

ORIGINAL ARTICLE

Outpatient therapeutic chronic opioid consumption in Italy: a one-year survey

Luca MICELI¹*, Rym BEDNAROVA², Miriam DI CESARE³,
Elisabetta SANTORI³, Marco SPIZZICHINO³, Lidia DI MINCO³, Renato BOTTI³,
Massimo CASCIELLO³, Giorgio DELLA ROCCA¹

¹Department of Anesthesia and Intensive Care, University of Udine, Udine, Italy; ²Health Agency Number 2, Pain Medicine and Palliative Care, Gorizia, Italy; ³Ministry of Health, Rome, Italy

*Corresponding author: Luca Miceli, via Ottobono 4, 33100 Udine, Italy. E-mail: miceli.luca@aoud.sanita.fvg.it

ABSTRACT

BACKGROUND: In Italy since the 38/2010 law concerning Palliative Care and pain therapy has been promulgated, the consumption of opioids started increasing. However, despite the availability of a large amount of data regarding opioid prescription, a database including all patients on chronic opioid therapy does not yet exist.

METHODS: Retrospective analysis of analgesic opioid consumption was performed between January 2013 and December 2013 using the data of national refunded medications for outpatients, collected by Italian Ministry of Health. We considered patients on chronic opioid therapy those patients with at least three opioids prescriptions in three consecutive months and/or six opioid prescriptions in six even not consecutive months in the observation period. We considered cancer patients those with neoplasm exemption code in the scheduled prescription and/or patients with at least one ROO prescription (rapid onset opioids, approved in Italy for Break Through cancer Pain-BTeP- only). We also calculated the patient's morphine daily mean dose (MED) converting all prescribed opioids in equivalent of morphine using specific conversion tables.

RESULTS: This census revealed a total of 422,542 patients in chronic therapy with opioids, of those 369,961 with chronic non-cancer pain and 52,581 with chronic cancer pain. This represents about 4% of the estimated requirement in Italy for both groups based on previous surveys regarding the prevalence of chronic pain.

CONCLUSIONS: Relatively to MED, We found that in Italy chronic cancer pain patients receive doses similar to patients with cancer pain in other Literature reports, whereas patients with chronic non-cancer pain received lower dosages.

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In Italy since the 38/2010 law regarding Palliative Care and pain therapy has been promulgated, the prescription of opioid drugs was increasing.¹ The same trend was documented worldwide.² Therefore, analysis of national analgesic consumption can provide useful information about pain medication use trends and might enable us to better understand behavior associated with drug prescription.

Analysis of opioid consumption is particularly important, since opioids are key medications for the treatment of moderate to severe pain, and some of them are listed by the World Health Organizations as essential drugs.³

In Italy despite the availability of many data regarding total opioid prescriptions, a database including all patients on chronic opioid therapy still does not exist.

In other words, we can identify the total prescribed opioid amount but we do not know

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how many patients are using those drugs, and in which proportion opioids are distributed among them.

We also do not know the mean opioid dose (MED) prescribed to patients on chronic therapy with these drugs.

Identifying appropriateness related to adequacy in terms of amounts and trends of opioid consumption provides precious data for evaluating policy and economic changes.⁴

The aim of the study was to describe the prescription patterns in patients on chronic opioid therapy in term of number of chronic patients and opioid dosage prescribed. Data, based on register of outpatients refunded prescriptions obtained from Italian Ministry of Health, are registered between January 2013 and December 2013.

Materials and methods

Retrospective analysis of analgesic prescriptions was carried out between January 2013 and December 2013 using data of national refunded medications for outpatients, furnished by Italian Ministry of Health (Office number III, Head Quarter Health Planning). According to the ATC classification (Anatomical, Therapeutic, Chemical) system data was collected from N02A group (central analgesics), with exception of acetaminophen alone. Parenteral formulations and in-hospital prescribed drugs were excluded from the collected data.

Drugs records included the following substances, alone or in combination: morphine (except intravenous formulations), oxycodone, hydromorphone, codeine, tramadol, fentanyl (except intravenous formulations), tapentadol, and buprenorphine except sublingual formulations.

