

# Abuse and misuse of prescription opioids: is it only an American problem? An observational study on an Italian casuistry

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## Abstract

Medical use of prescription opioids has steadily increased since the 1990s, particularly in the U.S.A. and Canada, along with abuse of these substances and significant increases in rates of addiction and death related to prescription opioids. The American authorities speak of an “addiction epidemic” and are launching a series of countermeasures to better address the problem. In Europe, there is an increasing use of prescription opioids and related problems, but the European context is much less dramatic than the American and Canadian ones. Nevertheless, based on the data, it cannot be ruled out that a similar crisis will occur on the Old Continent. The aim of this study is to analyze the Italian context to better understand whether there is a possibility of an addiction epidemic.

Twenty-four cases of death of people under treatment with prescription opioids have been retrospectively analyzed. Toxicological samples were collected with routine methods during the autopsy, followed by systematic screening for substances by diverse methods. Volatile compounds were identified using gas chromatography-flame ionization detection (GC-FID). Medical drugs and drugs of abuse were identified via the use of gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-tandem mass spectrometry (LC-MS-MS).

Of a total of 24 subjects, 14 died due to an overdose of Tramadol, while 7 died due to an overdose of Buprenorphine and 3 due to a Fentanyl overdose. The most used drug was Tramadol. Histological examination was performed with hematoxylin/eosin staining, though no significant findings emerged apart from widespread edema and focal sclerosis of the myocardium, and interstitial and alveolar edema of the lungs.

Our data show that attention must be paid to prescription opioids. European institutions, as soon as possible, must implement preventive measures that avoid the recurrence of the North American situation.

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## Introduction

According to the definition of the International Association for the Study of Pain, pain can be defined as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” (1,2). Clinically, pain can be distinguished in acute, chronic, and procedural (3,4). Acute pain is intended to alert the individual to an ongoing tissue injury: it is usually localized, short-lived (a few days), of known cause, and often responds very well to treatment. Chronic pain lasts much longer and can persist even when the nociceptive stimulus ceases, has an important emotional component, and is limiting for the social life of the patient; the treatment of chronic pain is much more complex. Procedural pain is associated with diagnostic/therapeutic investigations, and it is related to fear and anxiety. Therapeutic management of procedural pain is currently effective, even if pain management strategies could be intricate (2,5). Pain is currently considered a fifth vital sign; therefore, its correct evaluation and its adequate and prompt treatment are considered essential for the well-being of patients (6-8). The insertion of pain among the vital parameters has surely favored the spread of analgesic drugs, including opioids. Prescription opioids are excellent tools to treat chronic pain of oncological origin, in particular, cancer pain from moderate to severe (9-11). However, these drugs are not at all free from serious side effects. The most frequent are depression, confusion, sleepiness, dizziness, low levels of testosterone, nausea, and vomiting, dry mouth, tolerance, physical and psychological addiction (12-14). In recent years, there has been a significant increase in the use of these drugs to treat chronic non-cancer pain, despite the high risk of side effects and the lack of studies demonstrating the long-term efficacy of these medications for this type of pain (15,16). Besides pain, one of the most common reasons for opioid prescription is the treatment of addictions to other opioids such as heroin (17). Regarding the non-medical use of these drugs, there are two groups of subjects: those who start using opioids under prescription and only then develop a substance abuse disorder, and those who immediately start using these drugs outside the prescription.

From the middle of the years '90 in the United States there has been a gradual increase in drug abuse/misuse and overdose deaths involving prescription opioids (18-20). The situation has become so dramatic that the American authorities speak of an "addiction epidemic" (21). These kinds of overdose deaths rose from 3,442 in 1999 to 17,029 in 2017. In recent years, the trend has shifted, and in 2019 the number of deaths dropped to 14,139 (18). After an initial decrease occurred in 2012-2013, there was a new peak until 2016, when the number of deaths from opioids prescription overdoses stabilized. The most implicated medications in opioid overdoses deaths are Methadone, Oxycodone, and Hydrocodone (18).

The decrease in prescription opioid overdose-related deaths was favored by restrictive policies applied by the US government as well as by the publication of guidelines governing the use of prescription opioids. Indeed, the CDC, in 2016, published the Guidelines for Prescribing Opioids for Chronic Pain (22). The objective is to provide primary care physicians with recommendations for the management and treatment of chronic non-cancer pain and on the prescription of opioid drugs in the treatment of adult patients on an outpatient basis.

