

## ORIGINAL ARTICLE

# Increase of high-risk tramadol use and harmful consequences in France from 2013 to 2018: Evidence from the triangulation of addictovigilance data

Anne Roussin<sup>1,2</sup>  | Thomas Soeiro<sup>1</sup>  | Charlotte Fouque<sup>1</sup> | Emilie Jouanjus<sup>1,3</sup>  | Elisabeth Frauger<sup>4</sup> | Nathalie Fouilhé<sup>5</sup> | Michel Mallaret<sup>5</sup> | Joëlle Micallef<sup>4</sup>  | Maryse Lapeyre-Mestre<sup>1,2</sup>  | the French Addictovigilance Network (FAN)

<sup>1</sup>Département de Pharmacologie Clinique et Médicale, Centre d'évaluation et d'information sur la pharmacodépendance-Addictovigilance, Centre Hospitalier Universitaire de Toulouse, France

<sup>2</sup>Pharmacologie en Population Cohortes et Biobanques, Centre d'Investigation Clinique 1436, Université de Toulouse, France

<sup>3</sup>CERPOP, Université de Toulouse, INSERM, France

<sup>4</sup>Aix-Marseille Université, Assistance publique-Hôpitaux de Marseille, Inserm, Inst Neurosci System, UMR 1106, Service de pharmacologie clinique et Pharmacovigilance, Centre d'évaluation et d'information sur la pharmacodépendance-Addictovigilance, Marseille, France

<sup>5</sup>Département de Pharmacologie Médicale, Centre d'évaluation et d'information sur la pharmacodépendance-Addictovigilance, Centre Hospitalier Universitaire Grenoble Alpes, France

## Correspondence

Prof. Anne Roussin, Département de Pharmacologie Clinique et Médicale, Centre d'Addictovigilance, Faculté de Médecine, 37 allées Jules Guesde, 31000 Toulouse, France.

Email: [anne.roussin@univ-tlse3.fr](mailto:anne.roussin@univ-tlse3.fr)

## Funding information

Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM

[Correction added on 12 July 2022, after first online publication: The copyright line was changed.]

**Aims:** The aim of this paper is to assess recent developments in non-medical tramadol use, tramadol use disorder, illegal procurement and deaths.

**Methods:** This study used repeated cross-sectional analysis of data collected nationwide from 2013 to 2018. Analysis was conducted through multisource monitoring of the French Addictovigilance Network of: (1) validated reports of high-risk tramadol use, (2) record systems collecting information from toxicology experts investigating analgesic-related deaths (DTA) and deaths related to substance abuse (DRAMES), and pharmacists for forged prescriptions (OSIAP), and (3) survey of drug users, with investigation of patterns of use while visiting addiction-specialised institutions (OPPIDUM).

**Results:** Despite a plateauing level of tramadol exposure in the French population, the proportion of tramadol reports increased 1.7-fold (187 cases in 2018, 3.2% (95% confidence interval [CI]: 2.74–3.63%), versus 1.9% (95% CI: 1.49–2.42% in 2013). Trends were similar in OSIAP: 11.9% of forged prescriptions in 2018 (95% CI: 10.56–13.45%); 1.7-fold increase; in OPPIDUM: 0.76% (95% CI: 0.55–1.02); 2.2-fold increase; and DRAMES: 3.2% of drug abuse-related deaths in 2018 (95% CI: 1.89–5.16) versus 1.7% in 2013 (95% CI: 0.65–3.84). Tramadol was the primary opioid in analgesic-related deaths in DTA (45% in 2018). Two profiles of high-risk tramadol users were identified: (1) patients treated for pain or with tramadol persistence when pain disappeared (mainly women; mean age 44 years), and (2) individuals with non-medical use for psychoactive effects (mainly men; mean age 36 years).

**Conclusion:** The triangulation of the data obtained through addictovigilance monitoring evidenced a recent increase in high-risk tramadol use. These findings have a practical impact on the limitation of the maximal duration of tramadol prescriptions.

FAN associated collaborators: Anne Batisse, Cécile Chevallier, Amélie Daveluy, Sylvie Deheul, Christine Fournier-Choma, Marylène Guerlais, Reynald Le Boisselier, Marie-Christine Pérault Pochat, Sophie Roy, Juliana Tournebize

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. *British Journal of Clinical Pharmacology* published by John Wiley & Sons Ltd on behalf of British Pharmacological Society.

## KEYWORDS

abuse, addiction, addictovigilance, death, dependence, forged prescription forms, non-medical use, opioids, substance use disorder, tramadol

## 1 | INTRODUCTION

Non-medical use of prescription medicines with desirable psychoactive effects (also referred to as misuse) includes: use for self-medication, recreational, or enhancement purposes, with or without a medical prescription, and outside accepted medical guidelines.<sup>1,2</sup> In a systematic literature review on the misuse of medicines in the EU between 2001 and 2011, codeine and tramadol were the most prevalent among the different categories of substances cited.<sup>3</sup> Whereas the magnitude of substance use disorders could differ between countries, it was always related to the level of utilisation of these substances.<sup>4,5</sup>

Tramadol is an atypical opioid analgesic as it also inhibits the reuptake of serotonin and norepinephrine.<sup>6</sup> The metabolite M1 of tramadol (O-desmethyl tramadol) produced in the liver by the polymorphic CYP2D6 has a 200–500 higher affinity for mu-opioid receptor and a more potent activity at this receptor than its parent.<sup>7</sup> Reinforcing effects of oral tramadol have been observed in clinical studies.<sup>8,9</sup> In a human drug discrimination study, an acute oral 200 mg dose of tramadol discriminated opioid effects, while the higher 400 mg dose exerted mixed behavioural effects of an opioid agonist and stimulant.<sup>10</sup> In a human functional magnetic resonance imaging study, an acute 50 mg dose of tramadol enhanced brain activity associated with reward anticipation in the nucleus accumbens.<sup>11</sup> In the 2018 critical review report concerning tramadol, the Expert Committee on Drug Dependence of the World Health Organization (WHO) pointed out evidence of increasing tramadol addiction liability.<sup>12</sup> The United Nations Office on Drugs and Crime has raised an alarm about the soaring rates of addiction to tramadol in many countries in Africa (in particular in Western and Northern Africa) and increasing non-medical use in Asia in 2018.<sup>13</sup> Non-medical use can drive tramadol use disorder and overdose-related deaths. According to the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system based on multiple data sources over 20 years, tramadol medicine has been misused at the same level as methadone, buprenorphine and fentanyl (prescription forms) in the United States.<sup>14</sup> After adjustment for availability, tramadol use in a way not directed by the healthcare provider was observed to be lower than codeine in several European countries (Germany, Italy, Spain, and the UK) in 2018.<sup>15</sup> However, in Italy, tramadol use to get high was endorsed at a higher rate than codeine, morphine and oxycodone by patients entering substance use treatment in the survey of entrants to treatment programmes (OTPS) from 2015 to 2018.<sup>15</sup> Whereas the Euro-Den Plus project data evidenced that emergency hospital presentations related to tramadol abuse in a context of non-medical use were lower than for other opioids, a great variability has been observed in sentinel hospitals across Europe for 2014–2017.<sup>16</sup>

### What is already known about this subject

- Tramadol can lead to severe tramadol use disorder and overdose-related deaths.
- Non-medical tramadol use for its psychoactive effects is associated with major public health problems in many countries, particularly in Africa and the Middle East.

### What this study adds

- The data triangulation of the addictovigilance monitoring of tramadol in France evidenced an increase in non-medical use, tramadol use disorders, illegal procurement and related deaths between 2013 and 2018, despite a stable level of exposure in the French population.
- For patients with initial exposure for pain treatment, psychological symptoms of withdrawal, craving and non-medical use for desirable psychoactive opioid and/or stimulant effects play a leading role for ongoing tramadol use when pain disappears. They represent driving factors for the development of a severe primary substance use disorder.
- Prescribers often consider tramadol to have a low potential for substance use disorder.
- However, its use for desirable psychoactive effects when pain disappeared could be a risk factor for initiating a substance use disorder.

