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## THERAPIES

### HEADING: COVID-19

## Addictovigilance contribution during COVID-19 epidemic and lockdown in France

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## **Abstract**

Addictovigilance is a safety monitoring targeted at substances with potential for abuse and dependence. This vigilance was involved during the period of COVID-19 epidemic due to the significant changes in access to drugs and psychological disruption caused by the pandemic and lockdown. This article aims to present the different steps implemented by the French Addictovigilance network in collaboration with the French Health authorities from March to May 2020, including monitoring of potential harmful events, and scientific communication. The first events were identified through the continuity of the networking between the French addictovigilance centres and their partners: community pharmacies, general practitioners, specialized structures and emergency wards. As soon as the lockdown began, first cases of overdoses (lethal or not) were reported with opioids, mainly with methadone, and other opioids (heroin, oxycodone, tramadol or antitussive codeine). Lockdown-related noteworthy events consisted in clinical cases or other relevant information for which lockdown clearly played an important role : among the many substances identified at least once, pregabalin, benzodiazepines, cannabis, cocaine and nitrous oxide were the most significant in terms of prevalence, seriousness or particularly specific to the lockdown context. Despite significant decrease in the activity and travel limited to vital needs, community pharmacies continued to identify falsified prescriptions in this period, highlighting an increase in suspicious requests for pregabalin, codeine and tramadol. In parallel, the French addictovigilance network continued its communications efforts in the period, issuing a newsletter on tramadol, a press release on methadone and naloxone, and participating in the COVID-19 frequently asked questions (FAQs) of the French Society of Pharmacology and Therapeutic website (<https://sfpt-fr.org/covid19> ). COVID-19 epidemic has been an important challenge for addictovigilance, and has proved that this monitoring is highly essential for alerting health professionals and health authorities to points of vigilance in the field of psychoactive substances.

## **KEYWORDS**

Addictovigilance; COVID-19; Lockdown; Abuse; Addiction; Psychoactive substances; Methadone; Pregabalin; Cocaine; Nitrous oxide

## Abbreviations

ANSM: French Medicine Agency

ASOS: *antalgiques stupéfiants et ordonnances sécurisées*

DRAMES: *décès en relation avec l'abus de médicaments et de substances*

DGS: French General Health Directorate

FAQ: frequently asked questions

MILDECA: governmental mission against drugs and addictive behaviours

N<sub>2</sub>O: nitrous oxide

OMT: opioid maintenance treatment

OPPIDUM: *observatoire des produits psychotropes illicites ou détournés de leur usage médicamenteux*

OSIAP: *ordonnances suspectes indicateur d'abus possible*

WHO: World Health Organization

## Introduction

Any safety monitoring system is part of a global approach aimed at identifying emergence or spread of a health risk. This health security approach involves the early detection of signals and their most rapid integration into an action system allowing an adapted, effective and early intervention to preserve the health of populations. In the context of pharmacovigilance and drug safety, new or unexpected adverse drug reactions should be detected as early as possible in order to further inform and secure the use of the drug, giving the general population and health professionals the opportunity of evidence-based information about these risks. In the context of COVID-19 epidemic, the French regional pharmacovigilance centres network ensured this mission [1], with an assessment maintained in its continuity, based on a pharmacological and medical characterization of cases, shared with a population-based approach integrating pharmacoepidemiological methods when possible, contributing to optimizing the level of evidence. Sharing and collaboration, both within and beyond the French Pharmacology and Therapeutics scientific community, was integral

within these special weeks and beyond (see frequently asked questions [FAQ] at <https://sfpt-fr.org/covid19>) [2-4].

In the addictovigilance context, the field is even wider and more heterogeneous [5-7]. In the first weeks of epidemic spread, most of the interrogations were related to the disease itself and to drugs with supposed antiviral properties or interactions with the immune system. Concerns about substances of abuse appeared as soon as lockdown occurred in France on March 17, 2020. This article aims to present the different steps implemented by the French Addictovigilance network in collaboration with the French Health authorities (the French Medicine Agency [ANSM]; the French General Health Directorate [DGS]; the governmental mission against drugs and addictive behaviours [MILDECA]) from this date, including scientific information, communication, and clinical and pharmacological monitoring of potential harmful events.

### **Brief reminder of the French addictovigilance system**

The French Addictovigilance Network was set up in the 1990s, in order to benefit from a proactive vigilance system targeted at substances with potential for abuse and dependence (except tobacco and alcohol), and to participate in a proactive and coordinated manner in the activities of the World Health Organization (WHO) expert committee on drug dependence [8, 9]. This vigilance is based on spontaneous notification by healthcare professionals of any serious case of misuse, abuse and drug dependence involving psychoactive substances, regardless of their nature or status [5, 10]. In addition to this passive monitoring subject to under-reporting, other sources of information have been developed to improve vigilance: systematic data collection on falsified prescriptions from pharmacies (*“ordonnances suspectes indicateur d’abus possible”*, OSIAP survey) [11, 12] and on secure prescription forms for narcotic drug prescriptions (*“antalgiques stupéfiants et ordonnances sécurisées”*, ASOS survey) [13], systematic data collection from patients seen in addiction specialized structures (*“observatoire des produits psychotropes illicites ou détournés de leur usage médicamenteux”*, OPPIDUM survey) [14], analysis of toxicological data on chemical submission [15] or on deaths in a medico-legal framework (*“décès en relation avec l’abus de médicaments et de substances”*, DRAMES survey) [16]. Addictovigilance can broaden the assessment of the potential for abuse and dangerousness of substances by specific analyses on large databases from the national health data warehouse [17, 18], or on ad hoc field studies [19-24]. The identification of

a potential signal from one or more of the sources described above makes it possible to anticipate an emerging problem and to assess its magnitude using a multi-source approach (Fig. 1) [5, 10].

### **Summary of regulatory measures potentially impacting people using psychoactive substances (medications or illicit substances)**

On March 16, in his first address on the extend of the epidemic in France, the French President announced, in a message broadcast to the nation, the implementation of travel restrictions, lockdown, and a state of emergency involving the redeployment of the entire healthcare sector to prioritize COVID-19 care from the following day. Among the different measures launched by the Government, several ones were intended to ensure continuous access for care, while limiting outing to what was strictly necessary (urgent medical care). In these conditions, both public and private medical sectors (general and specialized practitioners, nurses, most of other health professionals) decreased their activities, together with addiction specialized structures, in order to insure social distancing and prophylactic barrier measures to reduce the risks of viral contamination. For example, in many areas in France, several first line harm reduction structures [25] and addiction specialized centres modified their way of functioning, with limited access hours, redeployment of nurses and doctors for COVID care, remote consultations, *etc.*, all these changes leading to a degraded operating mode. Some other structures may have also closed their doors, in particular those offering conviviality space with coffee and food for homeless and vulnerable isolated people, because of the impossibility to ensure social distancing.

