

Research Paper

The impact of an easy access drug supply management policy law on the consumption and abuse of opioids in Catalonia: A population-based study



Neus Carrilero^a, Toni Mora^b, Anna García-Altés^{a,c,d,*}

^a Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS), Barcelona, Spain

^b Research Institute for Evaluation and Public Policies (IRAPP), Universitat Internacional de Catalunya (UIC), Barcelona, Spain

^c CIBER de Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain

^d Institut d'Investigació Biomèdica (IIB Sant Pau), Barcelona, Spain

ARTICLE INFO

Keywords:

Opioid use
CNCP
Opioid misuse

ABSTRACT

Background: Over the last two decades, the rise in opioid prescription has worsened health outcomes worldwide, increasing both levels of abuse and mortality rates. In order to reduce the scale of this public health problem, new policies have been implemented in many countries. In 2012, Spain adopted new legislation on opioid prescription (the ROE law), which meant that practitioners no longer needed to obtain extra authorisation in order to prescribe strong opioids. The objective of the paper is to assess the impact of this law on opioid use and abuse in Catalonia, Spain.

Methods: We established two measures of the use of strong and weak opioids: DDDs, and abuse. We used benzodiazepines and antidepressants as controls, and adjusted for age, sex, drug co-payment level, death or near death, cancer diagnosis, morbidity group, and type of prescription. The data were obtained from administrative and dispensing drug databases in a population of 7.5 million inhabitants. We estimated two-way fixed effects using difference in difference models.

Results: The ROE law impacted reducing the monthly use of strong opioids by 0.903 DDDs, representing a 3.15% decrease in the mean monthly use of strong opioids. However, abuse rose 1.86 times compared with the average pre-ROE value, which represents an increase of 11,190 months of opioid abuse (i.e., an 11.33% of all monthly opioids use).

Conclusion: The abolition of the duplicate prescription programme for strong opioids led to a reduction in the average monthly use of strong opioids, but an increase in abuse.

Introduction

There has been a huge rise in opioid prescription in recent years, mainly because of their wider use to treat chronic non-cancer pain (CNCP). This increase has occurred in spite of the serious risks they entail and a lack of evidence of their long-term effectiveness (Chou et al., 2015). Worldwide opioid prescription doubled from 2001 to 2013, while related health outcomes also worsened (Degenhardt et al., 2014; Majors-Foley, 2016). Indeed, the US officially declared an opioid overdose crisis in 2017, as a consequence of the increase in related deaths (more than 399,000) since 1999 (Scholl, Seth, Kariisa, Wilson, & Baldwin, 2019). Several different patterns based on geographical and sociodemographic characteristics have been reported in opioid prescription, use, abuse, and related death (Finkelstein, Gentzkow, & Williams, 2018; Schieber et al., 2019; Scholl et al., 2019).

European countries also report increases in prescription rates, the number of users, overdoses, and the number of high-risk opioid consumers (Bosetti et al., 2019; Curtis et al., 2019; Kalkman, Kramers, van Dongen, van den Brink, & Schellekens, 2019). In Spain, opioid use rose by 83.6% between 2008 and 2015 (from 7.25 defined daily doses (DDD)/1000 inhabitants per day to 13.31 DDD) (Agencia Española de Medicamentos y Productos Sanitarios, 2017). Between 2012 and 2016, the use of strong opioids (morphine, fentanyl, buprenorphine, tapentadol, etc.) rose by 49%, while the use of weak opioids (codeine and tramadol) increased by 42%. Tramadol, fentanyl, and tapentadol were the drugs with the greatest increases. Studies performed in specific regions in Spain also show upward trends both in opioid prescription and in intensity of treatment (Hurtado, García-Sempere, Peiró, & Sanfélix-Gimeno, 2020).

In an attempt to reduce the magnitude of this public health concern, many countries have implemented new regulations and policies. Some of these policies have been evaluated in previous work, mainly in the US (Buchmueller & Carey, 2018; Hartung et al., 2018; Mauri, Townsend, & Haffajee, 2020; Meara et al., 2016; Rhodes, Wilson, Robinson, Hay-

* Corresponding author.

E-mail address: agarciaaltes@gencat.cat (A. García-Altés).

den, & Asbridge, 2019). These studies have focused on indicators of opioid prescription, use, abuse, and health-related outcomes. According to some recent reviews, there is moderate evidence that drug supply management policies, including prescription drug monitoring programmes (PDMPs), reduce opioid prescription. However, the impact of specific policies varies according to the type of regulation, characteristics of the population, and the degree of strictness, which suggests that there is a complex social component in their effectiveness beyond their application. (Dasgupta, Beletsky, & Ciccarone, 2018; Fink et al., 2018; Mauri et al., 2020; Meara et al., 2016). It has also been stressed that the root causes of the opioid crisis do not lie only in supply management policies (which in some cases may have spillover effects) but may also include demand-side factors, such as the conduct of the pharmaceutical industry and healthcare providers (Alpert, Evans, Lieber, & Powell, 2019; Maclean, Mallatt, Rhum, & Simon, 2020).

