ansm
Agence nationale de sécurité du médicament
et des produits de santé

SITUATION REPORT

Use and Abuse of Opioid Analgesics

FEBRUARY 2019

This report was written by
Emilie Monzon and coordinated
by Nathalie Richard

Also participating in its preparation were:

- The Addictovigilance network of drug dependence assessment and information centres -
- The French observatory of analgesic medicines *(Observatoire Français des Médicaments Antalgiques)*
- Philippe Cavalié
- Aldine Fabreguettes
- Augusto Fernandez
- Sylvain Guého
- Karima Hider-Mlynarz
- Adrien Inoubli
- Marie-Caroline Pesquidous
- Charlotte Pion
- Philippe Vella

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LIST OF ACRONYMS USED IN THIS DOCUMENT

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ANSES	National agency for food safety, environment and labour *(Agence Nationale de Sécurité Sanitaire)*
ANSM	National Agency for the Safety of Medicines and Health Products *(Agence Nationale de Sécurité du Médicament et des produits de santé)* **NSAID** Non-steroidal anti-inflammatory drug
AP-TV	Anti-Poison and Toxicovigilance centres
ASOS	Narcotic analgesics and secure prescriptions *(Antalgiques Stupéfiants et Ordonnances Sécurisées)*
BNPV	National pharmacovigilance bank *(Banque Nationale de Pharmacovigilance)*
CEIP-A	Centre for evaluation and information on pharmacodependence - Addictovigilance *(Centre d'évaluation et d'information sur la pharmacodépendance - Addictovigilance)*
CNAMTS	The national health insurance fund for salaried workers *(Caisse Nationale d'Assurance Maladie des Travailleurs Salariés)*
DANTE	Decade of analgesics in France *(Décennie D'ANTalgiques en France)*
DGS	National health authority *(Direction Générale de la Santé)*
DRAMES	Deaths in relation to the abuse of medicines and substances *(Décès en Relation avec l'Abus de Médicaments et de Substances)*
DTA	Deaths due to analgesic toxicity *(Décès Toxiques par Antalgiques)*
EGB	Permanent sample of health insurance beneficiaries *(Echantillon Généraliste des Bénéficiaires)*
HAS	National supreme health authority *(Haute Autorité de Santé)*
HH	Home hospitalisation
InCa	National cancer institute *(Institut National du Cancer)*
LTC	Long term condition
MA	Marketing Authorisation
MILDECA	Interministerial mission against drugs and addictive behaviour *(Mission Interministérielle de Lutte contre les Drogues et les Conduites Addictives)*
NotS	Spontaneous notification
NSAID	Non-steroidal anti-inflammatory drug
OFMA	French observatory of analgesic medicines *(Observatoire Français des Médicaments Antalgiques)*
OPEMA	Observation of drug dependence in outpatient medicine *(Observation des Pharmacodépendances en Médecine Ambulatoire)*
OPPIDUM	Observation of psychotropic products, illicit or licit but diverted from their medicinal use *(Observation des Produits Psychotropes Illicites ou Détournés de leur Utilisation Médicamenteuse)*
OSIAP	Suspicious prescriptions, indicator of possible abuse *(Ordonnances Suspectes, Indicateur d'Abus Possible)*
OSM	Opioid substitution medication
RFS	French society for accompaniment and palliative care *(Société Française d'Accompagnement et de Soins Palliatifs)*
SFAR	French association for anaesthesia and intensive care *(Société Française d'Anesthésie et de Réanimation)*
SFETD	French society for the study and treatment of pain *(Société Française d'Etude et de Traitement de la Douleur)*
SNIIRAM	National inter-scheme health insurance information system *(Système National d'Information Inter-Régimes de l'Assurance Maladie)*

BACKGROUND

Improving the management of pain is a public health priority in France. Since 1998, a succession of action plans to address the issue of pain and its relief have been implemented.

A broader provision and use of opioid medications in the treatment of pain has greatly contributed to the overall improvement in pain management. These medicinal products, while most often used rationally, have a high potential for abuse and dependence, and their misuse is associated with serious consequences for public health.

Opioid analgesics are responsible for a large and growing number of fatal overdoses worldwide. The World Health Organization (WHO) reports that this phenomenon has increased in recent years, in particular due to the increase in opioid consumption in the management of chronic non-cancer pain.

North America in particular has for several years been confronted with an increase in deaths related to the consumption of opioids, from both medical prescriptions and illicit sources. The first signs of this began in the United States in the 1990s with an increase in prescriptions for opioid analgesics and deaths due to their consumption. The numbers have only been increasing in the intervening period. The second and third waves of deaths started in 2010 and 2013 respectively, involving heroin and synthetic opioids (for example fentanyloids). Recent figures suggest that 115 Americans die each day from an overdose of opioids, whether licit or illicit (Source: Centres for Disease Control and Prevention). Opioids obtained on prescription were responsible for 17,087 deaths in 2016.

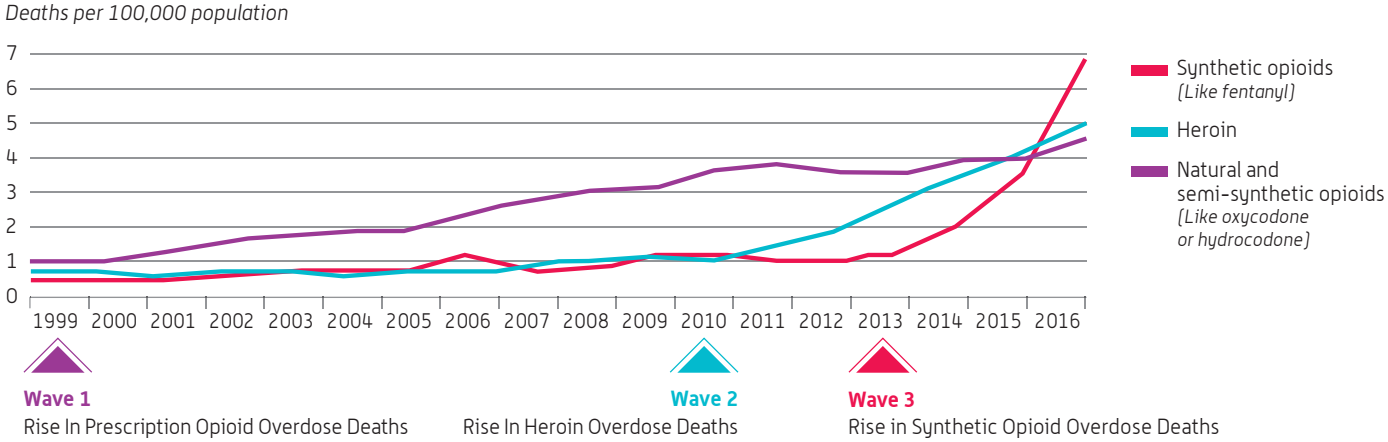
The situation in France is somewhat different, the conditions for prescribing, dispensing and managing opioid analgesics, along with the provision information to healthcare professionals and the general public having little in common with those encountered the United States.

In order to take stock of the situation in France, the ANSM hosted a symposium on the use and abuse of opioid analgesics on May 11, 2017. This day of partnership and exchange made it possible to gain a global vision of the issues raised, to carry out a synthetic analysis of the data and to make proposals with the overall aim of maintaining the positive benefit/risk ratio of these medicinal products. A number of stakeholders were invited and heard, including, health authorities, professional bodies and patient associations.

Although the situation is not comparable to that in the United States, a number of indicators call for increased vigilance on the part of both authorities and healthcare professionals.

This report presents the essential features of the data gathered at this meeting, along with additional considerations and proposals to improve the use, and reduce the misuse, of opioid analgesics.

3 WAVES OF THE RISE IN OPIOID OVERDOSE DEATHS
(source National Vital Statistics System Mortality File)



ABSTRACT

Several opioid analgesic products are marketed in France. High street pharmacy sales and hospital use figures, health insurance reimbursement data, and date on prevalence and incidence all show an increase in their consumption. This increase is an indicator of recent improvements in the management of pain. As a result:

- **In 2017, the most consumed analgesics in France were non-opioids [paracetamol, aspirin and non-steroidal anti-inflammatories (NSAIDs)] (78%), followed by weak opioid analgesics (20%)[1] which were consumed ten times more than strong opioids (2%)[2].**
- **In 2015, 9,966,944 French citizens (17.1% of the population) received a prescription for an opioid analgesic.**
- Consumption of weak opioid analgesics decreased overall due to the withdrawal of the combination dextropropoxyphene/paracetamol in 2011. Consumption of other weak opioids increased.
- **Tramadol is the most consumed opioid analgesic** (use increasing from 7.51 to 11.22 DDD/1000 inhabitants/day, an increase of + 68% between 2006 and 2017).
- **The opioid analgesic showing the greatest increase in use is oxycodone** (from 0.1 to 1 DDD/1000 inhabitants/day, a 738% increase between 2006 and 2017), a consumption rate close to that of **morphine sulphate, the strongest opioid analgesic available in the last 10 years.**
- **Users of analgesics are mostly women,** whether for weak or strong opioids (respectively 57.7% and 60.5% in 2015).
- Users of strong opioids are older than users of weak opioids (64 years and 52 years respectively).
- In 2015 treatment was initiated by a general practitioner in 59.1% of cases for weak opioid analgesics and in 62.9% of cases for strong opioids, and by a hospital doctor for 20.1% of weak opioids and 21% of strong opioids.
- Chronic use of opioid analgesics is higher with strong opioids (14.3% in 2015) than with weak opioids (6.6%).
- In 2017, prescribers of opioids were general practitioners (86.3% of weak opioids and 88.7% of strong opioids), dentists (2.8% and 0.3%), rheumatologists (2.2% and 1.7%) and orthopaedic surgeons (1.9 and 1.3%).
- The reasons for prescribing weak opioids are acute pain (71.1%), chronic pain (13.4%), back pain (8.1%), osteoarthritis pain (2.6%).
- The reasons for prescribing strong opioids are acute pain (50.1%), chronic pain (42.9%), back pain (21.6%) and pain related to osteoarthritis (7%).

(1) Examples of "weak" opioids analgesics: tramadol, codeine, opium.
(2) Examples of "strong" opioids analgesics: morphine, oxycodone, fentanyl.

Opioids have a major and undeniable place in the management of pain. However, increased consumption of opioid analgesics may be accompanied by serious complications:

- **The number of hospitalisations related to prescription-use opioid analgesics increased from 15 to 40 hospitalisations per million of the population between 2000 and 2017.**
- In the National Pharmacovigilance Bank (BNPV, see acronyms above), **the rate of notifications of opioid analgesic intoxication increased from 44/10,000 to 87/10,000 notifications between 2005 and 2016.** In 2016, the three substances most involved in such intoxications were tramadol, morphine and oxycodone.
- **The number of deaths related to opioid use increased from 1.3 to 3.2 deaths per million population between 2000 and 2015, with at least 4 deaths per week.**
- **The number of cases of opioid analgesic misuse reported to the addictovigilance network more than doubled between 2006 and 2015.**
- **Tramadol is the most common opioid analgesic appearing in reports of problematic use in the addictovigilance network, also being the most commonly implicated in death in the DTA and OSIAP surveys (see acronyms).**
- The problematic use of morphine and oxycodone differs from other opioids. In addition to patients initially treated for pain, a population with more male and young drug users emerges from the notifications reported in the French addictovigilance network.

The consumption of opioid analgesics has increased significantly in France over the last ten years. The modalities of care and supervision by prescribers, as well as the controlled nature of access to these medicines, have made it possible to avoid a crisis of the same magnitude as has occurred in the United States.

However, an increase in cases of misuse is observed, as are increases in intoxication and death related to the use of opioid analgesics.

This issue primarily affects patients having initially consumed an opioid analgesic **to relieve pain, and who go on to develop a primary dependence** on their treatment, and sometimes misuse. This profile concerns women more than men.

The ANSM wishes to recall that an opioid analgesic, **whether weak or strong,** exposes its user a risk of **dependence, abuse, misuse, overdose and respiratory depression, which can lead to death.**

Any opioid analgesic prescription should therefore be systematically accompanied by information for the patient concerning the treatment and its discontinuation, and **monitoring of the risks involved, even when it is initially prescribed in accordance with the conditions of the marketing authorisation.**

1

CONSUMPTION DATA EUROPE

Where does France sit ?

Five opioid analgesics are marketed in all European countries: codeine, tramadol, morphine, oxycodone and fentanyl. Other opioids (opium powder, buprenorphine, hydromorphone) are marketed in some but not all Member States.

Prescription and dispensing procedures differ from one country to another. The prescription of certain opioid analgesics may be restricted to specialists (Italy, Hungary, Czech Republic, Slovak Republic) or to doctors listed in a register (Germany).

The maximum duration of prescription can be between 5 and 14 days (Spain, Hungary, Czech Republic, Slovak Republic, Slovenia), one month (United Kingdom, Italy, Poland, Romania), between 60 and 90 days (Ireland, Latvia) or of unrestricted duration (Denmark, Finland, Germany, Portugal, Austria, the Netherlands, Sweden, Belgium). Supply may be reserved to certain administrative structures or recorded in a specific register, and the quantity delivered may be restricted.

France's place in Europe

An analysis of consumption of analgesics (non-opioids, weak opioids, strong opioids) carried out in 2015 in seven European countries (France, Germany, Italy, Spain, United Kingdom, Denmark and Sweden) has made it possible to highlight different consumption profiles. The sales data have been converted into DDD/1000 inhabitants/day in order to normalise for differences in packaging size and the dose of the different medicinal products marketed, along with the difference in population from one country to another. The full methodology is described in Hider-Mlynarz (2018).

The United Kingdom and Spain have a high overall consumption of analgesics. The United Kingdom is the leading consumer of opioid analgesics.

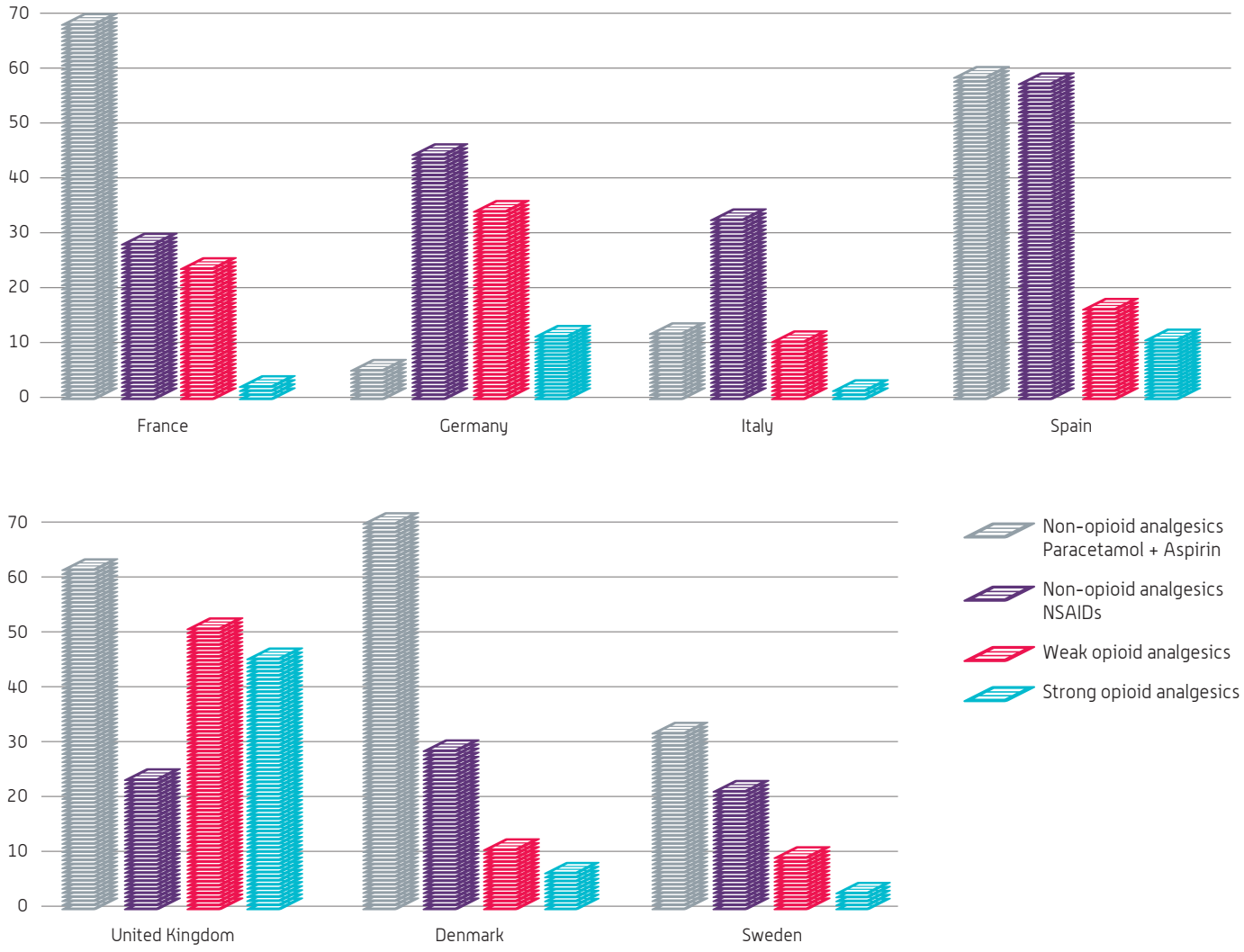
Among these seven countries, France is the third largest consumer of analgesics, and the second largest consumer of non-opioid analgesics behind Denmark. It is the fourth largest consumer of opioid analgesics behind the United Kingdom, Germany and Spain.

France ranks third in the consumption of weak opioids. Among these, tramadol is the most consumed in France, as in Germany, Italy, Spain and Denmark. Codeine in combination with paracetamol is the most consumed weak opioid in Sweden and the United Kingdom.

Strong opioid analgesics are least consumed in France and Italy. Fentanyl, morphine and oxycodone share the market for strong opioids.

DISTRIBUTION OF ANALGESIC USE IN 7 EUROPEAN COUNTRIES IN 2015

(source IMS MIDAS and public data)



(1) The Daily Defined Dose (DDD) is a recognised international unit of measurement based on a representation of the mean daily dose of a medicinal product in its indication for an adult weighing 70 kg. It is neither a recommended dose, nor a dose actually consumed or prescribed.