The rules for renewing prescriptions have been modified by several decrees (the first being published in the Official Journal on March 14, 2020 [26]), in order to prevent the health risks related to the abrupt interruption of chronic exposure to drugs, in a context of a reduced availability of prescribers during COVID-19 epidemic. Pharmacists were invited to issue even if the period of validity of a renewable prescription has expired, within the framework of the initially planned dosage, a number of boxes per prescription line guaranteeing the continuation of treatment, for a period not exceeding one month. These measures include specific provisions concerning medicinal products liable to be abused or misused, such as anxiolytic or hypnotic drugs, opioid maintenance drugs and other narcotic drugs or drugs falling under the regulations of narcotics. Along the successive decisions of the President and Government over time, these decrees were intended to be

prolonged during the period of the national state of health emergency. Table 1 summarizes the different situations concerning psychotropic and narcotic drugs (at the date of May 31, 2020).

### **Anticipated changes following the implementation of the whole population lockdown**

From March 17, 2020, some important problems rapidly appeared:

Because of the strict lockdown and repeated controls for any outing or trip, border shutdown for all extra European countries, but also with our immediate neighbours, drug trafficking has been drastically impacted, raising fears of an increase of episodes of withdrawal syndromes in the population of drug users. Opioid maintenance treatment (OMT) should be considered as an essential treatment during the COVID-19 pandemic, as significant risks to the community exist with an interruption of the stable provision of opioid treatment.

Difficulties for OMT drug provision have been expected with permanent changes of the prescribing and dispensing rules for narcotic drugs in the first days of lockdown, leading some patients to stock large amount of methadone at home. There may be an increased risk of opioid overdose arising from i) erratic access to OMT, ii) erratic access to illicit opioid supplies and iii) increased access to takeaway doses of methadone, which would have required the systematic prescription for take-home naloxone supplies [27].

There was also a growing concern about the risk of overdose with methadone (or of accidental exposure because of lockdown and provision of takeaway methadone at home), as methadone was already the first substance involved in drug abuse-related deaths before the disease outbreak, with an increasing trend in the last years [28]. Unfortunately, despite drug approval for forms of naloxone directly available without medical prescription in 2017, the level of use of takeaway naloxone from specialized structures or community pharmacies remains very low [27].

Psychological disturbances may occur due to the lockdown, with an increasing risk of misuse and abuse of psychoactive drugs in the population of drug users (including patients on OMT particularly vulnerable to these disruptions), but also in the general population [29]. Distress may result in some people increasing their substance use and subsequently require treatment (for example, alcohol use may increase). Changes in illicit drug supply may occur due to a range of complex interacting factors, with an increased demand for services. Alternately, some people who



use drugs may be less likely to request services during the pandemic, with an escalation of substance use during a time of distress.

Some not evidence-based and potentially deleterious “guidelines” were launched in order to anticipate withdrawals, with several dangerous recipes for substitution or techniques to make provisions of narcotic drugs. Such practices may bring new patterns of problematic use, including access to new psychoactive substances sold on the internet, with free home delivery services for using up stocks of illicit drugs.

Finally, in relation with the COVID-19 itself, concerns arose about risk of drug-drug interactions and QT prolongation with methadone potentially combined with chloroquine and hydroxychloroquine or azithromycin. Actually, when infected by SARS-CoV-2, older people, men and those with medical comorbidities (chronic pulmonary disease, cardiovascular disease, cerebrovascular disease, diabetes and a compromised immune system) present a much higher likelihood of acute respiratory distress, renal failure and death. Due to the respiratory and pulmonary tropism of SARS-CoV-2, people who smoke or vape tobacco or cannabis products were expected to be more at risk of pulmonary complications. Immune-suppressed people, for example, due to HIV infection or other chronic medication conditions, are also at increased risk for SARS-CoV-2 infection. Consequently, drug users with these conditions may be a subgroup more at risk.

### **Addictovigilance activities from the very beginning of lockdown**

We described the different events and facts collected and observed from mid-March to May 31, 2020. In the first days of lockdown, several concerns emerged in the field. The first events were identified through the continuity of the networking between the French addictovigilance centres and their partners (i.e. community pharmacies, general practitioners, specialized structures and emergency wards). By the second week of lockdown, several cases of methadone overdoses for people at home were reported, and falsified prescription forms to obtain hydroxychloroquine and azithromycin were also identified as OSIAP by different pharmacies on the French territory. These early signals have been transmitted to national health authorities, leading to the implementation of a weekly specific monitoring of noteworthy cases or events related to the COVID-19, related to the lockdown, and of all falsified or abnormal prescription forms reported through the OSIAP survey

during the period. This weekly monitoring was closely done between the French Addictovigilance Network and the ANSM [30]. The lessons of this weekly monitoring by conference calls and shared minutes of the meeting are presented in the following paragraphs. The Fig. 2 summarizes the highlights of this monitoring.

### **Periodical assessment of COVID noteworthy events (SIMAD-COVID)**

Detecting and identifying signals are a cornerstone for addictovigilance actors: they need to be able to label a piece of information received as a signal [5, 10, 20, 25, 31-33]. Signals suggesting a public health risk are collected and analysed in continuous manner in a surveillance process implemented by watchdog or public health structures, in a perspective of alert, anticipation and early action. In this framework, a signal is defined as a piece of information concerning a health phenomenon or exposure to a risk or hazard, which requires investigation in order to validate it and decide whether or not it should be considered as an alert. The signals observed in addictovigilance may be related to human cases (unusual deaths, symptoms or syndromes grouped in clusters); to psychoactive substances or associations thereof likely to have serious health consequences (presence of adjuvants, degree of purity, novelty of the substance or its usage) and to new ways of administration or new settings of use. Monitoring such noteworthy events is an important issue in addictovigilance.