In 2012, going against the worldwide trend in opioid regulations, Spain approved legislation to facilitate opioid prescription (known as the “ROE law”, ROE standing for “Official Opioid Prescription” or “*Receta Oficial de Estupefacientes*” in Spanish). Prior to the approval of this law, doctors could only prescribe opioids through a duplicate prescription programme, which required an Official Opioid Prescription (*Receta Oficial de Estupefacientes-ROE*) provided by their Official Medical Association or through the health authorities. If the medication was prescribed by the Spanish National Health System (NHS) an ordinary prescription was also required (plus the corresponding co-payment depending on the patient’s socioeconomic characteristics). Without the ROE, narcotics could not be dispensed at the pharmacy office. Thus, two prescriptions were required for dispensing a strong narcotic via the NHS: the ROE and the ordinary prescription.

The implementation of the 2012 law abolished the ROE as a requirement for the dispensing of strong opioids under electronic prescription through the NHS, switching from a duplicate copy prescription programme to an adapted electronic prescription system without any additional control. It also increased the validity of the prescription from one to three months of treatment (Royal Decree 1675/2012, 2012). Meanwhile, the electronic prescription system was gradually implemented. Although the ROE law was introduced to improve access for patients receiving treatment with opioids, little is known about the effect the law has had on prescription behaviours or on opioid use.

The objective of the paper is to assess the impact of the law on strong opioid use and opioid abuse. The analysis is based on data from Catalonia, one of Spain’s autonomous regions.

Methods

Setting

As in Spain as a whole, healthcare in Catalonia is organised as a National Health System, funded by taxes. All residents (7,488,275 as of 2017) are granted universal public healthcare coverage by law. Public healthcare spending represents 5.4% of Catalan GDP. The use of publicly funded healthcare services is free, with the sole exception of the drug supply system, which is based on a co-payment programme calculated according to the individual’s income (or, if appropriate, according to the social security benefits received). Each resident is assigned a personal healthcare ID, which can be used to trace their use of healthcare services and their prescribed and dispensed drugs.

In Catalonia, certain measures regarding drug prescriptions were implemented during 2012 and 2013. The region had previously introduced an electronic prescription system in 2006, which became fully available in the whole of the region in May 2010. The electronic prescription system was operated in tandem with the duplicate copy prescription up to February 2013. The drug co-payment system in Catalonia was reformed on 1 August 2012 for the active population, and on 1 October 2012 for pensioners. A capped drug co-payment of €1 per prescription with an annual limit was temporarily introduced on 23 June 2012, but was sus-

pended on 15 January 2013. Finally, the ROE law came into force in February 2013 (CatSalut, 2013) (see Fig. 1).

Study population

The study population comprised all residents in Catalonia using strong opioid drugs between March 2007 and December 2018; that is, a period of 70 months spanning the implementation of the ROE law. Any person over 15 years of age who had been dispensed any strong opioid, regardless of the duration of treatment or the number of prescriptions dispensed during the study period, was considered a strong opioid patient.

The main control variable was the use of weak opioids by strong opioid patients. However, given that individuals could switch from strong to weak opioids and vice versa, we also considered benzodiazepines or antidepressants used by all strong opioid patients as controls.

Data

Data were sourced from three different databases. The first was the Central Register of Insured Persons, an automated database that manages individual healthcare IDs and includes 99.6% of the population of Catalonia (7,570,452 individuals in 2019). This database allows individual identification of the level of drug co-payment and the economic benefits received via the social security system. The register provided us with our reference population and individual level information: age, sex, socioeconomic status, health area of residence, and date of death. The second was the Registry of the Minimum Basic Dataset, an administrative register containing detailed information on sociodemographic characteristics and medical diagnoses (coded using the International Classification of Diseases, 9th Edition). The registry includes all contacts an individual has with the public healthcare system: primary care, hospital care, emergency, mental health, and long-term care services. Third, and finally, the Electronic Prescription Database provided information on all prescriptions dispensed at community pharmacies to each patient, with the level of observation being prescriptions dispensed per month. Each event is associated with the patient’s health ID number, the ATC7 (WHOCC-ATC/DDD Index n.d) of the active ingredient, pharmaceutical form, defined daily doses (DDD), number of prescribers (number of different prescribers that each individual had), type of prescription (electronic or paper), and drug co-payment level.

Details on the drugs included in the study are provided in the Supplementary Material, Table 1a to c. First, the opioids included (strong and weak) were those available in community pharmacies in Spain for analgesic purposes: strong –N02AA01 (morphine) and N02AA03 (hydromorphone); N02AA05 (oxycodone), N02AA55 (oxycodone and naloxone); N02AB03 (fentanyl); N02AX06 (tapentadol); N02AB02 (pethidine); N02AE01 (buprenorphine) and N07BC51 (buprenorphine associations); and weak – N02AA52 (codeine associations), N02AJ06 (codeine and paracetamol), N02AJ07 (codeine and acetylsalicylic acid), N02AJ08 (codeine and ibuprofen); N02AJ13 (tramadol and paracetamol), N02AJ14 (tramadol and dextropropofen), N02AX02 (tramadol), and N02AX52 (tramadol, associations). These drugs were classified according to their pharmacological characteristics, analgesic potency, and dependence, as described in the 1961 Convention on Narcotic Drugs. Drugs included in list I of this Convention (grades i to v) were classed as strong or narcotic drugs and their dispensation required additional control. Drugs not included in list I were called weak and required a regular prescription. Some common opioid formulations were not included because their main indication in Spain is for the treatment of opioid dependence (e.g., methadone) or because they are not available (e.g., hydrocodone and oxycodone). Buprenorphine formulations are available in community pharmacies, but are only indicated for pain treatment. Second, the drugs derived from and related to benzodiazepine were: N05BA (benzodiazepine-anxiolytics), N05CD (benzodiazepine-



Fig. 1. Timeline of regulations in the drug management system in Catalonia during the period 2012–2013.

