting long-term opioid therapy for CNCP is limited.^{17,21,39} Physical dependence, tolerance development, and dose escalation are expected with prolonged use of opioids but, if not handled correctly by the prescriber, chronic opioid use may lead to misuse and addiction.^{4,5,46,53-55,63,64} A meta-analysis estimated that 3.3% of chronic pain patients managed with opioid analgesics developed abuse or addiction.²⁷ Doctor shopping represents one way to obtain a quantity of opioids greater than the therapeutic needs and the excess can be used either for unsupervised personal consumption or for diversion.^{35,45,46}

Doctor shopping means seeking multiple physicians to obtain prescriptions for the same drug.^{11,53,60} The increased use of opioid analgesics was correlated to an increase of diversion, abuse, and doctor shopping. In the United States from 1999 to 2007, a parallel increase in schedule II opioid prescription (approximately 150–280%) and opioid shopping behavior (approximately 111–213%) was reported.³³ Interestingly, overlapping prescriptions from multiple prescribers filled in multiple pharmacies have also been shown to be correlated with opioid abuse, injury, and death.^{13,45,53,72} In the United States among drug-related deaths for controlled substances, 25.2% were doctor shoppers and 17.5% were pharmacy shoppers.⁵³

The problem of opioid analgesic misuse is not limited to strong opioids and growing concerns have emerged regarding the problem of codeine, a weak opioid, because of its established potential of misuse. Codeine is the most commonly used analgesic opioid in the world³⁶ and in several European countries.¹⁰ Studies relating to codeine are often combined with general prescription opioid studies and therefore specific data focusing on codeine alone are scarce. However, over recent years, many reports of codeine misuse emerged from several countries including Australia,²⁹ New Zealand,⁵⁷ and the United Kingdom,⁶⁹ where codeine is also available 'over the counter' (without a prescription; OTC). In the United States, codeine misuse increased by 39% from 2004 to 2011.³ Case series of codeine deaths have been reported in the United States,³⁸ the United Kingdom, and Australia, where codeine-related mortality more than doubled in a decade, from 3.5 per million in 2000 to 8.7 per million in 2009.⁵⁹

In France, according to the number of boxes sold in 2013, codeine was the top-selling opioid analgesic and the third best-selling drug.¹ Codeine is used in combination with paracetamol to relieve mild to moderate pain and is also available OTC.

Although the potential for misuse of codeine is established, prospective studies assessing the magnitude of this risk are still lacking especially in CNCP.^{58,64,68} Several studies have suggested that long-term opioid therapy was associated with an increased risk of abuse and misuse^{18,54,72} but specific data on codeine are still

limited. The aim of this study was to assess the 1-year incidence of codeine shopping behavior in a cohort of CNCP patients and to identify the associated risk factors.

Methods

Study Design

This was a retrospective cohort study of CNCP patients treated with codeine in the period from 2004 to 2014 using anonymous data from a representative sample of the French health insurance database.

Data Source

Data came from the Échantillon Généraliste des Bénéficiaires (EGB) database, a representative 1/97th random sample of the population covered by the French national health insurance system.^{44,66} In 2014 the EGB database was comprised of almost 700,000 beneficiaries with more than 10 years of follow-up for some insured and has been widely used for public health and pharmacoepidemiological purposes for more than 5 years.^{6,22,25,28}

The EGB database contains administrative, medical, and pharmacy data. Administrative data include individual anonymous information on year of birth, long-term diseases (LTD) and the affiliation to free supplementary health insurance coverage (Couverture Maladie Universelle Complémentaire; CMUc). The attribution of the CMUc is only on the basis of the income, independently of the health status. Indeed, CMUc is attributed to unemployed and low-income insured and can be consequently used as a proxy for low-income status. In the French health care system, 30 major chronic diseases have been designated as LTD (ie, chronic diseases). The information recorded includes the chronic disease code and the associated International Classification of Disease (ICD)-10 codes. These chronic conditions represent proxies for comorbidity assessment. Pharmacy data comprise exhaustive claims for all reimbursed drugs dispensed in retail pharmacies (including dates of prescription/dispensation and supplied quantities). Medications are identified by their Anatomical Therapeutic Chemical class codes.

The use of the EGB for medical research has been approved by the Commission Nationale de l'Informatique et des Libertés, the French data protection authority.