Tramadol is currently not on the list of controlled substances regulated by the International Narcotics Control Board. In France, tramadol is a prescription-only medicine. The first signal of non-medical use of tramadol in France began to arise from the early 2010s, stressing the importance of this signal both in pain patients treated with tramadol and in users of psychoactive substances.<sup>17</sup> According to the atypical mechanisms of action of tramadol, identifying the reasons for non-medical use should help to find some ways to prevent high-risk tramadol uses with well-adapted responses in terms of regulations and/or clinical recommendations addressed to the prescribers.

The present study aimed to characterise the current situation for high-risk tramadol use in the context of pain treatment and for non-medical psychoactive use. Non-medical use, tramadol use disorder (dependence/abuse/addiction), illegal procurement and deaths were analysed based on national addictovigilance data with triangulation of

vigilance reporting and dedicated programmes in general or specific populations for the period 2013–2018.

## 2 | METHODS

### 2.1 | Addictovigilance monitoring

‘Addictovigilance’ is a contraction of the terms ‘addiction’ and ‘vigilance’. It has been introduced in the denomination of the French Addictovigilance Network.<sup>18</sup> Addictovigilance corresponds to the monitoring of medicines or other legal or illegal substances with abuse potential in the context of real life. For years, the French Addictovigilance Network has developed a proactive multisource approach to prevent population risks associated with substance use disorder (SUD).<sup>18</sup> The Addictovigilance regional centres are based in pharmacology departments of university hospitals. Health professionals must report any serious SUD to these centres.<sup>19</sup> These addictovigilance reports include age, sex, past medical history, past high-risk use of psychoactive substances and clinical features related to present substance use as patterns of this use. As for pharmacovigilance, the coverage of the declarants cannot be estimated and the number of recorded addictovigilance reports does not guarantee representativeness at the scale of the entire population. However, it is recognized worldwide that these systems are essential to provide safety alerts.

A strategy of mosaic surveillance, crossing information from spontaneous reports and dedicated pharmacoepidemiological surveys and record systems, enables in-depth analysis of each type of high-risk use.<sup>14,20</sup> The French Addictovigilance centres have implemented national programmes allowing a multidimensional analysis for a given substance.

These national programmes include the following:

1. OSIAP (‘Suspicious prescription form indicators of possible abuse’) programme, which investigates medicines identified on forged prescriptions presented in pharmacies.<sup>18,21</sup> From 2001 to 2004, a national network of volunteer community pharmacies was implemented on a national level to collect suspect prescriptions during two periods each year in May and November.<sup>18,21</sup> In addition, from 2005 to the present, all other suspect prescriptions identified outside these periods have been recorded in the same way and included in the global analysis with data collected in May and November. Consequently, participating pharmacies do not ensure the representativeness of the around 21 000 community pharmacies in France.
2. The OPPIDUM (‘Observation of illegal drugs and of the misuse of psychotropic medicines’) survey collects information (drug name, modalities of use, ways of procurement) on drug use in individuals with SUD and consulting in addiction-specialised centres.<sup>22</sup> This survey is conducted annually over one month. The number of addiction centres participating in the OPPIDUM survey increased from 168 in 2013 to 259 in 2018. One-third of the ambulatory

addiction centres that have included 77% of OPPIDUM individuals participated in the survey in 2015.<sup>23</sup>

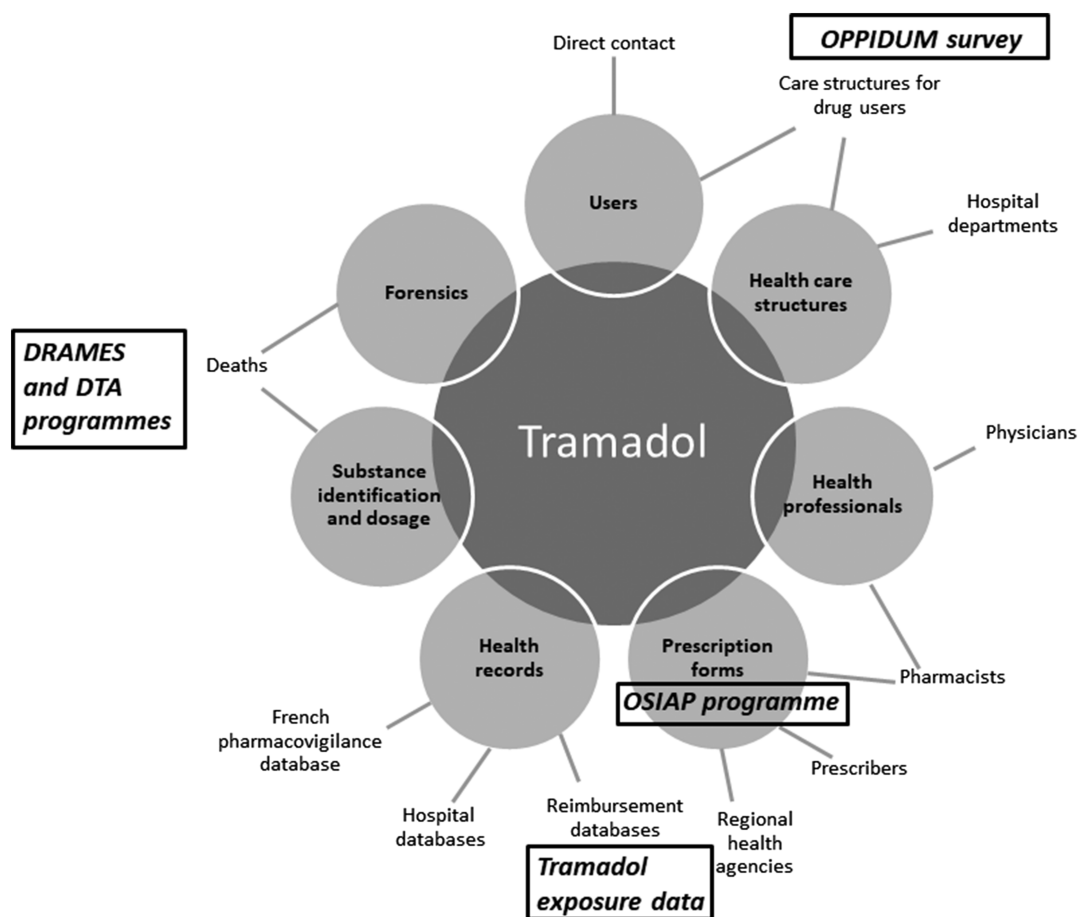
3. DRAMES (‘Death with abuse of psychoactive medicines or substances’) and DTA (‘Death related to analgesics in a therapeutic context’) national programmes analyse forensic data periodically transmitted by analytical toxicology laboratories in the context of abuse of psychoactive substances and patients treated for pain, respectively.<sup>24</sup> For a given case, each substance identified is subjected to a causality assessment, establishing the link between the substance and the cause of death. The strength of the causal connection is determined by a score, from high (level 1) to low (level 4). The causal link is made on blood concentrations (or other matrices if no blood) quantification and relies on the analysis from toxicology experts and published references. In the DRAMES programme, 19 analytical toxicology laboratories participated in 2013 and 27 in 2018. Concerning DTA, there were 14 and 21 in 2013 and 2018, respectively. The included cases came from 80% of the French geographic counties. For each fatality case, the record includes the sex and age, circumstance of death, autopsy data and if the deceased person was a psychoactive substance abuser.

Figure 1 provides an overview of the data sources used for each addictovigilance programme presented above in detail thanks to collaborations with partners on the interface with field data related to high-risk substance use and the potential related disorders.<sup>20</sup> For the present study concerning tramadol, Table 1 details the variables retained in the analysis.

### 2.2 | Tramadol exposure data

The exposure of the whole French population to medicine containing tramadol during the study period was estimated by drug reimbursement provided by the French National Health Insurance System.<sup>25</sup> The number of individuals in France who were dispensed at least once medicine containing tramadol and the level of tramadol exposure in the French population (defined daily dose [DDD]/1000 inhabitants/day) were computed by year.

High-risk tramadol uses were identified through addictovigilance reports with mention of: (1) tramadol use disorder (dependence [withdrawal symptoms or hospitalization for withdrawal]), abuse (daily doses higher than the 400 mg maximal recommended daily dose with deleterious consequences such as seizures, social or professional adverse consequences), and addiction, and (2) illegal procurement. High-risk uses were categorised into two profiles: individuals with pain (or when the pain disappeared, tramadol’s persistence was mainly to avoid withdrawal symptoms and because of craving) or non-medical use (for desirable psychological effects in the absence of pain or outside pain relief). This classification into profiles was discussed by two pharmacologists specialised in addictovigilance after reviewing each report narrative. Main characteristics (age, sex, initial use for pain, duration of use, abuse, harmful consequences and illegal



**FIGURE 1** Sources used for proactive tramadol addictovigilance monitoring

procurement) were compared using  $\chi^2$  (or Fisher's exact) tests and t-test for qualitative or quantitative characteristics, respectively.

