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Evaluation of Abuse and Dependence in Addiction Monitoring Systems: Tramadol as an example

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Abstract – The objective of this paper is to present an evaluation of the potential for abuse of and dependence on a drug from the data obtained from the different pharmacoepidemiological tools used by the French network for evaluation and information on pharmacodependence and addiction monitoring taking the example of tramadol. Comparison of the data from spontaneous reports with surveys in specific populations and with evaluations of indicators of diverted uses does not highlight a major problem of tramadol abuse and dependence in terms of public health, but stresses the importance of paying attention to the signal. This example of addiction monitoring of tramadol illustrates the interest of comparing results obtained from different validated sources. The implementation of repeated observational programs of abuse of and dependence on psychoactive drugs is an important aid to health authorities to define the content of the information to be delivered or regulatory decisions to reduce these problematic uses.

Abbreviations: see end of article.

1. Introduction

On account of their pharmacological characteristics, certain psychoactive substances have a potential for abuse (excessive, harmful use) and/or pharmacodependence (physical dependency evidenced by withdrawal symptoms on discontinuation, and also psychological and behavioral dependence (also named addiction). In the different stages of development of a new drug containing a psychoactive substance, determining its potential for abuse and dependence entails the confrontation of pharmacodynamic and pharmacokinetic data on the substance (*in vitro* and in animals) with clinical data (clinical trials). However this determination may be difficult, for instance when the characteristics of individual metabolisms can mean inter-individual variability of the pharmacological effects. In addition, the determination of abuse and dependence in clinical trials is subject to certain limitations, related in particular to patient selection bias (for instance subjects who are not representative of the population liable to present drug abuse or dependence), or else to insufficient numbers of exposed subjects when the potential for abuse and dependence is low. It is therefore necessary in such cases to implement surveillance of abuse and dependency in the general population once the drug is on the market. In France, the Centres of Evaluation and Information on Pharmacodependence-Addictovigilance (*Centres d'Évaluation et d'Information sur la Pharmacodépendance – Addictovigilance*, CEIP-A), the addiction monitoring network, takes on this

surveillance, implementing two approaches.[1] The first consists in collecting and analysing spontaneous notifications of cases of abuse and dependence. The second consists in conducting specific pharmaco-epidemiological surveys. Thus, by confronting all the data obtained via these two approaches, the expertise of the CEIP-A network enables the identification of emergent signals for abuse and/or dependence towards a psychoactive substance.

In order to illustrate the conduct of CEIP-A evaluations of abuse and dependency towards a psychoactive substance, this article presents recent data on tramadol, derived from different addiction monitoring tools.

Tramadol has been on the market in France since 1997 as a pain-killer for moderate to severe pain. Its desired and undesirable effects are linked to an agonist effect on mu opioid receptors (since its metabolite O-desmethyl-tramadol has much greater affinity than the parent molecule for receptor) and also to the inhibition of serotonin and noradrenaline reuptake.[2] This dual mechanism increases the risk of the appearance of undesirable side-effects, especially in case of excessive doses, and it raises the question of its potential for abuse and dependency which differs from that for other opioid substances.[3,4] Thus, while tramadol is classified among the mild opioid painkillers, it is an atypical opioid, and merely knowing its pharmacological mechanisms of action is not enough to assess its potential for abuse and dependence in real-life situations. In 2003, the World Health Organsiation (WHO) expert Committee on pharmacodependence indicated that the information available on tramadol abuse and dependency was insufficient to recommend international control of the drug, but that the information did warrant its continued surveillance. The Committee specified that from data obtained by the USA surveillance network, it could be thought that the potential for abuse of tramadol was comparable to that of codeine or dextropropoxyphene in that country.[5] In 2006 the same Committee considered that despite the considerable increase in the use of tramadol, the data was in favour of a fairly low potential for abuse of this substance.[6] It was subsequently, in the context of the recommendation by the European Medicines Agency (EMA) date June 25th 2009 concerning the market withdrawal of the association paracetamol-dextropropyphene in Europe, that the French drugs security agency (*Agence Française de Sécurité Sanitaire des Produits de Santé* [Afssaps], now *Agence Nationale de Sécurité du Médicament et des produits de santé* [ANSM]) asked the CEIP-A network to perform a yearly addiction monitoring procedure for tramadol. A transfer of the prescriptions of specialities containing dextropropoxyphene towards other fairly mild opioid pain-killers was indeed envisaged. The Toulouse CEIP-A was entrusted with the annual monitoring procedure for tramadol in France from 2010. *Via* the example of tramadol, this article sets out to present the complementary nature of the information provided by the different tools used in France for the determination of the abuse and dependence potential of a drug, and to provide an overview of problematic uses on the scale of the country as a whole.

2. Data on the evolution of abuse of and dependence on tramadol derived from the tools of the CEIP-A network

2.1. Spontaneous notifications of cases of abuse of and dependence on tramadol since 2009

One of the tools used by the CEIP-A network to assess the potential for abuse and dependence is the collection and analysis of serious cases of abuse and pharmacodependence, which in the terms of article R.5132-99 in the *Code de la Santé publique* must be notified to their local CEIP-A by any health professional, in similar manner to reporting in the area of pharmacovigilance.[1] These notifications make no mention of the name of the person exhibiting problematic use of a psychoactive substance. A refined analysis of these spontaneous notifications enables information on socio-demographic and clinical profiles to be gathered, information that is particularly useful in understanding phenomena of abuse and dependence.