Participants

All patients aged 18 years and older treated with codeine for at least 6 consecutive months (180 days) between January 1, 2004 and September 30, 2013 were included. The index date was the date of the first dispensation of this continuous sequence of at least 180 days of treatment. A continuous sequence was defined as an interval between 2 consecutive dispensations inferior to 35 days. This threshold of 35 days was on the basis of the fact that in France prescription drugs are dispensed for a maximum of 4 weeks and accordingly drugs prescribed for 3 months will be dispensed 3 times. To be

more specific to detect prescription interruption, 1 week was added to the maximum duration of prescription. The 6 months of continuous treatment period was used to identify chronic use of codeine in the absence of a specific code identifying the chronic pain status. For research purposes, pain lasting longer than 6 months is recommended to be defined as chronic pain.⁷⁰

Patients occasionally treated with codeine in the 6 months before the index date were excluded in order to select incident codeine users. Patients with a cancer condition were also excluded (according to the presence of a cancer-related ICD-10 code among the previously collected LTD) to ensure nonmalignant origin of pain. Patients were followed until September 30, 2014 allowing at least 12 months of follow-up for all included patients.

Study Data

Demographic data (year of birth, gender, date of death, LTD, and low-income status) were collected from this database.

Patients with mental health disorders were identified by ICD-10 codes ranging from F00 to F99, encompassing not only major depressive disorders but also anxiety, psychotic disorders, dementias, somatoform disorders, and addictive disease (alcohol use disorder, ICD-10 code F10; opioid use disorder, ICD-10 code F11). All these diagnoses were identified on initial entry into the cohort.

Data on dispensed medications (analgesic and psychotropic drugs) were extracted through Anatomical Therapeutic Chemical class codes. Strong opioids included morphine (N02AA01, N02AA51), fentanyl (N02AB03), oxycodone (N02AA05, N02AA55), methadone (N02AC52), pethidine (N02AB02), and buprenorphine (N02AE01). Weak opioids included tramadol (N02AX02, N02AX52), codeine (N02AA59), dihydrocodeine (N02AA08, N02AA58), dextropropoxyphene (N02AC04, N02AC54, and N02AC74), and opium (N02AA02). Psychotropic drugs corresponded to antidepressants (N06A), antipsychotics (N05A except N05AN), mood stabilizers (N05AN, N03AG01, N03AG02), anxiolytics (N05B), hypnotics (N05C), benzodiazepine derivatives (N03AE, N05BA, N05CD, N05CF), and drugs used in nicotine, alcohol, and opioid dependence (N07BA, N07BB, N07BC). Previous use was defined as at least 1 drug dispensation in the 3 months before the index date. Concurrent use was defined as at least 1 drug dispensation concomitant with codeine dispensations.

Outcome Measures

An episode of shopping behavior was defined as at least 1 day of overlapping prescriptions from 2 or more prescribers and filled in 3 or more pharmacies. This definition has been used in previous research.¹²⁻¹⁴ The number of shopping episodes during the follow-up period and time to first episode of shopping behavior were also assessed.

Statistical Analyses

Data were expressed as frequencies and associated percentages for categorical data and as mean \pm SD or

as median and interquartile range (IQR) for quantitative data. The 1-year incidence rate of codeine shopping behavior was estimated using the Kaplan–Meier method. For Kaplan–Meier analysis, the index date was considered as the starting date, and the date of first doctor shopping episode (or of last information, ie, death, end of treatment, switch to another analgesic, or end of follow-up) as the ending date. Buprenorphine maintenance treatment, well known to be abused through doctor shopping in France,^{49,52} was used as positive control and diuretics (not known to have abuse potential) as negative control.¹¹ The temporal trend in codeine shopping behavior between 2004 and 2014 was also assessed using a Poisson regression analysis.

Factors associated with the risk of codeine shopping behavior were analyzed and associated *P* values were computed with a Cox univariate model for which corresponding hazard ratios (HRs) are shown with their 95% confidence intervals (CIs). Multivariate analysis was developed with a Cox proportional hazard model of the factors considered significant in univariate analysis (entered into the model if *P* < .15) accordingly to clinically relevant variables such as age and gender. The corresponding adjusted HRs are shown with their 95% CIs.

All statistical analyses were performed using SAS for Windows version 9.3 (SAS Institute, Inc, Cary, NC).

Results

A total of 1,958 CNCP patients treated for at least 6 months with codeine were included (Fig 1).