SIMAD-COVID was the national periodical assessment with the aim to proactively monitor and share occurrence of fatal and non-fatal overdoses due to opioid medications (methadone, opioid analgesics) or opioid substances (heroin) or other illicit drugs (cocaine). As soon as the lockdown began, first cases of overdoses were reported with opioids, mainly with methadone, and to a less extent, with heroine and other opioid analgesics (oxycodone, tramadol) or cough syrups containing codeine. Until May 31 methadone was the most reported drug among overdoses. Interestingly, several characteristics of methadone overdose have emerged: i) accessibility of methadone by storage from family/friends at home was often reported ii) occurrence of overdose among opioid naïve subjects (never previously exposed to opioids or return to use after cessation) iii) occurrence among vulnerable subjects (homelessness, migrants, patients with psychiatric comorbidities) iv) methadone used outside its labelling in France, for anxiolytic or analgesic purposes iv) take-home naloxone was exceptionally used in the period. It is important to note that during this period the

price for street methadone remained relatively low, suggesting continued accessibility during the lockdown period compared to illicit drugs. Heroin overdoses were also observed in several areas, often among previous heroin users (around 40-45 years old) leading to severe opioid toxidromes (acute renal failure, rhabdomyolysis, haemodialysis). The same trend was observed with cocaine leading to cardiogenic complications including a patient with COVID-19 myocarditis. Overdoses were reported among young adults after tramadol use alone or associated with other drugs (cannabis) or after concomitant codeine and promethazine use (purple drank).

### **Periodical assessment of lockdown related noteworthy events (SIMAD-Confinement)**

Lockdown related noteworthy events “SIMAD confinement” consisted in clinical cases or other relevant information for which lockdown clearly played an important role, and concerned all other substances, whatever their nature (medications, illicit drugs, diverted drugs). During the lockdown period and until May 31, 2020, 231 reports were collected by the 13 French addictovigilance centres all over the country, including oversea territories.

Among the many substances identified at least once in these reports, pregabalin, benzodiazepines (including Z drugs), cannabis, cocaine and nitrous oxide (N<sub>2</sub>O) were the most significant in terms of prevalence, seriousness or particularly specific to the lockdown context.

- First signals of abuse of pregabalin (a gabapentinoid close to gabapentin, approved for the treatment of neuropathic pain, epilepsy and generalized anxiety disorder) were reported in France from 2011 with falsified prescriptions, medical nomadism and diverted use for psychoactive effect [34-36]. The French addictovigilance monitoring of pregabalin has shown, at the end of 2018, a dramatic increase in the number of cases of abuse, with the emergence of a population of young abusers. During the whole lockdown period and then afterwards, reports came from medical doctors who were urgently requested for prescription of pregabalin by young people, often minors, including migrants. This pregabalin addiction was not clearly identified before by these health professionals, since in the recent past reports came only from community pharmacists reporting abnormal prescription of Lyrica®. During the period, several cases of overdose were reported with pregabalin, including one requiring hospitalization with dyspnoea and hallucinations in a 17-year-old male.

- Benzodiazepines and Z-drugs were expected to be highly consumed during the beginning of the lockdown in France, because of social isolation or psychological troubles due to the lockdown with the potential increase of marital conflicts and domestic violence. No withdrawal syndrome was reported (renewal of prescriptions was possible along the period), but abuse or misuse (with alcohol or other psychoactive substances) were reported. Clonazepam alprazolam, oxazepam and zolpidem were the most frequently reported.

- Several reports concerned N<sub>2</sub>O indicating persistent diverted use during the lockdown due to i) a shortage of other substances in some areas and ii) a need to consume due to inactivity. On the other hand, difficulties to easily obtain large quantities of N<sub>2</sub>O cartridges led a 24-year-old male to abuse cocaine because of his craving. During the lockdown, it would appear that home deliveries have been made easier with Internet orders. Neurological complications with sensory-motor axonal polyneuropathies were also observed in the period, highlighting the spread of this new phenomenon of N<sub>2</sub>O addiction that has appeared in recent months [37].

- Unexpectedly, reports concerning cocaine were numerous (more over than with heroine or cannabis), while supply constraints could be considered as the same as for other illicit substances. Actually, this accessibility varied according to the regions, with cocaine easily available in some ones and with a wide disparity in cocaine concentration. The above described case of switching N<sub>2</sub>O to cocaine illustrates this greater availability of cocaine, with modified supply chains (home delivery instead of buying on the street from dealers).

- Cannabis supply was expected to be more difficult during lockdown. Some patients reported withdrawal symptoms due to supply difficulties or an increase in prices, while others abused cannabis in a context of anxiety related to the outbreak. Cases of accidental poisoning in children under 2 years of age who have accidentally ingested cannabis have been also reported.

In addition to these most frequent substances, other reports confirm that after a short period of waiting, the drug trade has adapted to lockdown, and cases of abuse, misuse or deleterious consequences of use were reported with synthetic cathinone 3-MMC (n = 7), amphetamines (n = 8), LSD, ketamine and GHB (n = 1 each). Finally, even if the number of reports seems quite low, it should be borne in mind that there is often a delay in reporting (cases that have occurred since lockdown break have not been reported by May 31, 2020) and that under-reporting in this area is very significant [38].

## **Periodical assessment of diverted prescription forms (OSIAP COVID)**

The two first reports collected through the OSIAP survey concerned out of date and falsified hydroxychloroquine prescription forms (presented during the first week of lockdown), in the context of media coverage about its hypothetical efficacy on Sars-CoV-2 [1, 2]. This first signal has been forwarded to the ANSM at the end of March. From this date, all suspected falsified prescription forms identified by community pharmacies and reported to the 13 addictovigilance centres were centrally analysed weekly and compared to the information collected at the same period in 2019. As a reminder, OSIAP is one of the national program implemented by the French addictovigilance network in the 1990s to record all falsified prescriptions presented to a network of community pharmacies located all over the country [11, 12]. This monitoring program has been useful to identify addictovigilance signals or characterize the abuse potential of prescription drugs [32, 39-41]. Usually, OSIAP are periodically collected each year (in May and November) on a voluntary basis by sentinel pharmacies [12]. Outside these proactive collection periods, OSIAP are continuously reported by community pharmacies, regional health authorities or medical/pharmacy councils. The OSIAP intensive data collection planned for May 2020 was cancelled due to the lockdown. Between March 16 and May 31, 2020, 178 falsified prescription forms were reported by community pharmacies to the French addictovigilance network, in a context of a significant decrease in the activity and travel limited to vital needs. This frequency must be considered with caution, as falsified prescriptions are often reported with a significant delay each year. In comparison, 634 prescription forms were collected in the same period in 2019, including the intensive data collection in May [12, 42]. Fig. 3 presents the main frequently reported drugs during the COVID-19 monitoring by weeks, compared to the same period in 2019 (estimated through the information available on May 31, 2020). During this period, the most frequently reported drugs were pregabalin, antitussive codeine syrup and analgesic codeine and tramadol. Pregabalin and codeine syrups were mainly requested by a population of young males. This profile was similar to that observed in the COVID and the lockdown noteworthy events, highlighting the emergence of a little-known population to health professionals [43-45].