Data from the included prescriptions were: anonymous patient personal identification code, region of residence, ticket exemption code (if present), sex, age, ATC prescribed, date of prescription, dose of the prescribed drug and number of packages prescribed.

Patient's age was presented divided in multiple groups of five year each (for example 50-54 years, 55-59 years).

We defined "a chronic opioid user" a patients that, within the twelve months of survey, received at least 3 opioids prescriptions in three consecutive months (according to the International Association for the Study of Pain – IASP – definition of chronic pain)⁵ and/or six opioid prescriptions in six months within the twelve months of survey, even in non-consecutive months.

We first divided the patients in three groups: total patients (who received at least one opioid prescription in the 2013), cancer patients and non cancer patients, identifying cancer patients those having the neoplasm Italian ticket exemption code in the single prescription and/or those that received in 2013 year at least one breakthrough cancer pain (BTcP) drug prescription, approved in Italy exclusively for cancer pain (fentanyl citrate, fentanyl buccal tablets, fentanyl sublingual tablets, fentanyl nasal spray).

We also analyzed the monthly chronic patients distribution (from three to twelve months according to chronic opioid user definition described above).

Subsequently all opioid prescribed for each patient were converted using specific conversion tables^{6,7} in MED (morphine equivalent dosage) and them analyzed.⁸

Statistical analysis

Data are presented as absolute values, percentage or mean±standard deviation (SD); the mean dose of MED are represented as a value and IC 95 (interval of confidence 95%). Sex differences in opioid prescriptions and prescription trends in all patients, cancer and non-cancer ones, were analyzed with two-tailed Student *t* test for unpaired samples.

Results

A total of 2,520,382 patients had at least one opioid prescription between January 2013 and December 2013 (Table I), 422,542 (prevalence on total Italian population 0.7%) were patients on chronic opioid therapy (16.75% of total opioid prescription-receiving patients

TABLE I.—Chronic pain patients distribution: total (in bold) and monthly of opioid use; data divided also in chronic oncological and chronic non oncological patients.

Months of treatment	N.	Chronic patients	Chronic cancer patients	N.	Chronic non cancer patients	N.
1	1,513,049	0	58,505	0	1,454,544	0
2	378,333	0	26,271	0	352,062	0
3	175,110	53,667	16,351	8806	158,759	44,861
4	105,826	49,485	11,293	7860	94,533	41,625
5	74,682	46,008	8380	6854	66,302	39,154
6	58,242	58,242	6393	6393	51,849	51,849
7	46,938	46,938	5127	5127	41,811	41,811
8	39,714	39,714	4169	4169	35,545	35,545
9	35,108	35,108	3502	3502	31,606	31,606
10	31,256	31,256	3109	3109	28,147	28,147
11	29,642	29,642	2977	2977	26,665	26,665
12	32,482	32,482	3784	3784	28,698	28,698
Total	2,520,382	422,542	149,861	52,581	2,370,521	369,961

in 2013). We then divided chronic patients in two groups: cancer patients (according to the above mentioned criteria) reaching 52,581 patients (2.08% of total opioid users, prevalence on total Italian population 0.08%) and non-cancer patients 369,961 (representing 14.67% of total patients on opioid therapy, prevalence on total Italian population 0.62%).

A demographic description of sex and age distribution (Figure 1) in chronic patients shows that most of the patients are over 65 years old, mainly females for each age class.

Such distribution differs when we analyze

those patients dividing them in cancer and non cancer subgroups: cancer patients have a minor mean age and do not present significant sex difference (Figure 2), non-cancer patients on the other hand are mainly elderly females (Figure 3).

The two tailed *t* Student test for unpaired samples showed a $P < 0.05$ in sex distribution for all age clusters from 50-54 in overall chronic patients and in non-cancer patients (Figures 1, 3).

