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Original Research

Trends in fatal poisoning among medical users of analgesics in France from 2013 to 2022: an analysis of the DTA register

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ABSTRACT

Objective: To describe analgesic-related deaths in France and report trends over a 10-year period.
Study design: The DTA (*"Décès Toxiques par Antalgiques"*) register is a French database of analgesic-related deaths among people without a history of drug abuse, reported by forensic toxicology experts.
Methods: We included analgesic-related deaths occurring from January 2013 to December 2022 in France. Subject demographic characteristics and medical history, forensic autopsy findings, and toxicology reports were evaluated.
Results: Among the 1036 deceased individuals (mean [SD] age, 48.3 [15.6] years), there were slightly more women than men (M:F sex ratio, 0.89:1). Over the entire study period, tramadol was the leading cause of death, ahead of morphine. A relative increase in oxycodone-related mortality was observed (from 6.8% in 2013 to 21.1% in 2022) compared to a progressive decrease in tramadol, morphine, and codeine-related deaths (from 43.2%, 31.1% and 24.3% in 2013 to 37.5%, 26.6% and 20.3% in 2022, respectively). However, no statistically significant variations were found (Chi-squared tests of homogeneity). Other analgesics (buprenorphine, dihydrocodeine, fentanyl, gabapentin, ketamine, methadone, nefopam, and pregabalin) were also implicated in deaths, but with low and stable rates over the period studied.
Conclusions: In France, no increase in fentanyl-related deaths and only a non-significant increase in oxycodone-related deaths were observed over the period 2013–2022. Tramadol was the leading cause of analgesic-related deaths throughout this period. Although close monitoring is still required, particularly for oxycodone, our data do not support the hypothesis of an opioid crisis in France.

Introduction

Worldwide, drug poisoning constitutes a public health concern, highlighted by the opioid epidemic currently raging in the United States, which has become the leading cause of accidental death in that country. The crisis began in the late 1990s when pharmaceutical companies introduced new opioid analgesics, reassuring the medical community that patients would not become addicted. This subsequently led to the widespread diversion and misuse of these

Abbreviations: ANSM, French National Agency for the Safety of Medicines and Health Products; CNBAE, *Compagnie Nationale des Biologistes et Analystes Experts* [National Society of Biologists and Analysis experts]; DDD, Daily Defined Dose; DTA, *Décès Toxiques par Antalgiques* [Toxic Deaths from Analgesics]; EUDA, European Union Drugs Agency; FAN, French Addictovigilance Network.

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medications before it became clear that they could indeed be highly addictive.[1] There is extensive debate as to whether Europe is facing a comparable opioid crisis and the possible contribution of analgesic prescriptions.[2] Although the situation currently seems less problematic than in the US, across Europe it is heterogeneous, with some countries (such as the United Kingdom) reporting significantly more opioid-related mortalities than others.[3] In addition, the Europe-wide summaries that are available, such as the annual European Union Drugs Agency (EUDA) report, do not provide detailed analysis per country and per analgesic, which are essential for effective monitoring and for the development of targeted prevention and treatment programs. For example, tramadol (an opioid medication used to treat moderate to severe pain) was implicated in less than 5% of reported deaths due to overdose across 12 European countries in 2021.[4] In contrast, for years it has been the most widely used opioid and the leading cause of accidental analgesic-related deaths reported to the French pharmacovigilance system,[5] suggesting that better surveillance and toxicological investigation might increase the detection of deaths associated with analgesic prescriptions on a country-wide scale.