Table 1

Characteristics of monthly opioid use before and after the ROE law. Catalonia, March 2007 to December 2018.

	Before the ROE law		After the ROE law	
	(N = 11,515,881) Women(mean, SD)	(N = 3422,429) Men(mean, SD)	(N = 17,812,854) Women(mean, SD)	(N = 5561,294) Men(mean, SD)
DDD				
Weak opioids	13.83 (15.36)	12.47 (16.39)	13.76 (13.90)	12.52 (12.70)
Strong opioid	27.43 (33.75)	30.65 (45.62)	23.71 (31.58)	27.49 (48.86)
Benzodiazepines	43.94 (48.93)	43.64 (57.10)	39.64 (39.98)	40.21 (48.46)
Antidepressants	50.32 (37.12)	48.26 (37.75)	45.40 (32.21)	43.79 (33.31)
DDD/per 1000 inhabitants per day				
Weak opioids	7.25 (2.63)	2.59 (1.04)	10.86 (3.73)	4.32 (1.58)
Strong opioid	2.90 (1.51)	1.44 (0.98)	5.59 (2.33)	2.45 (1.37)
Benzodiazepines	123.44 (26.99)	58.61 (14.35)	122.31 (28.64)	59.84 (15.36)
Antidepressants	120.05 (27.06)	46.66 (11.7)	132.08 (28.28)	52.77 (12.07)
Abuse [¶]				
Opioids	0.057 (0.23)	0.059 (0.24)	0.058 (0.23)	0.053 (0.22)
Benzodiazepines	0.047 (0.21)	0.047 (0.21)	0.033 (0.18)	0.037 (0.19)
Antidepressants	0.163 (0.37)	0.156 (0.36)	0.122 (0.33)	0.121 (0.33)
% users [†]				
Weak opioids	1.58 (0.50)	0.63 (0.22)	2.40 (0.72)	1.05 (0.37)
Strong opioids	0.33 (0.17)	0.14 (0.07)	0.75 (0.31)	0.28 (0.12)
Benzodiazepines	9.70 (1.92)	4.38 (0.95)	10.29 (1.83)	4.76 (0.93)
Antidepressants	7.34 (1.66)	2.82 (0.70)	8.86 (1.59)	3.47 (0.69)
% electronic prescription				
Weak opioids	0.38 (0.49)	0.33 (0.47)	0.95 (0.21)	0.94 (0.24)
Strong opioids	0.31 (0.46)	0.26 (0.44)	0.98 (0.14)	0.97 (0.17)
Benzodiazepines	0.46 (0.50)	0.42 (0.49)	0.98 (0.15)	0.96 (0.19)
Antidepressants	0.49 (0.50)	0.45 (0.50)	0.98 (0.13)	0.97 (0.17)
Age				
Weak opioids	68.38 (15.36)	63.73 (16.89)	68.32 (15.33)	63.69 (16.27)
Strong opioids	73.70 (13.73)	68.72 (14.08)	74.39 (13.69)	68.61 (14.40)
Benzodiazepines	69.56 (14.10)	66.86 (15.05)	69.53 (14.14)	65.80 (15.02)
Antidepressants	67.41 (14.47)	65.04 (15.61)	68.20 (14.48)	64.71 (15.55)
Socioeconomic status [§]				
More disadvantaged	0.026 (0.16)	0.015 (0.12)	0.061 (0.24)	0.043 (0.20)
Disadvantaged	0.912 (0.28)	0.881 (0.32)	0.816 (0.39)	0.749 (0.43)
Less disadvantaged	0.061 (0.24)	0.103 (0.30)	0.122 (0.33)	0.205 (0.40)
Not disadvantaged	0.001 (0.03)	0.001 (0.04)	0.001 (0.04)	0.003 (0.05)
Average co-payment level ^{††}	9.138 (16.47)	10.869 (17.89)	13.494 (14.19)	15.279 (16.00)
GMA risk				
No risk	0.089 (0.28)	0.109 (0.31)	0.163 (0.37)	0.190 (0.39)
Minor risk	0.460 (0.49)	0.315 (0.46)	0.410 (0.49)	0.317 (0.46)
High risk	0.333 (0.47)	0.389 (0.49)	0.305 (0.46)	0.309 (0.46)
Very high risk	0.117 (0.32)	0.186 (0.39)	0.121 (0.33)	0.183 (0.38)
N ^o . prescribers				
Weak opioids	1.890 (0.68)	1.939 (0.65)	1.795 (0.62)	1.851 (0.61)
Strong opioids	1.994 (0.88)	2.202 (0.99)	1.873 (0.79)	2.052 (0.91)
Benzodiazepines	1.805 (0.72)	1.854 (0.75)	1.718 (0.63)	1.762 (0.66)
Antidepressants	1.816 (0.72)	1.873 (0.75)	1.741 (0.66)	1.791 (0.69)
Cancer diagnosis	0.038 (0.19)	0.077 (0.27)	0.071 (0.26)	0.135 (0.34)
Close to death	0.021 (0.14)	0.061 (0.24)	0.020 (0.14)	0.046 (0.21)

[¶] Abuse: 0 no abuse; 1 abuse. Strong and weak opioid abuse considered as daily consumption of >120 MED, antidepressants as >60 mg fluoxetine equivalents and benzodiazepines as >40 mg diazepam equivalents.

[†] % users month: percentage of all users of each drug type in Catalonia.