2

NATIONAL CONSUMPTION DATA

Sales figures

Opioid analgesics marketed in 2017

The following table lists the pharmaceutical products containing an opioid, indicated in the management of pain, and available in France in 2017. Opioid analgesics reserved for hospital administration only are not included in this report.

LIST OF OPIOID ANALGESICS AVAILABLE IN FRANCE IN 2017

Active substance	Name of marketed products	Route of administration	Posology
Medical prescription mandatory			
Codeine + paracetamol	Algicalm, Algisedal, Codoliprane, Codeine Claradol, Compralgyl, Codeine Dafalgan, Gaosedal, Klipal Codeine, Lindilane	Oral	20 mg, 25 mg, 30 mg, 50 mg
Codeine + ibuprofen	Antarene with codeine	Oral IR	30 mg, 60 mg
Codeine + paracetamol + aspirin	Novacetol	Oral IR	10 mg
Codeine + paracetamol + caffeine	Migralgine, Prontalgine	Oral IR	20 mg
Codeine + aspirin + caffeine	Sedaspir	Oral IR	20 mg
Dihydrocodeine	Dicodin	Oral IR	40 mg
Nalbuphine	Nalpain and generics	Injectable	20 mg/2 ml
Opium (powder)	Lamaline, Izalgi	Oral IR Rectal	10 mg, 25 mg 15 mg
Tramadol	Topalgic, Contramal, and generics	Oral DS Oral IR Oral PR	100 mg/ml 50-100 mg 50-100-150-200-300 mg
Tramadol	Topalgic, Tramadol Lavoisier	Injectable	50 mg/ml, 100 mg/ml, 100 mg/2ml
Tramadol + paracetamol	Ixprim, Zaldiar and generics	Oral IR	37,5 mg, 75 mg
Tramadol + dexketoprofen	Skudexum	Oral IR	75 mg
Secure medical prescription required			
Buprenorphine	Temgesic	Sublinguale	0,2 mg
Long-acting fentanyl	Durogesic, Matrifen and generics	Transdermal	12-25-50-75-100 µg/heure
Fentanyl fast-acting (citrate)	Abstral, Actiq, Breakyl, Effentora, Instanyl, Pecfent, Recivit	Transmucosal	100 à 1200 µg
Hydromorphone	Sophidone	Oral PR	4 mg, 8 mg, 16 mg, 24 mg
Morphine (hydrochloride/sulfate)	Lavoisier, Renaudin, Aguettant, Cooper	Injectable	0,1-1-10-20-40-50 mg/ml
Morphine (sulphate)	Actiskenan, Sevredol, Oramorph	Orale DS Orale IR	10 mg/5 ml, 20 mg/1 ml, 30 mg/5 ml, 100 mg/5 ml 5-10-20-30 mg
Morphine (sulphate)	Skenan PR, Moscontin	Oral PR	10-30-60-100-200 mg
Oxycodone	Oxynorm, Oxynormoro and generics	Oral DS Oral IR Injectable	10 mg/ml 5-10-20 mg 10-50 mg/ml
Oxycodone	Oxycontin and generics	Oral PR	5-10-15-20-30-40-60-80-120 mg
Pethidine	Pethidine, Renaudin	Injectable	50 mg/ml
Tapentadol	Palexia	Oral	50-75-100 mg

For the oral route: **DS:** drinkable solution, **IR:** immediate release, **PR:** sustained release.

Opioid analgesics are primarily available for oral administration (capsule, film-coated, effervescent, immediate-release or sustained-release tablet) or injection. An oral solution is available for tramadol, morphine and oxycodone, with one suppository form for opium powder.

Fentanyl is prepared in a variety of forms: a patch form for prolonged transdermal action and several transmucosal forms for rapid action (sublingual or gingival tablet or with an oral applicator, as an orodispersible film or a nasal spray solution).

Note that the marketing of pethidine is soon to be discontinued, at the request of the laboratory. Due to the existence of numerous therapeutic alternatives with a clearly established favourable benefit/risk ratio, the ANSM is not opposed to this decision.

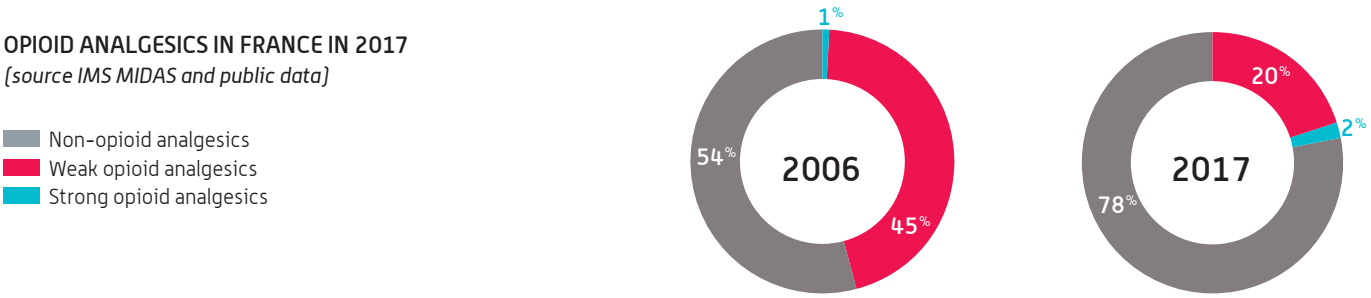
Consumption in 2017

In 2017, the most consumed analgesics in France were non-opioids [paracetamol, aspirin and non-steroidal anti-inflammatories (NSAIDs)] (78%), followed by weak opioid analgesics (20%) which were consumed ten times more than strong opioids (2%).

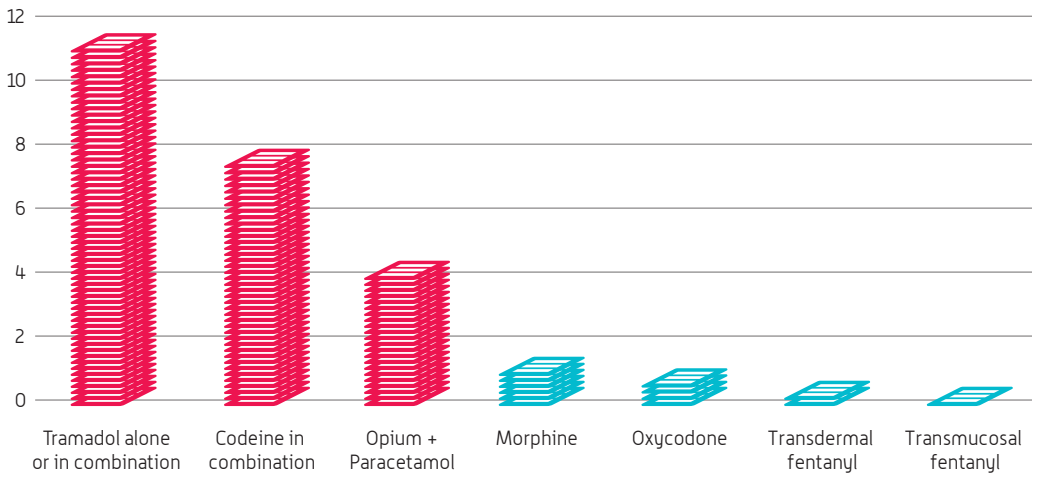
In 2017, the most commonly used opioid analgesic in France was tramadol, both in the high street pharmacies and hospitals, then codeine in combination and paracetamol in combination with opium powder.

Then come **morphine, the first strong opioid analgesic,** then **oxycodone**, which is nearly as widely consumed as oral morphine in high street pharmacies, and injectable morphine in hospitals.

OPIOID ANALGESICS IN FRANCE IN 2017
(source IMS MIDAS and public data)



THE PRINCIPAL OPIOID ANALGESICS CONSUMED
(DDD/1000 inhab./D)



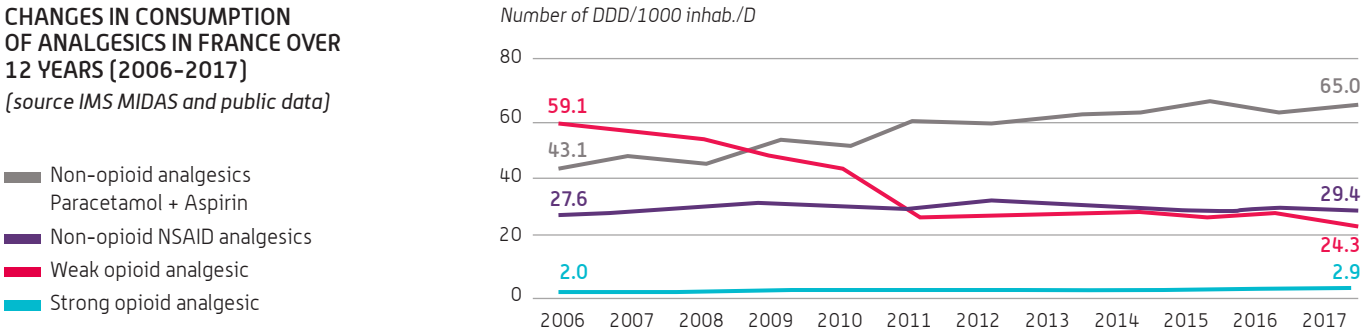
Changes in consumption over 12 years (2006-2017)

Non-opioids have been the most consumed analgesics in France for 12 years. Their share has steadily increased from 54% in 2006 to 78% in 2017. This growth became more pronounced in 2011, the year the dextropropoxyphene/paracetamol[1] combination was withdrawn from the market. The ANSM recommended paracetamol as the first-line replacement for mild to moderate pain and weak to strong opiates for more severe pain.

During this same period, the consumption of weak opioids fell by 59%, both in high street pharmacies and in hospitals, with a steeper drop in 2011. Despite this overall decrease, the consumption of each of the remaining weak opioids on the market (tramadol, codeine, opium powder) increased.

Lastly, although still much lower than for other analgesics, the consumption of strong opioids increased by 45% between 2006 and 2017.

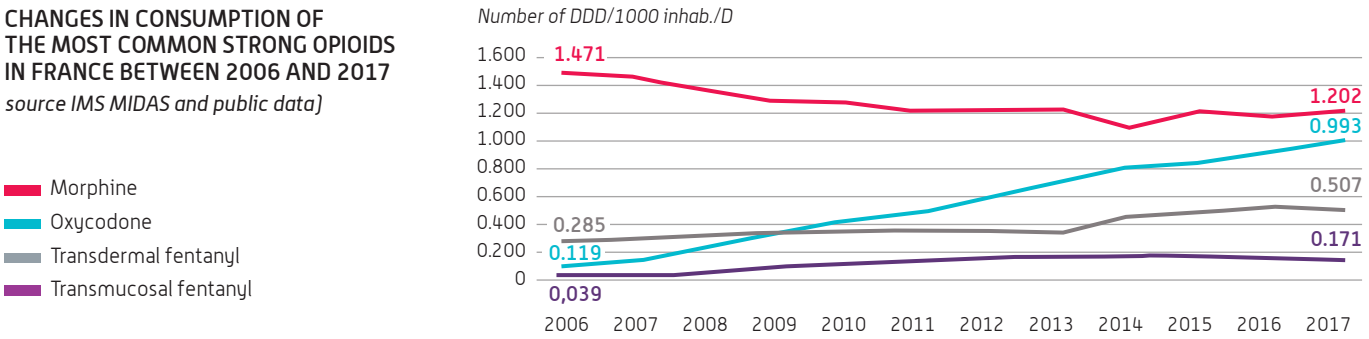
CHANGES IN CONSUMPTION OF ANALGESICS IN FRANCE OVER 12 YEARS (2006-2017)
(source IMS MIDAS and public data)



CHANGE IN CONSUMPTION BY SUBSTANCE

- The consumption of **tramadol** alone or in combination increased significantly (+ 68% between 2006 and 2017), but exclusively in high street pharmacies, and has stabilised since 2013. The data will have to be confirmed in the next few years.
- **Codeine** in combination also saw an increase in consumption in high street pharmacies between 2006 and 2014 (+ 84%), then falling by 30% between 2016 and 2017, following the regulatory measure of July 2017 making its prescription mandatory (see section on the abuse of medicinal products containing codeine in adolescents and young adults, chapter 5.4.4.1). In hospitals, codeine accounted for only 13% of analgesics consumed in 2017.
- Over 10 years, use of the **opium-paracetamol** combination doubled in pharmacies, and almost tripled in hospitals.
- **Morphine** is the most commonly used strong opioid analgesic, despite an 18% decrease in its consumption between 2006 and 2017. In hospitals, it represented 50% of consumption in 2017, followed closely by oxycodone (37%).
- **The sharp increase in the consumption of oxycodone (+ 738% between 2006 and 2017)** brings it close to that of morphine. The profile of change in use of oxycodone is identical in pharmacies and hospitals.
- **Transmucosal fentanyl** increased more significantly (339%) than **transdermal fentanyl** (+ 78%) which remained the least used product in pharmacies and hospitals in 2017 (25% and 11% of strong opioid analgesics respectively).

CHANGES IN CONSUMPTION OF THE MOST COMMON STRONG OPIOIDS IN FRANCE BETWEEN 2006 AND 2017
source IMS MIDAS and public data)



(1) This measure followed the decision of the European Commission of 14 June 2010, calling for the withdrawal of all products containing dextropropoxyphene from the European market within a maximum period of 15 months. The EC decision followed the conclusions of a review of available safety and efficacy data carried out by the EMA (European Medicines Agency), which considered evidence of the superiority of paracetamol-dextropropoxyphene compared to paracetamol alone to be insufficient in view of the risk of death in case of accidental or voluntary overdose.

CHANGES IN CONSUMPTION OF WEAK AND STRONG OPIOIDS BETWEEN 2006 AND 2017 IN PHARMACIES AND HOSPITALS

(source IMS MIDAS and public data)

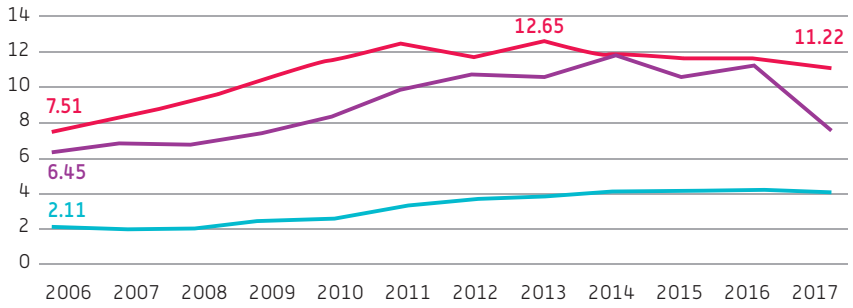
Tramadol alone or combined

Codein in combination

Opium + Paracetamol

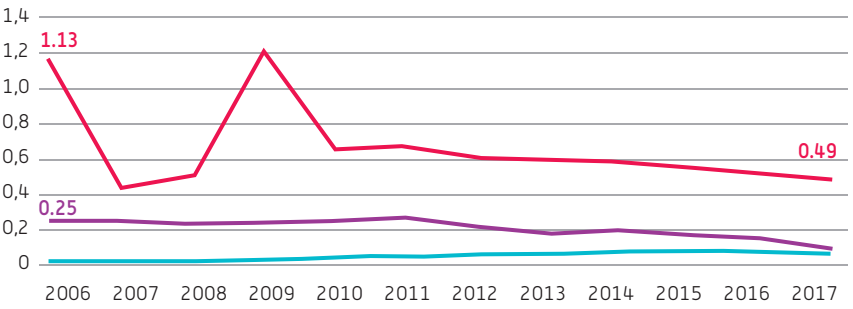
Change in consumption of the main weak opioids between 2006 and 2017 in high street pharmacies in France

Number of DDD/1000 inhab./D



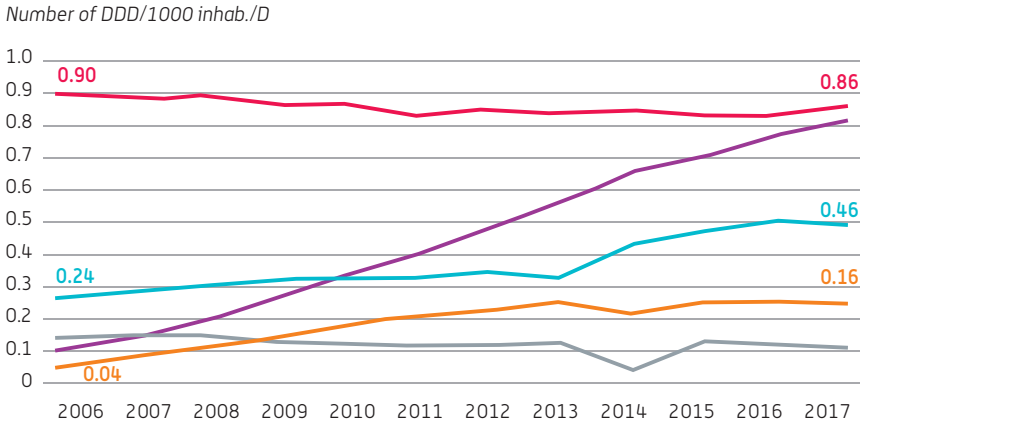
Change in consumption of the main weak opioids between 2006 and 2017 in hospitals in France

Number of DDD/1000 inhab./D

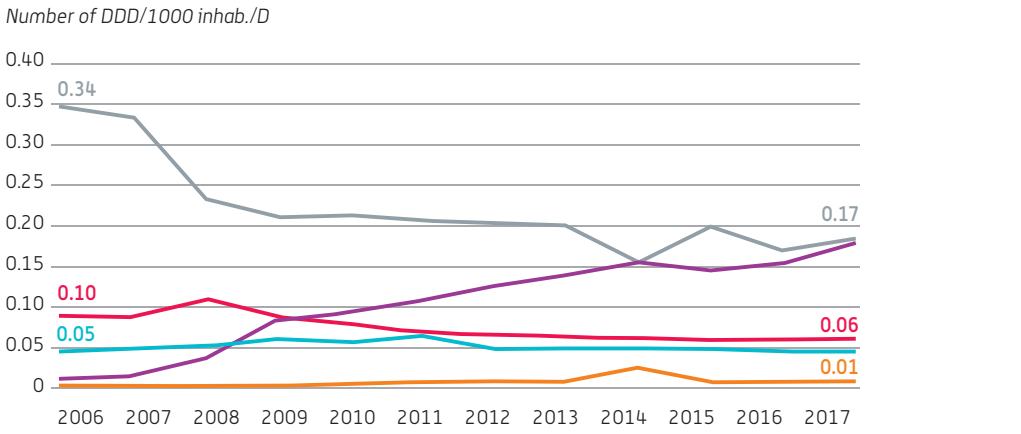


Oral morphine
Oxycodone
Transdermal fentanyl
Transmucosal fentanyl
Morphine for injection

Change in consumption of the main strong opioids between 2006 and 2017 in high street pharmacies in France



Change in consumption of the main strong opioids between 2006 and 2017 in hospitals in France

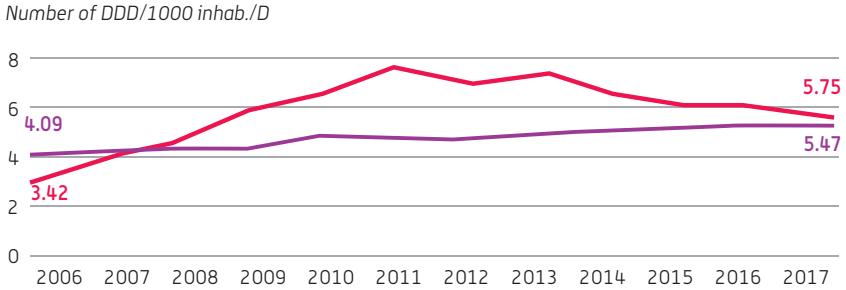


CHANGES IN TRAMADOL CONSUMPTION OBTAINED BY PRESCRIPTION FROM HIGH STREET PHARMACIES

Although the overall consumption of tramadol alone or in combination has tended to stabilise since 2013, the proportion of tramadol alone obtained from the pharmacy is constantly increasing, while that of tramadol in combination has decreased since 2013.