The CDC drew up 12 recommendations:

1. non-pharmacological and non-opioid drug therapy is preferable in the treatment of chronic pain.
2. Before initiating chronic pain treatment with opioids, physicians should establish treatment goals with patients.
3. before and during opioid therapy, physicians should discuss with patients the risks and benefits associated with opioid therapy.
4. when deciding to start treatment with opioid drugs, doctors should prescribe immediate-release formulations.
5. when deciding to start treatment with opioid drugs, doctors should prescribe the lowest effective dose.
6. when opioids are used to treat acute pain, doctors should prescribe the minimum effective dose for the expected duration of painful symptoms (often 3 days, or less).
7. physicians should evaluate the benefits and damage with patients 1-4 weeks after initiation of therapy or dose increase, in case of prolonged therapy every three months or more frequently.
8. Before and during opioid therapy, physicians should assess for each patient the risk factors for the potential associated damages.
9. doctors should examine the history of prescriptions to determine whether the patient is receiving a dose or combination of opioids at high risk of overdose.
10. before initiation of therapy, and at least once a year during therapy, physicians should submit the patient to a urine toxicology test to analyze prescribed drugs, other drugs, and possible drug use.
11. doctors should avoid prescribing opioids and benzodiazepine analgesics at the same time.
12. doctors should provide patients with an opioid disorder with treatment based on clinical evidence.

These guidelines represent a step towards achieving a balance between the needs of patients with chronic pain and the risks related to an excessive prescription of opioid

drugs. So, given the decline in the number of deaths in recent years, it seems that the publication of these guidelines and the increased media attention to these deaths have produced tangible results.

In Europe, the use of prescription opioids is much lower than in the United States (23,24). Consequently, evidence about the use, misuse, or abuse of prescription opioids in Europe is still poor. Moreover, European authorities, such as the European Monitoring Centre on Drugs and Drug Abuse, are more focused on heroin than on non-medical use of prescription opioids (25).

Among the European nations, UK represents the one with the greatest use of opioids, which is beginning to undergo a trend similar to the American one (26). In Italy, opioid use, although low, has been considerably increasing in recent years: between 2000 and 2010 the purchase of prescription opioids has raised by 292% (27). The latest available Italian report from the National Observatory on the use of medicines indicates a steady increase in prescriptions of major opioids for pain management in terms of change in the ratio of defined daily dose (DDD) ratio from 2014 to 2019 (28).

The Italian trend, even if currently very far from the American one, is beginning to arouse worries. Therefore, the Italian Society of Pharmacology has published a position paper on opioid use for pain management where it calls for great care to be taken in avoiding the risk of abuse and, at the same time, ensuring that all patients with chronic pain have access to treatment (29). Drugs that can be prescribed in Italy in a simplified way for pain therapy (also in parenteral formulations) are Buprenorphine, Codeine, Dihydrocodeine, Fentanyl, Hydrocodone, Hydromorphone, Methadone, Morphine, Oxycodone, Oxymorphone, Sufentanyl for sublingual administration, and Tapentadol. Evidence about deaths associated with prescription opioids is poor in Italy. This work aims to contribute to the analysis of this trend and underline that prescription opioids may become an issue also in the European context.

## Material and methods

A detailed retrospective review of the autopsy and toxicology reports was conducted at the Legal Medicine and Forensic Institutes of "Sapienza" University of Roma and University of Pisa to find cases of prescription opioid-related deaths. The autopsies and toxicological analysis have been carried out between January 2014 and June 2021. It was not possible to analyze the years before 2014 because prescription opioids were not routinely searched. The initial list of cases was compiled based on a search including the terms "overdose", "opioid", "synthetic opioid", finding over 139 cases. Subjects who tested positive for other substances other than opioids have been excluded, except in cases where they were associated with non-steroidal anti-inflammatory drugs (NSAIDs) because the combined use of these drugs with opioids for pain therapy is frequent. Only cases involving deaths related to the use of prescription opioids were included in the final dataset. After the vetting process, 24 different case numbers were found, which pertained to deaths related to the use of prescription opioids. The reasons for the consumption, when identified, have often been

recovered through interviews with family members or from medical records.

All subjects were completely autopsied at the Legal Medicine and Forensic Institutes of the "Sapienza" University of Roma and University of Pisa 24-48 hours after death. In all cases, toxicological samples were prepared by routine methods (30,31), followed by a systematic screening for substances by diverse methods. Volatile compounds were identified using gas chromatography-flame ionization detection (GC-FID). Medical and abuse drugs were identified via the use of gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-tandem mass spectrometry (LC-MS-MS). Brain, heart, lung, liver, spleen, and kidney tissues were sampled during the autopsy and then histologically examined to exclude other causes of death.