[§] Socioeconomic status: More disadvantaged (on social benefits and/or no employed person in the home), disadvantaged (<€18,000 annual income), less disadvantaged (€18,000–100,000 annual income), not disadvantaged (>€100,000).

^{††} Average co-payment level: Average prescription co-payment (0–100%).

hypnotics), and N05CF (benzodiazepine-non-hypnotic); Finally, the antidepressants were the drugs referred to by the code N06A.

Outcomes

At an individual level, we defined two indicators as proxies of consumption: DDDs and abuse, which were analysed separately. DDD is a standardized measure that captures the consumption of any drug and allows to adequately comparing them. DDD was calculated by all type of drugs (weak opioids, strong opioids, benzodiazepines, and antidepressants). Abuse was defined as monthly individual opioids dispensed above an average daily morphine-equivalent dose (MED) of 120 mg (Finkelstein, Gentzkow, & Williams, 2018; Dowell, Haegerich, & Chou, 2016; Meara et al., 2016). We computed this indicator for opioids (adding together both strong and weak opioids), benzodiazepines, and antidepressants using conversion tables to transform mg for each active substance according to its strength (see Supplementary Material Table 1a).

Next, benzodiazepine abuse was established by identifying individuals with monthly drug dispensation that resulted in an average daily diazepam-equivalent above 40 mg, using conversion tables to determine the mg of each active substance (see Supplementary Material Table 1b). With regard to antidepressants, abuse was established by identifying “high antidepressant users”, that is, any individual with monthly drug dispensation that resulted in an average daily fluoxetine-equivalent consumption of above 60 mg, using conversion tables to determine the mg of each active substance (see Supplementary Material Table 1c).

Covariates

Finally, as control variables that might affect opioid use, we took into account age, sex, death or near death, a cancer diagnosis over the study period, morbidity group according to the Adjusted Morbidity Groups classification (Dueñas-Espín et al., 2016), socioeconomic status (most disadvantaged: on social benefits and/or no employed person in the home; disadvantaged: <€18,000 annual income; less disadvantaged: €18,000–€100,000 annual income; not disadvantaged: >€100,000 annual income), drug co-payment level (from 0% to 100%) of each prescription, type of prescription (electronic or paper), and number of prescribers.

Analysis

We estimated difference by means of two-way fixed effects difference models, introducing dummy variables for all the policy measures of interest and their interactions with the four drug types considered (weak opioids, strong opioids, benzodiazepines, and antidepressants). Two-way fixed effects accounted for individual fixed effects, given that we had repeated cross-section values per individual for any kind of drug, and fixed effects relative to health area levels. The models considered error terms and standard errors were clustered at health area level.

$$Y_{d,i,t} = X_{i,t}\beta + drug_d\theta_1 + euro_i\gamma_1 + cp_i\gamma_2 + Roe_law_i\gamma_3 + electronic_{i,t}\gamma_4 + electronic_{i,t} \cdot Roe_law_i\gamma_5 + trend_t + \alpha_i bha_i + \epsilon_{i,t,d}$$

where Y indicates the variable of interest (DDD and abuse) by drug d , individual i in time t (months) whereas X_i is a set of observable characteristics (gender, age, average co-payment rates, cancer condition, death or near death, SEP and GMA). Age was introduced non-linearly and we also accounted for a non-linear tendency (trend). The *euro* dummy represents the introduction of € co-payment from July 2012 to January 2013, *cp* indicates the new co-payment scheme in Spain after August (active population)/October (pensioners) 2012, *electronic* indicates the type of prescription and *Roe_law* denotes the period in which the ROE policy was applied only to strong opioids (from February 2013). Our main coefficient of interest is γ_3 . Although the € co-payment

measure and the new co-payment measures affected all drugs, the ROE law had an impact only on strong opioids.

The variable *drug* identifies the kind of drug considered. In this regard, for DDDs we included weak and strong opioids, benzodiazepines, and antidepressants, and for abuse all opioids together, plus benzodiazepines and antidepressants for all users of strong opioids during the period considered (March 2007–December 2018). Finally, we considered two-way fixed effects accounting for: (i) individual fixed effects (α_i) given that we repeated cross-section values per individual for any kind of drug, and (ii) the fixed effects that might condition the probability of prescription based on common practices of medical doctors at basic health area level (bha_i). Individual fixed effects remove time-invariant characteristics such as gender from equations. Obviously, the models considered error terms ($\epsilon_{i,t,d}$) and standard errors were clustered at *bha* level given that more medical decisions and experiences are shared at this aggregated level.

Finally, we performed sensitivity analyses for a specific subsample; individuals whose co-payment level was not affected by the policy measure starting in August or October 2012 or by the € co-payment during 23 June 2012–15 January 2013 period. Assessing this population allowed us to capture the impact of the ROE law on individuals who were not affected by other measures introduced in the period studied.

Results

The study included 2,133,208 individuals, of whom 322,610 (58% female) were exclusively strong opioid users. From March 2007 to December 2018, data registers revealed that 15,736,905 monthly opioid prescriptions were dispensed (71.48% to women), the most common being for weak opioids (79.77%). Women used 71.26% of weak opioids and 72.35% of strong opioids. The number of individuals using both opioids and benzodiazepines was 995,782 (66.76% female), while 650,968 used both opioids and antidepressants (72.66% female).