Total opioid prescriptions (Table II) during the observation period in Italy has been

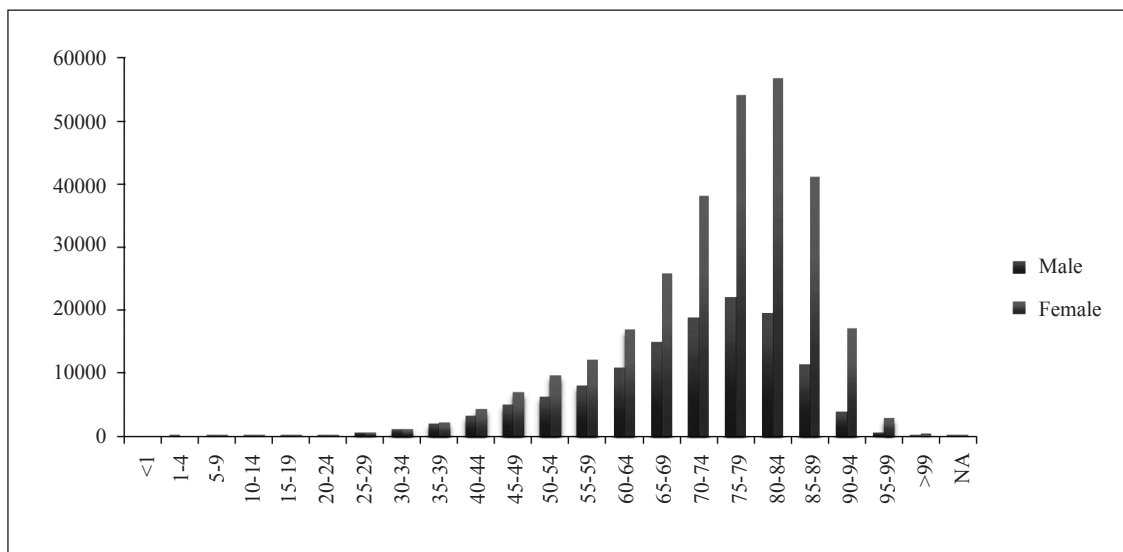


Figure 1.—Age and sex distribution in chronic opioid users. X axis: age groups (years); Y axis: number of patients.

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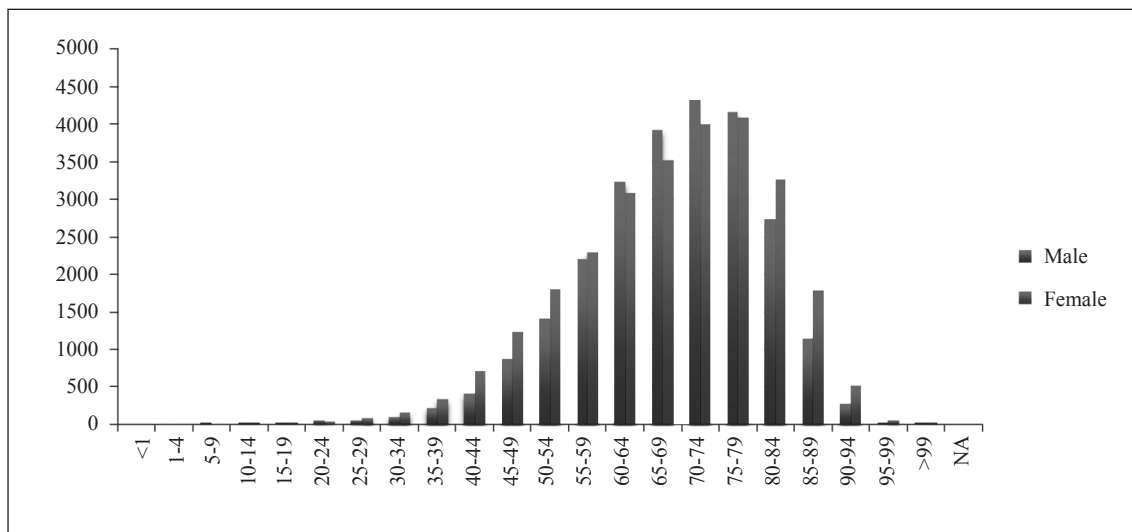


Figure 2.—Age and sex distribution in chronic neoplasm opioid users. X axys: age groups (years); Y axys: number of patients.