Description of the Study Population

The mean age of included patients was 62.7 ± 16.1 years, approximately two-thirds (63.2%) of them were women, and 6.1% were low-income patients. Among included patients, 10.1% presented mental health disorders, 2.1% a history of substance use disorders, and only .6% presented a history of opioid use disorders (Table 1).

Incidence of Shopping Behavior

During overall follow-up, 65 patients developed at least 1 episode of shopping behavior. The 1-year incidence rate of codeine shopping behavior was 4.03% (95% CI, 3.07–5.28), compared with .17% (95% CI, .13–.22) for diuretics and 8.45% (95% CI, 7.02–10.15) for buprenorphine maintenance treatment.

The first shopping episode occurred in a median time of 190 (IQR = 112–351) days. This median time was 190 (IQR = 113–295) days for women and 175 (IQR = 85–443) days for men with no statistically significant difference (*P* = .81). Just under one-third of patients (*n* = 18) developed only 1 episode of shopping behavior during follow-up and most of the patients were several-time shoppers (*n* = 47): there were 24 (36.9%) with 2 to 10 episodes and 23 (35.4%) with >10 episodes (Table 2).

When examining the temporal trend in codeine doctor shopping, the prevalence of codeine shopping behavior more than tripled between 2004 and 2014, but was not

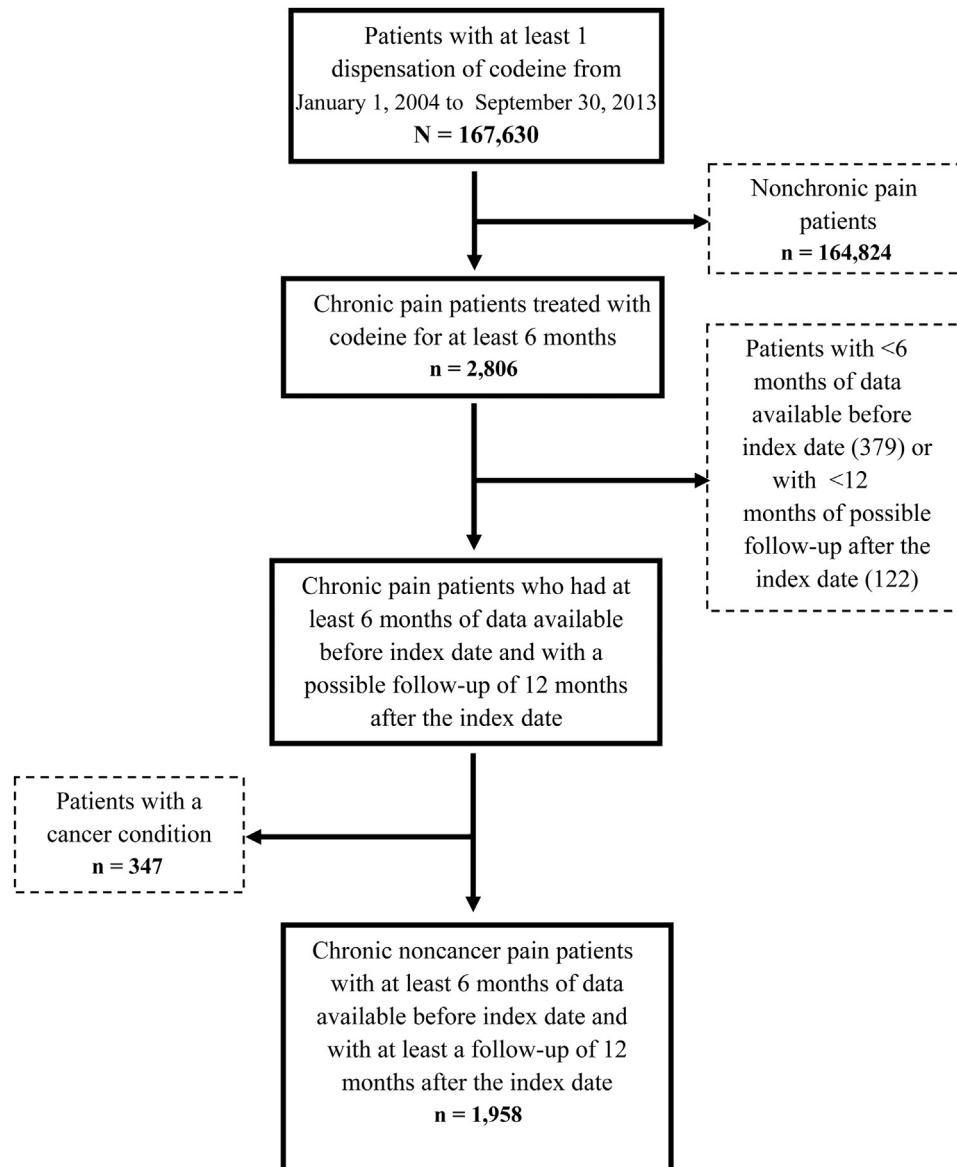


Figure 1. Flow diagram of included patients.

statistically significant ($P = .08$), increasing from 2.01% in 2004 to 6.29% in 2014.