Compared to the US crisis, no significant increase in oxycodone or fentanyl-related deaths was observed during the period 2011–2021 among drug users in France.[6] However, no study has explored trends in fatal analgesic poisoning among people without a history of drug abuse, while oxycodone was the opioid analgesic with the greatest increase in use between 2006 and 2017 in France (from 0.1 to 1 DDD/1000 inhabitants/day).[5] Although the prevalence remains low in the general population (0.4%), oxycodone consumption rate is close to that of morphine, which is the most widely used strong analgesic for many years in France, despite a 18% decrease in morphine consumption between 2006 and 2017.[5,7] The number of tramadol users remained stable between 2014 and 2018 in France, with 5.9 million users in 2018, while tramadol use decreased annually in quantity from 2014 (11.9 DDD/1000 inhabitants/day) to 2018 (10.5 DDD/1000 inhabitants/day).[8] Codeine in combination with paracetamol is the second most commonly used opioid analgesic in France, with an increase in consumption between 2006 and 2014 (+84%), then falling by 30% between 2016 and 2017.[5]

The purpose of this study is to present the trends in the analgesics implicated in fatal poisoning among people using analgesics for medical purposes (i.e., excluding drug abusers) in France over a 10-year period, from 2013 to 2022.

Methods

Data source

The DTA (*"Décès Toxiques par Antalgiques"*) register is a database of drug-related deaths designed to identify the analgesics involved and estimate trends in the number of these deaths. The register is based on the voluntary reporting of data on deaths for which toxicology experts (throughout France) have performed analyses. Post-mortem toxicological analyses are performed as part of the search for the cause of death, but only at the request of the judicial authorities. Consequently, when there is no suspicion of drug involvement in a death, a toxicological analysis is generally not requested. The Grenoble Addictovigilance Centre (coordinator of this register since 2013) examined each reported case to determine the drug or drugs involved in the death.

Data collection

Data were collected using a form completed by the forensic toxicologist containing the following items: the demographic characteristics; medical and substance abuse history of the subject; the circumstances in which the body was found; the results of the autopsy and pathological analyses; identification of the substances found in the analysis of biological samples and their quantification in blood or other matrices if blood was not available; the probable cause of death.

These data made it possible to classify each case into: direct cause of death (toxic cause alone, usually overdose; or toxic cause with related pathology) or indirect drug-related death (*e.g.*, falling from a high place while under the influence of a drug). Indirect drug-related deaths are not included in this study.

Inclusion criteria

The DTA register includes deaths due to a standard list of psychoactive analgesics: buprenorphine, codeine, dextropropoxyphene (although it was withdrawn from the French market in 2011), dihydrocodeine, fentanyl, gabapentin, hydromorphone, ketamine (used off-label for pain), morphine, nalbuphine, nefopam, methadone (licensed in France for pain from August 2020), oxycodone, pethidine, pregabalin, and tramadol.

Non-inclusion criteria

The following are not included in the DTA register: deaths due to drug intoxication by users with a documented history of substance abuse; cases in which another cause not related to an analgesic was found; cases with insufficient documentation (*e.g.*, no known cause of death); and cases without any drug testing (in the absence of blood, analyses of other matrices such as bile or muscle are needed).

Causality (death associated with substance use)

For each case examined, each substance present in the blood underwent a causality analysis.

In order to differentiate substance(s) involved in the death, from other substances found in the blood (or other matrix), each substance was graded[9–11] as follows: lethal concentration = level 1; toxic concentration = level 1 or 2 depending on other substances present; therapeutic concentration = level 1, 2, 3, or 4 depending on other substances present; sub-therapeutic concentration = no score assigned.

In the present study, only level 1 substances were considered as the cause of death. In addition, depending on the number of substances involved, the score was subdivided into: 1.0 when only one drug was involved (*e.g.*, tramadol without any other substance); 1.1 corresponding to one predominant drug (including active metabolites) amongst others (*e.g.*, morphine at a toxic concentration combined with benzodiazepine at a therapeutic concentration); 1.2 corresponding to 2 co-dominant drugs present (*e.g.*, oxycodone at a toxic concentration combined with benzodiazepine at a lethal concentration); 1.3 corresponding to 3 or more co-dominant drugs present (*e.g.*, tramadol combined with at least 2 other substances all at toxic or lethal concentrations).

According to this grading scheme, a combination of analgesics could be considered as the cause of death. For each case, the causality of the drug(s) was independently assessed by two toxicology experts. In case of disagreement, the advice of a third expert was sought.