## **Communication related to COVID 19 – lockdown**

The French addictovigilance network has published a national newsletter on addictovigilance news for several years (“*Bulletin d’addictovigilance*”), which was issued four times in 2019 (January, April, September and October) and once in 2020 (January). Table 2 summarizes the different topics discussed in these newsletters, which highlight the emergence or confirmation of addictovigilance signals in the recent months. In retrospect, the majority of bulletins have addressed substances that had been a problem during lockdown.

Throughout the lockdown and then, communication by the French addictovigilance network remained active with release of new national communications.

### **Bulletin number 14 (April 6, 2020)**

The last issue of the national addictovigilance bulletin was entitled: “Limitation of the prescription period of tramadol: how did we get there”. This bulletin presented a summary of the data collected in France on tramadol between 2013 and 2018 and summarized the key elements which have led in particular to limit the duration of prescription of this drug. From April 15, 2020, the maximum prescription period for analgesics containing tramadol has been reduced from 12 to 3 months. Continuation of treatment beyond 3 months will require a new prescription.

### **Press release on methadone (April 14, 2020)**

Following the results of the national addictovigilance monitoring of methadone, the French Addictovigilance network has published a press release on the need to maintain access to methadone during the lockdown period, while ensuring the safety of its use. Methadone is a mu opioid receptor agonist indicated for the substitution of opioid dependence. In France, for at least the past ten years, it has been the most frequently retrieved substance during the toxicological analyses of those involved in deaths linked to the excessive use of psychoactive substances (DRAMES Survey). The lockdown period may increase the risks linked to exposure to this drug in naïve-opioid subjects including children and those around them not treated with methadone. It

should be remembered that the potentially lethal dose of methadone ingestion in a person who has never used opioids is estimated at 1 mg/kg body weight.

The national addictovigilance review presented in November 2019 observed a constant increase in deaths and overdoses involving methadone, in parallel with increasing reports of misuse and illegal obtaining. From 2008 to 2018, methadone was the direct cause of at least 1,274 deaths (confirmed by autopsy and toxicological analysis according to the DRAMES results), with a maximum of 163 deaths in 2018. Methadone remains the first substance quantitatively implicated in deaths in France far ahead of heroin, cocaine and buprenorphine. These deaths have occurred in different contexts (naïve subjects or occasional consumers, with too rapid escalation dose during initiation of treatment, overconsumption, association with respiratory depressants, intravenous injection

The press release focused on the risk of overdose, due to the larger dispensed quantities, methadone “storage”, consumption of larger quantities of methadone or other respiratory depressants (alcohol, benzodiazepines, other opioids, *etc.*), resort to illegal obtaining, risk of overdose in the event of resumption of methadone after a few days off, risk of serious poisoning in children or naïve subjects. The press release also highlighted the risk of QT prolongation increased because high doses of methadone itself and because of combination with drugs or substances which also modify QT: domperidone, macrolides (erythromycin, clarithromycin, *etc.*), antidepressants (citalopram, escitalopram), antihistamines (hydroxyzine), antipsychotics (haloperidol, quetiapine), as well as drugs currently tested against COVID-19 in hospitals (hydroxychloroquine, azithromycin, lopinavir/ritonavir) or other psychoactive substances such as cocaine.

In order to minimize these risks, the press release insisted on warning about purchase of these drugs outside the pharmaceutical circuit, and on the need to report treatment with methadone in case of hospitalization for Sars-CoV-2 suspicion. The press release also insisted on the urgent need to increase the distribution of naloxone to methadone consumers (see brochure about where and how find naloxone; Fig. 4).

### **Contribution to COVID-19 FAQs of the French Society of Pharmacology & Therapeutics**

On March 16, 2020, the French Society of Pharmacology and Therapeutics has launched a national FAQs website at <https://sfpt-fr.org/covid19>, focused on the proper use of drugs during the COVID-

19 pandemic [4]. The French addictovigilance network has joined the scientific council and has participated to document the responses to each question related to addictovigilance.

One topic of the FAQs was about opioid maintenance treatment, because drugs approved in this indication (methadone and buprenorphine) should be considered as essential medications during the COVID-19 pandemic, and significant risks to the community exist with an interruption of the stable provision of opioid treatment. Another topic was related to the accessibility of naloxone take home in France. Another topic gave information on the risk to switch to other substances (cannabidiol or gabapentin) to manage cannabis withdrawal or to switch to opioid analgesics outside medical management for non-cancer pain [46]

## Conclusion

COVID-19 epidemic has been an important challenge for addictovigilance. Only part of the events that took place during this period have been reported to the French addictovigilance network, and it is likely that in the coming weeks or months the number of overdoses or deaths related to substance abuse will be higher than described in this article. This is of particular concern for methadone, heroin and pregabalin, but also for cocaine and nitrous oxide which seem to be more accessible than expected in this period. This Addictovigilance monitoring has proved to be indispensable for warning health professionals at the local and regional level in order to limit the risk for users, and for alerting health authorities at the national level to points of vigilance in the field of psychoactive substances.

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## **Disclosure of interest**