CHANGES IN TRAMADOL CONSUMPTION BETWEEN 2006 AND 2017 IN HIGH STREET PHARMACIES

Tramadol alone
Tramadol in combination



3

NATIONAL CONSUMPTION DATA

National health insurance data

In 2015, 17.1% of French residents benefited from the reimbursement of an opioid analgesic by the National Health Insurance, which equates to an estimated **9,966,944 patients receiving a prescription for an opioid analgesic** (Barreau, 2017).

The data presented are from the DANTE study (*une Décennie D'ANTalgiques En France* - "A decade of analgesics in France"), funded by the ANSM and carried out by the addictovigilance network under the coordination of the CEIP-A[1] in Bordeaux. The first results available relate to the changes in supply in the adult population between 2006 and 2015, according to reimbursement data from the National Health Insurance body (the EGB [2] sample, see acronyms).

Recently published national consumption data support the results of the DANTE study and provide additional data on the characteristics of the prescriptions issued. This study is part of the POMA project (Prescription opioids misuse assessment in chronic pain patients) funded by the ANSM (Chenaf, 2018).

Two other sources supplement this data — a survey made by the addictovigilance network on narcotic analgesics and secure prescriptions (ASOS, see acronyms above), and a study on self-medication, carried out in high street pharmacies in the context of the DANTE study.

Changes in supply between 2006 and 2015

The main objective of the DANTE study was to describe the use and changes in use of analgesics over a period of 10 years, presenting the characteristics of the users, the substances used and the modalities of their prescription and supply.

An analysis of "reimbursed supply" resulting from National Health Insurance-reimbursed medical prescription, was carried out on one hand in subjects receiving at least one analgesic unit during the year, and on the other hand in new subjects starting treatment. The number of subjects (the sample size) in this study increased by 8% between 2006 (392,985 subjects) and 2015 (424,559 subjects).

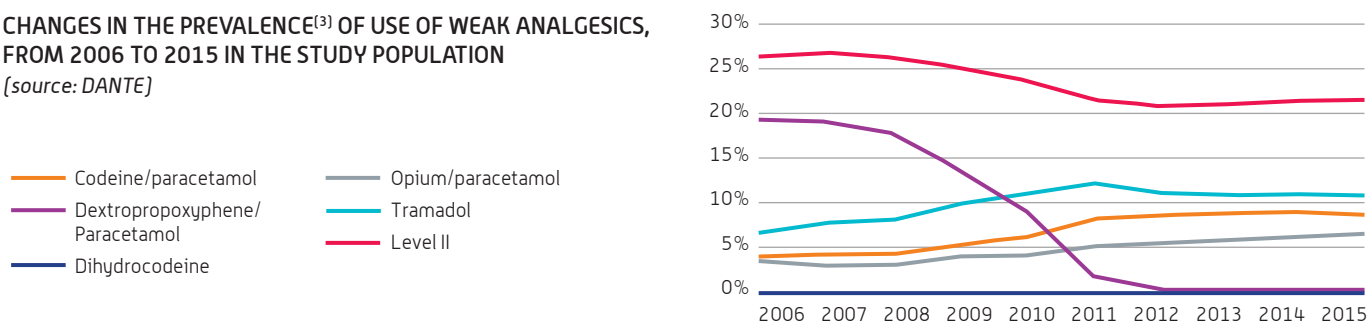
DATA FOR SUBJECTS RECEIVING AT LEAST ONE ANALGESIC UNIT IN THE COURSE OF THE YEAR

National Health Insurance reimbursement data between 2006 and 2015 from the DANTE study confirms the sales data (see previous chapter): the consumption of all analgesics combined increased and non-opioid analgesics are used to a much greater extent (prevalence 59.8% in 2015) than weak opioid analgesics (21.3%) and strong opioid analgesics (1.2%). Consumption of weak opioid analgesics decreased in 2011 (-18%) and then stabilised despite an increase in all weak opioids (with the exception of dihydrocodeine and dextropropoxyphene) and finally, strong opioid analgesic use showed a strong increase between 2006 and 2015 (+150%).

Products consumed

- **Tramadol is the most commonly used opioid analgesic.** The increase in its consumption since 2006 (x1.7) is the result of an increase in tramadol alone; the combination tramadol/paracetamol has actually been decreasing since 2011.
- The second most consumed opioid is **codeine**, in combination with paracetamol, which showed the greatest increase (x2.3), followed by **opium** in combination with paracetamol (x1.9).
- The use of strong opioid analgesics over the period 2006-2015 is very low (< 1%) compared to non-opioid analgesics and weak opioids.
- **Morphine** remains the most commonly consumed strong opioid (prevalence 0.6%).
- **The opioid showing the largest increase (x 8) is oxycodone,** reaching the same level as fentanyl in 2015 (prevalence 0.4%). While the prevalence remains low, there were nonetheless ten times more patients in raw numbers in the EGB having been supplied with oxycodone in 2015 than in 2006.
- Regarding fentanyl. Transdermal fentanyl was the most commonly consumed presentation (93.1% in 2015) despite a doubling of fast-acting (transmucosal) fentanyl between 2006 and 2015 (13.4% in 2015). The gross number of subjects in the EGB receiving transmucosal fentanyl was thus multiplied by 3.

CHANGES IN THE PREVALENCE[3] OF USE OF WEAK ANALGESICS, FROM 2006 TO 2015 IN THE STUDY POPULATION
(source: DANTE)



(1) CEIP-A: Centre for Evaluation and Information on Pharmacodependence - Addictovigilance. There are thirteen such centres, and they form the addictovigilance network of the ANSM. The purpose of addictovigilance is to monitor, evaluate, prevent and manage the risk of abuse, dependence and misuse related to consumption of any product (medicinal or other), substance or plant having a psychoactive effect, excluding ethyl alcohol and tobacco (Article L5133-1 of the Public Health Code amended by Ordinance No. 2017-51 of 19 January 2017).

(2) EGB (see acronyms): Permanent sample of health insurance beneficiaries, a sample of 1/97th of the population protected by National Health Insurance cover.

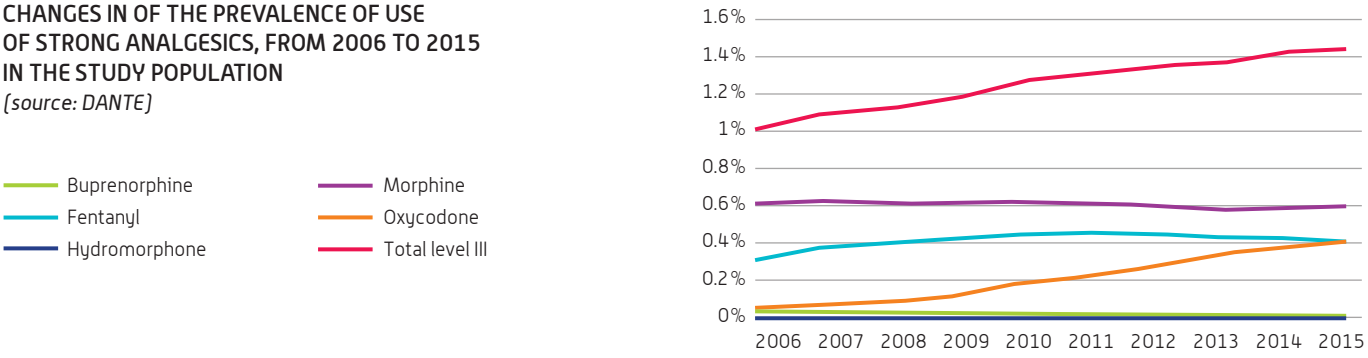
(3) The "prevalence" is an estimate of the number of patients receiving at least one analgesic unit during the year.

SWITCHING FOLLOWING THE DISCONTINUATION OF DEXTROPROPOXYPHENE

Approximately 74% of patients treated with the combination dextropropoxyphene/paracetamol were no longer receiving analgesic within 6 months following discontinuation.

The majority of those continuing to take an analgesic thereafter received either a non-opioid or a weak opioid analgesic.

CHANGES IN OF THE PREVALENCE OF USE OF STRONG ANALGESICS, FROM 2006 TO 2015 IN THE STUDY POPULATION
(source: DANTE)



Profile of consumers

In 2015, most users of analgesics were women, for both weak opioids (57.7%) and strong opioids (60.5%). Users of strong opioids are older than users of weak opioids (64 years and 52 years respectively). Prescriptions are most frequently issued in the context of an ongoing long-term condition (LTC) (69.3% and 34.5%). The patients concerned were more often hospitalised during the year of prescription (57.6% and 31%) and had consulted a medical specialist (other than a general practitioner) (79.4% and 74.6%).

The proportion of chronic users of analgesics (defined by having been supplied more than 9 units of weak opioids or 11 of strong opioids during the year) is higher for strong opioids (14.3%) than for weak opioids (6.6%). Finally, 0.39% of strong opioid users were prescribed at least one medical act of palliative care, compared to 0.05% of weak opioid users.

A study conducted by the French observatory of analgesic medicines (OFMA, see acronyms above) over the period 2014–2017 using the same health insurance reimbursement database (the EGB) showed that in 2017, acute pain was the reason for prescription for the majority of weak opioids (71.1% vs. 50.1% for strong opioids) and chronic pain for the majority of strong opioids (42.9% vs. 13.4% for weak opioids). Back pain and osteoarthritis accounted for 21.6% and 7% of strong opioid prescriptions respectively (8.1% and 2.6% of weak opioid prescriptions) (Chenaf, 2018).

Prescribers of opioid analgesics in 2017 were general practitioners in the vast majority of cases (86.3% of weak opioids and 88.7% of strong opioids), then dentists (2.8% and 0.3%), rheumatologists (2.2% and 1.7%) and orthopaedists (1.9% and 1.3%).

DATA CONCERNING SUBJECTS STARTING AN ANALGESIC TREATMENT

The 2015 incidence data[1] show that 22.9% of patients included in the EGB started a non-opioid analgesic treatment in that year. 13.6% started a weak opioid analgesic treatment and 0.84% a strong opioid treatment. A small increase in the rate of "new patients" is observed for strong opioids (0.77% in 2013 and 0.84% in 2015). This rate increases with age for strong opioids, contrary to analgesics in all classes.

Products consumed

- Tramadol remains the most consumed opioid analgesic (with an increased tendency for tramadol alone and a decrease in the tramadol-paracetamol combination), followed by codeine in combination with paracetamol.
- Opium showed a slight increase between 2013 and 2015.
- Next we find strong opioids, with morphine, oxycodone (increasing), and fentanyl.

Le profil des consommateurs

In 2015, new users of weak and strong opioids were predominantly women (55.1% and 58.7% respectively). New users of strong opioids were older (median age 63 years) than weak opioid users (48 years), and 30.9% of new strong opioid users were 75 years of age or older.

The primary prescriber of analgesics was a general practitioner for 59.1% of weak opioids and 62.9% of strong opioids, followed by hospital doctors for 20.1% of weak opioids and 21% of strong opioids.

(1) The incidence is the estimate of the number of patients supplied at least one unit of analgesic during the year under review, having not received an analgesic during the 12 months preceding the index date.

Narcotic analgesics and secure prescriptions
(Antalgiques Stupéfiants et Ordonnances Sécurisées - ASOS)

ASOS is a survey of the addictovigilance network coordinated by the CEIP-A in Bordeaux. This is an annual cross-sectional study of high street pharmacies, analysing prescriptions that contain narcotic analgesics.

The results of this study are in line with the analysis of sales figures and health insurance data with regard to strong opioid analgesics. In 2017, of 444 questionnaires collected, the most cited narcotic analgesics were morphine (37.3%), oxycodone (31.9%), transdermal fentanyl (26.5%) and fast-acting fentanyl (3.7%).

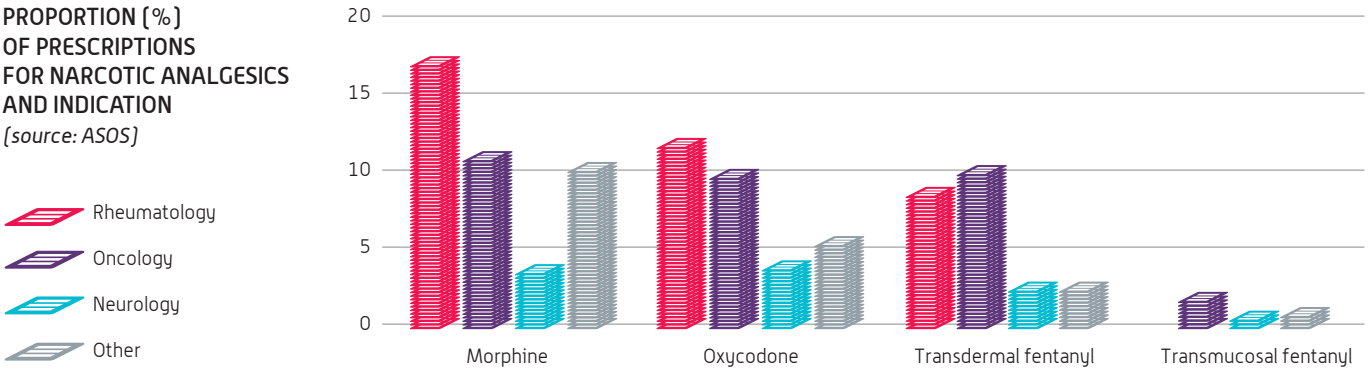
The mean age of patients was 65.9 years, 33.5% were over 75 years of age, and 58.6% were women.

The pain treated was chronic (62.2%), acute (21.6%) or both (1.8%) (not known to the pharmacist in other cases). Local care was reported in 8.6% of cases.

The indication was rheumatological (36.5%), oncological (30.3%), other (post-operative pain, amputation, wounds, ulcers) (19.9%), neurological (11.7%), and opioid substitution (1.6%).

Prescribers were primarily general practitioners (81.3%), then oncologists (5.4%), rheumatologists (2%), pulmonologists (1.4%), surgeons (1.1%) and anaesthetists (1.1%).

PROPORTION (%) OF PRESCRIPTIONS FOR NARCOTIC ANALGESICS AND INDICATION
(source: ASOS)



Self-medication with analgesics

In 2016, four analgesics were available as medical prescription optional (MPO) products allowing self-medication (use of medication without a medical prescription): paracetamol, aspirin, ibuprofen and codeine (the decree putting an end to excepted doses of codeine was published in July 2017). In a national study by the addictovigilance network involving high street pharmacies, an anonymous self-questionnaire was given to frequent patients presenting at the pharmacy with a spontaneous request for a specific analgesic to relieve current pain. This study took place over one week in October 2016.

Two hundred and fifty-one (251) questionnaires were returned for paracetamol, 239 for aspirin and 237 for ibuprofen.

Codeine was the subject of 222 questionnaires including 220 (99.1%) for the codeine/paracetamol combination. The mean age was 45.6 ± 13.4 years (18 to 90 years), and 67.6% were women.

One hundred and sixty-five patients (74.3%) reported that codeine was the treatment they used most frequently in case of pain.

The main reasons for purchasing codeine reported by patients were headaches/migraine (46.4%), back pain (21.2%) and toothache (11.7%).

For a given pain episode, 60.8% of patients took at least one other analgesic before turning to codeine.

Among those who answered the question about the beginning of their consumption (188), 35.6% had been consuming codeine for more than 3 years and 29.7% for between 3 months and 3 years.

Of the 194 patients who answered the question about the frequency of doses, 21.6% reported taking codeine daily, 27.3% several times per week and 51% less than once per week.

Sixty-four percent (64%) of patients took 40 mg of codeine per dose and 22.8%, 20 mg per dose (data provided for 114 patients). Note that 14 patients (12.3%) took 50 mg or more per dose.

Taking into account the dose of each codeine product, 26 patients consumed a total dose greater than that recommended, either by taking a higher dose, more doses, or more frequent doses. **Thus, in 2016, 13.3% of patients self-medicating with codeine and having answered the questions were in a situation of overdose.**

4

THE PLACE OF OPIOID ANALGESICS
in the management of pain

The potency of opioid analgesics

Morphine is one of the alkaloids constituting opium, a product extracted from the poppy plant. In the body, codeine, pholcodine, codethyline and heroin are transformed into morphine. Many substances synthesised chemically resemble morphine either in their structure or their activity. These molecules, grouped together, are the "opioids." The term "opiate" is theoretically reserved for natural derivatives of opium only.