Statistics

Chi-square tests of homogeneity were performed for selected drugs (over the whole period). All analyses were conducted with R software (version 3.6.3), and its tidyverse meta-package, including

the ggplot2 package for plotting. Smoothed curves correspond to LOESS (locally estimated scatterplot smoothing) curves obtained using ggplot2. In order to take into account the multiplicity of comparisons for homogeneity tests, the statistical significance threshold for *P*-values was adapted using a Bonferroni correction (P value < 0.0025).

Results

From January 2013 to December 2022, 1036 cases were included. Subject characteristics are presented in Table 1. The overdose mortality rate was slightly higher among women (M:F sex ratio, 0.89:1) and the mean [SD] age was 48.3 [15.6] years, ranging from 1 to 99 years. A progressive increase in the age of the subjects is observed over time. A psychiatric illness (anxiety, bipolar disorder, depression, schizophrenia, suicide attempts, etc.) was associated with 32.6% of deaths and 7.0% of subjects were being treated for a life-threatening illness such as cancer.

Over the course of the study period, the participation of toxicology experts increased, representing almost half of the 101 French counties in 2022 (Table 1).

The trends in drug-related deaths involving a single drug (1.0), a predominant drug (1.1), or multiple co-dominant drugs (1.2 and 1.3) are presented in Fig. 1. Over the whole period, tramadol remained the leading cause of death, ahead of morphine, reaching 43.2% ($n = 32$) in 2013 and 37.5% ($n = 48$) in 2022. The incidence of morphine-related deaths decreased from 31.1% ($n = 23$) in 2013 to a minimum of 22.3% ($n = 25$) in 2020. The incidence of codeine-related deaths decreased from 24.3% ($n = 18$) in 2013 to 20.3% ($n = 26$) in 2022. In contrast, the incidence of oxycodone-related deaths increased from 6.8% ($n = 5$) in 2013 to 21.1% ($n = 27$) in 2022, exceeding that of codeine in 2018 and 2022. However, no statistically significant variations were found over the period: tramadol ($P = 0.19$), morphine ($P = 0.89$), codeine ($P = 0.18$), and oxycodone ($P = 0.12$). Details of the Chi-square homogeneity tests are included in eTable 1. Interestingly, over the whole period the curves for tramadol and codeine, both weak opioids, seem to mirror each other.

The incidence of deaths due to other analgesics (buprenorphine, dihydrocodeine, fentanyl, gabapentin, ketamine, methadone, nefopam, pregabalin) remained low and stable over the study period.

Discussion

Our data do not support the hypothesis of an opioid crisis in France, with no statistically significant variations observed in the incidence of fatal poisoning among users of analgesics for medical purposes over the period 2013–2022.

An analysis of the consumption of analgesics (non-opioids, weak and strong opioids) carried out in 2015 across seven European countries (Denmark, France, Germany, Italy, Spain, Sweden and United Kingdom) highlighted different consumption profiles. Strong opioid analgesics were least consumed in France and Italy compared to the other countries, but France ranked third in the consumption of weak opioids. Among these, tramadol was the most consumed weak opioid in France, as in Germany, Italy, Spain, and Denmark.[7,12] Accordingly, for many years tramadol has been the leading cause of fatal poisoning among people with no history of addiction in France. Our results are consistent with a high-risk tramadol use driven by both opioid and non-opioid mechanisms of action, including effects on serotonin reuptake.[13] More specifically, we identified two profiles of high-risk tramadol use: (1) patients treated for pain or with continuation of tramadol when pain disappeared (mainly women; mean age 44 years), and (2) individuals with -non-medical use, including for recreational purposes (mainly men; mean age 36 years). For patients with initial medical use, symptoms of withdrawal, craving and desire for opioid and/or stimulant effects play a leading role in their pursuing of tramadol use and the development of a severe primary substance use disorder.[8] Despite this risk, prescribers often considered tramadol as having a low potential for substance use disorder. Consequently, in France, the maximum prescription period for analgesics containing tramadol was reduced from 12 months to 3 months in 2020, which may have contributed to the relative reduction in tramadol-related mortality observed from 2021 in our study. More recently, packs of only 10 or 15 tablets are marketed from 2024 to limit the risk of misuse, dependence and overdose-related deaths.