Characteristics of Codeine Shoppers

Among codeine shoppers, 13.9% visited 2 different prescribers, 44.6% visited 3 to 5, and 41.5% more than 5 prescribers. Almost one-third (32.3%) of shoppers filled their prescriptions in 3 to 6 different pharmacies whereas 35.4% frequented 7 to 10, and the other one-third (32.3%) more than 10 pharmacies (Table 3). Shoppers were younger with a mean age of 41.1 ± 10.7 years (vs 63.5 ± 15.8 years for the nonshoppers; $P < .001$) and were more often low-income patients than nonshoppers (24.6% vs 8.0%; $P < .001$). Shoppers also presented a higher frequency of previous history of opioid or substance use disorders and mental health disorders (Table 1).

Risk Factors of Codeine Shopping Behavior

Univariate analysis results are presented in Tables 4 and 5. Considering general characteristics (Table 4), younger age, low-income status, history of opioid use disorders, and history of substance use disorders were positively associated with codeine shopping behavior. Considering analgesic and psychotropic drugs, previous use of strong opioids and previous and concurrent use of anxiolytic benzodiazepines were significant risk factors (Table 5).

In multivariate analysis (Fig 2), age remained strongly associated with codeine shopping behavior; HR = 7.29 (95% CI, 4.28–12.42), $P < .001$ for patients younger than 40 years versus older than 40 years. Mental health disorders were also associated with shopping behavior (HR = 2.25; 95% CI, 1.08–4.67, $P = .030$). Considering other medications, the risk of developing shopping behavior was higher among concurrent users of

Table 1. Characteristics of Included Patients, Codeine Shoppers, and Nonshoppers

	ALL PATIENTS (N = 1,958)	CODEINE NONSHOPPERS (N = 1,893)	CODEINE SHOPPERS (N = 65)	P
Age, y				
Mean ± SD	62.7 ± 16.1	63.5 ± 15.8	41.1 ± 10.7	<.001
Median (Q1–Q3)	63.0 (51–76)	64.0 (52–76)	41.0 (33–46)	<.001
Gender				.283
Male	720 (36.8)	692 (36.6)	28 (43.1)	
Female	1,238 (63.2)	1,201 (63.4)	37 (56.9)	
Low-income status				<.001
Yes	168 (8.6)	152 (8.0)	16 (24.6)	
No	1,790 (91.4)	1,741 (92.0)	49 (75.4)	
History of alcohol dependence				.287
Yes	24 (1.2)	23 (1.2)	1 (1.5)	
No	1,934 (98.8)	1,870 (98.8)	64 (98.5)	
History of opioid use disorders				.008
Yes	11 (.6)	8 (.4)	3 (4.6)	
No	1,947 (99.4)	1,883 (99.6)	62 (95.4)	
History of substance use disorders				.009
Yes	43 (2.1)	37 (1.9)	5 (7.7)	
No	1,916 (97.9)	1,856 (98.1)	60 (92.3)	
Active chronic liver disease				.107
Yes	35 (1.8)	32 (1.7)	3 (4.6)	
No	1,923 (98.2)	1,861 (98.3)	62 (95.4)	
Arthritis				.662
Yes	81 (4.1)	79 (4.2)	2 (3.1)	
No	1,877 (95.9)	1,814 (95.8)	63 (96.9)	
Mental health disorders				<.001
Yes	197 (10.1)	180 (9.5)	17 (26.2)	
No	1,761 (89.9)	1,713 (90.5)	48 (73.8)	

Abbreviation: Q, quartile.

NOTE. Data are presented as n (%) except where otherwise noted.

anxiolytic benzodiazepines with a HR = 3.12 (95% CI, 1.55–6.26, P = .001). Previous use of strong opioids was also identified as a statistically significant risk factor, HR = 2.94 (95% CI, 1.24–6.98, P = .015).