Table 1 presents the individual characteristics of opioid users. With regard to the outcomes, average monthly DDD was lower for all drugs after the implementation of the ROE law, although post implementation of the €1 co-payment, all drugs showed a decrease in DDDs with the exception of strong opioids (see Fig. 2). The DDD/1000 inhabitants per day and the percentage of users by month showed increases after the ROE law, irrespective of the drug considered.

The average age of strong opioid users was 74 years (± 14) for women and 69 (± 14) for men, both pre- and post-legislation, and was higher than in weak opioid users. After the ROE law, the number of less disadvantaged users of strong opioids decreased and the number of disadvantaged users increased, in both sexes. It was also notable that women's use was more related to lower socioeconomic levels than men, in both periods. Finally, the average frequency of cancer and of patients close to death were below 1%.

Figs. 2 and 3 show monthly DDDs trends. A decrease in monthly individual use of all drugs is observed, which, combined with the growing sum of DDDs, reflects a higher number of users per month over time (see Supplementary Material Figure 2). In terms of population use (see Table 1 and Supplementary Material Figure 3), strong opioid DDD/1000 inhabitants per day increased by 221.39% for women and by 137.74% for men over the period 2007–2018. Indeed, like DDDs, DDD/1000 inhabitants per day decreased after €1 co-payment for all drugs except strong opioids. Over the period following the implementation of the ROE law, the use of benzodiazepines and antidepressants stabilised, but the use of both strong and weak opioids continued to rise.

The ROE law was associated with a reduction in strong opioid DDDs but an increase in opioid abuse. Tables 2 and 3 display the marginal effects on DDDs and abuse for each policy measure in the general population and in subsample. The estimated reduction in strong opioid use in the general population was 0.903 DDD, which represents a 3.15% decrease compared with the average monthly consumption before the

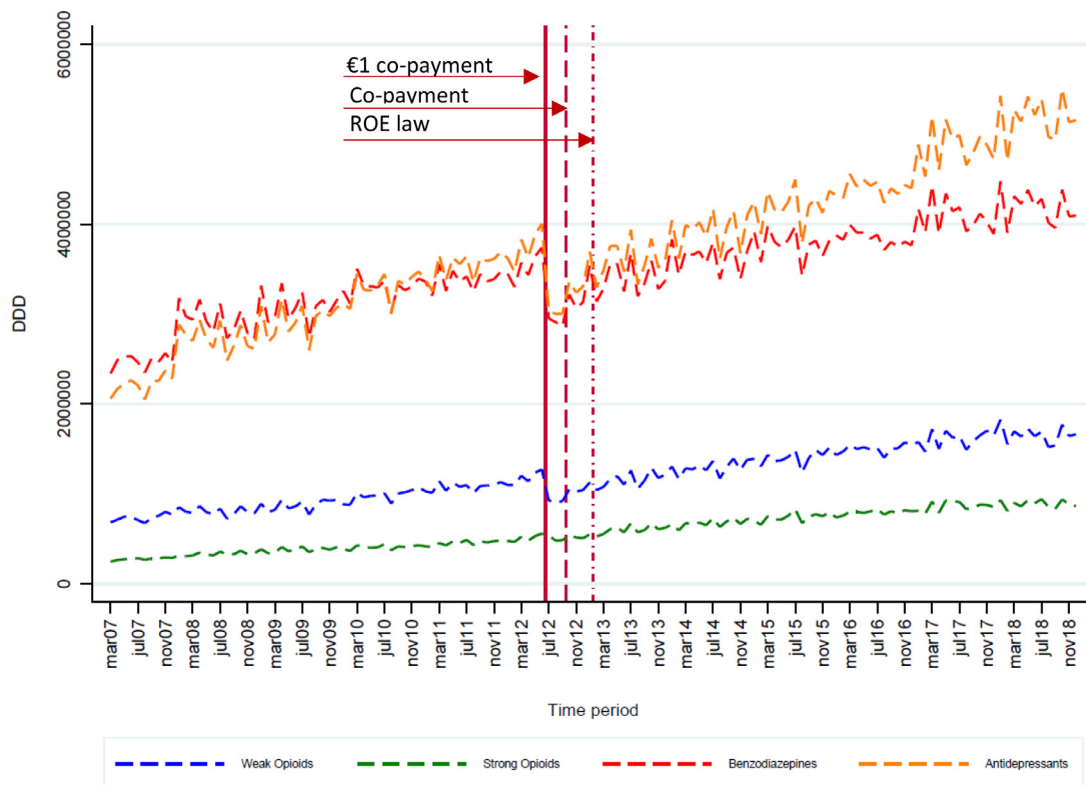


Fig. 2. Evolution of the monthly total number of DDDs by drug. Catalonia, March 2007 to December 2018.

* Use by strong opioid patients.

Solid line: €1 co-payment per prescription period (23 June 2012 to 15 January 2013); Dash line: New co-payment scheme (1 October 2012); Dash-dot line: ROE law (1 February 2013).