Authors have no competing interest to declare

## References

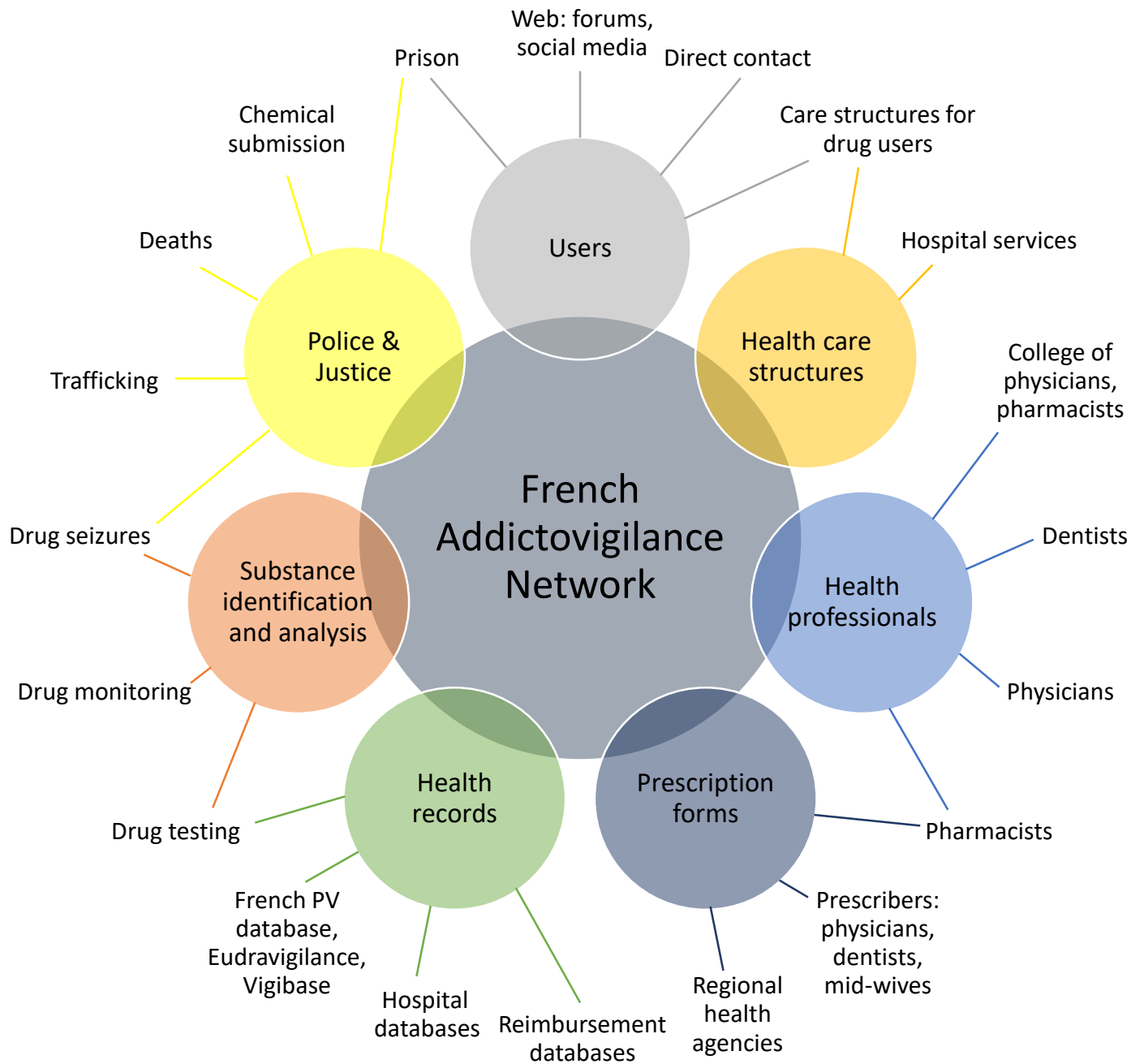
- [1] Grandvuillemin A, Fresse A, Cholle C, Yamani S, Dautriche A, French network of regional pharmacovigilance c. Adverse drug reactions of hydroxychloroquine: Analysis of French pre-pandemic SARS-CoV2 pharmacovigilance data. *Therapies* 2020;S0040-5957(20)30089-5. doi: 10.1016/j.therap.2020.05.001.
- [2] Gerard A, Romani S, Fresse A, Viard D, Parassol N, Granvuillemin A, et al. "Off-label" use of hydroxychloroquine, azithromycin, lopinavir-ritonavir and chloroquine in COVID-19: A survey of cardiac adverse drug reactions by the French Network of Pharmacovigilance Centers. *Therapies* 2020;S0040-5957(20)30091-3. doi:10.1016/j.therap.2020.05.002
- [3] Micallef J, Soeiro T, Jonville-Béra AP, French Society of Pharmacology T. Non-steroidal anti-inflammatory drugs, pharmacology, and COVID-19 infection. *Therapies* 2020;S0040-5957(20)30092-5. doi: 10.1016/j.therap.2020.05.003.
- [4] Larrouquere L, Gabin M, Poingt E, Mouffak A, Hlavaty A, Lepelley M, et al. Genesis of an emergency public drug information website by the French Society of Pharmacology and Therapeutics during the COVID-19 pandemic. *Fundam Clin Pharmacol* 2020 Jun;34(3):389-96.
- [5] Jouanjus E, Gibaja V, Kahn JP, Haramburu F, Daveluy A. Signal identification in addictovigilance: the functioning of the French system. *Therapie* 2015;70(2):113-31.
- [6] Jouanjus E, Mallaret M, Micallef J, Ponte C, Roussin A, Lapeyre-Mestre M. Comment on: "Social media mining for toxicovigilance: automatic monitoring of prescription medication abuse from Twitter". *Drug Saf* 2017;40(2):183-5.
- [7] Jouanjus E, Micallef J, Mallaret M, Lapeyre-Mestre M. Comment on: An insight into Z-drug abuse and dependence: an examination of reports to the European Medicines Agency database of suspected adverse drug reactions. *Int J Neuropsychopharmacol* 2019;22(8):528-30.
- [8] Baumevieille M, Perri-Plande J, Miremont-Salame G, Daveluy A, Haramburu F. From psychoactive medicines to addictovigilance in French Public Health Code (1990-2017). *Therapies* 2019;74(3):375-82.
- [9] Baumevieille M, Miremont G, Haramburu F, Maurain C, Bégau B. The French system of evaluation of dependence: establishment in a legal system. *Therapie* 2001;56(1):15-22.
- [10] Micallef J, Jouanjus E, Mallaret M, Lapeyre Mestres M. Safety signal detection by the French Addictovigilance Network: Innovative methods of investigation, examples and usefulness for public health. *Therapie* 2019;74(6):579-90.