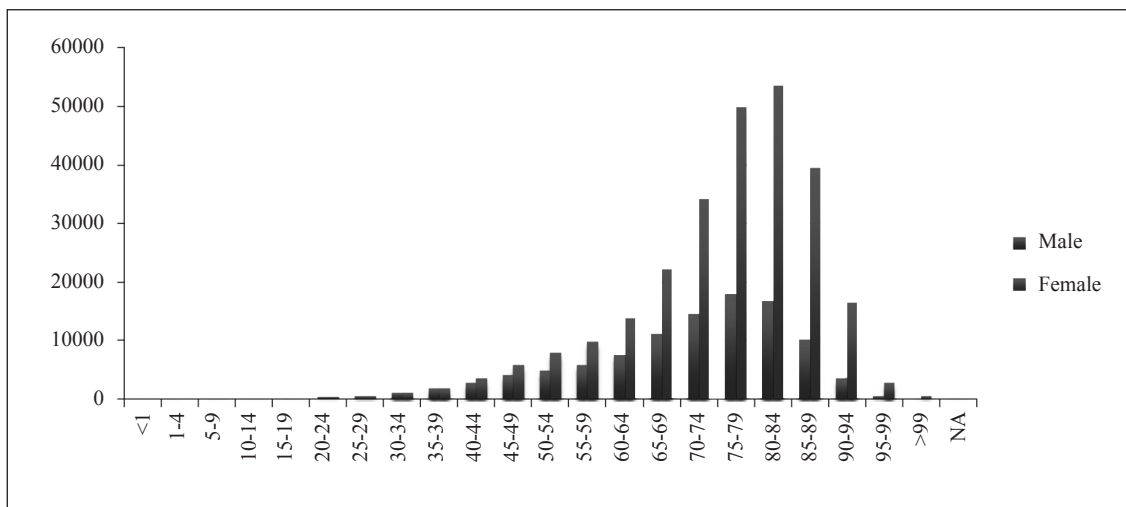


Figure 3.—Age and sex distribution in chronic non oncological opioid users. X axys: age groups (years); Y axys: number of patients.

9,323,790, of those 5,622,172 were for chronic users (60.3%), and the remaining 3,701,618 (39.7%) for non-chronic patients.

The seven most prescribed opioids in general population were the following (in descending order): weak opioids (codeine 35.2% and tramadol 21.5%), oxycodone 18.6%, fentanyl 11.1%, tapentadol 6.1%, morphine 2.4%.

In chronic patients however codeine was

less prescribed (27.3%) in favor primarily of oxycodone (21.5%) and fentanyl (15.2%).

The mean number of annual opioid prescription per patient was 3.7±2.5; the non-chronic patients had a mean of 1.8±0.9 annual prescriptions, chronic patients 13.3±8.1 prescription per year, with a mean of 20.6±14.5 prescriptions in chronic cancer patients.

Finally we measured the mean daily opioid

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TABLE II.—Opioids prescribed in Italian patients, total and divided in chronic and non-chronic users.

ATC code	Total patients	Chronic patients	Non-chronic patients
N02AA59 – Codein	3,279,702	1,535,361	1,744,341
N02AX02 – Tramadol	2,006,886	1,204,805	802,081
N02AA05 – Oxycodon and oxycodon+ naloxon	1,085,582	757,439	328,143
N02AB03 – Fentanyl	1,038,030	856,347	181,683
– transdermal	797,366	648,718	148,648
– other (ROOs-rapid onset opioids for BTcP)	240,664	207,629	33,035
N02AA55 – Oxycodone+ acetaminophen	654,366	449,646	204,720
N02AX06 - Tapentadol	568,329	326,995	241,334
N02AA01 – Morphine	228,090	168,991	59,099
– syrup	89,513	64,811	24,702
– others	138,577	104,180	34,397
N02AX52 - Tramadol, associations	183,093	100,516	82,577
N02AE01 - Buprenorphin	169,150	136,103	33,047
N02AA03 - Idromorfon	103,085	83,901	19,184
N02BE51 – Acetaminophen, others associations	7153	1810	5343
N02AG01 – Morphine and antispasmodic	274	256	18
R05DA04 – Codein	38	2	36
N07BC51 - Buprenorphin, associations	12	0	12
Totale	9,323,790	5,622,172	3,701,618

ATC: anatomical therapeutic chemical.

