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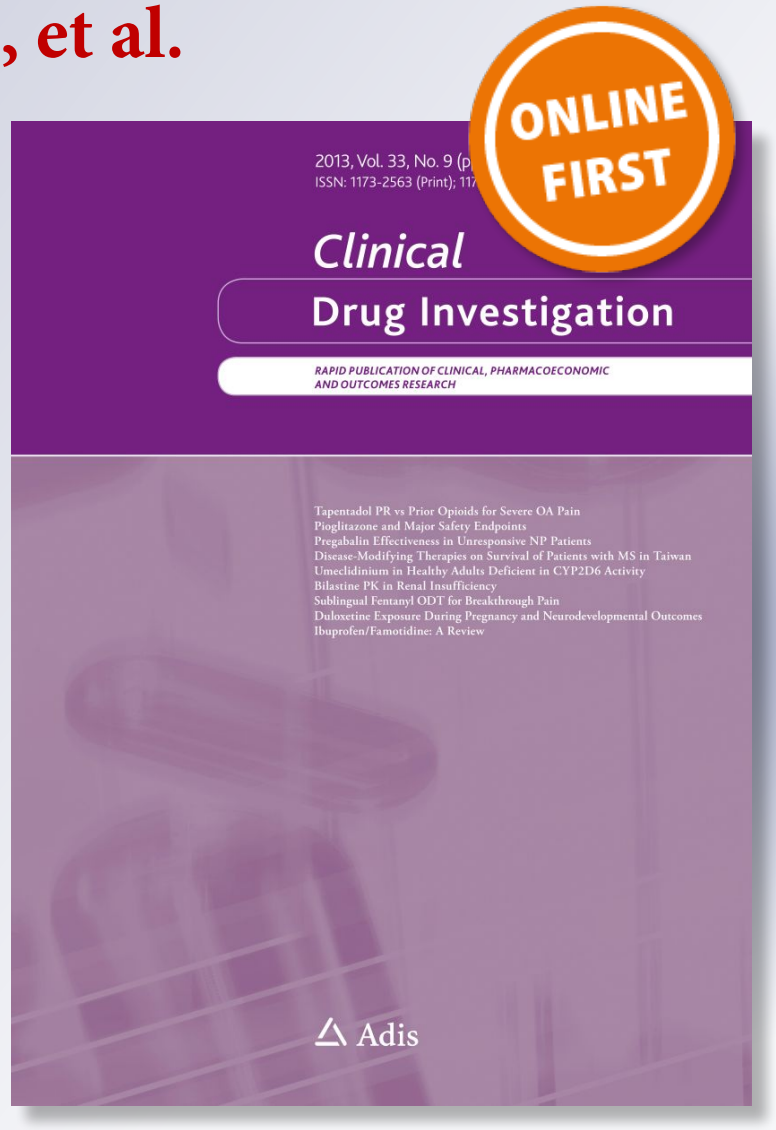

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ORIGINAL RESEARCH ARTICLE

Prescribing Trends of Codeine-containing Medications and Other Opioids in Primary Care After A Regulatory Decision: An Interrupted Time Series Analysis

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Abstract

Background and Objectives In 2014, the Italian Medicines Agency (AIFA) amended the summary of product characteristics of codeine-containing medications limiting their use for maximum three days. This study attempted to clarify the impact of AIFA intervention on prescribing trends and appropriateness of use of codeine-containing medications and other opioids.

Methods Using the Health Search Database, a quasi-experimental interrupted time series analysis was conducted to evaluate changes in prescribing trends and appropriateness of use of codeine-containing medications and opioids between 2013 and 2015.

Results Prescribing trends of codeine-containing medications significantly decreased (on average, − 352 days of treatment per month of observation), while long-acting opioids (LAOs) had an overall increase. Trends of inappropriate prescriptions significantly increased for two LAOs (i.e. tapentadol, naloxone-oxycodone), both before and after AIFA intervention.

Conclusion The use of paracetamol-codeine combination was effectively decreased in Italy because of AIFA intervention. Instead, prescriptions of tapentadol and oxycodone-naloxone stably increased over the study period irrespective of regulatory intervention. Given that the choice of the most appropriate opioid therapy is not straightforward, especially in elderly and/or comorbid patients, general practitioners should consider carefully alternative therapies on the bases of regulatory interventions.