Ethical approval and informed consent form were not needed since the material (biological fluid and tissue samples) was collected during judicial autopsies. Privacy rights of human subjects are observed, data are presented anonymously.

## Results

The results of toxicological tests, on blood from the femoral vein, are summarized in table n. 1, while table n. 2 shows the main characteristics of our sample.

Of a total of 24 subjects, 14 died of an overdose of Tramadol (in one case also traces of Methadone and its metabolite EDDP were found), while 7 died of an overdose of Buprenorphine (in one case also traces of Methadone's metabolite, EDDP, were found) and 3 of Fentanyl overdose. Of the deceased, 70,8% (17) were males, while 29,2% (7) were females. The most frequently identified drug in the blood was Tramadol, followed by Buprenorphine and Acetaminophen. Other substances were less frequently found, as shown in Table n. 2.

In all cases, the autopsy did not reveal any organ abnormality that could explain deaths. At histological examinations with hematoxylin/eosin staining no significant findings emerged apart from widespread edema, focal sclerosis of the myocardium, and interstitial and alveolar edema of the lungs.

## Discussion

According to studies on the American population, the risk of prescription opioids abuse is closely related to the following risk factors: intake of high daily doses of painkillers, history of mental illness or substance abuse (included alcohol), and overlapping prescriptions from multiple pharmacies (32-34). It has also been shown that the same use of these drugs for the treatment of heroin addiction is related to an increased risk of developing substance use disorders. The patient, therefore, paradoxically passes from heroin addiction to prescription opioid addiction (35). Moreover, it appears that more than 80% of heroin addicts have started using an opioid prescription (36,37).

The subjects identified through our retrospective analysis died of Tramadol, Buprenorphine, or Fentanyl overdose. Fentanyl is a potent synthetic opioid that is often used for chronic pain, particularly chronic oncological pain. This opioid is widely abused in the United States, where the use of illegal preparations of Fentanyl has become widespread (38,39). Recently there has been an increase in abuse/misuse of Fentanyl (or its derivatives, Cyclopropylfentanyl and Methoxyacetylfentanyl) in Europe, both legal and illegal. This led EMCDDA to monitor Fentanyl and its derivatives (40).

Buprenorphine is an oripavine derivative used for the treatment of acute and chronic pain and as a treatment for opioid cessation. It acts as a partial agonist on mu receptors and as an antagonist on kappa receptors. This dual effect makes this drug safer than other opioids; that is why it is used as replacement therapy in opioid dependence (41). Buprenorphine is often used in combination with Naloxone, and this also emerges from our study. This dual formulation is intended to avoid the misuse, therefore intravenously, of sublingual tablets (42). In fact, Naloxone is a mu receptor antagonist and when taken intravenously induces the typical withdrawal symptoms in drug addict patients. On the contrary, if taken orally, it is inactivated.

Tramadol is a synthetic opioid used to treat acute and chronic pain. In addition, to be a mu receptor agonist, it is also a norepinephrine and serotonin reuptake inhibitor. This triple-action potentiates the inhibitory effect on pain transmission (43). There is also a dual Tramadol/Acetaminophen formulation for the treatment of moderate-severe pain (44). Of the 14 subjects who died of Tramadol overdose analyzed in this study, 6 also had traces of Acetaminophen in biological fluids. Given its effectiveness and manageability, also linked to a lower risk of the onset of side effects typical of other opioids prescriptions, Tramadol has quickly become one of the most used opioid drugs for pain treatment (45). Despite its relative safety, this drug is not free from even very serious side effects, including the risk of intoxication and overdose (46). Moreover, Tramadol, like other opioids, can also induce addiction (47,48). Despite of the increase in cases of Tramadol abuse/misuse (in the USA it has gone from 892 accesses to the Emergency Department related to the Tramadol of 2005 to 5,181 in 2011 (49), the International Narcotic Control Board (INCB) has not yet included this drug in the list of internationally controlled opioids (50). Also, in Italy the Tramadol is not subject to the regulation of opioid drugs: to buy it is sufficient a simple medical prescription. In 2017 the World Health Organization's Expert Committee on Drug Dependence has reviewed Tramadol for the sixth time: following this last review, the Committee recommends placing Tramadol under international control (51).