### 2.3 | Ethics

In France, addictovigilance forms part of compulsory safety monitoring regulated by law.<sup>19</sup> Patient informed consent is not required as internationally stated for the collection of data required for safety monitoring. All the data records were collected under the agreement of the National Committee for Privacy.<sup>26</sup>

The data included in this analysis do not provide any individual information, except for sex, age, and date of the event. No information allowing potential re-identification (initials, location of residence, exact date of birth) is recorded. Consequently, linking data between spontaneous reporting, forged prescriptions or toxicological analysis of death is not possible.

### 2.4 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.<sup>27,28</sup>

## 3 | RESULTS

### 3.1 | Trends in tramadol exposure in the French population from 2013 to 2018

The number of tramadol users in France plateaued from 2014 to 2018 (with a decrease for tramadol associated with paracetamol and an increase for tramadol alone), with 5.9 million users in 2018, while tramadol exposure decreased annually in quantity from 2014 (11.9 DDD/1000 inhabitants/day) to 2018 (10.5 DDD/1000 inhabitants/day) (Figure 2). The decrease of tramadol exposure was accounted for by a reduction in tramadol associated with paracetamol.

### 3.2 | Trends in high-risk tramadol use, illegal procurement and deaths from 2013–2018

#### 3.2.1 | Trends in reported high-risk use according to addictovigilance reports and the OPPIDUM survey

The proportion of tramadol case reports among all the reports of high-risk substance use to the French Network of Addictovigilance increased 1.7-fold from 2013 to 2018 (Table 1 and Figure 3A).

**TABLE 1** Evolution of the characteristics of tramadol reports and cases registered in each of the programmes in the French addictovigilance network between 2013 and 2018

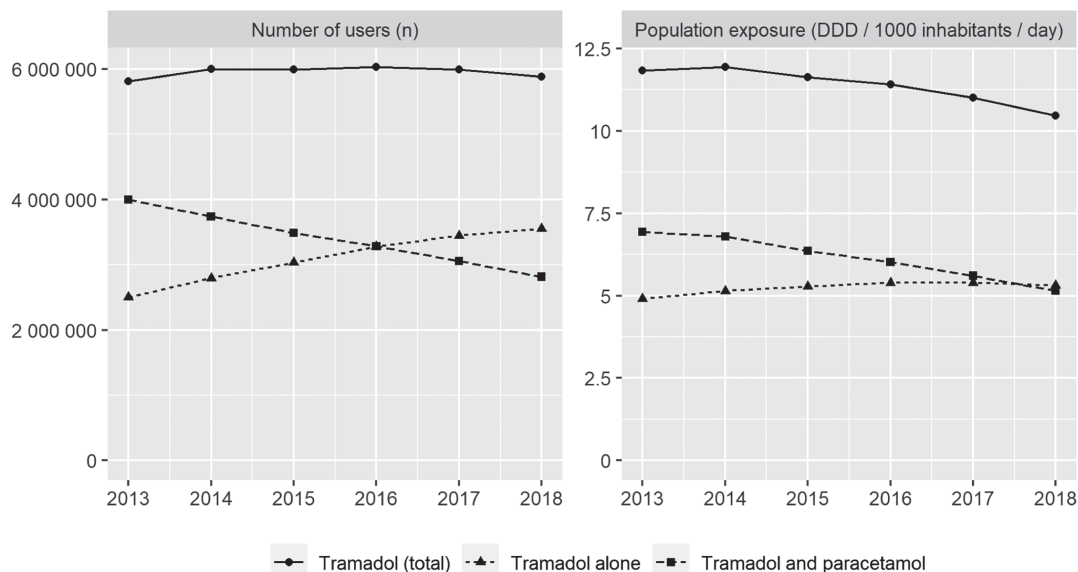
|   | Reports                       |                                | OSIAP            |   |
|---|-------------------------------|--------------------------------|------------------|---|
|   | 2013                          | 2018                           | 2013             | 2018  |
| Tramadol/total reports (%) [95% CI]   | 64/3347 (1.9%)<br>[1.49-2.42] | 187/5916 (3.2%)<br>[2.74-3.63] | 1.7 fold<br>of % | 233/1950<br>forged prescriptions (11.9%)<br>[10.56-13.45] |
| Mean age $\pm$ SE (years)<br>[min-max]  | 40.4 $\pm$ 25.5<br>[17-68]    | 37.8 $\pm$ 12.3<br>[14-81]     |                  | 46.1 $\pm$ 15.6<br>[25-80]                                |
| Adolescents<br>( $<$ 18 years)  | 2 (3%)                        | 13 (7%)                        |                  | 0   |
| Male (%)  | 34 (53%)                      | 103 (55%)                      |                  | 17 (33%)  |
| Duration of use $>$ 1 year  | 20 (31%)                      | 73 (39%)                       |                  | -   |
| Polysubstance use   |                               |                                |                  | -   |
| Tramadol-only medicines (% of citations)  | 50 (78%)                      | 150 (80%)                      |                  | 27 (52%)  |
| Tramadol associated with paracetamol (% of citations)                             | 12 (19%)                      | 43 (23%)                       |                  | 27 (50%)  |
| Tramadol abuse ( $>$ 400 mg/d)  | 20 (31%)                      | 87 (46.5%)                     |                  | -   |
| Tramadol procurement by forged prescription or other<br>illegal ways <sup>a</sup> | 12 (19%)                      | 50 (27%)                       |                  | 100%  |
| Tramadol substitution by buprenorphine or methadone                               | 6 (9%)                        | 21 (11%)                       |                  | -   |
| Tramadol as first SPA with dependence   | -                             | -                              |                  | -   |
| Mean age $\pm$ SE (years) of first SPA dependence                                 | -                             | -                              |                  | -   |
| Tramadol nasal administration   | 0                             | 3 (2%)                         |                  | -   |
| Tramadol injection  | 0                             | 1 (0.5%)                       |                  | -   |

<sup>a</sup>Doctor shopping, theft deal, gift, and internet.

TABLE 1 (Continued)

|  | OPPIDIUM                          |                                   | DRAMAS              |                                  | DTA                 |                                 |
|--|-----------------------------------|-----------------------------------|---------------------|----------------------------------|---------------------|---------------------------------|
|  | 2013                              | 2018                              | 2013                | 2018                             | 2013                | 2018                            |
| Tramadol/total reports (% [95% CI])  | 18/5245 people (0.3%) [0.21–0.53] | 41/5412 people (0.8%) [0.55–1.02] | 2.2 fold /of %      | 15/464 deaths (3.2%) [1.89–5.16] | 1.9 fold /of %      | 49/109 deaths (45%) [35.8–54.4] |
| Mean age ± SE (years) [min-max]  | 36.7 ± 11.3 [22–61]               | 41.9 ± 10.7 [19–67]               | 40.2 ± 14.7 [26–62] | 36.6 ± 16.3 [17–69]              | 47.1 ± 19.4 [13–92] | 51.6 ± 18.4 [16–91]             |
| Adolescents (< 18 years)   | 0                                 | 0                                 | 0                   | 1 (7%)                           | 3 (9%)              | 1 (2%)                          |
| Male (%)   | 13 (72%)                          | 28 (68%)                          | 2 (40%)             | 9 (60%)                          | 14 (44%)            | 18 (36%)                        |
| Duration of use > 1 year   | 8 (44%)                           | 22 (54%)                          | -                   | -                                | -                   | -                               |
| Polysubstance use  | 13 (72%)                          | 32 (78%)                          | -                   | -                                | -                   | -                               |
| Tramadol-only medicines (% of citations)                                       | 12 (67%)                          | 39 (95%)                          | -                   | -                                | -                   | -                               |
| Tramadol associated with paracetamol (% of citations)                          | 6 (33%)                           | 3 (7%)                            | -                   | -                                | -                   | -                               |
| Tramadol abuse (> 400 mg/d)  | 1 (6%)                            | 1 (2%)                            | -                   | -                                | -                   | -                               |
| Tramadol procurement by forged prescription or other illegal ways <sup>a</sup> | 7 (39%)                           | 14 (34%)                          | -                   | -                                | -                   | -                               |
| Tramadol substitution by buprenorphine or methadone                            | -                                 | -                                 | -                   | -                                | -                   | -                               |
| Tramadol as first SPA with dependence  | 2 (11%)                           | 10 (24%)                          | -                   | -                                | -                   | -                               |
| Mean age ± SE (years) of first SPA dependence                                  | 23.0 ± 10.8                       | 25.4 ± 9.5                        | -                   | -                                | -                   | -                               |
| Tramadol nasal administration  | 0                                 | 1 (2%)                            | -                   | -                                | -                   | -                               |
| Tramadol injection   | 0                                 | 0                                 | -                   | -                                | -                   | -                               |