Key Points

Prescription trends of codeine-containing medications in Italy significantly decreased because of AIFA intervention, while two long-acting opioids had an increase over the entire study period.

Trends of inappropriate prescriptions increased for tapentadol, naloxone-oxycodone over the entire study period irrespective of regulatory intervention.

The choice of the most appropriate opioid therapy is not straightforward, especially in elderly and/or comorbid patients.

Niccolò Lombardi and Alfredo Vannacci contributed equally.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40261-019-00767-8) contains supplementary material, which is available to authorized users.

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1 Introduction

Codeine-containing medications are authorized in Europe for the management of pain in adult and pediatric patients. They are commonly used in combination with other analgesics such as anti-inflammatory and other non-opioid medications with the aim of increasing the analgesic effect due to the synergic mechanisms of action.

Although there is an established use of codeine, gaps of knowledge persist on codeine effectiveness and safety [1, 2]. In 2012, after an extensive revision of literature and evaluation of data resulting from pharmacovigilance activities, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) claimed that the analgesic effect of codeine was not superior to that of other analgesics in the management of post-operative pain in children. PRAC therefore concluded that codeine still had a role in the treatment of acute pain in the pediatric population, but given the concerns about its risks, its use had to be limited to the management of moderate/acute pain in case of non-responsive therapy with other analgesics. The PRAC indicated a dosage range from 0.5 to 1 mg/kg as appropriate in children, and a duration of use limited to 3 days. Finally, the PRAC limited the use of codeine to children aged 12 years or older, since its conversion into morphine in children younger than 12 years is quali-quantitatively variable, making this population at major risk of side effects (e.g. life-threatening respiratory depression) [3].

In March 2014, the Italian Medicines Agency (AIFA), in agreement with the EMA, amended the summary of product characteristics (SPCs) of codeine-containing medications limiting the use of such a medication for 3 days at most [4, 5], and extending this alert to adult population.

Despite this regulatory decision on codeine-containing medications, evidence on their effectiveness and safety is still debated, and no formal investigation has been conducted on the effect of SPCs changes on prescribing behavior.

We therefore attempted to clarify the impact of AIFA regulatory intervention on codeine-containing medications in terms of reduction of the related prescriptions and prescribing trend and/or appropriateness of use of other opioids therapies.

2 Subjects and Methods

2.1 Data Source

We adopted the Health Search Database (HSD), a longitudinal observational database established in 1998 by the Italian College of General Practitioners and Primary Care, containing the electronic patient records from approximately 1000 general practitioners (GPs) homogeneously distributed across Italy. Computer-based patient records collected by a selected group of 800 GPs, who met standard quality criteria regarding the levels of data entry (i.e. levels of coding, prevalence of selected diseases, rates of mortality, and years of recording), were included in the present study. These GPs covered almost 1 million patients, and were geographically distributed to include patients' representative of the whole Italian population and to ensure the completeness and consistency of medical records [6–10].

Records consisted of demographic details; medical information, such as diagnoses, drugs and diagnostic test prescriptions; specialist referrals; life-style characteristics and mortality. These data were linked through a unique anonymous individual identification number.

All diagnoses were coded according to the International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM). To complement the coded diagnoses, GPs are enabled to add free text.

Information on drug prescriptions includes the name of the prescribed drug (i.e. active substance and/or brand name), the correspondent Anatomical Therapeutic Chemical (ATC) code along with the related defined daily dose (DDD), the date of prescription, and number of days' supply. The ATC/DDD is a validated classification system from the World Health Organization (WHO) [11], considered the standard reference for coding medications in several countries. Every prescription is associated with specific diagnoses (i.e. indication of use).

A number of epidemiological studies have been conducted using HSD [12–15].

2.2 Study Population

The study population was selected from active patients registered with GPs from a sample of 800 GPs homogeneously distributed across Italy who showed high up-to-standard quality criteria for data entry.

We formed a cohort of patients treated with paracetamol-codeine (ATC codes: N02AA59, N02AJ06), and/or opioids (ATC codes: N02A*) between January 1, 2013 and December 31, 2015. We considered only opioids available in Italy in the aforementioned period, and that could be prescribed by GPs.