- [11] Jouanjus E, Guernec G, Lapeyre-Mestre M. Medical prescriptions falsified by the patients: a 12-year national monitoring to assess prescription drug diversion. *Fundam Clin Pharmacol* 2018;32(3):306-322.
- [12] Boeuf O, Lapeyre-Mestre M, French Network of Centers for E, Information P. Survey of forged prescriptions to investigate risk of psychoactive medications abuse in France: results of OSIAP survey. *Drug Saf* 2007;30(3):265-76.
- [13] Daveluy A, Sauvaget L, Bastien A, Lapeyre-Mestre M, Collin C, Richard N, et al. Tamper-resistant prescription forms for narcotics in France: Should we generalize them? *Fundam Clin Pharmacol* 2018;32(5):571-7.
- [14] Frauger E, Pochard L, Boucherie Q, Giocanti A, Chevallier C, Daveluy A, et al. Surveillance system on drug abuse: Interest of the French national OPPIDUM program of French addictovigilance network. *Therapie* 2017;72(4):491-501.
- [15] Djezzar S, Questel F, Burin E, Dally S, French Network of Centers for E, Information on P. Chemical submission: results of 4-year French inquiry. *Int J Legal Med* 2009;123(3):213-9.
- [16] Brisacier AC, Palle C, Mallaret M. Décès directement liés aux drogues. In: Toxicomanie OFdDe, (Ed.), 2019: 1-8. <https://www.ofdt.fr/BDD/publications/docs/eftxabz7.pdf>. [Accessed June 18, 2020 (8 pp.)].
- [17] Dupui M, Micallef J, Lapeyre-Mestre M. Interest of large electronic health care databases in addictovigilance: Lessons from 15 years of pharmacoepidemiological contribution. *Therapies* 2019;74(2):307-14.
- [18] Daveluy A, Micallef J, Sanchez-Pena P, Miremont-Salamé G, Lassalle R, Lacueille C, et al. Ten-year trend of opioid and non-opioid analgesic use in the French adult population. *Br J Clin Pharmacol* 2020 Jun 4. doi: 10.1111/bcp.14415:
- [19] Auffret M, Rolland B, Behal H, Labreuche J, Jouanjus E, Bordet R, et al. A capture-recapture method for estimating the incidence of off-label prescriptions: the example of baclofen for alcohol use disorder in France. *Therapies* 2019;74(6):645-50.
- [20] Gentile G, Jegou M, Spadari M, Griffiths K, Jouanjus E, Micallef J. Identification and tracking of Addictovigilance signals in general practice: which interactions between the general practitioners and the French Addictovigilance Network? *Fundam Clin Pharmacol* 2018;32(6):643-51.
- [21] Daveluy A, Geniaux H, Baumevielle M, Letinier L, Matta MN, Lazes-Charmetant A, et al. Parachuting psychoactive substances: pharmacokinetic clues for harm reduction. *Addict Behav* 2018;78:173-7.

- [22] Peyriere H, Eiden C, Mallaret M, Victorri-Vigneau C. Medical complications of psychoactive substances with abuse risks: Detection and assessment by the network of French addictovigilance centres. *Therapie* 2016;71(6):563-73.
- [23] Batisse A, Eiden C, Peyriere H, Djeddar S, French Addictovigilance N. Use of new psychoactive substances to mimic prescription drugs: The trend in France. *Neurotoxicology* 2020;79:20-4.
- [24] Nguyen TL, Boudemaghe T, Leguelinel-Blache G, Eiden C, Kinowski JM, Le Manach Y, et al. Identifying Life-Threatening Admissions for Drug Dependence or Abuse (ILIADDA): derivation and validation of a model. *Sci Rep* 2017;7:44428.
- [25] Moracchini C, Frauger E, Pauly V, Nordmann S, Thirion X, Micallef J. Les CAARUD, lieux privilégiés d'émergence de signaux pour l'addictovigilance. *Therapie* 2012;67(5):437-45.
- [26] Ministère des solidarités et de la santé. Arrêté du 19 mars 2020 complétant l'arrêté du 14 mars 2020 portant diverses mesures relatives à la lutte contre la propagation du virus COVID-19. JORF n°0069 du 20 mars 2020. 2020. <https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000041737443&categorieLien=id>. [Accessed June 18, 2020].
- [27] Frauger E, Kheloufi F, Boucherie Q, Monzon E, Jupin L, Richard N, et al. Intérêt de la mise à disposition de la naloxone auprès des usagers de drogues pour le traitement d'urgence de surdosage d'opioïdes. *Therapie* 2018;73(6):511-20.
- [28] Frauger E, Fouilhé Sam-Lai N, Mallaret M, Micallef J. Améliorer la balance bénéfices/risques de la méthadone en respectant ses spécificités pharmacologiques. *Therapies* 2019; 74(3):383-8.
- [29] Mengin A, Alle MC, Rolling J, Ligier F, Schroder C, Lalanne L, et al. Psychopathological consequences of confinement. *Encephale* 2020;22:S0013-7006(20)30075-0. doi: 10.1016/j.encep.2020.04.007.
- [30] ANSM. Pharmacovigilance et addictovigilance dans le contexte du COVID-19 : une surveillance renforcée.2020. [https://www.ansm.sante.fr/Declarer-un-effet-indesirable/Systemes-de-vigilances-de-l-Agence/COVID-19-Dispositif-renforce-de-Pharmacovigilance-et-d-Addictovigilance/\(offset\)/0](https://www.ansm.sante.fr/Declarer-un-effet-indesirable/Systemes-de-vigilances-de-l-Agence/COVID-19-Dispositif-renforce-de-Pharmacovigilance-et-d-Addictovigilance/(offset)/0). [Accessed June 18, 2020].
- [31] Pauly V, Lapeyre-Mestre M, Braunstein D, Rueter M, Thirion X, Jouanjus E, et al. Detection of signals of abuse and dependence applying disproportionality analysis. *Eur J Clin Pharmacol* 2015;71(2):229-36.

- [32] Ponte C, Pi C, Palmaro A, Jouanjus E, Lapeyre-Mestre M, French Addictovigilance N. Early signal of diverted use of tropicamide eye drops in France. *Br J Clin Pharmacol* 2017;83(8):1791-800.
- [33] Tournebize J, Gibaja V, Frauger E, Authier N, Seyer D, Perri-Plandé J, et al. Le mésusage du fentanyl en France : 2010 à 2015. *Therapies* 2019;25:S0040-5957(19)30174-X. doi: 10.1016/j.therap.2019.11.002.
- [34] Driot D, Chicoulaa B, Jouanjus E, Dupouy J, Oustric S, Lapeyre-Mestre M. Pregabalin use disorder and secondary nicotine dependence in a woman with no substance abuse history. *Therapie* 2016;71(6):575-8.
- [35] Driot D, Jouanjus E, Oustric S, Dupouy J, Lapeyre-Mestre M. Patterns of gabapentin and pregabalin use and misuse: Results of a population-based cohort study in France. *Br J Clin Pharmacol* 2019;85(6):1260-9.
- [36] Lapeyre-Mestre M, Dupui M. Drug abuse monitoring: which pharmacoepidemiological resources at the European level? *Therapie* 2015;70(2):147-65.
- [37] French Association of Addictovigilance C, Micallef J, Mallaret M, Lapeyre-Mestre M, Daveluy A, Victorri-Vigneau C, et al. Warning on increased serious health complications related to non-medical use of nitrous oxide. *Therapies* 2020;17:S0040-5957(20)30005-6. doi: 10.1016/j.therap.2020.01.002.. 2020.
- [38] Jouanjus E, Pourcel L, Saivin S, Molinier L, Lapeyre-Mestre M. Use of multiple sources and capture-recapture method to estimate the frequency of hospitalizations related to drug abuse. *Pharmacoepidemiol Drug Saf* 2012;21(7):733-41.
- [39] Frauger E, Pauly V, Pradel V, Rouby F, Arditti J, Thirion X, et al. Evidence of clonazepam abuse liability: results of the tools developed by the French Centers for Evaluation and Information on Pharmacodependence (CEIP) network. *Fundam Clin Pharmacol* 2011;25(5):633-41.
- [40] Peyriere H, Eiden C, Micallef J, Lapeyre-Mestre M, Faillie JL, Blayac JP. Slow-release oral morphine sulfate abuse: results of the postmarketing surveillance systems for psychoactive prescription drug abuse in France. *Eur Addict Res* 2013;19(5):235-44.
- [41] Micallef J, Frauger E, Palmaro A, Boucherie Q, Lapeyre Mestres M. Example of an investigation of an "emergent" phenomenon in addiction vigilance: the case of methylphenidate. *Therapie* 2015;70(2):191-202.
- [42] Jouanjus E, Guernec G, Lapeyre-Mestre M, French Addictovigilance N. Medical prescriptions falsified by the patients: a 12-year national monitoring to assess prescription drug diversion. *Fundam Clin Pharmacol* 2018;32(3):306-22.