Discussion

The main result of this study is that codeine shopping behavior was encountered in 4% of CNCP patients in the first year of treatment in a large representative cohort of the French general population.

This study provides useful data where studies are limited.^{58,64} Indeed, the well established potential for dependence of codeine and the increasing awareness of its misuse contrast with the scantiness of research on prevalence of problematic use of codeine in CNCP patients, as stated by Van Hout et al in a recent review.⁶⁸ Data are particularly scarce in France where only 2 studies are available: in 2013 a cross-sectional study in community pharmacies reported that misuse of codeine analgesics concerned 6.8% of the patients exposed.⁵⁸ A 2009 French survey using questionnaires from pharmacies detected codeine abuse during the past month in 7.5% of patients.⁵⁰ In a Norwegian study

Table 2. Frequency of Shopping Episodes, Number of Patients Involved, and Duration of Codeine Treatment

NUMBER OF SHOPPING EPISODES DURING OVERALL FOLLOW-UP	NUMBER (%) OF CODEINE SHOPPERS	MEDIAN DURATION OF CODEINE TREATMENT (IQR)
1	18 (27.7)	420 (336–613)
2	10 (15.4)	295 (268–401)
3–5	10 (15.4)	420 (292–817)
6–10	4 (6.2)	358 (242–644)
11–20	5 (7.7)	1,158 (496–1,743)
21–30	5 (7.7)	1,054 (525–1,445)
>30	13 (20.0)	839 (676–1,008)
Total	65 (100)	522 (313–992)

Table 3. Number of Codeine Prescribers and Pharmacies Involved By Patients Who Developed Shopping Behavior During Overall Follow-Up

NUMBER OF DIFFERENT PRESCRIBERS	NUMBER OF DIFFERENT PHARMACIES			
	3–6	7–10	>10	TOTAL
2	6 (9.2)	2 (3.1)	1 (1.5)	9 (13.9)
3–5	13 (20.0)	14 (21.5)	2 (3.1)	29 (44.6)
>5	2 (3.1)	7 (10.8)	18 (27.7)	27 (41.5)
Total	21 (32.3)	23 (35.4)	21 (32.3)	65 (100%)

NOTE. Data are presented as n (%).

Table 4. Univariate Analysis of Patients' General Characteristics Associated With Codeine Shopping Behavior

VARIABLE	SHOPPING BEHAVIOR		HR	95% CI	P
	%	(N/N)			
Age, y					
≤40	16.8	(32/190)	9.07	5.54–14.84	<.001
>40	1.9	(33/1,768)		Reference	
Low-income status					
Yes	9.5	(16/168)	3.56	2.02–6.27	<.001
No	2.7	(49/1,790)		Reference	
Gender					
Female	3.0	(37/1,238)	.83	.50–1.37	.483
Male	3.9	(28/730)		Reference	
History of alcohol dependence					
Yes	4.2	(1/24)	1.11	.15–8.03	.917
No	3.3	(64/1,934)		Reference	
History of opioid use disorders					
Yes	27.3	(3/11)	10.13	3.16–32.49	<.001
No	3.2	(62/1,947)		Reference	
History of substance use disorders					
Yes	11.9	(5/42)	3.77	1.51–9.42	.004
No	3.1	(60/1,916)		Reference	
Active chronic liver disease					
Yes	8.6	(3/35)	3.33	1.04–10.66	.042
No	3.2	(62/1,923)		Reference	
Arthritis					
Yes	2.5	(2/81)	.58	.14–2.40	.457
No	3.4	(63/1,877)		Reference	
Mental health disorders					
Yes	8.6	(17/197)	3.42	1.96–5.97	<.001
No	2.7	(48/1,761)		Reference	

Abbreviations: n, number of codeine shoppers; N, number of total patients.

on new codeine users, .3% of patients became persistent users and .08% probable problematic users. Case series of codeine deaths have been particularly reported in Australia,⁵⁹ where the current situation appears alarming: codeine was the most dispensed opioid in 2011³⁷ and Roxburgh et al reported that codeine-related mortality in Australia more than doubled in a decade, mostly driven by a sharp increase in accidental overdoses.⁵⁹ Those who had accidentally overdosed were more likely to have a history of substance abuse and chronic pain.