Early signals of diversion have been observed in recent years for extended-release oral morphine.[14,15] However, according to our study, these signals have not been reflected by an increase in the number of deaths among prescription morphine users.

The majority of the population using codeine in a problematic manner were female (58%), mean age 40 years, and the main reason

Table 1
Number of subjects included, demographic characteristics, place of death, medical history of individuals, and number of French counties[a] covered per year.

Characteristics	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	Total
Participants, No. (%)	**74**	**66**	**82**	**83**	**104**	**107**	**144**	**112**	**133**	**131**	**1036**
A single (1.0) or a predominant drug (1.1) involved	45 (60·8)	40 (60·6)	50 (61·0)	47 (56·6)	61 (58·7)	73 (68·2)	85 (59·0)	65 (58·0)	80 (60·2)	80 (61·1)	626 (60·4)
Two or more co-dominant drugs (1.2 or 1.3) involved	29 (39.2)	26 (39.4)	32 (39.0)	36 (43.4)	43 (41.3)	34 (31.8)	59 (41.0)	47 (42.0)	53 (39.8)	51 (38.9)	410 (39.6)
Age, mean (SD), y.	**45.8 (16.2)**	**48.3 (12.9)**	**42.8 (13.6)**	**48.9 (13.3)**	**48.3 (15.3)**	**50.6 (17.4)**	**48.5 (13.5)**	**49.4 (17.0)**	**49.2 (16.4)**	**48.8 (17.2)**	**48.3 (15.6)**
Sex ratio (male:female)	**0.95**	**0.74**	**1.00**	**1.18**	**1.21**	**0.67**	**0.73**	**0.75**	**0.68**	**1.34**	**0·89**
Place of death, No. (%)											
Home	66 (89.2)	42 (63.6)	70 (85.4)	64 (77.1)	82 (78.8)	87 (81.3)	111 (77.1)	91 (81.3)	111 (83.5)	110 (84.0)	834 (80.5)
Public road		10 (15.2)	1 (1.2)	3 (3.6)	2 (1.9)	7 (6.5)	6 (4.2)	2 (1.8)	6 (4.5)	5 (3.8)	42 (4.1)
Hospital	4 (5.4)	3 (4.5)	2 (2.4)	2 (2.4)	3 (2.9)	5 (4.7)	6 (4.2)	1 (0.9)	4 (3.0)	5 (3.8)	35 (3.4)
Jail		1 (1.5)	1 (1.2)							2 (1.5)	4 (0.4)
Other/unknown	4 (5.4)	10 (15.2)	8 (9.8)	14 (16.9)	17 (16.3)	8 (7.4)	21 (14.6)	18 (16.1)	12 (9.0)	9 (6.9)	121 (11.7)
Known medical history, No. (%)											
Psychiatric history, including suicide attempts	26 (35.1)	20 (30.3)	27 (32.9)	31 (37.3)	39 (37.5)	34 (31.8)	50 (34.7)	30 (26.8)	38 (28.6)	43 (32.8)	338 (32.6)
Life-threatening illness	4 (5.4)	7 (10.6)	7 (8.5)	6 (7.2)	8 (7.7)	4 (3.7)	14 (9.7)	6 (5.4)	9 (6.8)	8 (6.1)	73 (7.0)
Counties represented, No. (%)	**30 (29.7)**	**31 (30.7)**	**36 (35.6)**	**36 (35.6)**	**32 (31.7)**	**42 (41.6)**	**46 (45.5)**	**40 (39.6)**	**41 (40.6)**	**48 (47.5)**	**NA**

NA, not applicable.
[a] France is divided into 101 counties (called departments).