TABLE III.—Mean daily morphine equivalent dose (MED) in chronic cancer and non-cancer patients.

Chronic patients	Number	Morphine equivalent dose (MED) (mg)	
		Mean daily MED	IC 95%
Neoplasm*	50,925	79.47	IC95% 78.51-80.43
No neoplasm**	351,764	30.13	IC95% 29.99-30.27

IC: interval of confidence.

*in 1656 patients it has not been possible to measure the MED.

**in 18197 patients it has not been possible to measure the MED.

dose (expressed in MED) in chronic patients, in both, cancer and non-cancer subgroups (Table III): as a results the mean dose in non-cancer patients was (Table III) 30.13 mg/morphine/daily compared to 79.47 mg/morphine/daily in chronic cancer patients (Student's *t*-test $P < 0.001$). In 1656 prescriptions for cancer patients and in 18,197 prescriptions for non-cancer patients the MED it was not possible

to calculate, because the ROOs (rapid onset opioids) formulation of fentanyl, don't have a defined conversion value.

We add a flowchart to describe the classification of total opioid patient users in chronic opioid users and acute opioid users for presumed cancer and non-cancer pain and the distribution of those prescriptions (Figure 4).

Discussion

Presented data show (Table I) that between January 2013 and December 2013 the number of chronic prescriptions of opioids in Italy was 422,542 (prevalence of 0.7%, divided in chronic non cancer pain 0.62% and chronic cancer pain 0.08%) compared to 2,520,382 non-chronic opioid prescription. The chronic use of opioid painkillers in Italy hence is still

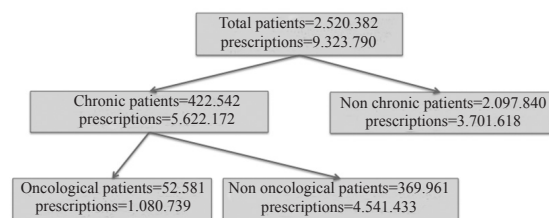


Figure 4.—Flowchart to describe the classifications of total opioid user patients in chronic and acute opioid users and in cancer and non-cancer pain.

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an exception rather than a rule, despite various warnings, hidden and explicit campaigns that aim to emphasize elevated chronic use and an abuse potential coming from USA.⁹ More than 80% of the chronic users suffer non-cancer pain, a fact that might sign of a cultural change in physician behavior, probably promoted by Italian law 38/2010¹⁰ that encourages- at least in initial phase of pain management- and simplifies opioid prescription for moderate to severe pain independently of its origin. This trend emerges despite the widespread opiophobia that still relegates Italy to the bottom of chronic consumers list in Europe.¹¹

The prevalence of patients with chronic non cancer pain (with moderate to severe intensity) in Italy is approximately 20% namely (12,000,000 residents),¹² of those 422,000 during the observation period were receiving prescriptions for their health problem with an appropriate drug (at least until a target oriented care for pain relief was available), representing about 4% of potential candidates, in consideration that Italian population is approximately 60,000,000 citizens (National Institute of Statistics).¹³

In patients with cancer having a prevalence of about 3.5% (National Institute of Statistics-13), 60% are estimated to face mild to severe pain¹⁴ and 53.000 patients are on chronic opioid treatment, being again about 4% only of potential candidates (estimated 1.3 million people).

This means that 96% of chronic pain patients, both of cancer and non-cancer origin, can unlikely have access to appropriate pain therapy at least until the correct diagnosis and specific treatment are performed.

Table II shows that all patients including chronic and the non chronic opioid users were treated in 50% of cases with weak opioids, whereas in chronic opioid users strong opioids predominate on weak opioids; this fact could be due to the pain being more severe when chronic compared to the probably less severe acute pain. The Tables I, II highlight that 17% of the patients taking opioids in 2013 received 60% of the total prescriptions. This data underline the numeric importance of chronic pain

patients in terms of use of public resources (a small number of patients-about 422,000 compared to 2,500,000 of total patients-recruit the greatest part of the prescriptions – about 5.600.000 compared to over 9,200,000 total prescriptions).