This study also identified several independent risk factors and partially fills a knowledge gap on identification of risk profiles of codeine misusers. The main risk factors associated with codeine shopping behavior were younger age, mental health disorders, concurrent use of anxiolytic benzodiazepines, and previous use of strong opioids. Indeed, codeine shoppers were younger and patients younger than 40 years had a risk 7 times higher than others of developing shopping behavior. These results confirm the strong relationship between younger age and opioid abuse, misuse, or dependence reported in several studies.^{7,23,54,63} Furthermore, 26.2% of codeine shoppers presented mental health disorders and this comorbidity was a significant risk factor. Studies reported that patients with high risk of opioid use disorders have greater frequency of reported mental health disorders, which is a strong predictor of

Table 5. Univariate Analysis of Opioid Analgesic and Psychotropic Drug (Previous and Concurrent) Use Associated With Codeine Shopping Behavior

ITEM	SHOPPING BEHAVIOR		HR (95% CI)	P
	%	(N/N)		
Antidepressants, previous use				
Yes	3.72	(22/591)	1.24 (.74–2.08)	.411
No	3.15	(43/1,367)		Reference
Antidepressants, concurrent use				
Yes	4.29	(30/699)	1.45 (.89–2.38)	.138
No	2.78	(35/1,259)		Reference
Antipsychotics, previous use				
Yes	6.78	(8/118)	2.03 (.97–4.27)	.061
No	3.10	(57/1,840)		Reference
Antipsychotics, concurrent use				
Yes	3.97	(6/151)	1.26 (.54–2.92)	.592
No	3.27	(59/1,807)		Reference
Mood stabilizers, previous use				
Yes	5.41	(2/37)	1.84 (.45–7.54)	.397
No	3.28	(63/1,921)		Reference
Mood stabilizers, concurrent use				
Yes	8.51	(4/47)	1.73 (.54–5.53)	.354
No	3.19	(61/1,911)		Reference
Hypnotic BZD, previous use				
Yes	4.46	(21/471)	1.65 (.98–2.78)	.061
No	2.96	(44/1,487)		Reference
Hypnotic BZD, concurrent use				
Yes	4.40	(28/637)	1.52 (.93–2.49)	.097
No	2.80	(37/1,321)		Reference
Anxiolytic BZD, previous use				
Yes	4.56	(30/658)	1.81 (1.11–2.95)	.018
No	2.69	(35/1,300)		Reference
Anxiolytic BZD, concurrent use				
Yes	5.46	(46/843)	3.02 (1.80–5.17)	<.001
No	1.70	(19/1,115)		Reference
Strong opioids, previous use				
Yes	6.90	(6/87)	2.39 (1.03–5.56)	.042
No	3.15	(59/1,871)		Reference
Strong opioids, concurrent use				
Yes	1.92	(2/104)	.50 (.12–2.06)	.338
No	3.40	(63/1,854)		Reference
Weak opioids, previous use				
Yes	3.15	(14/445)	.88 (.49–1.60)	.683
No	3.37	(51/1,513)		Reference
Weak opioids, concurrent use				
Yes	4.71	(20/425)	1.24 (.72–2.13)	.446
No	2.94	(45/1,533)		Reference

Abbreviations: n, number of codeine shoppers; N, number of total patients; BZD, benzodiazepines.

opioid abuse and dependence.^{23,42,56} Concurrent use of anxiolytic benzodiazepines was also linked with a higher risk of shopping behavior. The association between benzodiazepines and opioid misuse is highlighted in several studies^{30,34} and higher levels of anxiety have been reported in opioid abusers.⁶¹ In the United States benzodiazepines were involved in 31% of the opioid-analgesic poisoning deaths in 2011, up from 13% of the opioid-analgesic poisoning deaths in 1999.¹⁵ Several studies reported a similar relationship specifically with weak opioids.^{31,59,73}