Opioids mimic the effects of endogenous opioids (endorphins, enkephalins, dynorphins). Several peripheral and central opioid receptors have been identified. Each opioid interacts on these receptors in different ways, as complete or partial agonists and antagonists.

Opioids have an analgesic effect, which is exploited for the symptomatic treatment of pain.

According to a difference in pharmacological potency and the intensity of the pain evaluated, a distinction has been made between weak and strong opioids. The undesirable effects of the two groups are very largely the same: constipation, nausea, vomiting, respiratory depression, impaired alertness, tolerance, dependence.

Moreover, it is important to remember that following conversion of doses using factors of equi-analgesia, their effects (in particular their undesirable effects) can be comparable. For example, 400 mg tramadol/day = 80 mg morphine/day.

The risk of overdose and acute respiratory depression, as well as long-term dependence, is therefore common to all opioids, be they weak or strong.

The so-called "weak" opioids appear on List I of poisonous substances and the "strong" opioids also appear on the list of substances classified as narcotics.

Conditions of prescription and supply for opioid analgesics

In France, all opioid analgesics available at high street pharmacies require a medical prescription. Supply by secure prescription applies to narcotics but also to buprenorphine, a List I opioid, subject in part to the regulation of narcotics due its known misuse (falsified prescriptions, abuse, dependence). In addition, the maximum duration of any prescription may be limited, and the supply split in time.

CONDITIONS OF PRESCRIPTION AND SUPPLY FOR OPIOID ANALGESICS AS OF SEPTEMBER 1, 2018

PRESCRIPTION	Medical prescription mandatory (List I)	◆ Codeine in combination ◆ Dihydrocodeine ◆ Nalbuphine ◆ Opium (powder) ◆ Tramadol alone and in combination, oral route ◆ Nalbuphine	Maximum prescription 28 days-renewal possible
	Medical prescription mandatory (List I), prescription restricted	◆ Tramadol for injection	Initial bimonthly hospital prescription - Reserved for use in emergency situations, in accordance with Article R5121-96 of the Public Health Code
SECURE PRESCRIPTION	Medical prescription mandatory, with secure prescription (List I partly subject to the regulation of narcotics)	◆ Buprenorphine	Maximum prescription 28 days - renewal possible
	Medical prescription mandatory - secure prescription (narcotic)	◆ Hydromorphone ◆ Morphine (sulphate), oral route ◆ Oxycodone, oral route ◆ Tapentadol	Maximum 28 days - renewal prohibited
	Medical prescription mandatory (narcotic) and prescription restricted	◆ Morphine (sulphate and hydrochloride) for injection ◆ Oxycodone for injection	Prescription limited to 7 days, or 28 days when administered using active infusion systems - renewal prohibited
		◆ Pethidine	Prescription limited to 7 days - prohibited renewal
	Medical prescription mandatory on secure prescription (narcotic) and supply restricted	◆ Long-acting fentanyl	14 days, split supply
		◆ Fast-acting fentanyl	7 days, split supply

Types of pain indicated

Weak opioid analgesics are indicated in moderate to severe acute pain **following the failure of non-opioid analgesics, or in cases where the pain requires management with an opioid.** Some may also be used in the treatment of chronic pain (dihydrocodeine and tramadol).

Strong opioid analgesics are indicated in more severe pain and preferentially **following failure of weak opioid analgesics.** Some are indicated for acute pain only (pethidine and tapentadol) and others for both acute and chronic pain (morphine and oxycodone).

Due to its presentation as a "patch," long-acting fentanyl is reserved for the management of severe chronic pain requiring continuous administration.

Two opioids are **reserved for pain due to cancer:** hydromorphone and fast-acting or transmucosal fentanyl (Abstral, Actiq, Breakyl, Effentora, Instanyl, PecFent and Recivit). The latter is only for use in the treatment of paroxysmal pain episodes in adult patients using opioids to treat chronic cancer-related pain otherwise controlled by background opioid treatment.

Although the type of pain is not always clear in the indication, the High Authority for Health (HAS, see acronyms) has estimated, on the basis of available data, that the Medical Benefit (MB) of buprenorphine, long-acting fentanyl, morphine and oxycodone is of central importance in the management of severe pain and/or refractory cancer pain, as well as in neuropathic and post-operative pain, osteoarthritis of the knee or hip and chronic low back pain, as a treatment of last resort after failure of other medicinal and non-medicinal measures.

In contrast, **the Medical Benefit appears not to be sufficient in other situations of chronic non-cancer and non-neuropathic pain, particularly in chronic inflammatory rheumatism, represented mainly by rheumatoid arthritis and spondyloarthritis.** (All opinions of the Transparency Commission are available on the HAS website[1]).

Opioid analgesics used in children

Few opioid analgesics have a presentation as a solution suitable for oral administration as a function of weight in children.

- Morphine presented as an oral solution (multi-dose and single-dose vials) can be used in infants from 6 months of age. However, only the multidose presentation (Oramorph 20 mg/1ml) allows doge adjustment according to the weight of the child - all other oral solutions are presented in single dose containers of 10 mg, 30 mg and 100 mg, each for 5 ml of solution. The ANSM met with the laboratory to discuss the provision of single-dose, low dose presentations (1 and 2 mg) more appropriate for paediatric use.

  After opening, the capsules (Actiskénan immediate release and Skénan prolonged release) can be used in infants from 6 months of age by mixing their contents in food. The microgranules of the Skénan capsules keep their prolonged action properties. Morphine tablets (Moscontin and Sevredol), for their part, are prohibited in children under 6 years of age due to the risk of false route.
- Tramadol is also presented as an oral solution in a dropper bottle (100 mg/ml) with use possible in children from 3 years of age and a dose defined according to weight. In view of the large number of medication errors reported with the dropper bottle, the ANSM asked the laboratory to develop a less concentrated formulation and a presentation with a pipette graded in mg, more suitable for paediatric use.
- Buprenorphine, sublingual tablet (Temgesic) and hydromorphone can be used exceptionally in children 7 to 15 years of age.
- Codeine has been contraindicated in children under 12 years of age since 2013.
- Regarding the injectable forms, **morphine for injection is the only opioid analgesic that can be administered from birth,** then pethidine from 6 months, and nalbuphine from 18 months.
- Transdermal fentanyl (12 and 25 g/h) may be administered to children over 2 years of age already receiving a dose equivalent to at least 30 mg morphine orally per day.

(1) https://www.has-sante.fr

OPIOID ANALGESICS AUTHORISED FOR USE IN CHILDREN

(see also the Summary of Product Characteristics for each medicinal product on the public pharmaceutical database - http://base-donnees-publique.medicaments.gouv.fr)

Oral form	
Morphine	Child over 6 months of age for adapted oral forms (oral solution, capsule) Child over 6 years of age for non-adapted oral forms (tablet)
Tramadol	From 3 years of age for the oral solution From 12 or 15 years for other oral forms
Buprenorphine	Contraindicated in children < 7 years Exceptional use between 7 and 15 years
Hydromorphone	Contraindicated in children < 7 years Exceptional use between 7 and 15 years
Codeine	From 12 years of age, contraindicated in children < 12 years
Dihydrocodeine	Contraindicated in children < 15 years
Opium	Contraindicated in children < 15 years
Oxycodone	Reserved for adults
Tapentadol	Reserved for adults
Injectable form	
Morphine	From birth
Péthidine	Contraindicated in children < 6 months
Nalbuphine	Data insufficient for children < 18 months of age
Buprénorphine	Contraindicated in children < 15 years
Tramadol	Contraindicated in children < 15 years
Oxycodone	Reserved for adults
Other forms	
Transdermal fentanyl	From 2 years
Opium suppository (Lamaline)	Contraindicated in children < 15 years
Fast-acting fentanyl	Reserved for adults

MEDICINAL MANAGEMENT OF PAIN IN CHILDREN: AN ALTERNATIVE TO CODEINE

(*Prise en charge médicamenteuse de la douleur chez l'enfant : alternative à la codéine.* HAS, JANUARY 2016)

Following reports of death and serious undesirable effects, following tonsilectomy in the majority of cases, codeine has been contraindicated in children under 12 years of age since 2013.

In 2016, the HAS published its recommendations for good practice "Medicinal management of pain in children: an alternative to codeine." When opioid analgesia is required in a child under 12 years of age, the molecule of choice in case of severe pain, or in case of failure of less powerful analgesics, is morphine. Low doses should be proposed at the start of treatment (0.1 mg/kg/dose) in children under 1 year of age, and monitoring must be increased. Tramadol may be considered in children over 3 years of age, although its metabolism follows the same route as codeine in part, and serious undesirable effects can occur.

ORAL TRAMADOL SOLUTION IN CHILDREN: AWARENESS OF MEDICATION ERRORS

[*Solution buvable de tramadol chez l'enfant : attention aux erreurs médicamenteuses.* ANSM, JUNE 2016]

In children, cases of fatal errors of administration have been reported. These errors are essentially related to difficulties in understanding by patients and those in their family/care networks of the dose prescribed by the doctor, potentially leading to significant overdose of tramadol.

In 2016, the ANSM issued a reminder to healthcare professionals of the importance of clear dose instructions, and to parents of the importance of strict compliance with the doctor's prescription, requesting:

- **prescribing physicians:**
  - to write-out the dose in terms of the **number of drops per dose,** the **number of doses per day,**
  - to inform parents of the need to strictly adhere to the doses prescribed,
  - to remind parents of the need to keep this medicine out of the sight and reach of children,
  - to inform parents of the signs of overdose, and of the need to consult a doctor or an emergency service immediately in case of appearance of these signs, in particular upon the first administration to the child.
- **pharmacists:**
  - to ensure that the **prescribed dose** is expressed as a **number of drops per dose,**
  - to inform the parents of the need to respect the dose prescribed,
  - **to write the number of drops to be administered per dose on the box or the bottle,**
  - to remind parents how a dropper bottle works,
  - to inform parents of the need to immediately consult a doctor or an emergency service in case of signs of overdose.
- **parents:**
  - to respect the doctor's prescription,
  - to ask the advice of a doctor or a pharmacist if in doubt about the prescription or the operation of the dropper bottle,
  - to keep the medication out of the sight and reach of children,
  - to consult a doctor or emergency department immediately if signs of overdose (vomiting, disturbances of consciousness, breathing difficulties etc.) occur.

Principal recent recommendations regarding the good use of opioid analgesics in France

Two recommendations from French professional bodies regarding the correct use of opioid analgesics have recently been published. These are recommendations on the use of strong opioids in chronic non-cancer pain (CNCP) of the French society for the study and treatment of pain (Société Française d'Étude et de Traitement de la Douleur - SFETD) published January 2016, and an update of the recommendation on post-surgical pain by the French association for anaesthesia and intensive care (Société Française d'Anesthésie et de Réanimation - SFAR) published 2017 (see Annexes 1 and 2).

The SFEDT reported a moderate efficacy for strong opioids in chronic non-cancer pain (lower limb osteoarthritis, chronic low back pain, herniated disc etc.) and in peripheral and central neuropathic pain.

It recommends that strong opioid treatment should not be pursued beyond 3 months in the absence of pain relief, improvement of function or quality of life, and not to exceed 150 mg morphine equivalent per patient per day without the advice of a specialist.

In addition, it recommends that strong opioids should not be used in fibromyalgia or in the treatment of primary headaches and migraine, and that fast-releasing transmucosal fentanyl forms should not be used in the management of chronic non-cancer pain.

On the use of opioids perioperatively, the SFAR recommends prescribing a strong opioid (morphine or oxycodone), preferably orally, in case of severe postoperative pain or in case of pain insufficiently relieved by lower-level analgesics, and this regardless of the patient's age.

The HAS has also published a fact sheet, Good use of pharmaceuticals: medicines for breakthrough pain due to cancer (HAS, July 2014[1]).

No recent recommendations are available regarding the correct use of weak opioid analgesics or for the management of acute pain. However, following the withdrawal of dextropropoxyphene, recommendations were published by the SFAR, the SFETD and Afssaps in 2011 on the management of moderate to severe pain in adults. It is recalled that the analgesic of choice in mild to moderate acute nociceptive pain is paracetamol, NSAID or weak opioid analgesic in moderate to severe pain, and weak or strong opioid in very severe pain, according to the clinical context and the urgency of obtaining relief.

Very recently, the National Academy of Medicine published a report "Chronic pain in France. Recommendations of the National Academy of Medicine for better care of patients" (Queneau, October 2018[2]).

(1) https://www.has-sante.fr/portail/upload/docs/application/pdf/2014-07/fbum_adp_maj_juillet2014.pdf
(2) http://www.academie-medecine.fr/wp-content/uploads/2018/10/apr%C3%A8s-vote-Rapport-Douleurs-chroniques-12-10-2018-2.pdf

5

RISKS ASSOCIATED WITH THE USE OF OPIOID ANALGESICS

Undesirable effects and main risks

THE MOST COMMON UNDESIRABLE EFFECTS

Undesirable effects related to the use of opioid analgesics are listed in the Summary of Product Characteristics for each product, available on the public medicines database[1]. The most common are constipation, drowsiness, nausea and vomiting, difficulty breathing, headache, confusion, dysphoric effects, dry mouth.

For example, 222 codeine questionnaires were analysed in the DANTE study (see also Chapter 3). Patients taking codeine daily or several times per week (95 of 222 patients) were asked if they experienced any undesirable effects. More than a third (n = 33) answered in the affirmative. Undesirable effects reported were drowsiness (n = 10), nausea (n = 5), constipation (n = 5) and abdominal pain (n = 5). Nine patients cited other undesirable effects, of which three indicated psychoactive effects (dependence, addiction or withdrawal).

RISK OF OVERDOSE

An excessive dose of opioid is manifested by central nervous system depression (drowsiness, coma), respiratory depression (decreased respiratory rate) and myosis (contraction of the pupil). Overdose can lead to the death of the patient. This risk is increased in case of concomitant intake of alcohol or sedatives (benzodiazepines, neuroleptics, sedative antidepressants, antihistamines, central antihypertensives, baclofen, thalidomide, morphine-based cough suppressants, opioid substitution medication)[2].

The management of an opioid overdose consists in administering the antidote, the mu opioid receptor antagonist naloxone, to reverse the effect of the opioid.

RISK OF PROBLEMATIC USE, ABUSE AND DRUG DEPENDENCE

The consumption of opioids presents a risk of abuse[3] and dependence, whether weak or strong opioid analgesics are concerned, whether the patient is naive to opioid treatment or not, has a history of substance use disorders or not, and whatever the duration of the treatment. Any opioid analgesic prescription should therefore be followed-up for these specific risks.

OPIOID ANALGESICS AND DRIVING

In France, a classification of active substances liable to impair the ability to drive a vehicle, was established in 2005 and updated in 2013 and 2017, in the form of a pictogram indicating the level of risk, affixed to the external packaging of all medicinal products concerned[4]. Opioid analgesics are categorised as level 2 **"Be very careful.** Do not drive without the obtaining the advice of a health-care professional".

PARTICULAR RISKS

Fentanyl patch: risks of medication error

Due to reported cases of accidental exposure or overexposure to transdermal fentanyl, particularly in children, the colour of Durogesic patches has been changed to improve their visibility on the skin, to better distinguish the dose, and thus limit these risks. (ANSM information bulletin of 15 December 2016).

Rapid action fentanyl: risk of intoxication in children

Transmucosal fentanyl is available in various presentations that may be attractive to children. A toxicovigilance survey reports 13 cases of accidental exposure in children under 12, including 10 cases of exposure involving transmucosal presentations. Rapid management allowed a favourable outcome. Transmucosal presentations are made available for use in packaging resistant to tampering by children. Nonetheless, in view of the risk of death in children, these devices should never be used in front of children or left within their reach (source: Anti-Poison and Toxicovigilance centres).

(1) http://base-donnees-publique.medicaments.gouv.fr/
(2) Thésaurus : http://www.ansm.sante.fr/var/ansm_site/storage/original/application/a90a7e83a649086c46aa73ea1f9e1b56.pdf
(3) Abuse refers to the intentional, persistent or sporadic excessive use of medicinal or other products mentioned in Article R. 5121-150, accompanied by harmful physical or psychological reactions (Art R5121-152 amended by Order No. 2013-923 of 16 October 2013)
(4) Order of 8 August 2008, issued for the application of Article R. 5121-139 of the Public Health Code, giving a complete list of all active substances having effects on the ability to drive or use machines.

Opium powder, tramadol and codeine in combination with paracetamol: risks related to paracetamol

In cases of intentional or involuntary intoxication by products combining codeine, tramadol or opium powder with paracetamol, medical management including the administration of N-acetylcysteine was necessary in certain cases due to the specific toxicity, especially to the liver, of paracetamol.

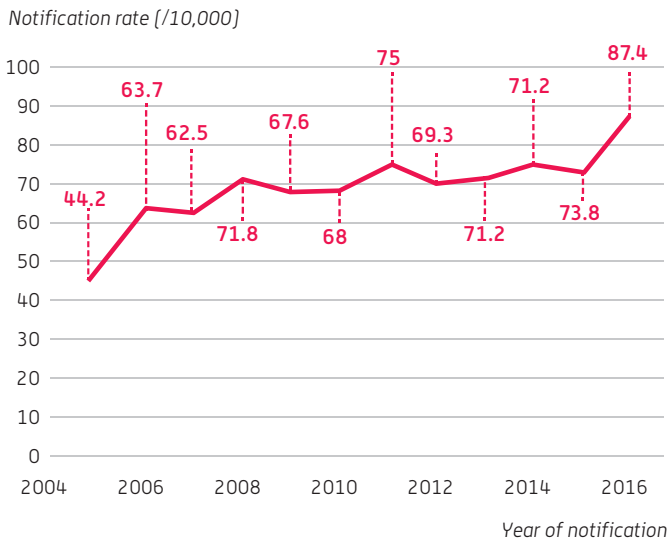
The ANSM wishes to reinforce the information presented on the outer packaging of medicines containing paracetamol, in order to raise awareness among patients and healthcare professionals of the additional hepatic risks related to the misuse of opioid analgesics in presentations combined with paracetamol. To this end, on 20 August 2018, the ANSM launched a public consultation regarding the warning messages to appear on the packaging, and harmonising the wording thereof to help prevent this hepatic risk. The conclusions should be published soon.