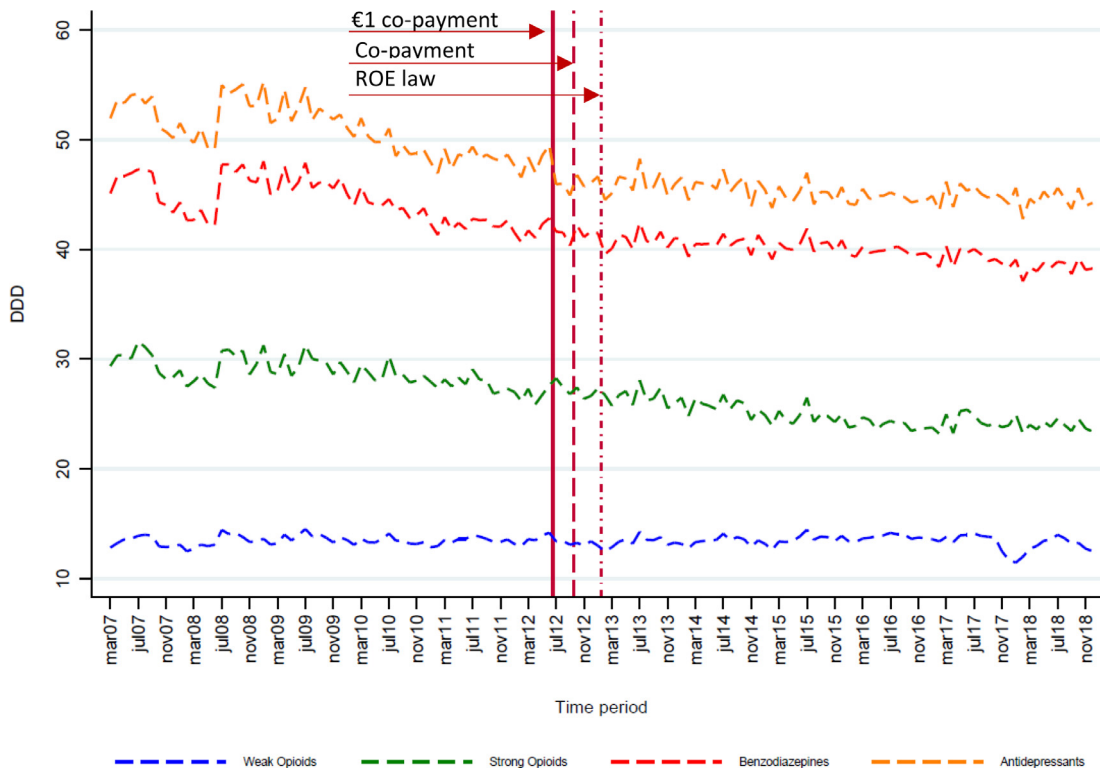


Fig. 3. Evolution of the individual monthly average number of DDDs by drug. Catalonia, March 2007 to December 2018.

* Use by strong opioid patients.

Solid line: €1 co-payment per prescription period (23 June 2012 to 15 January 2013); Dash line: New co-payment scheme (1 October 2012); Dash-dot line: ROE law (1 February 2013).

Table 2
Two-way fixed effects DiD marginal effects in DDD and for specific subsample. Catalonia, March 2007 to December 2018. Catalonia.

	Overall	No change in co-payment scheme and €1 co-payment ^{††}
Strong opioids	7.668 (0.212)***	10.436 (0.314)***
Benzodiazepines	24.735 (0.193)***	29.913 (0.200)***
Antidepressants	28.904 (0.167)***	26.179 (0.252)***
ROE law	-0.903 (0.221)***	-0.685 (0.305)**
€1 co-payment	0.060 (0.047)	0.437 (0.086)***
New co-payment	1.945 (0.066)***	0.912 (0.118)***
Electronic prescription	2.273 (0.121)***	2.601 (0.154)***
N°. observations	37,658,393	14,421,288
N°. individuals	1,479,143	633,823
Adj. R2	0.3910	0.3822
Root MSE	29.22	32.38

Note: Regressions include non-linear trend, non-linear age, close to death, cancer condition, number of prescribers, average drug co-payment, adjusted morbidity group, and socioeconomic status. We considered an interaction between ROE law and electronic prescription.

^{††} No change in co-payment and €1 co-payment: individuals not affected by the co-payment or the €1 co-payment. *** Significant at 1% ** Significant at 5% * Significant at 10%.

Table 3
Two-way fixed effects DiD marginal effects in abuse and for specific subsample. Catalonia, March 2007 to December 2018.

	Overall population	No change in co-payment scheme and €1 co-payment ^{††}
Benzodiazepines	-0.004 (0.001)***	-0.022 (0.001)***
Antidepressants	0.088 (0.001)***	0.074 (0.002)***
ROE law	0.107 (0.002)***	0.117 (0.003)***
€1 co-payment	0.006 (0.000)***	0.014 (0.001)***
New co-payment	0.005 (0.000)***	-0.005 (0.001)***
Electronic prescription	0.000 (0.001)	0.003 (0.001)***
N°. observations	37,311,970	14,421,288
N°. individuals	1,477,622	633,822
Adj. R2	0.2414	0.2711
Root MSE	0.23	0.25

Note: Regressions include non-linear trend, non-linear age, close to death, cancer condition, number of prescribers, average drug co-payment, adjusted morbidity group, and socioeconomic status. We considered an interaction between ROE law and electronic prescription.

^{††} No change in co-payment and €1 co-payment: individuals not affected by the co-payment or the €1 co-payment. *** Significant at 1% ** Significant at 5% * Significant at 10%.

ROE law. In the subsample of patients whose co-payment level or €1 co-payment did not change, the reduction in use was 2.37%.

Regarding opioid abuse, the increase is 1.86 times the average value prior to the ROE law. The estimated coefficient (increase of 0.107) represents a rise of 11,190 months of opioid abuse (11.33% of all monthly opioids use). In the subsample of patients whose co-payment level or €1 co-payment did not change, monthly opioid abuse increased by 12.39%.