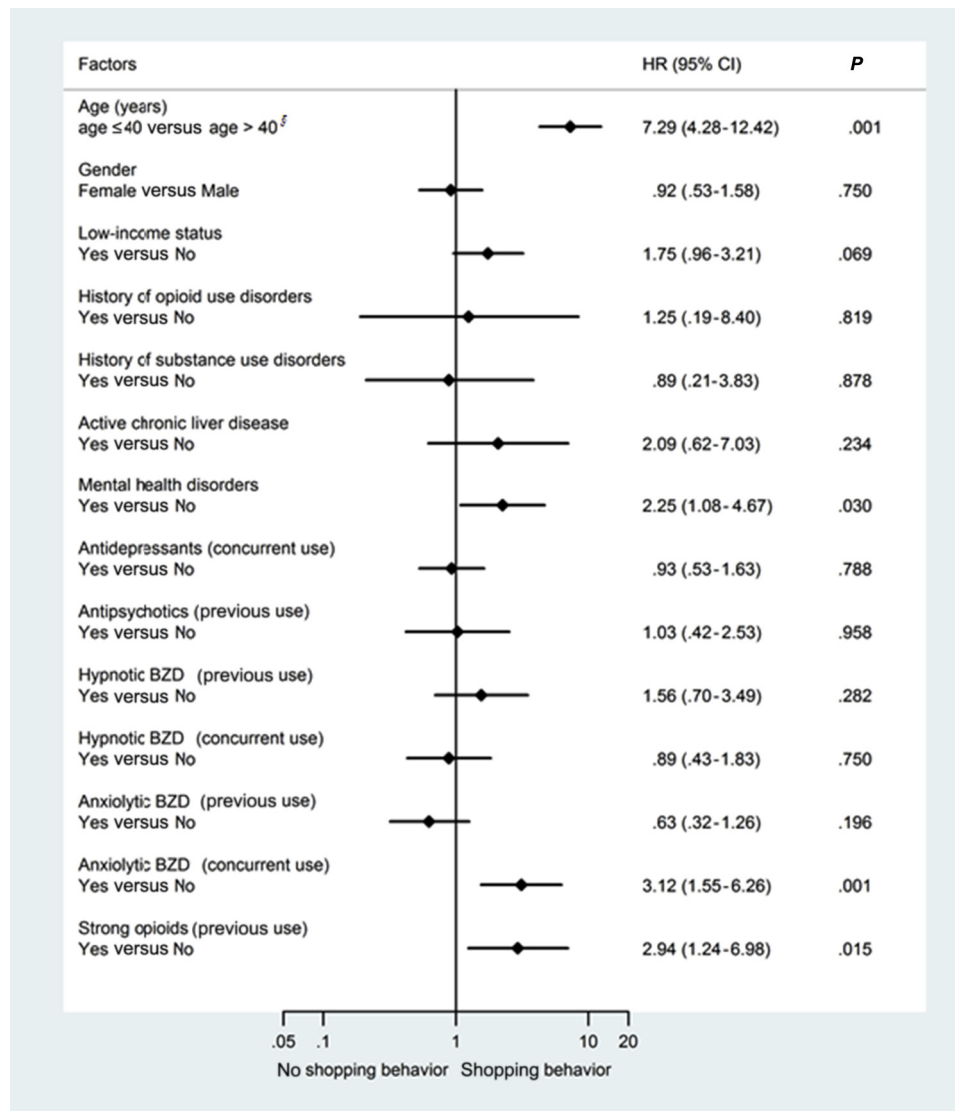


Figure 2. Multivariate analysis of risk factors associated with codeine shopping behavior in CNCP patients. § 'Age >40' category represents the reference group (ie, patients aged ≤40 years have a more than 7-fold higher incidence of shopping behavior than patients aged >40 years). Abbreviation: BZD, benzodiazepines.

Previous use of strong opioids was associated with a greater risk of developing shopping behavior and these findings are consistent with literature, which reported a greater risk of use disorders in opioid non-naïve subjects.^{11,12,56} Rice et al showed that having filled 1 to 5 opioid prescriptions in the previous 12 months was associated with an odds ratio of 2.23 (95% CI, 1.99–2.51) for being diagnosed with a substance use disorder.⁵⁶ Cepeda et al reported that patients with a history of previous opioid use had a risk 10-fold greater of developing opioid shopping behavior.^{11,12}

Interestingly, this study did not find a significant association between alcohol use disorder and codeine shopping. A similar result was reported in a large Australian prospective case series study examining morbidity associated with codeine misuse: most patients had no previous history of substance use disorder or alcohol treatment history.²⁹ This suggests that there may be differences in the substance use profile between codeine-dependent

patients and strong prescription opioid-dependent patients, as stated by Nielsen et al in a recent case series of 135 patients⁴⁷: stimulant and cannabis use were more frequent in the strong opioid group and the codeine group was less likely to report a history of heroin use (odds ratio = .16; 95% CI, .07–.40).

Strengths and Limitations

To our knowledge, this is the first study to assess the incidence of codeine shopping behavior in a French cohort of CNCP patients.