Poisoning and death by opioid analgesics in the BNPV

National pharmacovigilance bank (BNPV, see acronyms above) notifications concerning accidental intoxication with opioid analgesics between 2005 and 2016 were analysed. The substances studied were morphine, fentanyl, oxycodone, hydromorphone, buprenorphine (low dose), tramadol, codeine, opium powder and dihydrocodeine. Intentional intoxication, cases involving opioid substitutions and those attributed to opioids specifically used perioperatively in the hospital situation, were excluded.

The rate of notifications of intoxication by opioid analgesics, calculated as a percentage of the total annual number of notifications, increased significantly between 2005 and 2016 from 44 per 10,000 to 87 per 10,000 notifications.

CHANGES IN NUMBERS OF NOTIFICATIONS OF OPIOID ANALGESIC INTOXICATION BETWEEN 2005 AND 2016 IN THE BNPV
(source IMS MIDAS and public data)



- **2,762 cases of intoxication by opioid analgesics were reported in the BNPV between 2005 and 2016: 49% relate to weak opioids, 47% to strong opioids and 4% to a combination of both.**

  Of these, 78% were considered serious (91% for strong opioids and 68% for weak opioids). The median age of subjects concerned was 73 years [51–83 years] and 67% were women. Pain was reported in 43.3% of cases, and cancer in 15.7%.

  Notification rates by substance are stable for codeine, morphine and fentanyl. A significant increase in notifications of accidental intoxication was, however, observed for tramadol (+139%), opium powder (+757%) and oxycodone (+1229%).

  In 2016, the three substances most involved in such intoxications were tramadol, morphine and oxycodone.

- **304 deaths by opioid analgesic intoxication were identified in the BNPV.**

  Of these deaths, 63.5% were attributed to strong opioid analgesics, 29% to weak opioids and 7.5% to a combination of the two. The median age of the subjects concerned was 68 years [49–82]. Most were men (53%). On the other hand, in the group of cases attributed to weak opioids, women were in the majority (53%). The overall change in the rate of notification of such deaths was stable, with a decreasing trend for morphine. The two substances most implicated in accidental death by overdose were tramadol and morphine.

Hospitalisations and deaths related to the use of opioid analgesics in France

DATA FROM THE MEDICALISATION OF INFORMATION SYSTEMS PROGRAM *(Programme de médicalisation des Systèmes d'Information - PMSI)*

The PMSI is a tool dedicated to the description and medico-economic measurement of hospital activity. The use of this tool by the OFMA has made it possible to extract the number of hospitalisations related to accidental intoxication by opioid analgesics (Chenaf, 2018).

Between 2000 and 2017, the number of hospitalisations related to the prescription of opioid analgesics increased by 167% from 15 (n = 881) to 40 hospitalisations (n = 2586) per million population.

DATA FROM THE CENTRE FOR EPIDEMIOLOGY OF MEDICAL CAUSES OF DEATH *(Centre d'Epidémiologie sur les Causes Médicales de Décès - CépiDC)*

The CépiDC, is an INSERM laboratory (the French national medical research body). One of the missions of the CépiDc is the annual production of statistics regarding medical causes of death in France (540,000 deaths per year), via a comprehensive national hospital database.

Analysis of CépiDC data on deaths related to opioid use between 2000 and 2015 was conducted by the OFMA, (Chenaf, 2018).

Deaths from opioid use increased by 146% from 1.3 (n = 76) to 3.2 deaths (n = 204) per one million of the population, representing at least four deaths per week. The number of deaths due to unintentional overdose of opioid analgesics tripled between 2000 and 2015, from 8.5% to 15% of all fatal overdoses over this period.

The results also show that the use of high doses (> 150 mg morphine equivalent) or "doctor shopping" behaviour (see also chapter 5.4.3) are associated with a three times greater risk of death (all causes).

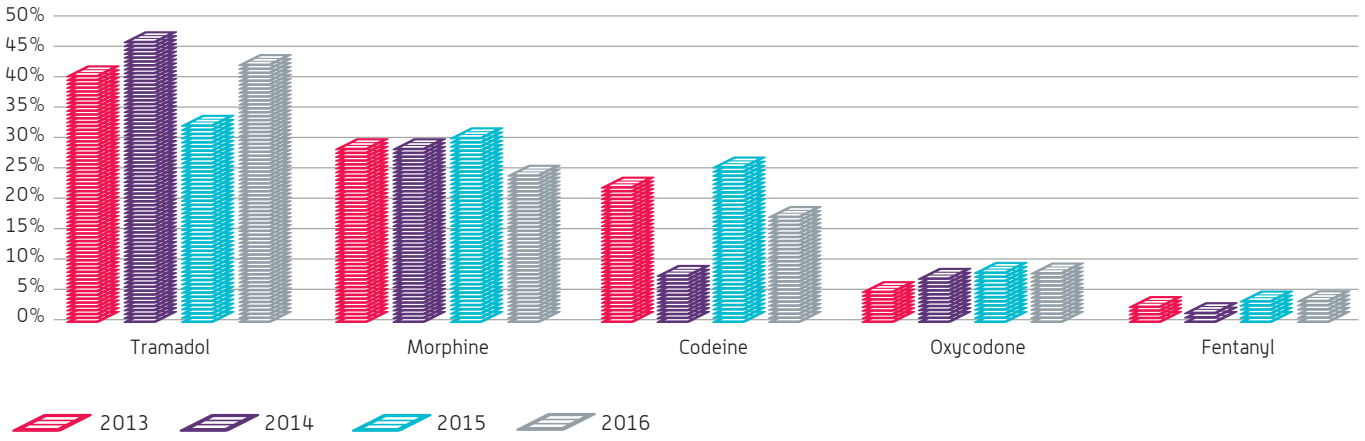
INVESTIGATION OF TOXIC DEATHS DUE TO ANALGESICS

DTA (deaths due to analgesic toxicity, see acronyms above) is an annual survey carried out by the Addictovigilance network, set up in 2013 and coordinated by the CEIP-A in Grenoble. This survey collects reports of deaths in which a toxicological analysis revealed the involvement of an analgesic medicinal product.

Data is collected from a national network of expert toxicologists working as volunteer analysts. This survey is relatively new, and the rate of data collection is still rather low (94 cases in 2016 including 84 deaths directly related to the products in question and 10 deaths indirectly related to the product), which may mean that the number of deaths is underestimated. However, the results are sufficiently reproducible from one year to another for certain trends to be revealed.

In the last four years, the analgesic most often directly implicated in death is tramadol (37 deaths in 2016) followed by morphine (22 deaths), codeine (16 deaths) and oxycodone (8 deaths). In 2016, in the 5th and 6th positions are paracetamol, the first non-opioid analgesic (5 deaths) then fentanyl (4 deaths) (See full table in Annex 3).

SHARE OF THE MAIN OPIOID ANALGESICS INVOLVED IN DIRECT DEATHS *(source DTA)*



Demographic and clinical analysis shows that in 2016, 53% of deaths involved males and the mean age was 50.5 years.

A pathology was associated with the case in 63% of the deaths, of which 51% involved a psychiatric illness (depression, schizophrenia, bipolar disorder etc.), 32% involved pain alone and 12% were related to another serious illness (cancer, epilepsy etc.).

Among those directly related to the product, deaths were of toxic origin without further precision (75%) or occurred in a suicidal context (24%) (unknown in one case).

DEATHS IN RELATION TO THE ABUSE OF MEDICINES AND SUBSTANCES

Deaths in relation to the abuse of medicines and substances (DRAMES, see acronyms above) is an annual survey conducted by the addictovigilance network, set up in 2010 and coordinated by the CEIP-A in Grenoble. This survey collects information on deaths among drug users from a network of expert toxicologists working as volunteer analysts. Although not exhaustive, the data from this study have become a reference at the national level, and also in European evaluations, notably with the EMCDDA[1], and internationally.

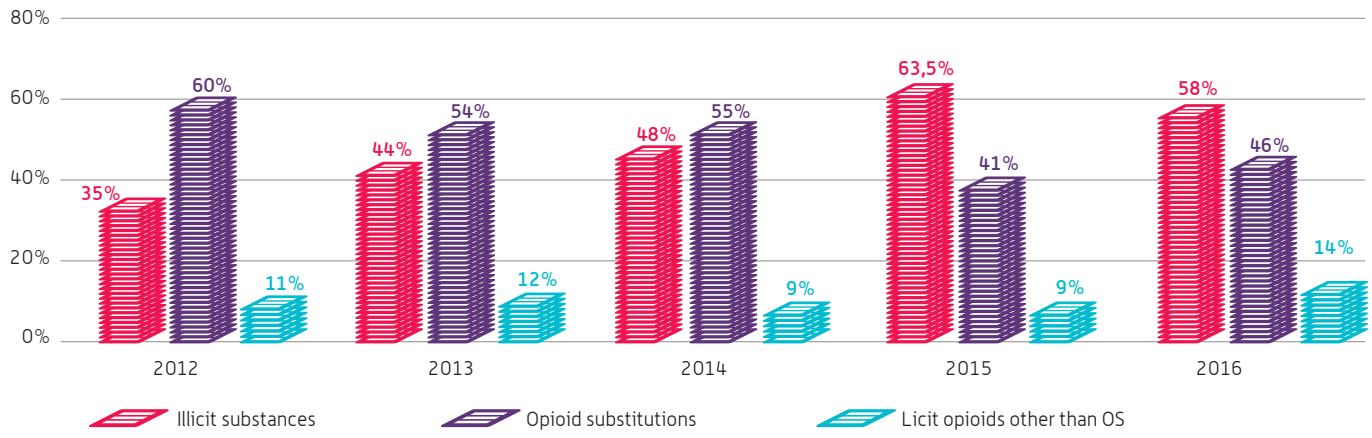
Direct deaths (directly related to the product consumed) were primarily related to opioid substitution products (OS) until 2014. In the 2015 and 2016 surveys, illicit substances (opioids and non-opioids) claimed first position, potentially with several substances involved in the same death.

In 2016, of direct deaths (406 deaths) were related to the abuse of licit opioids other than OS in 14% of cases (58 deaths). This rate has been increasing compared to 2014 and 2015 - the trend will have to be confirmed in 2017 and 2018.

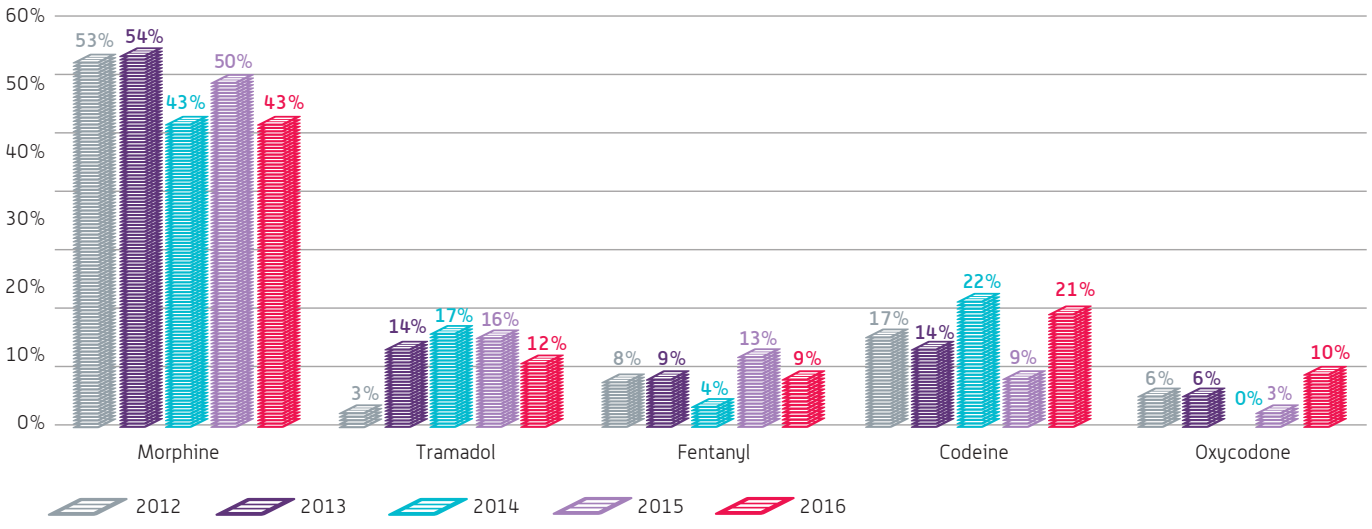
Morphine has been the opioid analgesic most commonly involved in direct deaths for several years (25 deaths in 2016). This can be explained by its heavy misuse by drug users (see Chapter 5.4.4.7). It should be noted that the increase in the number of deaths in 2016 due to the abuse of codeine (12 deaths) and oxycodone (6 deaths), is a trend to be followed in the next few years.

Demographic and clinical analysis of the data in this study shows that, in 2016, deaths primarily concerned men (86%), with a mean age of 37.4 years and with a history of substance abuse in 51% of cases. The population is more masculine and also younger than the DTA survey.

SHARE (%) OF SUBSTANCES INVOLVED IN DIRECT DEATHS *(source DRAMES)*



SHARE (%) OF OPIOID ANALGESICS IN ALL DIRECT DEATHS RELATED TO THE USE OF LICIT OPIOIDS *(source DRAMES)*



(1) European Monitoring Centre for Drugs and Drug Addiction - http://www.emcdda.europa.eu/

Problematic use of opioid analgesics

The most consumed opioid analgesics (codeine, tramadol, opium powder, morphine sulphate, oxycodone, transmucosal fentanyl and transdermal fentanyl) are monitored by the CEIP-A, the addictovigilance network of the ANSM.

Data analysed by the addictovigilance network come from different sources:

- Spontaneous notifications (NotS) of cases of abuse, dependence, misuse and abuse reported by healthcare professionals,
- Annual surveys of the network:
  - Observation of psychotropic products, illicit or licit but diverted from their medicinal use (OPPIDUM, see acronyms) which collects information on the modalities of consumption of psychoactive substances by users frequenting specialised care structures for drug users,
  - Observation of drug dependence in outpatient medicine (OPEMA, see acronyms) which collects information on the modalities of consumption of psychoactive substances by users from a network of general practitioners,
  - Suspicious prescriptions, indicator of possible abuse (OSIAP, see acronyms) carried out by a network of sentinel high street pharmacies,
  - Soumission Chimique ("Chemical Submission", "Date Rape Drug"), which collects cases of administration for criminal or delinquent purposes of psychoactive substances without the knowledge of the victim or under threat, from a network of expert toxicologists/analysts.

In addition to these studies, the results of the DRAMES, DTA and ASOS[2] surveys are presented earlier in this report.

Opioid analgesics appear little in the Chemical Submission survey, which is not presented in this report. The annual results of this survey are available online, as are those of all other surveys carried out by the addictovigilance network[3].

The clinical analysis of spontaneous notifications crossed with the results of the various surveys by the addictovigilance network, makes it possible to highlight several problematic uses of opioid analgesics, which may be different from one substance to another.

SUSPICIOUS PRESCRIPTIONS, INDICATOR OF POSSIBLE ABUSE (OSIAP)

OSIAP collects and analyses suspicious prescriptions submitted to a network of sentinel high street pharmacies.

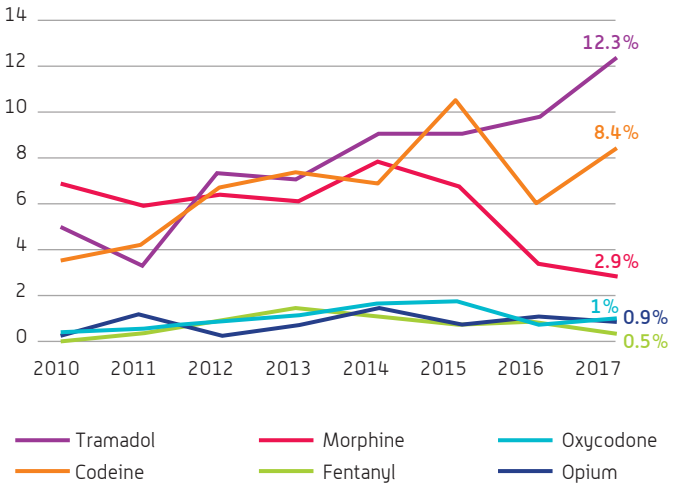
Possible indicators of abuse include prescription theft, falsification (photocopying, computer-generated images, scans), prescription non-compliant with legislation, suspicious writing, inconsistency, non-secure prescription form, added lines, spelling mistakes, unusual doses, modifications (of dose, number of boxes, duration of treatment), overlapping prescriptions or any context that leads the pharmacist to doubt the prescription (for example refusal to present the National Health Insurance card).

For the period 2010–2017, the opioid analgesics for which a suspicious prescription were reported were tramadol (616 cases), codeine (504 cases), morphine (397 cases), oxycodone (77 cases), opium (65 cases) and fentanyl (60 cases).

- **The rate for tramadol has been rising steadily since 2011, being the first opioid analgesic cited in the survey in 2016 (9.7%) and 2017 (12.3%),**
- Codeine takes second place, although certain products containing codeine were not subject to a mandatory medical prescription before July 2017,
- The rate for morphine has been falling since 2014, reaching its lowest level in 2017 (2.9%),
- After a steady increase, the rate for oxycodone decreased in 2016 (0.8%) and remained low in 2017 (1%),
- The rate for opium has remained stable, at around 1% since 2015,
- Despite an increase in 2013, fentanyl remains low overall (0.5% in 2017).