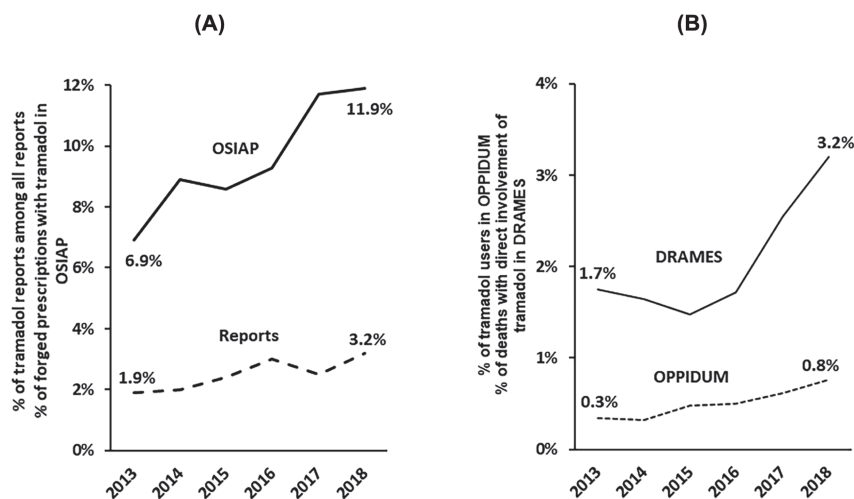
<sup>a</sup>Doctor shopping, theft deal, gift, and internet.



Anonymous and aggregated data are available through the Open platform for French public data (Open Medic).

**FIGURE 2** Tramadol exposure in the French general population and number of users from 2013 to 2018

**FIGURE 3** 2013–2018 evolution of tramadol high-risk uses evidenced by addictovigilance monitoring: (A) in general population and (B) in individuals with SUD



(A) Reports of cases of high-risk tramadol use to the French Addictovigilance Network (% of tramadol reports among all reports) and annual national OSIAP records (% of forged prescription with tramadol presented in community pharmacies).

(B) Annual national OPPIDUM survey (% of tramadol users in individuals with SUD seen in specialised addiction centres) and DRAMES records (% of deaths with direct involvement of tramadol in substance abusers).

The total number of cases reported to the addictovigilance centres and recorded in each national programme varied annually. Therefore, the annual evolution of tramadol data is expressed in percentage.



The proportion of individuals with tramadol use in the OPPIDUM survey was 2.2-fold higher in 2018 than in 2013 (Table 1 and Figure 3B). Among all the substances reported as the first drug responsible for SUD in this population, tramadol proportion increased from 0.08% (95% CI: 0.026–0.19) in 2013 to 0.6% (95% CI: 0.41–0.84) in 2018.

### 3.2.2 | Trends in illegal procurement using data from addictovigilance reports, OPPIDUM and OSIAP record systems

Whereas medical prescription represented the principal way of tramadol procurement, addictovigilance reports and OPPIDUM survey data have highlighted an increase in doctor shopping, pharmacy hopping and use of forged prescriptions. Some other ways of procurement were also described: stolen treatment from close family, deal, gift and the internet. The most striking indicator of a rise in the illegal procurement of tramadol is the regular increase of forged prescriptions being presented in pharmacies. The rate of prescriptions containing tramadol alone or associated with paracetamol increased 1.7-fold between 2013 and 2018 (Table 1 and Figure 3A). This increase concerned mainly tramadol alone (Table 1).

### 3.2.3 | Trends in deaths using data from DRAMES and DTA record systems

The proportion of tramadol-related fatalities recorded in DRAMES was the highest in 2018, with 3.2% of 464 deaths (Table 1 and Figure 3B), vs 4.5% for morphine-related deaths. In 2018, tramadol was judged responsible for death in five cases when other substances were considered non-responsible. For the remaining 10 cases, tramadol was involved in fatalities together with other substances identified.

In DTA, tramadol ranked first among opioid analgesics directly involved in deaths (including suicide) of patients treated for pain and without a history of drug abuse. In 2018, tramadol was directly involved in 45% of the 109 deaths, followed by morphine (29%). Among the 49 deaths: in four cases, tramadol was the only detected substance involved; in 26 cases, tramadol was judged responsible while other detected substances were not; in 19 other deaths, tramadol was qualified responsible together with other substances.

## 3.3 | Profiles of tramadol users in addictovigilance reports in 2018

Two main profiles can be distinguished from the 187 cases recorded in 2018: patients treated for pain and individuals with non-medical use of tramadol to exert its psychoactive effects ( $n = 178$ , Table 2). In addition, nine reports concerned tramadol intoxications with suicidal ideation or attempt, particularly in minors and young adults (Table 2).

## 3.4 | Profile of patients treated for pain and without non-medical tramadol use in 2018 ( $n = 49$ )

The tramadol users were mainly women, and the mean age was 44 years (Table 2). The duration of tramadol use was long (up to 13 years). There was a high proportion of abuse and dependence in a context of pain. When the pain disappeared, the persistent use of tramadol was mainly to avoid withdrawal symptoms and because of craving. For 8.2% of the patients in this group, a substitution by buprenorphine or methadone was reported (tramadol being the only opioid used).

## 3.5 | Profile of individuals with non-medical tramadol use in 2018 ( $n = 129$ )

In the group 'non-medical users' we included: (i) patients first exposed to tramadol for pain relief and when pain disappeared continued to use tramadol only for its psychoactive effect (41% of the group), and (ii) those who started tramadol use for recreational purposes, to be high or for self-medication of psychological troubles.

The durations of use were long (up to 20 years). Adolescents represented 9% of the non-medical tramadol users, with getting high as the most frequently reported reason for use. In addition, tramadol was also used for sedative effects in the absence of cannabis or was taken after a period of non-medical use of codeine.

Tramadol dependence was reported in 64% of non-medical users, with withdrawal symptoms (including depressive symptoms and worsening of depression) and sometimes craving.

The proportion of men was higher, and the mean age was lower than in the group of patients treated for pain (Table 2). A past high-risk use of any substance was retrieved at a higher rate. The illegal ways of procurement of tramadol were also higher.

Two sub-groups of non-medical use were differentiated:

- 1- In the majority (59%,  $n = 76$ ), tramadol was used in association with other substances (medicines [mainly benzodiazepines, opioids and gabapentinoids] and/or illicit drugs). The most frequently expected psychoactive effects of tramadol were anxiolysis, sedation, and to be high. In some cases, the reports described a stimulant effect, disinhibition, use for festive context, well-being, and to hold on physically and psychologically. Past high-risk use of other opioids was described in 26.3% of the reports. In six of ten individuals starting substitution with buprenorphine or methadone, tramadol was the only opioid used.
- 2- For the other 53 individuals, tramadol was the only substance used. The reasons for use were anxiolysis and a stimulant effect. Less frequently, the reports mentioned tramadol use to get high, experience euphoria and sedation. Past high-risk use of other opioids was described in 15% of the reports. For all the five individuals starting substitution by buprenorphine, tramadol was the only opioid used.