Prescriptions of opioids (ATC codes: N02A*) have been evaluated by two pain experts (i.e. one GP and one pharmacologist) and were classified in long-acting opioids (LAOs) and short-acting opioids (SAOs) according to their pharmacokinetic characteristics and formulation type [16]. This approach was possible because every branded medication is identified by an individual code (AIC: Autorizzazione all'Immissione in Commercio), which has been assigned by the Italian Drugs Agency (AIFA) as marketing approval.

2.3 Outcome Definition

For each patient included in the cohort, we operationally calculated the number of prescribed days (i.e. overall mgs divided by the WHO DDD) of therapy for paracetamol-codeine combinations, and/or opioids. We therefore evaluated the impact of AIFA intervention, which came into force in March 2014 [5], on paracetamol-codeine combinations in terms of reduction of the related prescriptions and prescribing trends and/or inappropriateness of use of other opioid therapies. We evaluated the prescribing inappropriateness throughout a clinical evaluation performed by a group of experts, who considered the indication of use for each ATC, and the presence of previous prescriptions of other opioid medications.

2.4 Criteria of Inappropriateness

Prescription inappropriateness was assessed by a panel of experts comprising a GP, a pharmacologist, a pharmacoepidemiologist, and a pharmacist. It was based on the following criteria:

- LAO when used to treat "acute" diseases; namely, we identified coded diagnoses coupled with descriptions suffixed with "algia" (e.g. arthralgia), and containing "acute" and not "chronic" terms;
- morphine (ATC codes: N02AA01, N02AA51), oxycodone (ATC codes: N02AA05, N02AA55), fentanyl (ATC code: N02AB03), buprenorphine (ATC code: N02AE01) and all LAOs used to treat patients with a diagnosis of "headache" and/or "migraine";
- episodic use of any opioid (defined as the absence of prescriptions in the previous or following 60 days);
- use of LAO with no prescription of SAO in the previous or following 30 days were considered inappropriate when used to treat osteoarthritis (OA) not specified as "acute" or "chronic".

Prescribing inappropriateness for paracetamol-codeine combinations, as SAO, was operationally defined according to criteria which were complimentary the aforementioned indicators (e.g. use of paracetamol-codeine combinations for chronic arthralgia).

2.5 Data Analysis

A quasi-experimental interrupted time series (ITS) analysis was conducted to examine the effect of AIFA intervention on paracetamol-codeine combinations. As outcome variables, we investigated the changes in trends of prescribed days along with inappropriateness of use of paracetamol-codeine combinations and other opioids. Monthly durations (in days) related to the overall and inappropriate prescriptions were compared for the pre- and post-intervention period using a *segmented regression* model. For this ITS analysis, GP is the analysis unit. That being said, the monthly durations (in days) of prescriptions was calculated by summing up all prescribed days being cumulated monthly by GPs' patients. This model estimated the parameters in a linear regression in which the errors were assumed to follow an autoregressive process after verifying the autocorrelation using the Durbin-Watson test [17–19].

To better maximize the visualization of change for prescribing trends of paracetamol-codeine combinations, statistical process control (SPC)—c-chart—was adopted [20–22] as well.

All models were tested considering the following aspects: (1) the latency of the impact of AIFA intervention, not considering its effects in the previous and following 3 months (from December 2013 to June 2014); (2) adjusting the model for variable to control for seasonality; (3) exclusion from the analysis of the *wild data points* (i.e. outliers) [19].

All statistical analyses were performed using the software STATA version 13.

3 Results

Prescription trends for paracetamol-codeine, and opioids (overall and stratified according to their pharmacokinetics and formulation types: LAOs and SAOs) between January 1, 2013 and December 31, 2015 are reported in Fig. 1. The demographic and clinical characteristics of LAOs and SAOs users at baseline (January 2013) are described in Online Resource 1.