- [43] Baumevieille M, Rambaud A, Perri-Plande J, Daveluy A. Pharmaciens d'officine, étudiants en pharmacie et demandes de médicaments à base de codéine : étude observationnelle. *Therapies*. 2019;S0040-5957(19)30188-X. doi:10.1016/j.therap.2019.12.006.
- [44] Bossard JB, Ponte C, Dupouy J, Lapeyre-Mestre M, Jouanjus E. Disproportionality analysis for the assessment of abuse and dependence potential of pregabalin in the French Pharmacovigilance database. *Clin Drug Investig* 2016;36(9):735-42.
- [45] Jouanjus E, Falcou A, Deheul S, Roussin A, Lapeyre-Mestre M. Detecting the diverted use of psychoactive drugs by adolescents and young adults: A pilot study. *Pharmacoepidemiol Drug Saf* 2018;27(11):1286-92.
- [46] Addictovigilance. Site de l'association française des centres d'addictovigilance. Addictovigilance, situation COVID-19. 2020. <http://www.addictovigilance.fr/Nouvel-article,470>. [Accessed June 18, 2020].



April 3, 2020: 1<sup>st</sup> Teleconference with ANSM  
"COVID-Notheworthy events"

Seven teleconferences with ANSM  
until May 31



Lockdown  
March 17,  
2020

"Arrêté"  
March 14,  
related to  
community  
pharmacies

Decree 2020-  
293 March 23

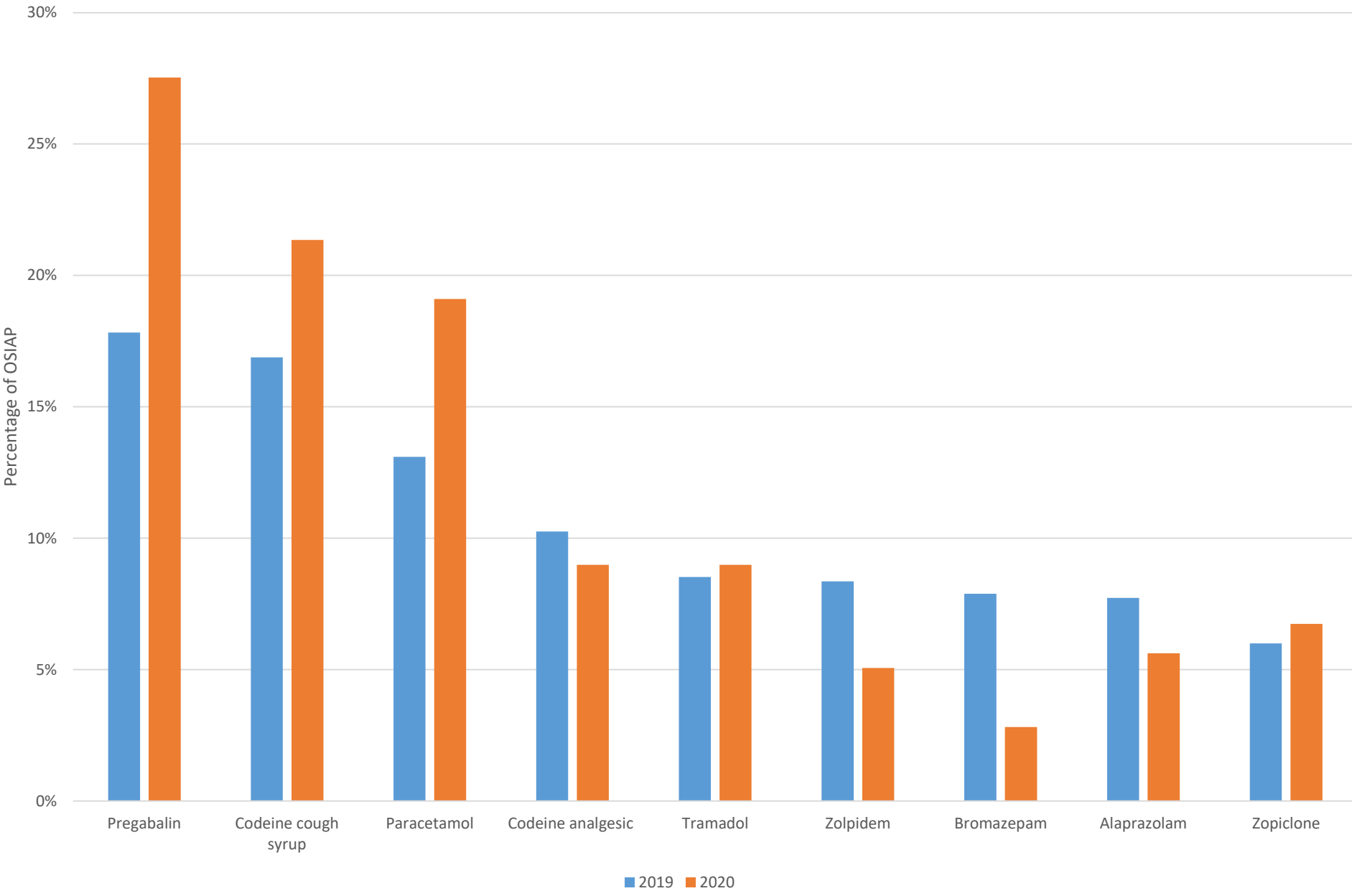
Health  
Emergency

Decree 2020-  
545 May 11  
Lockdown  
break

"Arrêté"  
March 14  
extendable  
up to June  
11

July 10, 2020 for methadone





L'Organisation mondiale de la santé (OMS) récence environ 70 000 décès par surdosage d'opioïdes dans le monde chaque année. Ces décès se déroulent dans 70 % des cas en présence d'un témoin. Dans ce contexte, l'OMS a encouragé les autorités de santé à mettre à disposition des personnes à risque d'overdose un antidote la naloxone. Cette mise à disposition s'accompagne d'un plan d'information et de formation sur les overdoses. Les décès par overdose sont évitables, la prévention repose sur une meilleure connaissance des risques et une meilleure prise en charge. A partir de juillet 2016, une forme nasale (Nalscue®) a été mise à disposition dans les services spécialisés (CAARUD, CSAPA ou service hospitalier). Depuis juin 2019, une nouvelle forme intramusculaire de naloxone (Prenoxad®) est disponible dans les services spécialisées et également en officine.