Regardless of the users' profile, the proportion of the reports involving tramadol alone (i.e., not associated with paracetamol) was



**TABLE 2** Characteristics of the two main profiles of individuals with high-risk use of tramadol in 2018

|   | Total population<br>(N = 187) <sup>a</sup> | Patients treated for pain<br>(n = 49) | Non-medical tramadol use<br>(n = 129) |
|---|--|---------------------------------------|---------------------------------------|
| Mean age ± SE (years)   | 37.8 ± 12.3                                | 43.6 ± 12                             | 36.3 ± 12.1 <sup>b</sup>              |
| [min-max]   | [14-81]                                    | [18-73]                               | [14-81]                               |
| Adolescents   | 13 (7.0%)                                  | 0                                     | 12 (9.3%) <sup>***</sup>              |
| Male (%)  | 103 (55.1%)                                | 19 (38.8%)                            | 78 (60.4%) <sup>***</sup>             |
| Initial use of tramadol for pain treatment                                      | 102 (54.5%)                                | 49 (100%)                             | 53 (41.1%)                            |
| <b>Duration of use</b>  |  |                                       |                                       |
| < 1 day   | 33 (17.6%)                                 | 10 (20.4%)                            | 16 (12.4%)                            |
| [1 day-3 months]  | 5 (2.7%)                                   | 1 (2%)                                | 4 (3.1%)                              |
| [3 months-1 year]   | 13 (7.0%)                                  | 5 (10.2%)                             | 8 (6.2%)                              |
| [1 year-2 years]  | 19 (10.2%)                                 | 6 (12.2%)                             | 13 (10.1%)                            |
| [2 years-10 years]  | 46 (24.6%)                                 | 9 (18.4%)                             | 36 (27.9%)                            |
| [10 years-20 years]   | 8 (4.3%)                                   | 4 (8.2%)                              | 4 (3.1%)                              |
| Abuse   | 87 (46.5%)                                 | 21 (42.9%)                            | 60 (46.5%)                            |
| Seizures  | 17 (9.1%)                                  | 3 (6.1%)                              | 14 (10.9%)                            |
| Tramadol-only medicines (% of citations)  | 150(80.2%)                                 | 39 (78%)                              | 103 (76.9%)                           |
| Tramadol associated with paracetamol (% of citations)                           | 43 (23%)                                   | 11 (22%)                              | 31 (23.1%)                            |
| Tramadol procurement by forged prescription or other illegal ways <sup>**</sup> | 50 (26.7%)                                 | 7 (14.3%)                             | 40 (31.0%) <sup>***</sup>             |
| Past high-risk use of any psychoactive substance                                | 73 (39%)                                   | 8 (16.3%)                             | 61 (47.3%) <sup>b</sup>               |
| Past high-risk use of other opioids than tramadol                               | 32 (17.1%)                                 | 4 (8.2%)                              | 28 (21.7%) <sup>***</sup>             |
| Hospitalisation for withdrawal  | 24 (12.8%)                                 | 5 (10.2%)                             | 19 (14.7%)                            |
| Tramadol substitution by buprenorphine or methadone                             | 21 (11.2%)                                 | 4 (8.2%)                              | 17 (13.2%)                            |

Chi<sup>2</sup> (or Fisher's exact) tests and t-test for comparison of qualitative or quantitative characteristics, respectively.

<sup>b</sup>Doctor shopping, stolen treatment, deal, gift, and internet.

<sup>a</sup>Including nine reports of tramadol intoxications with suicidal ideation or attempt: for 4 young individuals (16,18,19, and 28 years), an addiction to tramadol and to other psychoactive substances was described.

\*P < .05. \*\*P < .001. \*\*\*P < .0001.

high (around 80%) (Table 2). Tramadol abuse was frequently reported, with seizures in a similar proportion in the profile of patients treated for pain and in those with non-medical use (Table 2).

## 4 | DISCUSSION

The synthesis of addictovigilance data on tramadol for 2013–2018 highlights that high-risk tramadol use is on the rise in France, despite tramadol exposure plateauing among the population. Tramadol was the primary opioid analgesic involved in deaths of patients treated for pain (DTA programme) each year. The proportion of tramadol reports almost doubled in all other data sources. This analysis also exhibits two main profiles of tramadol users: (i) in the context of pain treatment and (ii) for non-medical psychoactive use. Whereas the two profiles of individuals presented distinct demographic characteristics, high-risk tramadol uses were similar: dependence and addiction

(withdrawal symptoms and craving) and abuse (with seizures and deaths as adverse consequences).

Compared to the 2009–2013 synthesis,<sup>17</sup> high-risk tramadol use has steadily increased, particularly for non-medical use. The reports highlighted the leading role of psychological symptoms of withdrawal and craving for tramadol in its persistent use. The durations of tramadol use were long, as reported in a recent US cohort study.<sup>29</sup>

An increase in the proportion of forged prescriptions mentioning tramadol alone (OSIAP) and tramadol alone users seen in addiction specialised centres (OPPIDUM) was observed between 2013 and 2018. Tramadol alone medicines contain higher dosages than tramadol associated with paracetamol and so are more attractive for psychoactive effects.

Reports of high-risk tramadol use to the French Addictovigilance Network added data to the literature by providing in-depth details on the tramadol effects sought after by the users that were mostly anxiolysis, sedation, as a stimulant and to be high.

Mixed opioid and stimulant effects of tramadol have been evidenced in clinical studies.<sup>10</sup> However, very little data on the positive psychological effects of tramadol issued from self-declarations of non-medical users exist in the literature. Two studies reported non-medical tramadol use to improve functioning ('to give energy, stay awake').<sup>30,31</sup> A single case report also described the stimulant/antidepressant-like effect with a binge pattern of tramadol use.<sup>32</sup> Due to the polymorphism of CYP2D6 producing the active opioid metabolite of tramadol, an inter-individual variability of monoaminergic and opioid effects of tramadol could occur, as for analgesic effects.<sup>8,33,34</sup> Tramadol use to get high or for psychoactive effect accounted for 1.2% of online discussions concerning tramadol coming from the UK in the RADARS System Web Monitoring Programme from 2014 to 2016.<sup>35</sup> Comments related to diversion (transfer of a prescription drug to an unlawful channel of distribution or use) accounted for 3.9% of the tramadol mentions.

This study highlights the role of tramadol use for stimulant and/or opioid psychoactive effects (well-being, euphoria, anxiolysis, hypnotic and forgetting problems) as a driving factor for primary SUD in patients treated for pain as in individuals with non-medical tramadol use. Tramadol self-medication for anxiety or depressive symptoms and use to cope with psychological problems seem to mostly concern tramadol consumption outside a pain context and without any other substance.

Tramadol withdrawal signs are often ignored by physicians. This study showed the leading role of psychological symptoms of withdrawal and craving for tramadol on its continuous use leading to a severe tramadol use disorder. Psychological effects of tramadol withdrawal were frequently represented by impaired well-being, anxiety, insomnia, irritability and depressive symptoms. Withdrawal symptoms appeared either in the context of discontinuation or dose reduction and were encountered in patients abusing tramadol and those with therapeutic doses. It has recently been suggested that an increase in withdrawal intensity during opioid treatment in chronic pain could be used to identify patients at risk of developing a prescription opioid use disorder.<sup>36,37</sup> Typical and atypical opioid signs of tramadol withdrawal have been observed.<sup>38</sup>

Interdependence between mood, opioid tolerance/dependence, and pain plays a crucial role in the difficult reversibility of dependence on opioid pain treatment.<sup>39,40</sup> Addictovigilance reports evidenced that patients first exposed to tramadol for pain relief are at risk of developing dependence on this substance (with or without tramadol use for psychoactive effects) leading to a primary SUD (or secondary SUD when they present a past high-risk use of any substance). In 41% of addictovigilance reports concerning non-medical tramadol users, initial exposure to tramadol for pain treatment was described, with a long course. The pathways of patients developing SUD after initial exposure to tramadol for pain can later lead the patients to search for care support management. Those pathways are supported by the results of the OPPIDUM survey, based on self-reporting of individuals consulting in addiction centres, where the proportion of citations of tramadol as the first substance with dependence increased 7.5-fold among all individuals with SUD from 2013 to 2018 (Figure S1 in the Supporting Information).

A recent systematic review on the abuse liability of tramadol in humans compared to other opioids highlighted that tramadol opioid positive effects were rated only with large doses of oral tramadol administered in individuals without opioid physical dependence across the 13 included studies.<sup>41</sup> A stimulant or antidepressant effect of tramadol was rated when lower doses were administered to individuals with opioid physical dependence, supporting our results obtained in the real-world context.