CHANGES IN THE RATE OF OPIOID ANALGESICS MOST FREQUENTLY CITED IN THE OSIAP SURVEY SINCE 2010

(source OSIAP)



(2) Deaths in relation to the abuse of medicines and substances, Deaths due to analgesic toxicity, Narcotic analgesics and secure prescriptions.
(3) http://ansm.sante.fr/Declarer-un-effet-indesirable/Pharmacodependance-Addictovigilance/Outils-de-surveillance-et-d-evaluation-Resultats-d-enquetes/(offset)/5#sp

Between 2010 and 2017, suspicious prescriptions were presented more by women for codeine (44.4% vs. 39.9% for men) and opium powder (55.4% vs. 27.7% for men). In contrast, men represented the majority for morphine (58.2% vs. 22.6% for women), oxycodone (56.9% vs. 29.3% for women) and fentanyl (45% vs. 21.6% for women). Regarding tramadol, the difference between men and women is less clear (42.4% women and 44.6% men)[1].

The mean age of requesters in ascending order was 35.3 years for morphine, 39.7 years for oxycodone, 39.9 years for tramadol, 44.1 years for codeine, 46.5 years for fentanyl and 51.7 years for opium powder.

The OSIAP results by substance for 2017 are given in Annex 5. (See also a study on falsified prescriptions in several European countries conducted in 2006-2007 [Lapeyre-Mestre, 2014]).

CONSUMPTION OF OPIOID ANALGESICS BY USERS ATTENDING SPECIALISED CARE CENTRES

OPPIDUM (see acronyms) is an annual study carried out among drug users attending specialised addictology care facilities. This study provides information on the use of substances in practice (product, dose, frequency, acquisition, suffering upon discontinuation, concomitant intake of alcohol, simple use-abuse-dependence, route of administration).

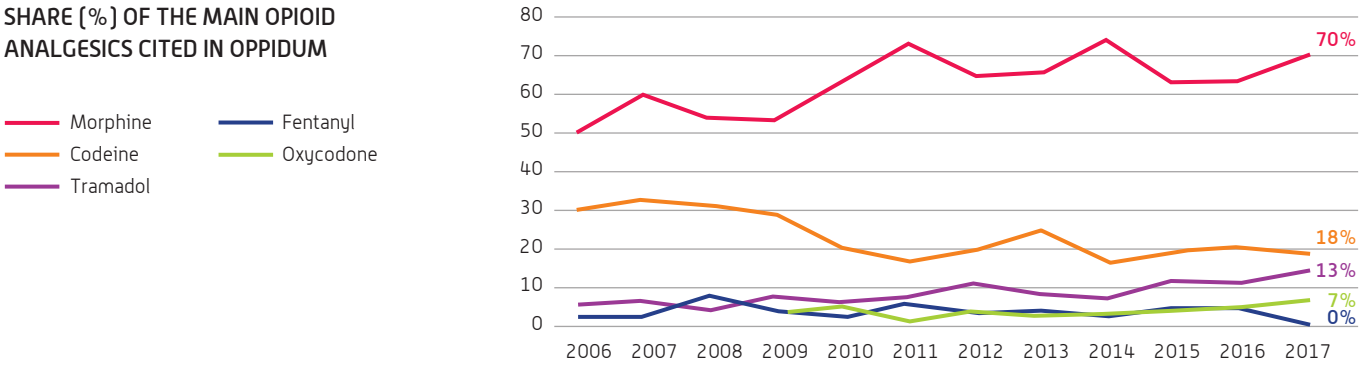
The users of this study are mostly dependent on opioids. The first products cited are opioid substitutions (OS) (55.5% in 2016 with 5997 cases), then illicit substances (37.9% in 2016) and drugs other than OS (6.6% with 717 cases).

Since 2006, the various OPPIDUM surveys have highlighted an increase in the proportion of opioid analgesic consumption from 2.8% of all citations in 2006 to 4.6% (246 subjects) in 2017.

The opioid analgesic most cited in OPPIDUM, is morphine, consistent with the population of drug users included in this study. The second opioid analgesic cited is codeine, then tramadol (constantly increasing), oxycodone (which has also tended to increase for over several years), and finally fentanyl, the share of which remains low.

The modalities of use of these opioids are characterised by an increase in the concomitant intake of alcohol (12% in 2006 and 29.3% in 2016), from suffering upon discontinuation (62.9% to 64.9%) and illegal means of acquisition (33.3% to 46%).

SHARE (%) OF THE MAIN OPIOID ANALGESICS CITED IN OPPIDUM



DOCTOR SHOPPING, AN INDICATOR OF MISUSE

The Doctor Shopping Quantity (DSQ), is the share of medicinal products obtained using overlapping prescriptions from different doctors. This indicator is calculated using data from the national health insurance database (SNIIRAM). An index greater than or equal to 1 suggests misuse of the medicinal product.

Analyses carried out on health insurance reimbursements in 2013 shows that the opioids with the highest indicators are morphine (4%), oxycodone (1.7%) and fentanyl (1.5%). The dose has an influence on the indicator, which increases to 8.4% for morphine 200 mg and 3.3% for oxycodone 80 mg, as does the formulation with 3.3% for transmucosal fentanyl and 4.1% for morphine extended release (Ponté, 2018).

A similar analysis conducted in a cohort of patients with chronic non-cancer pain over the period 2005–2013 reports an indicator of 1.0% for tramadol. A risk of doctor shopping is observed when the tramadol prescription is associated with recent initiation of treatment (risk x 8.5), age 40 or younger (x 7.4), and previous use of strong opioids (x 5.7) (Chenaf (b), 2016).

The same study for 2004–2014 reported an indicator of 4.03% for codeine. The risk factors associated with this doctor shopping are age 40 or younger (risk x 7.29), concomitant use of benzodiazepines (x 3.12), prior use of strong opioids (x 2.94) and mental disorder (x 2.25) (Chenaf (a), 2016).

Given the increased consumption of opioid analgesics since 2013, in particular tramadol and oxycodone, these results have probably changed.

(1) The remaining percentages represent missing data.

TREND BY SUBSTANCE

Compared to the total number of spontaneous notifications (NotS) reported to the addictovigilance network, the proportion of cases of problematic use of opioid analgesics is increasing, reaching 9.2% in 2015 (323 notifications in 2015) (Figure 16). This phenomenon is observed for all opioid analgesics.

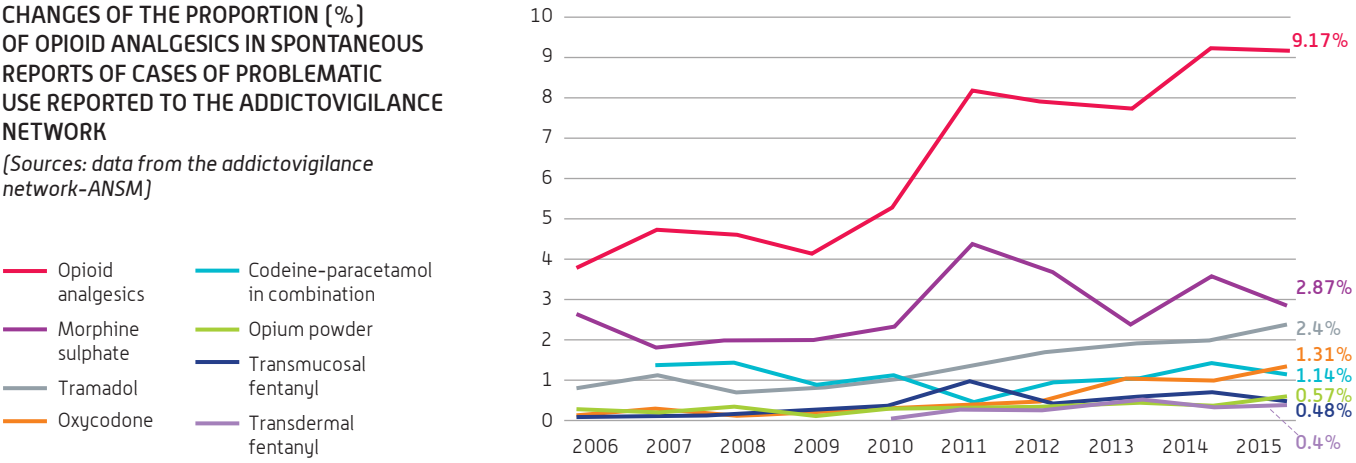
In 2015, **the most represented substance was morphine sulphate (2.9%), followed by tramadol (2.4%), which has been increasing steadily since 2008,** and oxycodone (1.3%), which has been increasing strongly since 2012, then paracetamol/codeine (1.1%), opium powder (0.6%), transmucosal fentanyl (0.5%) and transdermal fentanyl (0.4%).

Due to the significant under-reporting of cases, these data are not exhaustive, although their analysis over several year, allows trends, risks and signals to be highlighted, whether reproducible or emerging, which can be cross-correlated with other sources of data.

They must be also related to the number of patients treated. For example, the rates of spontaneous notifications involving transmucosal and transdermal fentanyl are similar - however, the number of patients treated with transmucosal fentanyl is much lower than that of patients treated with transdermal fentanyl.

CHANGES OF THE PROPORTION (%) OF OPIOID ANALGESICS IN SPONTANEOUS REPORTS OF CASES OF PROBLEMATIC USE REPORTED TO THE ADDICTOVIGILANCE NETWORK

(Sources: data from the addictovigilance network-ANSM)



Problematic use of codeine

Codeine in combination is the second most commonly used opioid analgesic in France.

The analysis of notifications reported to the addictovigilance network between 2007 and 2016 shows that the population using codeine in a problematic manner is rather female (58%), and the mean age is 40 years.

The reason for starting consumption is the treatment of pain (82%) followed by recreational use (7%), anxio-depressive disorders (6%) and opioid dependence (3%) (see also Roussin, 2013).

Codeine on medical prescription represents the majority of cases of problematic use reported to the network, (53%), even though prescription was not mandatory before July 2017. The proportion for open-sale codeine is 42%. Falsified prescriptions and theft are rather rare in spontaneous reports (3% and 1%, respectively), whereas in the OSIAP survey, codeine was the second opioid analgesic cited (see Chapter 5.4.1).

The duration of consumption is often highly variable, use sometimes being occasional or one-off, although in some cases it reaches 40 years (median: 4 years).

To a lesser extent, another problematic use of codeine is its recreational use among young people. In this scenario, codeine is mixed with other drugs and soda to obtain a drink commonly known as "purple drank" or "lean" (see box below).

Despite measures taken to inform and warn the public, this misuse has progressed rapidly, and in early 2017, two teenagers died. This led to all codeine-based products being placed under mandatory prescription by ministerial decree in July 2017. This regulatory measure also covers dextromethorphan, ethylmorphine and noscapine.

An update to the addictovigilance survey is under way to measure the impact of this measure. It appears to have reduced the misuse of products containing codeine and also allowed a previously unsupported codeine-dependent population to enter the health care system.

Study of self-medication with analgesics for which medical prescription is optional

The DANTE study (see Chapter 3) analysed 222 "codeine questionnaires" on self-medication with analgesics for which medical prescription is optional, 95 of which corresponded to regular users (daily or several times per week). Of these 95 patients, the following problematic situations related to the use of codeine were reported:

- tolerance (41%),
- need to increase the dose to relieve pain (32.6%),
- consumption of codeine when pain was not present (21%),
- an attempt or desire to quit (60%),
- codeine considered a source of problems by the patient (18%),
- continuation of use despite negative consequences on health (35%),
- at least 3 criteria for the problematic use of a DSM-V[1] positive substance (38.9%),
- a significant or compulsive desire to consume codeine, or "craving" (15%),
- consumption for a reason other than pain (14.7%), of which 11 subjects sought a positive psychoactive effect: dependence/to avoid signs of withdrawal without further precision (5 cases), anxiolysis/relaxation (2 cases), for well-being (2 cases), "to raise morale" (1 case), "to be more functional" (1 case). Three subjects did not specify the desired effect.

MISUSE OF MEDICINAL PRODUCTS CONTAINING CODEINE IN ADOLESCENTS AND YOUNG ADULTS

"Purple drank" or "lean" is a drink originally concocted from codeine, promethazine and carbonated drinks. It emerged in the United States in the late 1990s.

In France, the first signals were reported to the addictovigilance network in 2013. The symptoms associated with consumption of this mixture are disorders of alertness (drowsiness) and behaviour (agitation, confusional or delusional syndrome), generalised seizures and dependence.

In 2016, in view of the rapid increase in reports of misuse of these medicinal products by a particularly vulnerable population, the ANSM issued a warning to pharmacists, general practitioners, addictologists, emergency service physicians, paediatricians, doctors practising in family planning centres and maternal and child health centres, school and university health services, as well as to professionals practising in care associations for the prevention of drug use in young people.

In view of the persistence of these serious cases of abuse and misuse, which eventually led to two adolescent deaths, all medicinal products containing codeine, dextromethorphan, ethylmorphine or noscapine were added to the list of medicinal products available only by prescription on July 12, 2017.

See also:

- the information bulletin of 10 March 2016 on the ANSM website (https://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Usage-detourne-de-medicaments-antitussifs-et-antihistaminiques-chez-les-adolescents-et-les-jeunes-adultes-Point-d-Information)
- the information bulletin of 17 July 2017 on the list of medicines containing codeine, dextromethorphan, ethylmorphine or noscapine (https://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/L-ANSM-publie-la-liste-des-medicaments-contenant-de-la-codeine-du-dextromethorphane-de-l-ethylmorphine-ou-de-la-noscapine-desormais-disponibles-uniquement-sur-ordonnance-Point-d-Information)

Problematic use of tramadol alone and tramadol in combination with paracetamol

Tramadol alone or in combination with paracetamol is the most commonly consumed opioid analgesic in France. In recent years, the number of addictovigilance cases spontaneously reported to the CEIP-A network has been steadily increasing, from 14 in 2006 to 132 in 2016 (140 in 2017), despite consumption appearing to have stabilised since 2013. Of all notifications reported to the network, the percentage concerning tramadol more than tripled between 2006 (0.8%) and 2016 (3%).

In 2016, as many women as men (66/65) were concerned, and the mean age was 38.7 years. Note that since 2014, the mean age of subjects has been under 40 years whereas it was over or equal to 40 years in previous surveys. Nine notifications concerned minors (2 in 2014 and 1 in 2015).

The reason for starting to take tramadol was pain management (87% of reported cases), headache (2 cases in 2013, 3 cases in 2014, 4 cases in 2015 and 3 cases in 2016), an opioid dependence (3 cases in 2015 and 1 case in 2016).

(1) Diagnostic and Statistical Manual of Mental Disorders

The means of obtaining tramadol, indicated in 72 cases of 132, was medical prescription (71%).

Tramadol was consumed for purposes other than analgesia in 51 cases (38.6%); the misuse of tramadol in a context of multi-dependence in which psychoactive effects are actively sought is increasing, with 40 cases in 2016 (26 in 2015).

The proportion of cases for which the duration of consumption exceeds 2 years (compared to the number of cases where the duration is specified) has doubled since 2013: 38% in 2013, 50% in 2014 and 2015 and 77% in 2016.

In 2016, in 49% of the cases for which information is available, the quantity consumed was greater than that recommended in the marketing authorisation (45% in 2014 and 52% in 2015), and 8% of subjects consumed quantities greater than 3 g per day.

In 2016, 35/132 (27%) of cases reported withdrawal syndrome.

The problematic use of tramadol is also observed in the various surveys carried out by the addictovigilance network, particularly in the DTA and OSIAP surveys, in which it is the first opioid analgesic in question (see Chapters 5.2.1.2 and 5.3.2).

Despite small population samples from different sources of available data (spontaneous notifications, DTA, DRAMES, OPPIDUM, OSIAP), the information available all converges towards the same observation, being the emergence of non-negligible problematic use of tramadol, both in the general population for pain management, but also among drug users.

(See also Roussin, 2015 and Chenaf, 2016).

TRAMADOL AND WITHDRAWAL: DATA FROM THE ADDICTOVIGILANCE NETWORK

More than 50% of the symptoms (or signs) of tramadol withdrawal occur following therapeutic doses, sometimes even over very short periods (less than one week). Since the first OPPIDUM and OPEMA surveys, subjects consuming tramadol alone are dependent users of this substance, consumed daily at a therapeutic dose. In addition, more than half of the subjects taking tramadol included in the OPPIDUM and OPEMA surveys reported suffering upon discontinuation.

An analysis of the signs of withdrawal described in spontaneous reports to the addictovigilance network over a 6-year period (226 reports of signs of withdrawal), shows that the "psychological and psychic" signs (primarily anxiety disorders and symptoms) are more frequent than "physical" signs (for example pain, sweating). The "psychological and psychic" signs of withdrawal may be at the origin of persistent use of tramadol, and this is sometimes clearly specified.

Problematic use of opium powder

Opium alkaloids of are rapidly metabolised by the body, principally to morphine and morphine-6-glucuronide, which is some fifty times more active than the parent compound.

The rate of notifications involving opium powder is low, but increased from 0.25% in 2012 to 0.51% in 2015.

Among the cases from the last period of the addictovigilance survey (2012–June 2016), women were very predominantly represented (75%) and the mean age was 51 years.

Where information was given, the desired effect was uniquely analgesic 83% of cases, "other" in 8% and "both" in 8% of cases.

The most commonly used pharmaceutical form used is the capsule (59%) with 5 cases use by another route of administration not intended in the MA.

A history of psychiatric consultations was associated with 31% of cases, the most frequent being anxiety and depressive disorders. A history of concomitant abuse or overdose of other psychotropics (usually other medicinal products) was associated with 59% of cases.

The five reported cases of misuse of the route of administration concern 4 men and 1 woman younger than middle age, for specifically recreational purposes in 3 cases.

Doctor shopping and/or prescription falsification is reported in some 9% of spontaneous reports, and self-medication in 14%.

Signs of withdrawal, primarily neuropsychic disorders, are reported in 20% of cases, and an attempt to wean or reduce the dose in 46% of cases, about half of which were recorded in hospitals.

Death in the context of overdose with analgesic intent is also reported.

Problematic use of oxycodone

Oxycodone is the opioid analgesic seeing the largest change in consumption between 2006 and 2017, increasing by 738%. By 2017, it is was the second most consumed strong opioid analgesic, very close to morphine, although still far behind tramadol and codeine.

In parallel, between 2006 and 2015, the proportion of notifications involving oxycodone reported to the addictovigilance network increased constantly, with an accentuation of the phenomenon in 2013.

Over the period 2013–2015, notifications mostly involved men (60%), and the mean age was 40–45 years. Psychiatric comorbidity was present in 36% of cases, primarily anxiety and/or depressive disorders and a history of substance use was present in 41.2% of cases.