Following the AIFA update of SPC of codeine-containing medications, prescription trends were shown to increase for LAOs and to decrease for paracetamol-codeine-containing medications. Conversely, the prescription trend of all other SAOs was stable over the study period. The decrease in prescribing trend for paracetamol-codeine combinations was evaluated and confirmed by use of c-chart methodology (see Online Resource 2). As the counts of prescribed LAOs grew after the authority intervention (see Online Resource 3), trends of the different LAOs were explored, stratifying the analysis according to LAO-related ATC codes (Fig. 2). An increased trend in prescriptions was found for tapentadol (ATC code: N02AX06), and oxycodone-naloxone (ATC code: N02AA55) after March 2014.

A *quasi-experimental ITS* analysis was therefore performed for paracetamol-codeine combinations, tapentadol, and oxycodone-naloxone, which have shown a modified trend during the study period.

Table 1 shows the durations (days) of treatments with paracetamol-codeine, comparing the pre- and post-intervention periods. A significant reduction of monthly durations

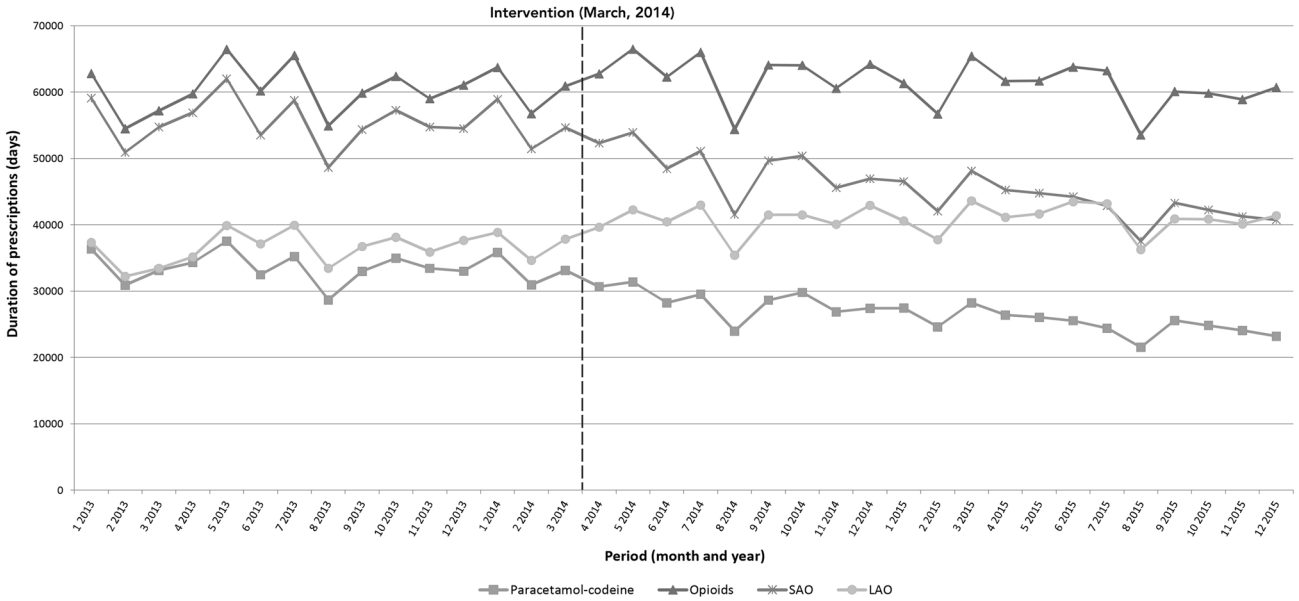

Fig. 1 Prescribing trends for paracetamol-codeine, and opioids (overall and stratified according to their pharmacokinetics) between January 1, 2013 and December 31, 2015. *LAOs* long-acting opioids, *SAOs* short-acting opioids

of treatment with paracetamol-codeine-containing medications was found in the post-intervention period [on average, −306.7 days per month (95% CI −541.6; −71.9)], with an overall reduction of −352 days of treatment for each month of observation ($p < 0.001$) over the entire study period.