Deleterious consequences of high doses of tramadol, mainly represented by seizures, impaired consciousness and respiratory depression,<sup>42,43</sup> were observed in these addictovigilance data. The most frequent adverse consequences of abuse were seizures. Tramadol lowers the seizure threshold, and the risk of seizures is higher in case of a history of seizures or with co-administration of other substances, as antipsychotics.<sup>44,45</sup>

#### 4.1 | Tramadol abuse and illegal ways of procurement

The WHO recently pointed out a global increase in tramadol non-medical use and abuse.<sup>12</sup> A significant number of lower and middle-income countries in Africa and the Middle East have to face severe public health issues due to the non-medical use of tramadol. In those countries, tramadol is by far the most common opioid misused due to its unregulated prescription and availability in pharmacies and mainly on the informal market.<sup>46-49</sup>

In France, illegal ways of tramadol procurement were evidenced through addictovigilance, mainly with increased doctor shopping, pharmacy hopping and forged prescriptions. According to the analysis performed in national databases, from 2010 to 2016, tramadol was one of the few opioids for which both the quantity and the proportion obtained by doctor shopping increased.<sup>50,51</sup>

#### 4.2 | Tramadol-related fatalities according to the profiles of the users

The higher rate of fatalities with tramadol than other opioid analgesics in the context of medical treatment (according to the DTA record system) could be explained as tramadol still represented the most common opioid analgesic used in France.<sup>52</sup>

There are very few published studies on unintentional poisoning, which is more frequent in drug abusers than in non-abusers. In Finland, by combining a nationwide post-mortem toxicology database and the register on reimbursed prescription medicines, fatal poisoning with tramadol was significantly higher in case of non-medical use (procurement without a prescription) and in the same range as for oxydone between 2011 and 2013.<sup>53</sup>

Tramadol overdose is associated with respiratory depression.<sup>42</sup> Fatalities due to cardiopulmonary arrest have been observed in cases of suicide with very high doses of tramadol (5–8 g) without any co-ingestion.<sup>54</sup> A review of case reports has indicated that the risk of

fatal overdose increases further when tramadol is abused concurrently with alcohol or other CNS depressants, including other opioids.<sup>55</sup>

In England and Wales, the increase of tramadol-related deaths has previously occurred within increased medical prescribing.<sup>56</sup> However, tramadol-related deaths increased between 2015 and 2017 in the US, in the context of a slight decrease of tramadol prescriptions between 2016 and 2017 when tramadol was the second most prescribed opioid in 2017.<sup>57,58</sup>

### 4.3 | Limitations and strengths

This study has some limitations. Compared to tramadol exposure, the number of reports is low with under-reporting bias.<sup>59</sup> Other biases can also be found, specific for each of the other record systems: (1) in OSIAP, the reporting of forged prescriptions by community pharmacists is voluntary, and their increasing number reported each year may be explained by an increase in forged prescriptions or an increase in the pharmacists' vigilance; (2) in OPPIDUM, drug use and way of procurement are self-reported by the patients; and (3) DRAMES and DTA record only the deaths with medico-legally analysis with substance dosages performed by analytical toxicology laboratories and the reporting is voluntary. Therefore, there is an under-reporting bias.

While the annual evolution of the recorded number of tramadol cases depends on the number of declarants, this influence should have concerned all high-risk substances. In the present study, we observed an upward trend in the proportion of tramadol reports among all the reported cases for spontaneous reporting, as well as for the OSIAP, OPPIDUM, DRAMES and DTA programmes. However, a notoriety bias for tramadol cannot be excluded that could have increased tramadol reports by spontaneous declarants as in DRAMES and DTA programmes. Despite the biases specific to each of these recording systems, the limitation of under-reporting of high-risk substance use and the underestimation of the tramadol high-risk cases and deaths, the strength of this study is a result of the triangulation of the data issued from distinct sources characterised by independent biases. For tramadol, the results from all these tools converge towards the same conclusion for the studied period 2013–2018. Therefore, the main strength of this study is the multisource approach provided by the French addictovigilance system, with real-world data. Mandatory spontaneous reporting has been implemented for many years in France, and all other population-based surveys and national programmes have been widely used to investigate high-risk substance use in the past.<sup>60–63</sup>

### 4.4 | Impact of the findings on policy-making

The leading role of multimodal, proactive vigilance with complementary tools to investigate high-risk substance use has been highlighted recently for post-marketing surveillance and proved its usefulness for rapid and adapted public health responses in some countries, such as the US.<sup>14,64,65</sup> The results of tramadol addictovigilance analysis prompted the French National Agency for Medicines (ANSM) to adapt

public health messages and address recommendations to health professionals and patients. These recommendations aimed to improve tramadol-appropriate clinical use, to inform on the risks of tramadol overdosing and on the necessity of gradually tapering at the end of the treatment.<sup>66</sup> Moreover, the maximal duration of tramadol prescription was limited to 3 months by French law in April 2020.<sup>67</sup> A Direct Healthcare Professional Communication addressed in January 2021 to the prescribers and pharmacists explained this regulation change. It could be expected that health professionals would be more aware of tramadol use disorders and their modalities of care.

## 5 | CONCLUSION

This addictovigilance analysis evidenced a recent increase in high-risk tramadol use with severe tramadol use disorders and deaths driven by its psychoactive effects used to fight withdrawal symptoms, self-medication for anxiety or depressive symptoms, or enhancement purposes in France. The expected impact of the recent national public health measures will be a decrease in the proportion of high-risk tramadol uses and the harmful consequences, particularly among individuals who start tramadol use for pain relief.

### ACKNOWLEDGEMENTS

We acknowledge all the participants in the addictovigilance monitoring system, in particular: the pharmacists (OSIAP programme), staff in specialised addiction care centres and harm reduction centres (OPPIDUM survey), analytical toxicology laboratories, and hospital departments of forensic medicine (DRAMES and DTA programmes).

The French Addictovigilance Network is funded annually by the Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM. The writing of this article was done in a public academic context, without specific financial support.

### COMPETING INTERESTS

The authors report no conflict of interests.

### CONTRIBUTORS

A.R. was responsible for the study conception. A.R., E.J., E.F., N.F., M.M., J.M. and M.L.M. contributed to the annual national tramadol Addictovigilance report. A.R. performed the multisource data analysis and interpretation. T.S. and C.F. analysed tramadol case reports. E.J. and M.L.M., E.F. and J.M., and M.M. and N.F. analysed the tramadol data of the OSIAP programme, OPPIDUM survey, and DRAMES and DTA programmes, respectively. A.R. and M.L.M. were responsible for the drafting of the manuscript. All authors reviewed and approved the final version of the manuscript.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## ORCID