### Ce qu'il faut savoir sur le Prenoxad®

- ❑ Prenoxad® est indiqué chez l'adulte dans le traitement d'urgence des surdosages aux opioïdes, caractérisés ou suspectés, se manifestant par une dépression respiratoire et/ou une dépression du système nerveux central, dans l'attente d'une prise en charge par une structure médicalisée.
- ❑ **Comment l'obtenir en officine et dans les structures? Toute commande s'effectue exclusivement auprès du dépositaire « Centre Spécialités Pharmaceutiques » (CSP) par e-mail ([commande\\_adv@csp-epl.com](mailto:commande_adv@csp-epl.com)) ou fax (04 73 69 89 43 ou 44) en y joignant un bon de commande (modèle non fourni, selon votre convenance). Pour toute demande de renseignement sur les commandes, contactez CSP (téléphone : 04 73 69 97 57). Les commandes de 2 kits ou plus sont exonérées de frais de ports.**
- ❑ Le prix d'achat est de 19,00 euros HT (23,16 euros TTC), remboursé à 65 % en cas de prescription.
- ❑ **Pour recevoir le matériel éducatif (vidéo, brochures, check-list) contacter le laboratoire :** au 06 74 67 10 40 ; mail : [prenoxad@ethypharm.com](mailto:prenoxad@ethypharm.com) ; Internet : <https://www.prenoxad.fr>
- ❑ Avec chaque kit sera transmis une brochure et la carte patient
- ❑ **Contenance du kit :** Un kit → Un patient → Un seul épisode de surdosage
  - ✓ Seringue pré-remplie avec 5 doses de 0,4mg, Injection IM
  - ✓ A chaque utilisation, administrer une dose (correspond à une graduation)

Deux aiguilles à assembler (la 2<sup>ème</sup> aiguille sert si la première est endommagée)

Une notice médicament avec informations et schémas explicatifs



Une seringue (contenant 5 doses délimitées par des lignes noires)

Une boîte en plastique rigide pour le transport

#### ❑ Modalités de délivrance

- ✓ 1/ Prescription médicale facultative mais remboursée si prescription
- ✓ 2/ Nécessité de **former** l'usager/tiers à son utilisation, informer des signes de surdosage et de l'importance de contacter les secours
- ✓ 3/ Remettre au patient la brochure patient et Carte patient

#### ❑ Que faire en cas d'overdose?



**Table 1.** Main points of regulatory changes concerning drug dispensing in community pharmacies during COVID-19 epidemic in France (on April 3, 2020)

	<b>Anxiolytic and/or hypnotic drugs</b>	<b>Opioid maintenance drugs: methadone (syrup, capsule), high dosage buprenorphine</b>	<b>Other narcotic drugs or drugs submitted to narcotic rules for prescribing and dispensing</b>
<b>Preconditions</b>	<ul style="list-style-type: none"> <li>- The last prescription form presents an expired validity period</li> <li>- Drugs have been dispensed during the last 3 consecutive months</li> </ul>		
<b>Discussions with the prescriber</b>	To inform the prescriber about the dispensing renewal	Prescriber's prior approval required (possible by phone or other contact)	Prescriber's prior written approval required
<b>Terms of renewal</b>			
<b>Location</b>	All community pharmacies	Pharmacy whose name is specifically reported on the prescription form	Pharmacy in which medications have been previously given to the patient
<b>Dose</b>	Doses similar to those written on the initial prescription	Doses and splitting procedures as initially prescribed	
<b>Duration</b>	Maximal duration of 28 days  Renewal possible up to June 11, 2020, except for methadone, renewal possible up to July 10, 2020 (end of the state of health emergency)		
<b>Action be taken</b>	Affix on the prescription the pharmacy stamp, the date of issue and the number of boxes dispensed		

**Table 2.** Information issued in the addictovigilance bulletins released in 2019 and 2020, available at <http://www.addictovigilance.fr>

Date	Topic	Main information
01/2019	Nitrous oxide	Signal of abuse and addiction with nitrous oxide in young people, with the emergence of an increasing number of serious neurological complications <sup>[37]</sup>
04/2019	Cocaine	Situation of cocaine abuse and addiction in France, in particular with a marked increase in psychiatric, cardiac and neurological complications
09/2019	Pregabalin	Extent of pregabalin misuse, abuse and addiction in France, with the emergence of a profile of very young misusers, often poly substances users, seeking for euphoria and high [35, 44] -Increasing risk of respiratory depression with opioids, even in morphine tolerant subjects
11/2019	OSIAP survey	Main results of the OSIAP survey in 2018, highlighting a recent increase in falsified prescriptions to obtain opioids (codeine analgesics, codeine in anti-cough drugs [43, 45], tramadol) and pregabalin
01/2020	Cannabidiol	Summary of the main pharmacological properties of cannabidiol, with focus on drug-drug interactions with psychoactive substances and the addictive potential of cannabidiol

OSIAP: *ordonnances suspectes indicateur d'abus possible*

**Figure 1.** Different sources of information collected and analysed by the French addictovigilance network to improve early signal identification and to assess changes in the patterns of use and complications related to psychoactive substances in France.

**Figure 2.** Timeline of events between the start of lockdown and monitoring of COVID outbreak.

**Figure 3.** Most frequently reported prescription drugs identified in falsified prescription forms (*ordonnances suspectes indicateur d'abus possible* [OSIAP]) during the COVID-19 monitoring by week (March-May 2020). Comparison with the corresponding period of March-May 2019

**Figure 4.** Naloxone leaflet accompanying the press release on the increased risk of methadone overdoses during lockdown  
[http://www.addictovigilance.fr/IMG/pdf/plaquette\\_information\\_addictovigilance\\_naloxone.pdf](http://www.addictovigilance.fr/IMG/pdf/plaquette_information_addictovigilance_naloxone.pdf).