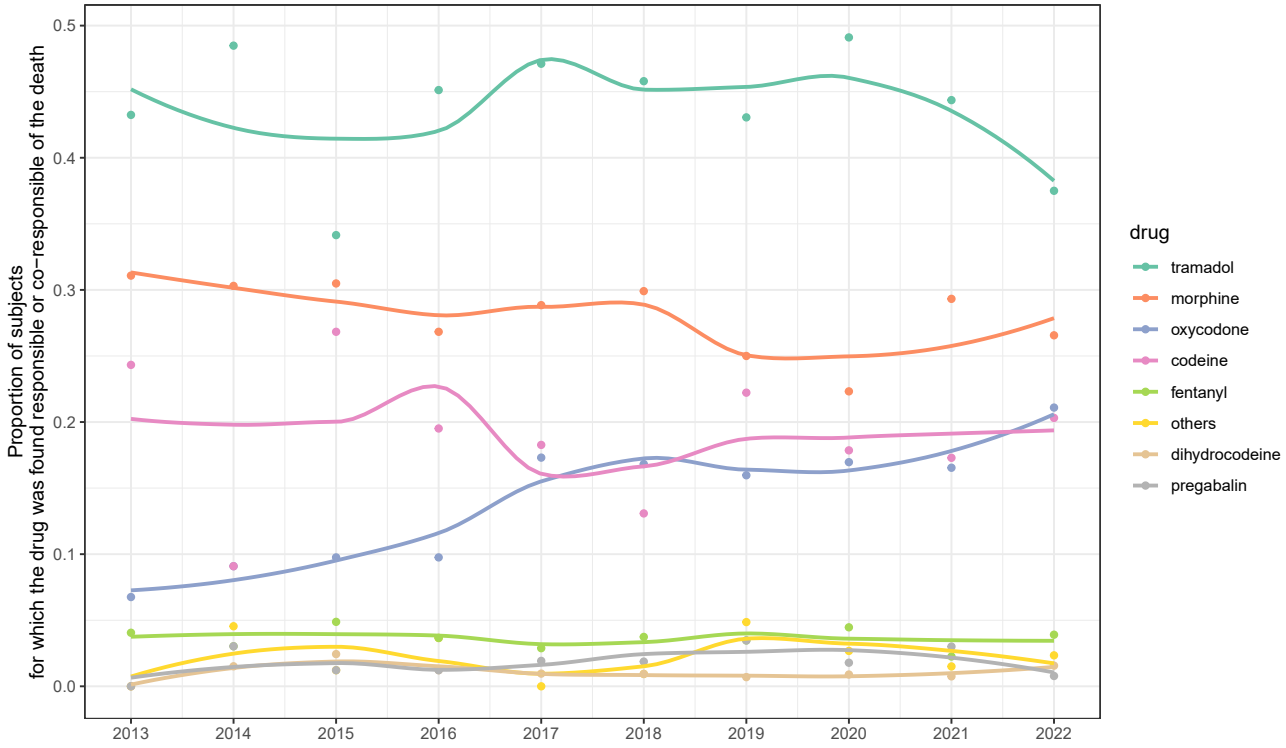

Fig. 1. Trends in analgesic-related deaths involving a single drug (1.0) or a predominant drug (1.1) or multiple co-dominant drugs (1.2 and 1.3) among medical users, France, 2013–2022. *Others include buprenorphine, dextropropoxyphene, gabapentin, ketamine, methadone, nefopam.

for starting consumption is for the treatment of pain (82%).[5] However, codeine is also misused by teenagers and young adults for recreative purposes in the form of the cocktail "Purple Drank" (or "Lean").[16] In France, this led to all codeine-based products being placed under mandatory prescription in 2017. A 30% drop in consumption was observed following this decision, which may have contributed to the relative reduction in codeine-related mortality observed from 2018 in our study.