Concerning the other policies, electronic prescription rose monthly strong opioids use by 2273 DDDs, a 7.90% increase compared with the period before the ROE law. Likewise, new co-payment rose by 1945 DDDs, a 6.76% increase. Monthly opioids abuse rose slightly after the implementation of the 1€ co-payment (estimated coefficient 0.006) and after the establishment of the new co-payment (estimated coefficient 0.005) reflecting increases of 0.63% and 0.53% in all monthly opioid use since the introduction of the ROE law.

As shown in the Supplementary Material, Table 2, the subsample with no change in co-payment levels comprised older users, a larger percentage of females and lower levels in the average co-payment (reflecting a higher presence of pensioners). This subsample also had poorer

health status (i.e., more cancer, and more individuals were died or were close to death).

Discussion

The results of the study showed that the ROE law, which facilitated access to drug supply, reduced strong opioid consumption but led to an increase in opioid abuse. For their part, the introduction of the electronic prescription and co-payment systems had the opposite effect, notably increasing strong opioid use.

To better understand these results, some context is required. Population ageing, common in many developed countries, has increased the rate of chronic pathologies, especially those related to pain. It is estimated that 12% of the adult population in Spain suffer from CNCP, which is one of the main reasons for contacts with the health system (Dueñas et al., 2015). The abolition of the need for an official opioid prescription (ROE) and the equalisation of the duration of prescription treatment to that of other drugs may have misled physicians into believing that strong opioids do not require any special control. Due to the high patient demand for pain treatment, physicians have expanded the types of medications that they prescribe, and now include strong opioids amongst their options. This widely accepted praxis has aroused criticism from the medical community, since strong opioids are not indicated as first-line drugs for the treatment of CNCP and their efficacy has been questioned (Jamison, Sheehan, Scanlan, Matthews, & Ross, 2014; Perelló Bratescu et al., 2020).

Multiple-copy prescription programmes were among the earliest monitoring programmes applied to reduce the misuse of controlled substances. They have been broadly implemented in the US since 1939, but have been gradually replaced by electronic prescription systems. Opioid control has moved over to electronic prescription systems or to other surveillance formulas such as PDMPs and single-copy programmes (Alpert et al., 2019). In Spain, a duplicate prescription programme was adopted in 1995: doctors were obliged to use the official form described above (the ROE) for dispensing through pharmacy offices, whereas other substances needed only an ordinary prescription (García Del Pozo, Carvajal, Rueda De Castro, Cano Del Pozo, & Martín Arias, 1999). Two copies of the prescription were needed, one for the doctor and the other for the pharmacy, which recorded the substance, dose, and patient data, and sent it to the drug monitoring agency. An ordinary paper prescription was also required in order to bill the patient according to his/her co-payment level and to reimburse the pharmacy.

The deployment of electronic prescription systems decreased the likelihood of duplicate and erroneous dosages, and addressed “doctor shopping” abuses (multiple opioid prescribers per patient) since physicians would know what medications patients had been prescribed. Furthermore, it established a dispensing scheme according to the prescribed dosage, avoiding the accumulation of medication by the patient and, therefore, misuse. However, despite the benefits of the electronic system with regard to stockpiling behaviours, it led to a controversial increase in use and had no effect on abuse. The electronic prescription system in Spain did not use any alarms to warn that strong opioids required control over their management. Practitioners may have been under a false sense of security regarding opioid use, which was reflected in an increase in prescriptions dispensed and users. Supplementary Figure 1 shows the trend in electronic prescription implementation by drug, and Fig. 2 shows the trend in relative percentage of users throughout Catalonia.

Opioid users have different profiles, and policies impact them in different ways (Dasgupta et al., 2018; Mauri et al., 2020; Meara et al., 2016). For instance, our results for the impact of the ROE law showed that the group of users whose co-payments status did not change, with a high presence of pensioners and women and with a worse clinical condition, presented less fall in average monthly DDD and the highest increase in abuse (though very close to the total strong opioid users). This population was not directly affected by other recent reg-

ulations such as co-payment or €1 co-payment, which have had an impact on the general population. In addition, other studies report that the effect of co-payment on demand for analgesic drugs aiming individuals whose co-payment status did not change has been minimal (Hernández-Izquierdo, González López-Valcárcel, Morris, Melnychuk, & Abásolo Alessón, 2019). For the €1 per prescription the effect was similar (García-Gómez, Mora, & Puig-Junoy, 2018). This allows us to create a subpopulation that was affected mainly only by the ROE law, and not by the other measures implemented at the time.

The implementation of four different policies in such a short time frame makes it difficult to discuss the effects of each one individually. For instance, increases in DDDs and abuse under the new co-payment may be due to a rebound effect caused by the stockpiling of control drugs under the €1 co-payment system (one month earlier) (García-Gómez et al., 2018) (see Fig. 2). This is particularly true in elderly and low income groups, which came to benefit from free full coverage after the new co-payment was implemented (Puig-Junoy, Rodríguez-Feijóo, López-Valcárcel, & Gómez-Navarro, 2016). However, the ROE law is the measure that changes the patients' participation the least, as its main effect was to relax the prescribing requirements and had little influence on demand, even though patients were the main beneficiaries. The law oversees the praxis of prescribers on the drug supply system while other policies, where demand was regulated by co-payments, affected patients' behaviours more directly.