On the American prescription opioids crisis, numerous studies have been published highlighting a dramatic situation that must be absolutely addressed in the best possible way (52-56). Numerous strategies have been undertaken in the United States, both to prevent and treat opioid-use disorders. For example, opioid formulations with abuse-deterrent properties (such as Buprenorphine-Naloxone formulation) and alternative opioid treatments for chronic pain management

Table 1. The results of the toxicological analysis performed on blood from the femoral vein in 24 cases of death related to the consumption of prescription opioids. The reason why the subjects were under treatment is also indicated when known.

	CASE (Reasons of the consumption)	DRUG	BLOOD (ng/ml)
1	Male (Treatment for opioids dependence. Injected suboxone)	Buprenorphine Free Buprenorphine Total Naloxone Free Naloxone Total	5,61 14,01 Neg. 1,57
2	Male (Treatment for opioids dependence. Injected suboxone)	Buprenorphine Free Buprenorphine Total Naloxone Free Naloxone Total	0,734 2,45 0,84 2,34
3	Female (Treatment for opioid dependence. Suboxone OS)	EDDP Buprenorphine Free Buprenorphine Total Naloxone Free Naloxone Total	63 1,68 2,88 0,89 3,34
4	Male (Unknown)	Buprenorphine Free Buprenorphine Total	2,57 5,98
5	Female (Unknown)	Fentanyl	44,8
6	Male (Pain Therapy Abuse)	Tramadol	2,2
7	Male (Unknown)	Tramadol Methadone EDDP	1,53 0,182 0,03
8	Male (Pain Therapy Abuse)	Tramadol Acetaminophen	1,41 33,1
9	Female (Pain Therapy Abuse)	Tramadol	0,507
10	Male (Unknown)	Tramadol	40,0
11	Male (Pain Therapy Abuse)	Tramadol Acetaminophen Ibuprofen	1,1 0,623 0,140
12	Male (Pain Therapy Abuse)	Tramadol	12,1
13	Male (Unknown)	Acetaminophen Tramadol	5,82 1,82
14	Male (Pain Therapy Abuse)	Acetaminophen Tramadol	2,69 1,19
15	Male (Unknown)	Buprenorphine Free Buprenorphine Total	0,926 3,87
16	Female (Pain Therapy Abuse)	Tramadol	2,4
17	Female (Pain Therapy Abuse)	Tramadol Acetaminophen	1,6 0,437
18	Male (Pain Therapy Abuse)	Buprenorphine Free Buprenorphine Total	0,8 3,25
19	Male (Unknown)	Fentanyl	49,1
20	Female (Pain Therapy Abuse)	Tramadol	2,7
21	Female (Unknown)	Fentanyl	43,8
22	Male (Pain Therapy Abuse)	Tramadol Acetaminophen	3,7 1,55
23	Male (Treatment for opioids dependence. Injected suboxone)	Buprenorphine Free Buprenorphine Total Naloxone Free Naloxone Total	0,872 4,52 0,97 2,85
24	Male (Pain Therapy Abuse)	Tramadol	4,8

Table 2. The main characteristics of the study's sample. EDDP indicates 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine.

Sample characteristics (n = 24)		N. of subjects
Sex	Female	7 (29.2 %)
	Male	17 (70.8 %)
Cause of death	Fentanyl overdose	3 (12.5 %)
	Buprenorphine overdose	7 (29.2 %)
	Tramadol overdose	14 (58.3 %)
Identified drugs	Ibuprofen	1 (4.2 %)
	Methadone and/or EDDP	2 (8.3 %)
	Fentanyl	3 (12.5 %)
	Naloxone	4 (16.7 %)
	Acetaminophen	6 (25 %)
	Buprenorphine	7 (29.2 %)
	Tramadol	14 (58.3 %)

such as cannabinoids, monoclonal antibodies, brain stimulation technologies, etc. have been proposed (57-59).