When duration of treatment with tapentadol in the pre- and post-intervention periods were analyzed (Table 1), we found an increase in both the pre- [+164.6 days per month (95% CI −3.9; +333.1)] and post-intervention period [+32.9 days per month (95% CI −160.6; +226.5)], although it was not statistically significant. The duration of treatment with oxycodone-naloxone had an overall increasing trend [+326.4 days per month (95% CI −64.7; +717.5)], which was not statistically significant, but the increase was lower in the post-intervention period (−98.8 days per month [95%

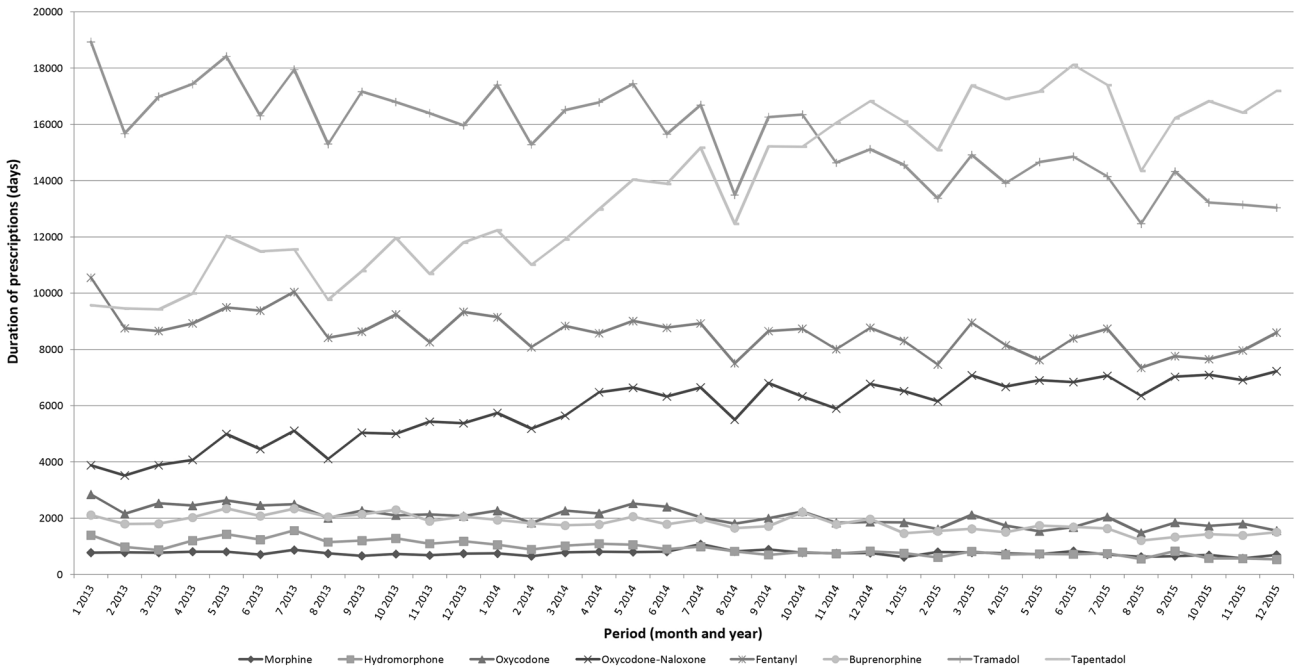

Fig. 2 Prescribing trends of long-acting opioids stratified according to active principles, between January 1, 2013 and December 31, 2015

Table 1 Trends of prescribed days for paracetamol-codeine combinations (SAOs), tapentadol (LAO), and oxycodone-naloxone combinations (LAOs) comparing the pre- and post-intervention periods according to interrupted time series analysis

Variable	Coefficient (95% CI)	*p* value
Paracetamol-codeine		
Pre-intervention trend	−45.3 (−257.8 to 167.3)	0.667
Post-intervention trend	−306.7 (−541.6 to −71.9)	0.012
Constant	33,916.2 (32,113 to 35,718.4)	<0.001
Tapentadol[a]		
Pre-intervention trend	164.6 (−3.9 to 333.1)	0.055
Post-intervention trend	32.9 (−160.6 to 226.5)	0.731
Constant	9616.9 (8164 to 11,069.5)	<0.001
Oxycodone-naloxone[b]		
Pre-intervention trend	144.3 (107.4 to 181.3)	<0.001
Post-intervention trend	−98.8 (−139.6 to −58.1)	<0.001
Constant	3614.2 (3301 to 3927.4)	<0.001

CI confidence interval, *LAOs* long-acting opioids, *SAOs* short-acting opioids

[a]Tapentadol prolonged-release tablets and capsules (LAO)

[b]Oxycodone-naloxone-prolonged release tablets (LAO)

CI −139.6; −58.1]) compared to the pre-intervention trend [+144.3 (95% CI +107.4; +181.3)] (Table 1).