In patients on chronic opioid therapy among strong opioids oxycodone alone or associated with naloxone is the mostly prescribed drug when non-cancer patients are considered.

Figures 1-3 shows that patients with chronic opioid therapy are elderly, with female predominance, a fact that might be explained by the prevalence of females in Italian population and furthermore is in accordance with other literature data.¹³⁻¹⁵

This fact in our opinion can be also explained by a cultural and socioeconomic phenomena where younger males, often affected by chronic pain, mostly benign, as already explained by Breivik *et al.*,¹² missed the attention of pain therapist.

Table III is fundamental to answer the question about the mean daily dose of opioid therapy: some data in literature¹⁵ showed a mean posology of about 86 morphine equivalent dose (MED) in cancer patients, being similar to data obtained in our study, and about 62 MED in non cancer patients treated with opioids for 6-12 months, being twice the MED revealed by our observation.

In Cepeda's work¹⁵ collected data from 48.986 patients in a 8 years period (2002-2008) in US, with a mean age of 44.5 years, similar to our results, and a prevalence of female sex, also similar to our findings. Moreover some differences in the age group might be related to the fact that in the US study data were collected from an insurance database in which patients over 65 years, low income patients and people not able to work are often excluded, whereas Italian data include all refunded prescriptions in the 2013 with no restrictions.

Others US studies^{16, 17} showed lower MED prescriptions respect to Cepeda's data, at least in particular subset patients (veterans). Edlund¹⁶ and Macey¹⁷ registered respectively a median MED of 21 mg/die — range 10-997 mg/die — (in the years 2009-2011) and av-

erage MED of 40.8±36.1 mg/die (in the year 2008) in long-term opioid users for chronic non-cancer pain. This data, newer than those of Cepada *et al.*, are lower than previous findings and closer to Italian and European data. This data furthermore can suggest a reduction opioid prescribing trend in US, especially in veterans suffering from chronic non-cancer pain.

In Germany, Marshall *et al* in a recent paper¹⁸ analyzed data from a large German medical health insurance organization and found a prevalence of long-term opioid prescription for chronic non-cancer pain of 1.3%, with a MED of 58 mg/die. These results are not considered a signal of “opioid epidemic” and the Authors recommend careful selection and continuous evaluations of these patients. The chronic non-cancer pain opioid prescription prevalence and the relative MED were lower (prevalence respectively 0.62% in Italy versus 1.3% in Germany and MED 30.13 mg/die in Italy versus 58 mg/die in Germany), for which the “opioid epidemic” risk appear to be less at present.

Limitations of the study

The database created is prescription based: We don't have a clinical confirmation of patient's pain intensity or a real documentation of the pain condition. We suppose that physicians signed only appropriate opioid prescriptions (namely for moderate to severe pain conditions).

The database does not include opioids prescribed during hospital admission and ward stay.

The definition of “cancer patients” is based and hence limited by the correct and complete compilation of all fields of the prescription as well as by a correct clinical prescriptive indication. This is important, especially for rapid onset opioids (ROOs), approved in Italy for BTP in cancer pain only, with the exclusion of ROOs prescription for Break Through Pain of non-cancer origin (several oral morphine formulations).

Conclusions

We performed a patient-based (number of users) analysis of the prescribing behavior in Italy during the 2013-year rather than number of opioid packages prescribed in the same period. This has led to a census of more than 422.000 patients on chronic therapy with opioids (about 50.000 cancer patients and 370.000 non cancer patients), representing nevertheless only 4% of the estimated pain therapy applicants.

Relatively to morphine daily dose our data (79.4 MED in cancer patients and 30.1 MED in non cancer patients) showed that in Italy cancer patients received adequate opioid doses, whereas the non cancer patients received minor opioid.

Key messages

— The study used a “number of patients”-centered data base of chronic opioids users instead of “number of drug-pack”-centered data base, already known in literature.

— This database collected all 2013 opioids prescription in Italy (about 9 million of records) provided by Italian Ministry of Health.

— The study analyzed and compared with other countries the mean MED (morphine equivalent dose) of opioids in the scheduled opioids chronic users.

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