Consumption started for the treatment of pain in 84 cases (73.7%). This pain is 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).

Acquisition of oxycodone was illicit in 18.4% of the notifications reported.

Hospitalisation for oxycodone withdrawal following a reassessment of treatment for chronic pain was reported in 31.6% of the notifications (with the exception of one case following recreational use). Among these hospitalisations with the objective of weaning, oxycodone was the only opioid consumed in 83% of cases. The duration of consumption varied between one year and eight years (median 3 years).

Recreational use with no involvement of pain is reported in 32 cases (7%) involving younger men (median age 27 years) and use of oxycodone as an opioid substitution outside the scope of the MA in 1.7% of cases.

Problematic use of long-acting fentanyl/transdermal patch

Between 2010 and 2015, transdermal fentanyl (patch) misuse increased tenfold. However, it remains the least-cited opioid analgesic (0.4%).

Analysis of these cases highlights two consumption profiles:

- Mainly for analgesic effects (73.8% of cases) by women (60.8%), mean age 49 years, with addictive and/or psychiatric history (45.6%), treated initially for chronic pain of non-cancerous origin (93.2%) and misusing their treatment,
- Seeking positive psychic effects other than analgesia (26.2% of cases) mostly men (81.5%), mean age 36 years, with addictive and/or psychiatric history (86, 9%) and having obtained the fentanyl patch illegally (60%).

The method of acquisition, when given, was medical prescription (64%), a falsified prescription (10%), theft/black market/gift (7%), self-prescription (2%), not prescribed but without any other information (2%).

For fentanyl obtained by prescription, the indication, when known, is chronic pain (89.6%) and acute pain outside the scope of the MA (10.4%). Among the chronic pain types mentioned are lumbar and neuropathic pain (65.2%), "other," including fibromyalgia (18.8%) and cancer (8.7%).

Use of route of administration other than that intended is reported in 13% of cases.

Weaning in a hospital environment is mentioned 40% of notifications and intoxication in 27 cases (18%), of which 25 were serious (hypotension, coma, respiratory depression, etc.). Eight deaths are reported in spontaneous reports, in addition to those from the DRAMES and DTA surveys.

Problematic use of fast-acting/transmucosal fentanyl

Analysis of abuse and addiction notifications reported to the addictovigilance network between 2013 and 2015 highlights the prescription of fast-acting fentanyl in indications and/or conditions not authorised by the MA. In other words, cases of abuse and dependence are reported in patients who should not have been exposed to fast-acting fentanyl[1].

Fast-acting fentanyl is thus used outside the scope of the MA for chronic and/or non-cancer pain (52%), with no or insufficient opioid background treatment (24%) or at excessive doses (26%). This use outside the scope of the MA had already been observed in previous surveys (Gibaja et al, 2015).

The notifications concern as many women as men, and the median age is 47.5 years. A psychiatric history is reported in 28% of cases, and a history of abuse, either prior or concomitant, is present in only 24% of cases. Doctor shopping and/or falsification of prescriptions is involved in 18% of cases.

In a little more than half of the reported cases, weaning or a reduction in the dose is reported, of which 43% occurred in the hospital environment.

In the DANTE study (see Chapter 3), the number of subjects having fast-acting fentanyl prescriptions not associated with a strong long-acting analgesic (at about 30 days) went from 21.9% of subjects supplied at least one unit of transmucosal fentanyl in 2006 to 24% in 2015. These results confirm those of the addictovigilance network, reporting use outside the scope of the MA.

(1) As a reminder, fast-acting transmucosal fentanyl products are indicated in the treatment of paroxysmal pain attacks in adult patients already receiving opioid treatment for chronic cancer pain.

Problematic use of morphine sulphate

Morphine sulphate is the most consumed strong opioid analgesic supplied by high street pharmacies, and has the highest rate of notifications, in particular concerning the product Skénan, which represents 81% of notifications.

Two populations are represented in the notifications.

The first group includes subjects having developed primary dependence following the prescription of morphine sulphate as an analgesic. In the last update of the survey (2013–2016) this population represented 16.2% of notifications (vs. 7.2% in the 1996–2013 survey). The mean age is 43.7 years. The route of administration is that intended.

The second group includes drug users who use morphine sulphate for recreational use or as an opioid substitution. They are mainly men (70%), and younger (median age between 35 and 38 years).

In more than half of these cases, the route of administration is other than that intended, being administered by injection, and large doses are consumed. Morphine sulphate is obtained from dealers in 53.6% of cases and by medical prescription in 46.2%. Poly-consumption of psychoactive substances and doctor shopping are frequently associated. Infectious, neurological and vascular complications are reported (see also Peyrière, 2016, 2013).

The prescription of morphine for opioid users long pre-dates the marketing of opioid substitutes (high dose methadone and buprenorphine) in the mid-1990s. This explains, among other things, the high proportion of morphine use compared to other opioid analgesics among drug users.

ANALYSIS OF USED SYRINGES:

A study carried out in 2014 by the CEIP-A in Marseilles analysed the contents of 254 syringes from nine different collection points (automatic collection machines, street litter and drop-in centres *[Centres d'Accueil et d'Accompagnement à la Réduction de Risques pour Usagers de Drogues - CAARUD]*).

An average of one to three different substances were found in each syringe. Among these were cocaine, buprenorphine, methylphenidate and cathinones (57%, 56%, 39% and 19% of syringes, respectively). Morphine was detected in 9% of syringes and heroin in 1% of syringes (Nordmann, 2015).

All cases of problematic use of opioid analgesics must be notified to the CEIP-A in your area
http://www.addictovigilance.fr/centres

6

ACTION PLANS IN PLACE TO PROMOTE GOOD USE AND REDUCE RISKS

Maintaining health surveillance

- The ANSM is intensively monitoring the most consumed opioid analgesics: codeine, opium powder, tramadol, oxycodone, morphine sulphate, transdermal fentanyl and fast-acting fentanyl. An assessment of follow-up studies is regularly carried out and presented to the ANSM (Technical Committees for Pharmacovigilance and Addictovigilance).
- Opioid analgesics are also the subject of a specific point in each of the annual surveys of the addictovigilance network (DRAMES, OPPIDUM, OSIAP, Soumission chimique), and also have their own specific surveys (DTA and ASOS)[1].
- The ANSM has funded a study on the use of analgesics in France and changes in their use over the last ten years. This is the DANTE study (see acronyms) carried out by the addictovigilance network under the coordination of the CEIP-A in Bordeaux. This study consists of four parts - a review of analgesic consumption in France from 2006 to 2015 (see results, chapter 3.1), an observational study on self-medication with analgesics for which medical prescription is optional (see chapter 3.3), an analysis of analgesic consumption from sales and supply data (in progress), and an analysis of analgesic misuse extracted from health insurance data (in progress).
- The French Observatory for Analgesic Medicines (OFMA, see acronyms) was created in November 2017 from projects funded by the ANSM. Its main missions are to participate in pharmaco-surveillance and to promote the correct use of analgesic medicinal products in France[2].
- The ANSM monitors and analyses medication errors and proposes, where necessary, solutions to reduce these risks (see example of fentanyl and tramadol patches in children) in consultation with the producing laboratories.

Reinforcing the information supplied with medicines, adapting their availability and their supervision

- The information given in the Summary of Product Characteristics, on the Labelling and in the Package Leaflet of each medicinal product is updated according to the new data.
- Medicinal product information documents distributed by pharmaceutical laboratories to healthcare professionals are systematically validated upstream by the ANSM. The advertising of prescription medicines to the general public is prohibited in France.
- The ANSM meets with Head Pharmacists and laboratory management to ensure the development and availability of safer and better-adapted presentations for the target patients:
  - Durogésic®, transdermal patch: change of the visual aspect of the patches to improve their visibility and reduce the risk of medication error (labelling modified on 15/12/2016)
  - Oramorphe®: development of a single-dose low dose (1 and 2 mg) presentation allowing better adapted paediatric use (in progress)
  - Tramadol®: development of a less concentrated formulation with a pipette graded in mg, allowing better-adapted paediatric use (in progress)
  - Oxynorm® 10 mg/ml, oral solution: modification of the oral syringe, formerly graded in ml, now graded in mg, allowing a direct correspondence between the posology in mg and the administration of the medicinal product (in progress)
- Regulations can also be introduced to reduce the most serious risks and ensure the safe use of opioid analgesics: in view of the persistence of serious cases of misuse and abuse of medicines containing codeine, dextromethorphan, ethylmorphine or noscapine by adolescents and young adults, these products have been included in the list of medicines available on prescription only (order of July 12, 2017).

(1) ASOS (Narcotic analgesics and secure prescriptions), DTA (Deaths due to analgesic toxicity), DRAMES (Deaths in relation to the abuse of medicines and substances), OPPIDUM (Observation of psychotropic products, illicit or licit but diverted from their medicinal use), OSIAP (Suspicious prescriptions, indicator of possible abuse) - see acronyms.
(2) http://www.ofma.fr/

Provision of naloxone, an antidote for opioid overdose, for patients and their families

- The Commission for Narcotics and Psychotropics of the ANSM gave a favourable opinion in 2015 (February 12) on the availability of naloxone, in nasal spray and injectable forms, accompanied by training in their use by users, their care networks and healthcare professionals. This provision, originally planned for drug users only, is intended to become broadly available to all patients treated with opioids.
- The ANSM has made ready-to-use naloxone available for use outside care structures and in the absence of a healthcare professional:
  - Early availability of the product Nalscue, solution for nasal spray in a single-dose container, through the granting of a Temporary Authorization to Use Cohort (ATUc) (26/07/2016)
  - Granting of several marketing authorisations: Nalscue, solution for nasal spray in single-dose container (28/07/2017), Nyxoïd 1.8 mg, nasal spray solution in single-dose container (11/11/2017), Naloxone Adapt 1.8 mg and 3.6 mg, solution for nasal spray (27/03/2018), Prenoxad, 0.91 mg/ml, solution for injection in pre-filled syringe (08/08/2018), Ventizolve 1.4 mg/dose, solution for nasal spray (08/10/2018)
  - Exemption from compulsory medical prescription for these products allowing their dispensation without prescription in pharmacies
  - Validation of training and information documents for healthcare professionals, patients and their care networks on the proper use of these products
- Online posting of several information bulletins (27/07/2016, 23/12/2016, 28/07/2017, 08/01/2018)

Reinforcing communications

- The ANSM publishes information bulletins on the risks related to drugs, including opioid analgesics, whenever health watch data highlights the appearance or the persistence of a risk signal. These information bulletins are also distributed to a network of healthcare professionals. Examples of information bulletins on opioid analgesics:
  - Generic transdermal patch devices containing fentanyl (10/12/2008)
  - Medicinal products containing dextropropoxyphene:
    - End of the European re-evaluation - gradual withdrawal of the dextropropoxyphene/paracetamol combination (25/06/2009)
    - New US data on cardiac risk in healthy volunteers (22/11/2010)
    - Gradual withdrawal of the MA (20/07/2010)
    - Withdrawal from the market on March 1st 2011 (13/02/2011)
    - Withdrawal of the product (01/03/2011)
  - Transmucosal fentanyl: Reminder of undesirable effects and the need to respect the indications (25/09/2013)
  - Fentanyl Transdermal Devices: Risk of potentially life-threatening accidental exposure (25/06/2014)
  - Risks related to the use of oxycodone (30/10/2014)
  - Oral tramadol solution in children: warning of the possibility of medication errors (16/06/2016)
  - Durogesic® (fentanyl): change in colour of the patch to limit the risk of medication error (15/12/2016)
  - Publication of a list of medicinal products containing codeine, dextromethorphan, ethylmorphine or noscapine now available only on prescription (17/07/2017)
  - Online publication of information sheets on the correct use of analgesics, developed by OFMA in partnership with the ANSM as part of Patient Safety Week from 26 to 30 November 2018 (Appendix 6)
  - Tramadol: increase in the number of deaths, cases of abuse and dependence (February 2019)
- On May 11, 2017, the ANSM organised a day of partnership and exchange on the use and misuse of opioid analgesics in France, bringing together health authorities (ANSM, DGS, MILDECA, CNAMTS, HAS, INCa, ANSES), professional bodies (SFAR, SFEDT, SFAP), patient associations (LCC, AFPric, AFVD), as well as the OFDT and ELSA France. This day made it possible to take stock of the data available in the presence of the parties most involved. The report of this meeting is available online on the ANSM website[1].

(1) https://www.ansm.sante.fr/var/ansm_site/storage/original/application/7eeb7817c7212668cafbac08023063c8.pdf

7

ACTION PLANS TO BE IMPLEMENTED, TO IMPROVE GOOD USE AND REDUCE RISKS

During the day of partnership and exchange on the use and misuse of opioid analgesics of 11 May 2017, several measures to improve the good use of these medicinal products and to reduce the risk associated with their prescription and consumption were proposed by various participants[1].

These measures are part of a wider intention to develop a national action plan on overdoses linked to the consumption of opioids, analgesics, substitutions (high dose methadone and buprenorphine) and illicit drugs (such as synthetic fentanyloids).

Actions emerging from the day of partnership and exchange, May 11, 2017

REINFORCE TRAINING OF HEALTHCARE PROFESSIONALS IN THE PRESCRIPTION AND SUPPLY OF OPIOID ANALGESICS

- Training of healthcare professionals - general practitioners, pain specialists, oncologists, radiotherapists, dental surgeons, addictologists, emergency services physicians, occupational health physicians, hospital and high street pharmacists, hospital and district nurses, medical, pharmacy, dentistry and other students
- Training on the different types of pain, their treatment, the risks and recommendations, the goal of comprehensive care, the need for interdisciplinarity, the semiology of abuse/addiction/misuse and strategies for screening

IMPROVING THE CARE PATHWAY

- The comprehensive care of pain and suffering:
  - Considerations of physical and psychological pain
  - Facilitate non-drug management (psychotherapy, hypnotherapy, physiotherapy, acupuncture, psychological support, sophrology, meditation etc.).
  - Specify the most relevant criteria for evaluating chronic pain and therefore the effectiveness of analgesic treatment.
  - Take into account the risk of misuse, abuse and dependency in the overall evaluation.
  - Re-evaluate treatment after 3 months maximum in chronic pain and consider discontinuation if ineffective.
- Develop interdisciplinary exchanges between healthcare professionals (pharmacists/general practitioners, emergency medicine specialists, occupational health/addictologist).
- Anticipate the consequences of developments of home hospitalisation (HH) and outpatient management, for example using "protocolized" discharge orders.
- Supervise pain management at home: GPs and nurses can assess pain and treatment by communicating with the original prescriber and make recommendations for best-use in each patient.

IMPROVE THE DISTRIBUTION OF INFORMATION TO HEALTHCARE PROFESSIONALS

- Relay the recommendations of professional bodies, health agencies and the Committee Against Pain (*Comité de Lutte contre la Douleur* - CLUD), important hospital relays for information on pain and analgesics.
- Distribute information via:
  - Prescription software
  - Health insurance company delegates and medical advisors
  - Shared interfaces between physicians, chronic pain care structures, addictologists and health agencies such that information is easily accessible and consolidated.

IMPROVE THE DISTRIBUTION OF INFORMATION TO THE GENERAL PUBLIC

- Inform patients about the different types of pain, their treatment, recommendations and care pathways
- Raise awareness of the structures and consultations in existence for the management of pain, and the addiction centres
- Raise awareness about the preconceived ideas and fears surrounding these treatments

IMPROVE KNOWLEDGE

- Elaboration of recommendations on the best-use of weak opioids and in acute pain
- Promote research and clinical trials on analgesics to expand the therapeutic arsenal
- Identify those populations at risk of misuse and intoxication
- Identify in-family self-medication and improve users' knowledge to reduce risks
- Expand access to naloxone to all patients treated with opioid analgesics
- Take into account the risk of abuse, dependence and misuse in the evaluation the medical benefit and added medical benefit (AMB)

(1) https://www.ansm.sante.fr/var/ansm_site/storage/original/application/7eeb7817c7212668cafbac08023063c8.pdf

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ANNEX 1

Summary of recommendations of good clinical practice of the French Society of Evaluation and Treatment of Pain (SFEDT see acronyms) of January 2016 on the use of strong opioids in chronic non-cancer pain (CNCP) in adults

RECO 1: STRONG OPIOIDS HAVE SHOWN MODERATE EFFICACY IN THE RELIEF OF CNCP IN THE FOLLOWING AETIOLOGIES:

- osteoarthritis pain of the lower limbs,
- refractory chronic low back pain (degenerative disc disease, spondylolisthesis, disc herniation or narrowed lumbar canal),
- peripheral or central neuropathic pain.

It is recommended that they be considered as a therapeutic option in these three situations, subject to the following recommendations.

RECO 2: IT IS RECOMMENDED TO INTRODUCE STRONG OPIOIDS ONLY AFTER:

1. An accurate diagnosis of the aetiology of chronic pain.
2. Failure of recommended first-line medicinal treatments administered at maximum tolerated effective doses (see Table 4).
3. Comprehensive care of the patient including psychological management in patients with depressive or anxious comorbidity, social, professional and rehabilitative management for osteoarthritis pain and chronic low back pain.
4. Decisions and objectives shared with the patient, who should be informed of the expected benefits and undesirable effects, to be included in a care contract between the prescribing physician and the patient.

RECO 3: IT IS RECOMMENDED NOT TO USE STRONG OPIOIDS IN THE TREATMENT OF SO-CALLED "DYSFUNCTIONAL DISEASES", AND ESPECIALLY IN FIBROMYALGIA.

RECO 4: IT IS RECOMMENDED NOT TO USE STRONG OPIOIDS IN THE TREATMENT OF PRIMARY HEADACHES, ESPECIALLY MIGRAINE.

RECO 5: IT IS RECOMMENDED NOT TO CONTINUE STRONG OPIOID TREATMENT BEYOND 3 MONTHS IN THE ABSENCE OF BENEFIT IN AT LEAST ONE OF THE FOLLOWING ASPECTS:

- Pain relief
- Improved function
- Improved quality of life

As an indication, the threshold of 30% improvement or a reduction of 2 points on a scale of 10 points are considered a moderate improvement, but clinically significant.