Applying the described criteria for inappropriateness, 29.4% and 15.7% of the prescribed days for LAOs were inappropriately used for acute pain and as sporadic use/first-line treatment, respectively. Prescribing inappropriateness was 10.1% of the prescribed days for paracetamol-codeine combinations. No statistically significant variations were observed for paracetamol-codeine-containing medications over the study period.

Table 2 Trends of inappropriate prescribed days for paracetamol-codeine combinations (SAO), and tapentadol (LAO) plus oxycodone-naloxone combinations (LAO), comparing the pre- and post-intervention periods according to interrupted time series analysis

	Coefficient (95% CI)	*p* value
Paracetamol-codeine		
Pre-intervention trend	−109.9 (−187.1 to −32.8)	0.007
Post-intervention trend	75.9 (−10.5 to 162.4)	0.083
Constant	4422.8 (3766.1 to 5079.5)	< 0.001
LAOs[a]		
Pre-intervention trend	46.2 (−9.2 to 101.6)	0.099
Post-intervention trend	6.4 (−54.2 to 67.1)	0.830
Constant	2329 (1918.7 to 2740.2)	< 0.001

CI confidence interval, *LAOs* long-acting opioids, *SAOs* short-acting opioids

[a]Tapentadol prolonged-release tablets and capsules and oxycodone-naloxone prolonged-release tablets

Regarding LAOs (i.e. tapentadol and oxycodone-naloxone), no significant differences were reported for the prescribed days contrasting pre- versus post-intervention phase. However, focusing on the two phases alone, a significant increase in the number of days of inappropriate prescriptions was observed in both periods for LAOs (Table 2), which was consistent with an increasing trend over the entire study period.

4 Discussion

To our knowledge, this is the first ITS analysis being conducted in a real-world primary-care setting evaluating the impact of a regulatory intervention on codeine-containing medications. This intervention was decided by AIFA in 2014, following an EMA pharmacovigilance assessment, introducing a new limitation for the use of codeine-containing medications in Italy [3, 5], related to both pediatric and adult populations.

In this context, our results confirmed a reduction of prescribing rates of codeine-containing medications in the observed population, with an average monthly reduction of −306 days in the post-intervention period, proving that Italian GPs effectively perceived the AIFA decision.

Concerning opioids safety, the alert raised in Europe was based on cases of obstructive sleep apnea observed in children who were treated with codeine after tonsillectomy [1, 2]. Furthermore, it is widely described in literature that patients who are ultra-rapid or extensive metabolizers of codeine have an increased conversion to morphine, which can result in toxic systemic concentration and may lead to severe adverse drugs reactions, particularly on breathing [23]. However, the ultra-rapid metabolizer phenotype has been estimated to be present in only 1–2% of patients, but the prevalence varies widely in different populations worldwide, ranging from 28% of North Africans, Ethiopians, and Arabs to 1% in Hispanics, Chinese, and Japanese [24–26]. In this respect, regulatory SPCs updates and guidelines should always take into account the specific population-related characteristics. In any case, GPs' choice of the best analgesic medication should be driven both by regulatory aspects and by a comprehensive assessment of patients [27]. In fact, there is evidence that codeine-containing products still represent an effective and safe therapeutic option in much of the adult population [28], when compared with other available medications used for the treatment of different types of pain [29, 30].