The 1-year incidence of codeine shopping behavior may seem like a low rate from a clinical perspective, but it represents a significant public health concern, because millions of individuals receive chronic weak opioid therapy for CNCP.⁸ Consequently, even a low rate of codeine misuse may result in a large number of serious adverse effects. Moreover, we recently showed

that the 1-year incidence rate of doctor shopping for tramadol in CNCP patients, using the same methodology, was 4-fold lower than for codeine,¹⁶ indicating that the codeine problem should be of interest and would need to be monitored. This is all the more important because an increasing trend in codeine shopping behavior is being observed in France since 2004. Internationally, responses to the problematic use of codeine have resulted in upscheduling and increased restrictions on the availability of OTC codeine. Restriction of pack sizes and brief interventions in pharmacies were also implemented.⁶⁵ However, in Australia, a recent study⁹ reported that codeine upscheduling to 'pharmacist only' in 2010 had no effect on misuse.

Codeine misuse is also a prescriber issue: other preventive strategies could focus on improving education of prescribers about effective and safe pain management. Several authors have suggested developing prescription monitoring programs to limit doctor shopping.^{2,17,41,55} A high level of monitoring is required to ensure that the effectiveness of chronic codeine therapy is properly reviewed on a regular basis. Patients should be reassessed periodically to re-evaluate the benefits versus risks, including aberrant substance-related behaviors.⁶¹ The identification of associated risk factors will provide tools to clinicians to screen patients before initiating chronic codeine treatment. Other strategies such as referring high risk patients to addiction and pain specialists and urine drug screening are suggested.⁴¹

Because codeine is available OTC, pharmacists may also have an important role to play in minimizing risks by advising consumers on the best pain management and harms.

The education of patients seems important as well: clarifying misconceptions around the supposed safety of codeine is important; patients should be informed of the addictive potential of codeine and should be warned of the risk of fatal overdose especially when combined with other drugs such as benzodiazepines.⁵⁹

The definition of doctor shopping used in this study is valuable because it has been explicitly linked to abuse in previous studies.^{13,40} Besides, numerous studies have shown that the index that incorporates excess dose supply and multiple prescribers and pharmacies appeared to be sensitive and specific for identifying patients with opioid abuse.^{13,45,51} Manchikanti et al showed that 90% of patients with drug abuse could be identified by excessive opiate needs, deception or lying to obtain controlled substances, and current or previous intentional doctor shopping.⁴³

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Nonetheless, this study has several limitations common to most health insurance claims databases. First, doctor shopping is not the sole way for opioid analgesics abuse. Indeed patients can also obtain large quantities of opioids through friends, family, internet, or illegal market.^{42,45,71} Second, another limitation is actually the alternative that one prescriber may voluntarily provide a substantial amount of codeine as requested by the individual patient, to avoid shopping behavior. Consequently, opioid abuse might be underestimated in this study. Third, it is noteworthy that in France preparations containing up to 20 mg of codeine can be dispensed without any prescription. Because codeine is indeed available as an OTC medicine, the rate of doctor shopping may be potentially underestimated because OTC drugs are not captured in our database. However, from 2008 to 2013, the proportion of prescribed and reimbursed codeine sales assessed from IMS Health drugs data represented more than 90% of overall codeine sales, which might limit the risk of an important underestimation of the risk of codeine shopping behavior. However, the problem of OTC in contributing to codeine misuse may not be minor. Indeed, the 2 sole French studies focusing on nonprescription codeine analgesics identified misuse in approximately 6.8 to 7.5% of patients, which is more than the estimation in the present study, but less than 20% of these patients were probable chronic pain patients. Interestingly, the literature has reported a wide profile of patients misusing codeine.⁶⁸ OTC codeine users may be a heterogeneous group, including not only chronic pain patients but also recreational use among university students, psychiatric patients, and addiction patients. Opioid-maintained patients have been identified as a particular cohort of dependent users, using codeine to alleviate withdrawals.⁶⁸ Because of the absence of specific monitoring systems, the exhaustive identification and characterization of OTC codeine misusers remains challenging. Fourth, the lack of detailed clinical information and the small sample size of shoppers may have been a limitation to identify further significantly associated risk factors. However, a number of risk factors commonly cited in other studies were identified.

Conclusions

Study findings call for vigilance considering the nontrivial incidence of codeine doctor shopping in France. Appropriate use from the perspective of patients and health care providers should be encouraged.

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1300 The Journal of Pain

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