Anne Roussin  <https://orcid.org/0000-0003-4541-3725>

Thomas Soeiro  <https://orcid.org/0000-0003-2604-9673>

Emilie Jouanjus  <https://orcid.org/0000-0002-3510-2475>

Joëlle Micallef  <https://orcid.org/0000-0002-7172-7835>

Maryse Lapeyre-Mestre  <https://orcid.org/0000-0002-5494-5873>

## REFERENCES

- European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Addressing the misuse of medicines. [https://www.emcdda.europa.eu/best-practice/briefings/addressing-misuse-medicines\\_en](https://www.emcdda.europa.eu/best-practice/briefings/addressing-misuse-medicines_en). Accessed February, 25, 2022.
- Cremers S, Wright DFB. Nonmedical use of prescription drugs. *Br J Clin Pharmacol*. 2021;87(4):1635-1636. doi:10.1111/bcp.14797
- Casati A, Sedefov R, Pfeiffer-Gerschel T. Misuse of medicines in the European Union: a systematic review of the literature. *Eur Addict Res*. 2012;18(5):228-245. doi:10.1159/000337028
- Rossow I, Bramness JG. The total sale of prescription drugs with an abuse potential predicts the number of excessive users: a national prescription database study. *BMC Public Health*. 2015;15(1):288. doi:10.1186/s12889-015-1615-7
- Roussin A, Palmaro A, Lapeyre-Mestre M. Weak opioid analgesics abuse and addiction: a comparison of pharmacology and pharmacoepidemiology of codeine, dihydrocodeine and tramadol. In: Preedy VR, ed. *Neuropathology of Drug Addictions and Substance Misuse*. London: Academic Press; 2016:375-391.
- Rickli A, Liakoni E, Hoener MC, Liechi ME. Opioid-induced inhibition of the human 5-HT and noradrenaline transporters in vitro: link to clinical reports of serotonin syndrome. *Br J Pharmacol*. 2018;175(3):532-543. doi:10.1111/bph.14105
- Gillen C, Haurand M, Kobelt DJ, Wnendt S. Affinity, potency and efficacy of tramadol and its metabolites at the cloned human mu-opioid receptor. *Naunyn Schmiedeberg's Arch Pharmacol*. 2000;362(2):116-121. doi:10.1007/s00210000266
- Zacny JP. Profiling the subjective, psychomotor, and physiological effects of tramadol in recreational drug users. *Drug Alcohol Depend*. 2005;80(2):273-278. doi:10.1016/j.drugalcdep.2005.05.007
- Babalonis S, Lofwall MR, Nuzzo PA, Siegel AJ, Walsh SL. Abuse liability and reinforcing efficacy of oral tramadol in humans. *Drug Alcohol Depend*. 2013;129(1-2):116-124. doi:10.1016/j.drugalcdep.2012.09.018
- Duke AN, Bigelow GE, Lanier RK, Strain EC. Discriminative stimulus effects of tramadol in humans. *J Pharmacol Exp Ther*. 2011;338(1):255-262. doi:10.1124/jpet.111.181131
- Asari Y, Ikeda Y, Tateno A, Okubo Y, Iijima T, Suzuki H. Acute tramadol enhances brain activity associated with reward anticipation in the nucleus accumbens. *Psychopharmacology (Berl)*. 2018;235(9):2631-2642. doi:10.1007/s00213-018-4955-z
- World Health Organization (WHO). Critical Review Report: Tramadol. Expert Committee on Drug Dependence Forty-first Meeting. Geneva, 12-16 November 2018. <https://www.who.int/medicines/access/controlled-substances/Tramadol.pdf?ua=1>. Accessed February, 25, 2022.
- United Nations World Drug Report 2018. New York, NY: United Nations Publication; 2018. <https://www.unodc.org/wdr2018/>. Accessed February, 25, 2022.
- Dart RC, Iwanicki JL, Black JC, Olsen HA, Severtson SG. Measuring prescription opioid misuse and its consequences. *Br J Clin Pharmacol*. 2021;87(4):1647-1653. doi:10.1111/bcp.14791
- Iwanicki JL, Schwarz J, May KP, Black JC, Dart RC. Tramadol non-medical use in Four European countries: a comparative analysis. *Drug Alcohol Depend*. 2020;217:108367. doi:10.1016/j.drugalcdep.2020.108367
- Layne KA, Dargan PI, Dines AM, et al. Acute toxicity related to misuse (nonmedical use) of tramadol: experience of the European Drug Emergencies Network Plus. *Br J Clin Pharmacol*. 2021;87(4):1668-1675. doi:10.1111/bcp.14408
- Roussin A, Doazan-d'Ouince O, Géniaux H, Halberer C, French Network of Centre for Evaluation and Information on Pharmacodependence (Addictovigilance Centres). Evaluation of abuse and dependence in addiction monitoring systems: tramadol as an example. *Thérapie*. 2015;70(2):203-221. doi:10.2515/therapie/2015014
- Jouanjus E, Gibaja V, Kahn JP, Haramburu F, Daveluy A. Signal identification in addictovigilance: the functioning of the French system. *Thérapie*. 2015;70(2):113-131. doi:10.2515/therapie/2015011
- Journal Officiel de la République Française (French Republic Official Journal). Décret n° 2019-1306 du 6 décembre 2019 sur les vigilances relatives aux produits de santé et les événements indésirables associés aux soins (Decree on health products and care adverse events-related vigilances). <https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000039457239&categorieLien=id/> Accessed February, 25, 2022.
- 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):528-530. doi:10.1093/ijnp/pyz033
- Jouanjus E, Guernec G, Lapeyre-Mestre M, French Addictovigilance Network. Medical prescriptions falsified by the patients: a 12-year national monitoring to assess prescription drug diversion. *Fundam Clin Pharmacol*. 2018;32(3):306-322. doi:10.1111/fcp.12356
- Frauger E, Moracchini C, Le Boisselier R, et al. OPPIDUM surveillance program: 20 years of information on drug abuse in France. *Fundam Clin Pharmacol*. 2013;27(6):672-682. doi:10.1111/fcp.12024
- Frauger E, Pochard L, Boucherie Q, et al. Surveillance system on drug abuse: interest of the French national OPPIDUM program of French addictovigilance network. *Thérapie*. 2017;72(4):491-501. doi:10.1016/j.therap.2017.01.010
- Micallef J, Mallaret M. Twenty-five years of the French Addictovigilance Network (FAN). *Thérapie*. 2016;71(4):375-378. doi:10.1016/j.therap.2016.05.001
- Moulis G, Lapeyre-Mestre M, Palmaro A, Pugnet G, Montastruc JL, Sailler L. French health insurance databases: what interest for medical research? *Rev Med Interne*. 2015;36(6):411-417. doi:10.1016/j.revmed.2014.11.009
- Commission Nationale Informatique et Libertés (CNIL). Référentiel relatif aux traitements de données à caractère personnel mis en œuvre à des fins de gestion des vigilances sanitaires. 2019. [https://www.cnil.fr/sites/default/files/atoms/files/referentiel\\_vigilances\\_sanitaires.pdf](https://www.cnil.fr/sites/default/files/atoms/files/referentiel_vigilances_sanitaires.pdf). Accessed February, 25, 2022.
- Alexander SP, Christopoulos A, Davenport AP, et al. The Concise Guide to PHARMACOLOGY 2021/22: G protein-coupled receptors. *Br J Pharmacol*. 2021;178(Suppl 1):S27-S156.
- Alexander SP, Kelly E, Mathie A, et al. The Concise Guide to PHARMACOLOGY 2021/22: Transporters. *Br J Pharmacol*. 2021;178(Suppl 1):S412-S513. doi:10.1111/bph.15540
- Thiels CA, Habermann EB, Hooten WM, Jeffery MM. Chronic use of tramadol after acute pain episode: cohort study. *BMJ*. 2019;365:l1849. doi:10.1136/bmj.l1849
- AbdelWahab MA, Abou El Magd SF, Grella CE, Enaba DA, Abdel Maqsood R. An examination of motives for tramadol and heroin use in an Egyptian sample. *J Addict Dis*. 2018;37(3-4):123-134. doi:10.1080/10550887.2019.1623650
- Peprah P, Agyemang-Duah W, Appiah-Brempong E, Akwasi AG, Morgan AK. "With tramadol, I ride like a Jaguar": a qualitative study of motivations for non-medical purpose tramadol use among