Beside showing a reduction in the prescription of codeine-containing medications, our results showed an increase of the prescriptions of two LAOs, namely tapentadol and oxycodone-naloxone, over the entire study period. In addition,

we had already observed a high level (around 30% of LAO-prescribed days) of inappropriateness for these medications before the intervention promoted by AIFA. Although LAOs can play a valuable role in the management of chronic pain [27] an improper use of these drugs could be associated with potential risks; evidence shows that chronic opioid therapy is associated with constipation, sleep-disordered breathing, fractures, and hypothalamic–pituitary–adrenal dysregulation [31]. In particular, the elderly seem to be the population most vulnerable to the side effects of opioids [32–36]. Because of these risks, the US Food and Drug Administration (FDA) required a Risk Evaluation and Mitigation Strategy (REMS) for extended-release/long-acting opioid analgesics [37]. Thus, while the AIFA intervention changed the way of prescribing paracetamol-codeine combinations, the contemporary growing trend of tapentadol and oxycodone-naloxone combinations should be debated.

Indeed, in Europe, especially following the new limitations added to the prescription of paracetamol-codeine combinations, the potential choice of LAOs as alternative medications could lead to an increased risk of LAO-related adverse events. In Italy, this prescribing trend could also represent an important economic burden, given the higher costs of LAOs compared to paracetamol-codeine medications. In fact, the price reimbursed by the Italian National Health Service for oxycodone-naloxone as fixed combination, ranges from EUR18.44 to EUR80.90 and that of tapentadol from EUR16.40 to EUR95.46; in contrast to the price for paracetamol-codeine combination, which is EUR3.96.

These findings may allow us to claim that the use of paracetamol-codeine in the management of mild-to-moderate pain in primary care, especially in older patients, can still represent a valid and safe therapeutic strategy. Furthermore, we recently demonstrated that patients with osteoarthritis who regularly (adherently) used paracetamol or paracetamol-codeine combinations had a statistically significant lower risk of being prescribed with other analgesic medications than irregular users over time [30].

The present study had several strengths. First, the Italian HSD, one of the largest general practice databases in Europe, contains reliable information on a large population assisted in primary care throughout Italy, resulting in a homogenous and country-representative data collection. Second, in the HSD, information on drug exposure is prospectively recorded by GPs, thereby minimizing any recall bias. Third, our findings are strengthened by the fact that HSD is able to capture the actual indication of use.

The limitations of this study include (i) as The prescription records only reflect what was prescribed and not what was actually consumed, drug prescription was used as a proxy of drug utilization. However, we aim to investigate GPs' prescribing behavior, which was not biased by the short-comings of this database. (ii) We identified inappropriate prescriptions by using criteria which were implementable in this data source, so other potential indicators, such as those related to actual measurement of pain level (i.e. WOMAC scale was poorly registered in primary care) might have been missed. As such, several cases of inappropriateness could have been underestimated in the present analysis. Nevertheless, we quantify a burden of inappropriateness (higher than 30%), which was not negligible, so allowing us to reliably identify this issue.

5 Conclusions

Our findings indicate that in recent years, the use of paracetamol-codeine medication has been discouraged among GPs in Italy because of AIFA intervention. Prescriptions of other opioids, namely tapentadol and oxycodone-naloxone steadily grew over time, irrespective of AIFA intervention. However, Italian GPs generally prescribe these medications in older and often co-morbid patients with OA, for whom the choice of the most appropriate opioid therapy is not straightforward, especially for LAOs [30]. GPs should therefore carefully consider alternative therapies in replying to regulatory intervention.

Compliance with Ethical Standards

Funding This work was supported by the Italian College of General Practitioners and Primary Care, who played no role in the study design, execution, analysis or interpretation of data, writing of the paper, or decision to submit the paper for publication.

Conflicts of interest Francesco Lapi provided consultancies in protocol preparation for epidemiological studies and data analyses for IBSA and Angelini. Claudio Cricelli provided clinical consultancies for IBSA, Angelini, Grunenthal, Alfa Wasserman, Pfizer, Prostrakan, Molteni, Dompè and Teva. Alberto Magni provided clinical consultancies for Bayer, Angelini, Doc and AlfaSigma. Niccolò Lombardi, Alfredo Vannacci, Alessandra Bettiol, Ettore Marconi, Serena Pecchioli, have no conflict of interest to disclose.

Ethical approval With regard to the classification and implementation of observational drug-related research, as issued by the Italian National Drug Agency (an entity belonging to the Italian Ministry of Health), the present study does not require approval by an Ethics Committee in Italy (Italian Drug Agency note dated 3 August 2007).

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