Our study showed that the population group not affected by any of the other policies (1€ co-payment, new co-payment scheme) also decreased DDD consumption, recovering –and even increasing– shortly afterwards when those measures were implemented on the overall population. No individuals in a population are free from being affected by a measure even if they are not the target population. Perceptions and fears of the possible increase in the cost of his medication may have led to changes in their behaviours. This contagion effect has been seen in others studies assessing the drug demand under new co-payment policies, even in populations outside the public health system (García-Gómez et al., 2018; Hernández-Izquierdo et al., 2019; Sánchez et al., 2015).

One of the limitations of the study may be the use of weak opioids, benzodiazepines, and antidepressants as controls. They were chosen for two main reasons. The first is that the use of these medications is closely associated with the profile of the narcotic patient (chronic pain, multiple morbidity, female sex, or advanced age) (Public Health England, 2020) so their use prior to the ROE law will presumably have presented the same trend as that of opioids. Second, they were not affected by the ROE legislation. Fig. 3 bears out the presence of this parallel trend before the implementation of the new policies, and it was also demonstrated by statistical tests ($F = 1.13$, p -value=0.286).

Another limitation is that no data on the duration of opioid treatment were available. However, this does not compromise the results obtained in our study, as they are based on monthly DDD and abuse (defined as MED), which are both related to the analgesic potency of the drug rather than to the duration of treatment. However, length of treatment should be explored in future research, as it may have undergone changes and also reflects consumption patterns.

Several measures of opioid use and potential abuse were constructed to determine the impact of the ROE law on strong opioids. While the simplest measure of hazardous use is the number of opioid prescriptions a patient has presented at any pharmacy in a fixed period, a more detailed measure of risky behaviour takes into account the strength of these prescriptions or their MED (Dowell, Haegerich, & Chou, 2016). Due to the lack of information on the specific medical diagnoses prompting the prescription of opioids and control drugs, as a reference we used the maximum daily consumption accepted by the clinical practice guidelines, established based on efficiency and security criteria (WHOCC - ATC/DDD Index, n.d.).

The evidence supporting the association between legislation to control opioid misuse and reductions in abuse indicators is limited (Mauri et al., 2020; Meara et al., 2016). The introduction of PDMPs

has slightly reduced volumes of opioid use and high opioid dosage per prescription and their related outcomes (Buchmueller & Carey, 2018; Cerdá et al., 2020; Rhodes et al., 2019). Drug supply management policies (i.e., regulatory policies limiting the maximum amount of opioid in each prescription and requiring extra authorisation to prescribe some high-risk opioid doses) has a significant impact on reducing abuse: they have been reported to reduce high-risk opioid prescriptions (by 1.7% in Hartung et al., 2018, or by 3.8% in Keast et al., 2018), but in return they also increase the number of low-dose prescriptions or long-term opioid use. However, drug supply management policies could be implemented the other way around, in order to facilitate drug prescription. For instance, the policy we evaluated here increased the treatment period for every prescription and reduced the control of opioid prescriptions, leading to a more intense use, and consequently to higher levels of abuse (up to 11.3% of all monthly opioids use) after the abolition of the ROE. In spite of the large contextual differences between studies, they all confirm that prescriptions of high-risk doses of opioids are the most sensitive to drug supply regulations. This effect is even more pronounced in individuals with a high demand, whether due to social or socioeconomic factors or to clinical need. These findings suggest that drug management in the high-demand group is in need of review, and that more attention should be paid to the different social and clinical profiles of users when policies are implemented.

Introducing obstacles to prescribing may reduce drug consumption and, thus, overdoses. Equally, however, it may obstruct compassionate pain management and increase provider burden (Selvy, 2019). Indeed, easing access to opioids for patients with chronic pain was the main aim of the ROE law introduced in 2012. Moreover, several studies have detected inequalities in opioid outcomes. For instance, the expansion of opioid use in the US has been shown to be medically inappropriate and has been linked to counties with the worst socioeconomic characteristics and least health insurance coverage (Baker, Bundorf, & Kessler, 2020). This suggests a need to focus on the social determinants and comorbidities of patients when tackling opioid overdose and related deaths (Dasgupta et al., 2018).

Beyond regulations in drug management, other demand and supply factors that have not been accounted for in this study may partly explain the increase in opioid use and number of consumers. These include the pressure placed on the physician by the patient, pharmaceutical marketing, physicians' attitudes and practice patterns, and changes in social perceptions of opioid consumption (Jamison et al., 2014; Maclean et al., 2020; Perelló Bratescu et al., 2020).

Although Catalonia has not reached alarming levels of opioid use, there is a clear need to consider the evidence regarding drug management systems. The evaluation of the ROE law has highlighted the limited use of monitoring tools in opioid prescriptions. The digitisation of prescription systems is an ideal environment for automatically determining high risk users according to the doses, addiction risk and type of opioid prescribed. This information should help physicians to improve their management of pain and prevent misuse. The provision of more training and the implementation of interdisciplinary approaches to pain management will benefit patients, while at the same time maintaining rational access to opioids.

Author contributions

NC had the idea for the article and performed the data extraction. NC and TM designed the study, constructed the database, performed the statistical analysis, and wrote the first draft of the article. AGA performed the final write-up of the article and coordinated the project.

As corresponding author, AGA had full access to all the data in the study and had final responsibility for the decision to submit for publication.

No medical writer or editor has been involved in the creation of the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics approval

Not applicable.

Declarations of Interest

The authors received no specific funding for this work.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.drugpo.2021.103562](https://doi.org/10.1016/j.drugpo.2021.103562).

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