- commercial vehicle operators in Kumasi, Ghana. *Subst Abuse Treat Prev Policy*. 2020;15(1):49. doi:10.1186/s13011-020-00292-4
32. Ferrari A, Tiraferri I, Palazzoli F, Licata M. Tramadol abuse in a binge pattern in a young depressed woman. *Eur Addict Res*. 2014;20(2):82-86. doi:10.1159/000353971
  33. Poulsen L, Arendt-Nielsen L, Brøsen K, Sindrup SH. The hypoalgesic effect of tramadol in relation to CYP2D6. *Clin Pharmacol Ther*. 1996;60(6):636-644. doi:10.1016/S0009-9236(96)90211-8
  34. Enggaard TP, Poulsen L, Arendt-Nielsen L, Brøsen K, Ossig J, Sindrup SH. The analgesic effect of tramadol after intravenous injection in healthy volunteers in relation to CYP2D6. *Anesth Analg*. 2006;102(1):146-150. doi:10.1213/01.ane.0000189613.61910.32
  35. Hockenull J, Black JC, Bletz A, et al. An evaluation of online discussion relating to nonmedical use of prescription opioids within the UK. *Br J Clin Pharmacol*. 2021;87(4):1637-1646. doi:10.1111/bcp.14603
  36. Coloma-Carmona A, Carballo JL, Rodríguez-Marín J, van-der Hofstadt CJ. The Adjective Rating Scale for Withdrawal: validation of its ability to assess severity of prescription opioid misuse. *Eur J Pain*. 2019;23(2):307-315. doi:10.1002/ejp.1305
  37. Coloma-Carmona A, Carballo JL, Rodríguez-Marín J, Pérez-Carbonell A. Withdrawal symptoms predict prescription opioid dependence in chronic pain patients. *Drug Alcohol Depend*. 2019;195:27-32. doi:10.1016/j.drugalcdep.2018.11.013
  38. Senay EC, Adams EH, Geller A, et al. Physical dependence on Ultram (tramadol hydrochloride): both opioid-like and atypical withdrawal symptoms occur. *Drug Alcohol Depend*. 2003;69(3):233-241. doi:10.1016/S0376-8716(02)00321-6
  39. Ballantyne JC, Sullivan MD, Kolodny A. Opioid dependence vs addiction: a distinction without a difference? *Arch Intern Med*. 2012;172(17):1342-1343. doi:10.1001/archinternmed.2012.3212
  40. Ballantyne JC. Assessing the prevalence of opioid misuse, abuse, and addiction in chronic pain. *Pain*. 2015;156(4):567-568. doi:10.1097/j.pain.000000000000105
  41. Dunn KE, Bergeria CL, Huhn AS, Strain EC. A systematic review of laboratory evidence for the abuse potential of tramadol in humans. *Front Psych*. 2019;10:704. doi:10.3389/fpsy.2019.00704
  42. Ryan N, Isbister GK. Tramadol overdose causes seizures and respiratory depression but serotonin toxicity appears unlikely. *Clin Toxicol (Phila)*. 2015;53(6):545-550. doi:10.3109/15563650.2015.1036279
  43. Habibollahi P, Garjani A, Shams Vahdati S, Sadat-Ebrahimi SR, Parnianfard N. Severe complications of tramadol overdose in Iran. *Epidemiol Health*. 2019;41:e2019026. doi:10.4178/epih.e2019026
  44. Miotto K, Cho AK, Khalil MA, Blanco K, Sasaki JD, Rawson R. Trends in tramadol: pharmacology, metabolism, and misuse. *Anesth Analg*. 2017;124(1):44-51. doi:10.1213/ANE.0000000000001683
  45. Babahajian A, Khomand P, Manouchehri F, et al. Seizure prevalence and its related factors in tramadol intoxication; a brief report. *Arch Acad Emerg Med*. 2019;7(1):e28.
  46. Salm-Reifferscheidt L. Tramadol: Africa's opioid crisis. *Lancet*. 2018;39(10134):1982-1983. doi:10.1016/S0140-6736(18)31073-0
  47. International Narcotic Control Board. Tramadol, review of the global situation. 2018. [http://www.incb.org/documents/News/Alerts/Alert7\\_on\\_Control\\_of\\_Psychotropic\\_Substances\\_June\\_2018.pdf](http://www.incb.org/documents/News/Alerts/Alert7_on_Control_of_Psychotropic_Substances_June_2018.pdf). Accessed February, 25, 2022.
  48. United Nation Office on Drugs and Crime (UNODC). World drug report 2019. [https://wdr.unodc.org/wdr2019/prelaunch/WDR19\\_Booklet\\_1\\_EXECUTIVE\\_SUMMARY.pdf](https://wdr.unodc.org/wdr2019/prelaunch/WDR19_Booklet_1_EXECUTIVE_SUMMARY.pdf). Accessed February, 25, 2022.
  49. Klein A, Patwardhan S, Loglo MGA. Divergences and commonalities between the US opioid crisis and prescription medicine mis/use in West Africa. *Int J Drug Policy*. 2020;76:102640. doi:10.1016/j.drugpo.2019.102640
  50. Ponté C, Lepelley M, Boucherie Q, et al. Doctor shopping of opioid analgesics relative to benzodiazepines: a pharmacoepidemiological study among 11.7 million inhabitants in the French countries. *Drug Alcohol Depend*. 2018;187:88-94. doi:10.1016/j.drugalcdep.2018.01.036
  51. Soeiro T, Lacroix C, Pradel V, Lapeyre-Mestre M, Micallef J. Early detection of prescription drug abuse using doctor shopping monitoring from claims databases: illustration from the experience of the French Addictovigilance Network. *Front Psych*. 2021;12:640120. doi:10.3389/fpsy.2021.640120
  52. Daveluy A, Micallef J, Sanchez-Pena P, et al. Ten-year trend of opioid and nonopioid analgesic use in the French adult population. *Br J Clin Pharmacol*. 2021;87(2):555-564. doi:10.1111/bcp.14415
  53. Haukka J, Kriikku P, Mariottini C, Partonen T, Ojanperä I. Non-medical use of psychoactive prescription drugs is associated with fatal poisoning. *Addiction*. 2018;113(3):464-472. doi:10.1111/add.14014
  54. Shadnia S, Soltaninejad K, Heydari K, Sasanian G, Abdollahi M. Tramadol intoxication: a review of 114 cases. *Hum Exp Toxicol*. 2008;27(3):201-205. doi:10.1177/0960327108090270
  55. Food and Drug Administration (FDA). "Full prescribing information-Ultram®". 2008. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2009/020281s032s033lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020281s032s033lbl.pdf). Accessed February, 25, 2022.
  56. Handley SA, Flanagan RJ. Drugs and other chemicals involved in fatal poisoning in England and Wales during 2000-2011. *Clin Toxicol (Phila)*. 2014;52(1):1-12. doi:10.3109/15563650.2013.872791
  57. Drug Enforcement Administration. Tramadol. 2018. [https://www.deadiversion.usdoj.gov/drug\\_chem\\_info/tramadol.pdf](https://www.deadiversion.usdoj.gov/drug_chem_info/tramadol.pdf). Accessed February, 25, 2022.
  58. Zebala JA, Schuler AD, Kahn SJ, Maeda DY. Desmetramadol is identified as a G-protein biased  $\mu$  opioid receptor agonist. *Front Pharmacol*. 2020;10:1680. doi:10.3389/fphar.2019.01680
  59. 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):733-741. doi:10.1002/pds.3280
  60. Victorri-Vigneau C, Dailly E, Veyrac G, Jolliet P. Evidence of zolpidem abuse and dependence: results of the French Centre for Evaluation and Information on Pharmacodependence (CEIP) network survey. *Br J Clin Pharmacol*. 2007;64(2):198-209. doi:10.1111/j.1365-2125.2007.02861.x
  61. Ponté C, Pi C, Palmaro A, Jouanjus E, Lapeyre-Mestre M, French Addictovigilance Network. Early signal of diverted use of tropicamide eye drops in France. *Br J Clin Pharmacol*. 2017;83(8):1791-1800. doi:10.1111/bcp.13272
  62. Eiden C, Vincent M, Serrand C, et al. Health consequences of cocaine use in France: data from the French Addictovigilance Network. *Fundam Clin Pharmacol*. 2021;35(2):455-465. doi:10.1111/fcp.12603
  63. Tambon M, Ponté C, Jouanjus E, et al. Gabapentinoid abuse in France: evidence on health consequences and new points of vigilance. *Front Psych*. 2021;12:639780. doi:10.3389/fpsy.2021.639780
  64. Schifano F, Papanti GD, Orsolini L, Corkery JM. The consequences of drug misuse on post-marketing surveillance. *Expert Rev Clin Pharmacol*. 2016;9(7):867-871. doi:10.1080/17512433.2016.1178571
  65. Throckmorton DC, Gottlieb S, Woodcock J. The FDA and the next wave of drug abuse—proactive pharmacovigilance. *N Engl J Med*. 2018;379(3):205-207. doi:10.1056/NEJMp1806486
  66. French National Agency for Medicines and Health Product Safety (ANSM). 2020. Tramadol: a measure to decrease misuse in France. <https://ansm.sante.fr/actualites/tramadol-une-mesure-pour-limiter-le-mesusage-en-france>. Accessed February, 25, 2022.



67. Journal Officiel de la République Française (French Republic Official Journal). JORF n°0013. Arrêté du 13 janvier 2020 fixant la durée de prescription des médicaments à base de tramadol administrés par voie orale (Decree on oral tramadol medicines duration of prescription). <https://www.legifrance.gouv.fr/eli/arrete/2020/1/13/SSAP2000655A/jo/texte>. Accessed February, 25, 2022.

#### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Roussin A, Soeiro T, Fouque C, et al. Increase of high-risk tramadol use and harmful consequences in France from 2013 to 2018: Evidence from the triangulation of addictovigilance data. *Br J Clin Pharmacol.* 2022;88(8): 3789-3802. doi:[10.1111/bcp.15323](https://doi.org/10.1111/bcp.15323)