RECO 6: IT IS RECOMMENDED NOT TO EXCEED 150 MG OF MORPHINE EQUIVALENT/DAY. A SPECIALIST OPINION IS RECOMMENDED FOR DOSES EXCEEDING 150 MG.

RECO 7: ALL STRONG OPIOIDS APPEAR TO BE SIMILAR IN EFFICACY, REGARDLESS OF THE INDICATION. IN THE CURRENT STATE OF KNOWLEDGE, NO ONE STRONG OPIOID IS RECOMMEND OVER ANY OTHER.

However, the choice of medicinal product must take into consideration:

- The ease of titration
- The cost (Table 7)
- Undesirable effects presented by the patient
- Data from current science
- Marketing authorisations
- Health insurance reimbursement

RECO 8: Digestive side effects are common with strong opioids. Discontinuation of treatment with strong opioids is more often due to the undesirable effects than inefficacy. It is strongly recommended to plan treatment for the most common side effects (constipation, nausea, vomiting) with anticipated symptomatic treatment added as lines on the prescription.

RECO 9: IT IS STRONGLY RECOMMENDED TO SEEK RISK FACTORS FOR OPIOID MISUSE PRIOR TO ANY PRESCRIPTION FOR STRONG OPIOIDS.

The risk factors for misuse are known. The "Opioid Risk Tool" is a quick and easy screening tool that can detect the potential risk of addiction. The existence of risk factors does not preclude prescription, but warrants increased attention and follow-up.

RECO 10: When monitoring a patient on long-term opioid treatment, it is recommended to look for misuse signals at each prescription renewal.

RECO 11: IN THE EVENT OF PROBABLE ADDICTION OR MISUSE OF A STRONG OPIOID, A SPECIALIST OPINION IS RECOMMENDED.

This may be given by an addictologist, a centre for the evaluation and treatment of pain or a psychiatrist.

RECO 12: In patients treated with strong opioids for CNCP, it is recommended to seek specialist advice in the following situations:

- **Before prescription:**
  1. In the absence of a precise aetiology explaining chronic pain.
  2. In case of associated psychiatric comorbidity.
  3. Faced with the presence of risk factors for misuse.
- **During the lifetime of the prescription:**
  4. Faced with pain that persists despite an increase in opioid consumption.
  5. Beyond 3 months of treatment
  6. Above 150 mg morphine equivalent Strong agreement

RECO 13: It is recommended to prefer sustained-release forms in CNCP. Small, immediate-release doses are indicated during the titration phase, especially in the elderly or in cases of renal or respiratory impairment

RECO 14: It is recommended not to prescribe transmucosal fentanyl (rapid release) forms in the management of CNCP.

RECO 15: It is recommended that the benefits and risks of continued treatment with strong opioids be evaluated at each prescription renewal. This evaluation will determine whether or not treatment can be continued. This is to be specified to the patient when initiating treatment with strong opioids.

Full version with methodology: http://www.sfetd-douleur.org/sites/default/files/u3349/recommandations/recos_opioides_forts_sfetd_version_longue.compressed.pdf

ANNEX 2

Development – Management of moderate to severe pain in adults – Recommendations after removal of dextropropoxyphene/paracetamol and dextropropoxyphene/paracetamol/caffeine combinations – SFR, SFEDT and Afssaps

KEY MESSAGES

- The overall evaluation of pain as experienced by the patient, along with the results yielded by the treatments taken, whether prescribed or self-medicated, are the prerequisites for the management of pain.
- The choice of treatment for nociceptive pain is guided by the intensity of the pain and its acute or chronic nature. It takes into account the efficacy and the risk profile of the analgesic treatment with regard to the clinical picture, the age of the patient and other concomitant treatments, in order to anticipate and prevent the risks of undesirable effects.
- **Acute nociceptive pains:**
  - Mild to moderate pain:
    - Paracetamol at optimal dose (minimum effective dose).
  - Moderate to severe pain::
    - Nonsteroidal anti-inflammatories at short-course analgesic doses, in the absence of contraindications

    OR

    - Level II analgesic treatment.
  - Intense pain:

    Analgesic treatment of level II, or level III in very intense pains, according to the urgency of obtaining relief and the clinical context.
- **Chronic pain with nociceptive component:**
  - Discontinuation of treatment with dextropropoxyphene/paracetamol (DXP/P) or dextropropoxyphene/paracetamol/caffeine (DXP/P/C) should be an opportunity to re-evaluate the pain, the patient's expectations and management of the medicinal products used.
  - Pain controlled with 2 and 4 capsules per day of DXP/P or DXP/P/C:
    - Paracetamol at optimal dose (minimum effective dose).
    - In case of insufficient efficacy: Low-dose level II analgesic treatment and progressive titration.
  - Pain controlled with a dose greater than 4 capsules per day DXP/P or DXP/P/C:

Medium-dose level II analgesic treatment, with or without paracetamol supplement, not exceeding a total dose of 3 or 4 g of paracetamol per day.

Treatment should be re-evaluated after one week: the dose of the level II analgesic treatment can be increased gradually, and the paracetamol supplement dose decreased accordingly.

- It is essential to remind the patient to comply with the medical prescription and not to take other analgesics without medical advice, in particular to avoid the risk of overdose when the same active substance, such as paracetamol, tramadol, codeine or a nonsteroidal anti-inflammatory drug, is present in several different medicinal products.

Full version: http://www.ansm.sante.fr/S-informer/Informations-de-securite-Lettres-aux-professionnels-de-sante/Specialites-contenant-du-dextropropoxyphene-retrait-du-marche-le-1er-mars-2011-Lettre-aux-professionnels-de-sante

ANNEX 3

Report of the National Academy of Medicine: Chronic pain in France. Recommendations of the National Academy of Medicine for better patient care

SUMMARY

Nearly 20 million French people (about 30% of the adult population) suffer from chronic pain refractory to conventional analgesic treatments.

France has been one of the first countries to be committed to work against chronic pain, with several governmental plans implemented.

However, the current state of play indicates that genuine threats exist to the management of chronic pain patients due to:

- retirements in the near future of many of the specialists having created and developed the specialised structures for chronic pain relief (*Structures Spécialisées Douleur Chronique* - SDC)
- and great difficulties in recruiting their successors.

The National Academy of Medicine makes the following recommendations:

1. Consolidate the existence of the 273 SDCs for the coming years.
2. Designate, within each Faculty of Medicine, a "University pain coordinator" attached to the "Therapeutics-pain medicine" sub-section of the National Council of Universities or to one of the major academic disciplines working with pain.
3. Ensure the renewal of these SDC teams with:
   - Physicians having received specialised training (*Formation Spécialisée Transversale* - FST) in pain medicine, in addition to their original specialised studies diploma (*Diplôme d'Etudes Spécialisées* - DES)
   - other caregivers (nurses, psychologists, physiotherapists, etc.) having received specialised pain training.
4. In addition to the essential initial training of all doctors and caregivers in the specificities of chronic pain, facilitate access to additional training on new non-drug, technological and psycho-social approaches.
5. Develop clinical and fundamental research through the implementation of strategic, political and organisational choices.

Full version: http://www.academie-medecine.fr/wp-content/uploads/2018/10/apr%C3%A8s-vote-Rapport-Douleurs-chroniques-12-10-2018-2.pdf

ANNEX 4

DTA: DEATHS DUE TO ANALGESIC TOXICITY *(Décès Toxiques par Antalgiques)*

Analgesic substances, direct deaths (Level 1 accountability (1.0 to 1.3)

Substances	2013 n = 76	2014 n = 67	2015 n = 82	2016 n = 84
tramadol	32 (42%)	32 (48%)	28 (34%)	**37 (44%)**
morphine	23 (30%)	20 (30%)	26 (32%)	**22 (26%)**
codeine	18 (24%)	6 (9%)	22 (27%)	**16 (19%)**
oxycodone	5 (6.5%)	6 (9%)	8 (10%)	**8 (9.5%)**
fentanyl	3	2	4	4
paracetamol	3	2	3	5
dihydrocodeine		1	2	1
pregabalin		2	1	1
dextropropoxyphene		1		1
ketamine				1
buprenorphine				1
Total[1]	**84**	**72**	**94**	**97**

DRAMES : DEATHS IN RELATION TO THE ABUSE OF MEDICINES AND SUBSTANCES

Décès en Relation avec l'Abus de Médicaments et de Substances)

Licit opioids excluding opioid substitutes, direct deaths 2012–2016 (Level 1 Accountability (1.0 to 1.3))

Substances	2012 n = 310	2013 n = 285	2014 n = 243	2015 n = 343	2016 n = 406
morphine	19	19	10[2]	16[2]	**25[2]**
tramadol	1	5	4	5	**7**
fentanyl	3	3	1	4	**5**
pholcodine	5	1	3	3	**2**
codeine	6	5	5	3	**12**
oxycodone	2	2		1	**6**
dextromethorphan					**1**
Total[1]	**36**	**35**	**23**	**32**	**58**

(1) Morphine origin known in 7 cases: 6 cases Skénan, 1 case Actiskénan
(2) Several substances may be present in the same case

ANNEX 5

OSIAP : SUSPICIOUS PRESCRIPTIONS, INDICATOR OF POSSIBLE ABUSE

(Ordonnances suspectes - indicateurs d'abus possible)

Characteristics of falsified prescriptions for opioid analgesics over the period 2010–2017

	Tramadol	Codeine	Morphine sulphate	Oxycodone	Opium powder	Fentanyl
Number of citations, 2010–2017	616	504	397	77	65	60
OSIAP rate in 2017	12,3 %	8,4 %	2,9 %	1 %	0,9 %	0,5 %
Characteristics 2010–2017:						
M/F[3]	**44,6 %** / 42,4 %	39,9 % / **44,4 %**	**58,2 %** / 22,6 %	**56,9 %** / 29,3 %	27,7 % / **54,4 %**	**45 %** / 21,6 %
Mean age	39,9 ans	44,1 ans	35,3 ans	39,7 ans	51,7 ans	46,5 ans
Prescription type:						
• Simple	**69,5 %**	**72,9 %**	11,5 %	16,7 %	**71,4 %**	9,5 %
• Two-zone	11,2 %	11,2 %	24,7 %	21,4 %	16,7 %	21,4 %
• Hospital	11,2 %	8,8 %	15 %	16,7 %	0	16,7 %
• Secure	8,0 %	7,2 %	**48,9 %**	**45,2 %**	11,9 %	**52,4 %**
Misuse indicators:						
• Change	7,6 %	6,1 %	3,3 %	4,1 %	**12,3 %**	6 %
• Addition	4,7 %	4,3 %	3,3 %	4,1 %	4,9 %	4,5 %
• Inadequate quantity	1,5 %	2,2 %	4,4 %	4,1 %	2,5 %	4,5 %
• Spelling mistake	3,6 %	2,7 %	2,4 %	4,1 %	1,2 %	6 %
• Handwriting	6,7 %	6,1 %	4 %	2,7 %	9,9 %	9 %
• Non-compliant prescription	1,6 %	1,3 %	9 %	5,5 %	7,4 %	11,9 %
• Inconsistency	1,1 %	0,9 %	2 %	2,7 %	1,2 %	1,5 %
• Theft	3,2 %	3,3 %	**16,5 %**	9,6 %	0	**16,4 %**
• Falsification	**50 %**	**49,6 %**	**35,4 %**	**28,8 %**	**43,2 %**	**28,4 %**
• Overlap	4,6 %	4,7 %	8,8 %	**15,1 %**	4,9 %	3 %
• Background	**14,2 %**	**18,8 %**	11 %	**19,2 %**	**12,3 %**	9 %
Principal products cited in 2017	• DCI (53 %) • Ixprim (25,8 %) • Topalgic (10,7 %)	• Dafalgan codeine (41,3 %) • Codoliprane (21 %) • Klipal codeine (20 %)	• Skénan (70 %)	• Oxynorm (54 %) • Oxycotin (31 %)	• Lamaline • Izalgi (1 citation)	• Durogesic (2 citations)

For any suspicious prescription, please contact the CEIP-A in Toulouse or the CEIP-A in your region.

(3) Rest "unspecified"

ANNEX 6

Information sheet on the correct use of opioid analgesics developed
by OFMA in partnership with the ANSM as part of Patient Safety Week from 26 to 30 November 2018.

Using medicines correctly
OPIOID ANALGESICS

Opioid painkillers are medicines that contain either **codeine, tramadol, opium, dihydro-codeine, morphine, oxycodone, fentanyl** or **hydromorphone**.

Opioid pain medicines can only be obtained on prescription, normally from your general practitioner for certain types of moderate to intense pain. Here are some vital facts about their use:

Using opioid analgesics:

- **Never increase the dose on your own initiative**: an overdose can be fatal (respiratory arrest)! Always talk to your doctor before changing the dose.
- Only take your opioid analgesic **for the period of time your doctor has told you to take it,** and only ever take it **for the specific pain for which it was prescribed.** This is very important, as these medicines can lead to addiction.
- **Never give your treatment to another person,** even if their signs of illness are the same as yours. It may harm them, and can even be fatal.

- **Constipation is the most common side effect of these medicines.** Speak to your doctor or pharmacist.
- **If the pain is not sufficiently and quickly relieved, tell your doctor.**
- **Never stop treatment abruptly without talking to your doctor,** as side effects may occur (intense symptoms of withdrawal syndrome, sweating, muscle aches, insomnia).
- **If you find that it is difficult or impossible to stop taking your opioid analgesic, or if you feel the need to increase the dose, tell your doctor or pharmacist at once.**
- **Do not drive vehicles or operate machinery without first asking your doctor for advice.**

ENSURING YOU TAKE PAIN MEDICINES ADEQUATELY

Patient safety week

ESSENTIAL INFORMATION

to ensure these medicines work well,
and to limit the risks

www.ofma.fr

#BonUsageMédicamentsAntidouleurs

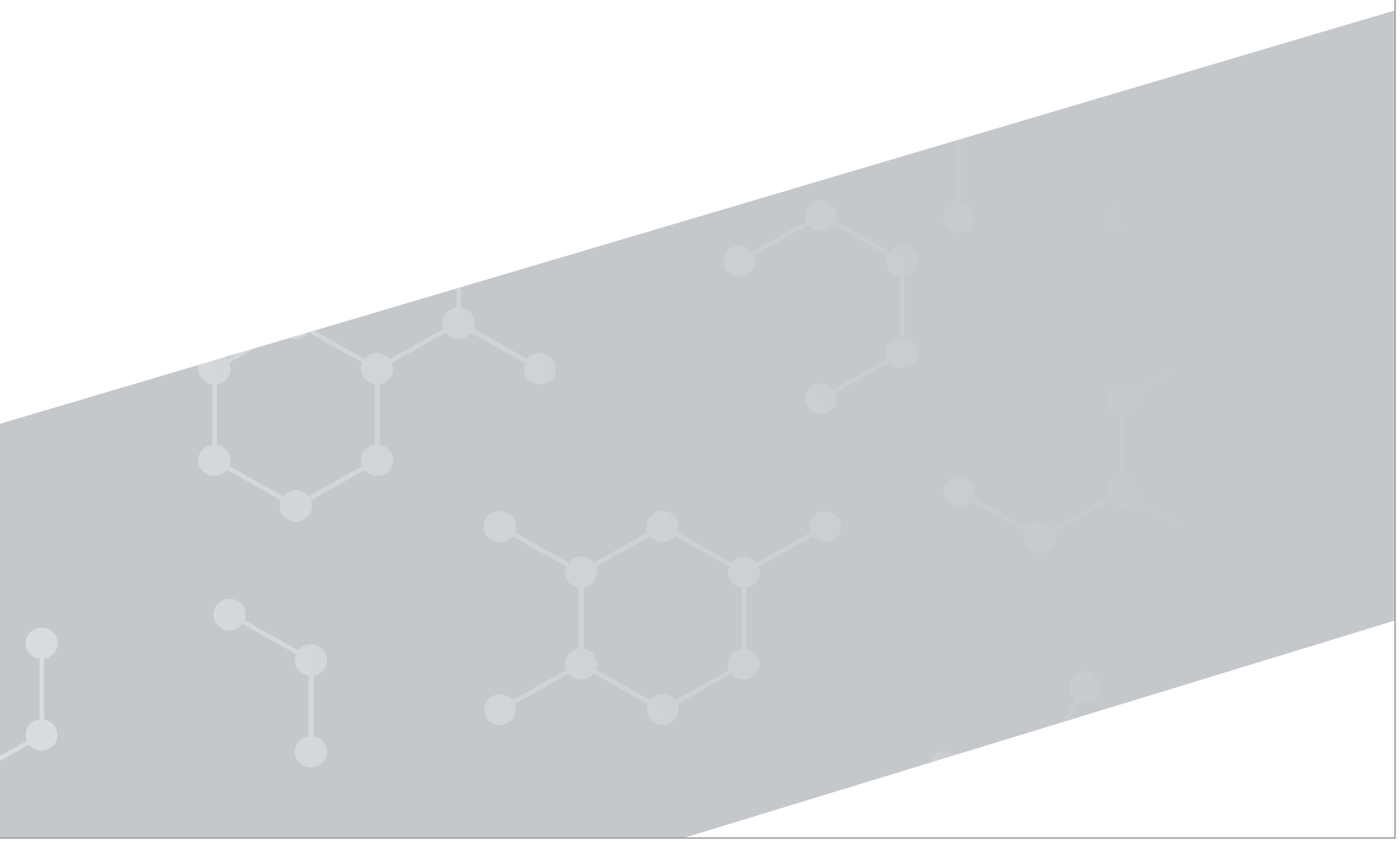
#BUMA

In partnership with: ansm, ARS, L'Assurance Maladie, SFETD, AFVD, SFSPO, Analgesia

Patients can report any side effects of pain medication on **signalement-sante.gouv.fr**

You can always ask for more information about your pain treatment at your pharmacovigilance or addictovigilance centre at: **rfcrpv.fr/contacter-votre-crpv** ou **addictovigilance.fr/centres**

Up-to-date bulletins and information sheets can be consulted on **base-donnees-publique.medicaments.gouv.fr**



143/147, boulevard Anatole France
F-93285 Saint-Denis Cedex
Phone: +33 (0) 1 55 87 30 00
@ansm

ansm.sante.fr

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