In Italy, opioid use is much lower than in the United States but also compared to the rest of Europe (58,60). Despite this, our study shows, in line with the very few studies related to the European situation, that there is the potential for a worsening of the Italian situation (24,62-64). The relatively low incidence of prescription opioids deaths in Italy could be explained by various elements. In this regard, it is important to note that in Italy there is wide use of NSAIDs for the treatment of chronic pain (65,66). Moreover, in Italy, only in 2010 the access to opioids for the treatment of chronic pain - also non-cancer - was facilitated and simplified by the law number 38/2010 ("Disposizioni per garantire l'accesso alle cure palliative e alla terapia del dolore" formally published in 2010 March 65). In particular, the law emphasizes the obligations to report the detection of pain within the medical record, training, and updating of health care professionals in the field of palliative care and pain therapy, simplification of procedures for access to medicinal products used in pain management. Surely the entry into force of law 38/2010 has favored the spread of opioid analgesic drugs; this is demonstrated by the various reports of the Observatory on the use of Medicines (OsMed) presented by the Italian Medicines Agency (AIFA) published from 2010 to 2020 (67). These documents indicate that the Defined Daily Dose (DDD/1000 inhabitants per day) of prescription opioids in Italy increased from 2.8 in 2010 to 5.2 in 2013. The latest OsMed report shows not only that this trend is confirmed, but also that curiously, from 2014 to 2019, there was a consistent decrease in DDD/1000 inhabitants per day for minor opioids alone or in combination from 2.5 to 2.0 and an increase for major opioids alone or in combination from 2.2 to 2.9 (plus 9.2% from 2018 to 2019) (67). The Organisation for Economic

Co-operation and Development (OECD) published a report updated to 2016 that shows a decrease in opioid-related deaths in Italy in the last years from 4.8 per million to 1.8 per million habitants (68). However, those data concern both prescription and illicit opioids. All these elements suggest that it would be at least reckless to underestimate the signals that even in Europe, and in Italy, there is the potential risk of an increase in prescription-opioid-related deaths. The need for a systematic report database to collect all available data on prescription opioids deaths is compelling, alongside a policy program to prevent and reduce their misuse/abuse impact on public health. In 2018, the Italian association of Pharmacology (Società Italiana di Farmacologia, SIF) published a position paper speaking out of concern about the abuse risk associated with prescription opioids (69). Another issue concerning prescription opioids is the possibility of medical responsibility claims. If the patient develops opioid abuse after a prescribed opioid treatment, the patient could ask for the opening of a prosecution against the physician who prescribed the drug. Moreover, the patient may claim the lack of information concerning the risk of developing an opioids abuse disorder after the discontinuation of the treatment. (70) To document the information process, a proper and adequate consent form may be necessary.

One limit of this work is that it is based on the casuistry of only two Legal Medicine Institutes, and it may not be representative of the entire Italian situation. Another limitation is the small period of time taken into consideration (only seven years, from January 2014 to June 2021). However, our study shows that particular attention should be paid to drugs considered to be "safer" such as Buprenorphine and Tramadol, also considering that, as already argued, for the latter, there are no specific regulations, unlike other opioid drugs. To prevent a crisis related to prescription opioids deaths, Europe, which is not exempt from an increase in the prevalence of opioid drugs, should implement a series of preventive measures also taking advantage of the American experience. First, the guidelines issued by the CDC should be used (22). Then, particular attention should be paid to the close monitoring and counseling of the patient undergoing opioid analgesic therapy before and during treatment. Indeed, as Jamison *et al.* showed, a cognitive-behavioral preventive approach could significantly reduce the risk of opioid abuse (71,72). Adequate education of health professionals on the risks and benefits of opioid drugs is another indispensable tool to avoid the misuse/misuse of these substances. Lastly, in chronic pain management, it is crucial to support research into the identification of safer opioid molecules that do not facilitate the development of addiction. To best define all the appropriate preventive measures is also fundamental from the point of view of medical liability: a doctor, in prescribing opioids, should have the tools to better assess the best behavior to be implemented.

## Conclusion

Our study, based on data collected by two Italian Forensic Institutes, although limited by a small case series, shows that the problem of opioid overdose deaths is also present in Italy. Even if the cases of opioid abuse seem to be lower than in the

United States, it has been shown that in Italy a public health problem could emerge in the coming years. Therefore, in the context of prescription opioids, it is certainly crucial to focus on achieving good clinical practices and on the appropriateness of prescribing. In addition, European institutions should carefully monitor the evolution of prescription opioid use and possibly implement strategies and policies aimed at preventing an epidemic similar to that in the United States. Furthermore, in the context of medical responsibility, it is essential to define the limits, benefits, risks, and alternatives of prescription opioids.

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**Institutional Review Board Statement:** The study did not require ethical approval. Data processing complies with the general authorization for scientific research purposes granted by the Italian Data Protection Authority (1 March 2012 as published in Italy's Official Journal no. 72 dated 26 March 2012) since the data do not entail any significant personalized impact on data subjects. Approval by an institutional and/or licensing committee is not required since experimental protocols are not applied in the study. All cases are judicial and ordered by local prosecutors.

**Informed Consent Statement:** No informed consent is required to use information from persons where the same information is strictly indispensable and relevant for scientific and research purposes.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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