In contrast, the incidence of oxycodone-related deaths increased over our study period. In parallel, the proportion of notifications involving oxycodone reported to the French Addictovigilance Network (FAN) constantly increased. In 73.7% of these, the drug was initially used to treat pain, described as "mixed" (39.3%), neuropathic pain (36.9%), fibromyalgia (7.1%), cancer pain (4.7%), pain due to "excess of nociception" (4.8%) and diffuse pain syndromes (2.4%) (not specified in other cases).[5] Our results are also consistent with the large increase in the number of subjects with "doctor-shopping" behavior for oxycodone (a channel for potential misuse).[17]

Fentanyl was of particular concern because of the central role it plays in the US opioid epidemic. However, according to our results, neither its frequent off-label use (oral transmucosal fentanyl formulations prescribed for non-cancer pain) nor the risk of primary fentanyl dependence[18] resulted in a significant increase in mortality.

Over the period studied, pregabalin was the only non-opioid analgesic regularly responsible for deaths, which is consistent with the related harms already reported in France (hospitalization for serious neurologic, psychiatric, or cardiac effects, requests for addictology support and deaths).[19]

In light of the US crisis, the multi-modal approach to pain treatment in France and the French legal framework restricting access to strong opioids may inspire similar approaches in other countries.[20] The challenge remains to encourage the proper use of opioids without regressing in terms of pain management. In this context, the use of brief questionnaires such as the Opioid Risk Tool (ORT) or the Prescription Opioid Misuse Index (POMI) is recommended to detect substance use disorders, including for weak opioids (*e.g.* tramadol or codeine).

To our knowledge, our study is the first to collect and analyze data on all deaths for which toxicology reports were available. The novelty of this study is also its target population, subjects without a history of drug abuse. Despite this, our study has several limitations, mainly due to the fact that in France, toxicological investigations are only performed if ordered by the judicial authorities and that the participation of toxicology experts in the DTA register is voluntary. Therefore, the drug-related deaths collected and described in the register are non-exhaustive. Nevertheless, the results are sufficiently reproducible from one year to another to reveal certain trends. However, the absolute number of reported drug-related deaths was low (131 cases in 2022), which might explain the absence of statistically significant results and did not allow us to conduct a sub-analysis by county. These limitations might be overcome by encouraging more experts to participate and including data from other French counties. In addition, even though suicidal and accidental poisonings are considered separate clinical entities, determining the intentionality (or not) underlying a lethal overdose is often challenging. Accordingly, both entities are included in the DTA register.

In conclusion, analgesic-related deaths are of concern in France, with tramadol being the leading cause of such deaths, and with oxycodone requiring close monitoring.

Author statements

Ethical approval

As this study was performed using routinely collected de-identified data it did not require any ethics committee approval, in line with the French regulations for mandatory reporting by

healthcare professionals (article R5132-102 of the Public Health Code).

This study follows the reporting guideline for case series studies: eligibility criteria are explicitly provided; appropriate statistics have been performed ensuring that the assumptions of the statistical methods are reasonable in this setting (Bonferroni correction); limitations and how these limitations could be overcome are explicitly discussed.

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Competing interests

None reported.

Author contributions

BR had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: BR, TW, HEG, NFSL.

Acquisition, analysis, or interpretation of data: BR, TW, VDT, JMG, HEG, NFSL.

Drafting of the manuscript: BR, TW, MM.

Critical revision of the manuscript for important intellectual content: MM, VDT, JMG, HEG, NFSL.

Statistical analysis: BR, MM.

Obtained funding: VDM, JMG, HEG, NFSL.

Administrative, technical, or material support: BR, TW, MM.

Supervision: VDT, JMG, HEG, NFSL.

Role of the funder/sponsor

The sponsor had no role in the design of the study, its execution, analyses, interpretation of the data, or decision to submit results.

Data sharing statement

Individual patient data that support the findings of this study are available from the corresponding author, upon reasonable request. Annual reports are available online on the ANSM website: https://ansm.sante.fr/page/resultats-denquetes-pharmacodependance-addictovigilance.

Additional contributions

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2024.08.019.

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