Although the number of cases of tramadol abuse and dependency has increased constantly over recent years, it is only a small fraction of abuse and dependency notifications overall (2.4% in 2013 [80/3280]). Between 2012 and 2013 the rate increased by 2.9%, but this increase did not exceed the increase in sales of pharmaceuticals containing tramadol, alone or in association with paracetamol, (5.9% between 2012 and 2013 according to ANSM).

The reports of abuse concerned tramadol both alone and in association with paracetamol (an association mentioned in 37% of the reports in 2012 and 20% in 2013). When known, the duration of tramadol use is prolonged. Thus in 2013 in around a quarter of the cases the duration of use of daily doses exceeded two years. Pain treatment accounts for the initiation of tramadol use for 30 to 50% of cases, depending on the year considered. However the persistence of usage appears to be frequently linked to the fear of experiencing withdrawal symptoms, or to a desire to experience the psychoactive effects of tramadol other than pain relief. Although it is not possible to distinguish between these different reasons, knowing how the drug was obtained makes it possible to know whether or not the use of the substance was under medical supervision. Thus the proportion of people engaging in "doctor shopping" and/or pharmaceutical nomadism to obtain tramadol concerned around one third of reports in 2011 and 18% in 2013. In addition, three cases of purchase of tramadol on a website were reported in 2012 and 2013.

Since the first monitoring survey of tramadol in France in 2010, three motives for notifications of problematic use of tramadol have been reported: i) signs of withdrawal syndrome at therapeutic doses or doses above the maximum recommended dose (400 mg/d), ii) misuse of tramadol for purposes other than pain relief in a medical setting, and iii) tramadol abuse. Information is sometimes lacking to enable concluding on one of these three types of problematic use. Likewise, patients can present more than one type.

2.1.1. Withdrawal symptoms in individuals dependent on tramadol

Since the first survey, the proportion of notifications mentioning withdrawal symptoms has ranged from 15 to 36%. In the notifications that do not report signs of withdrawal, it is often specified that the person was reluctant to discontinue the treatment. Cases of withdrawal reported in 2013 amount to around 20% of the notifications, and involve patients who, for about half, were taking tramadol at a therapeutic dose. Signs of withdrawal were noted when the treatment was discontinued or the dose reduced. Psychic withdrawal signs (impaired well-being, depression, anxiety, insomnia, craving, irritability) were frequently encountered. These signs were moreover often the reason why people continue to take tramadol.

2.1.2. Diversion of tramadol for purposes other than the management of pain in a medical setting

Here the proportion of subjects concerned increased markedly in notifications, from 12% in 2010 to 37% in 2011, thereafter stabilising around 30% in 2012 and 2013. The effects sought were stimulant, anxiolytic, hypnotic, or euphoric, improved well-being, forgetting problems, compensating for lack of strong opioids, or in one instance the desire for a dissociative effect. For half the cases in 2012 and one third in 2013 the initial use of tramadol was for pain management, and its misuse set in secondarily for the purpose of obtaining psychoactive effects. Alongside, the proportion of cases of diverted use of tramadol by users of psychoactive substance doubled between 2012 and 2013, rising from 6/22 to 13/22 notifications. Among these 13 notifications in 2013, six describe the use of tramadol in conjunction with strong opioids (including methadone and buprenorphine in substitution treatment). In one case it was noted that tramadol was used like codeine to counteract withdrawal of strong opioids.

2.1.3. Tramadol abuse

In one quarter of the notifications in 2013, the doses of tramadol taken were above the maximum recommended dose, with, in nine cases, doses over 1g/day to 6g/day. The motive of suicide attempt was explicitly concluded to in only two cases. Seven other cases of abuse were described among problematic users of psychoactive substances (medications and others) among who two died (tramadol was found at therapeutic doses in the autopsies). The other damaging consequences of the use of high doses of tramadol reported are convulsions, hallucinations, memory disturbances and headache. Harmful consequences of tramadol use on social and/or professional life are also reported.

In the yearly addiction monitoring procedures for tramadol, spontaneous notifications of abuse and dependence filed by pharmaceutical laboratories marketing drugs containing tramadol are also examined. Despite the constant increase in sales of tramadol, the number of cases reported has decreased. In 2013 only 10 cases reported from 18 laboratories were analysed, as compared to 27 in 2012.

Overall, the data on tramadol abuse and/or dependence on the basis of notifications by pharmaceutical laboratories are similar to those obtained by the CEIP-A network.

2.2. Data on tramadol abuse and dependence from results of the CEIP-A network specific tools

2.2.1. The OSIAP survey

The suspicious prescriptions suggesting possible abuse (*ordonnances suspectes, indicateur d'abus possibles*, OSIAP) survey is a data collection system enabling identification of the medications that are misused or diverted by way of falsified prescriptions presented to dispensing pharmacists. The methods and the results of this survey in France and in Europe have been widely published in the literature.[7-9]

In relation to all medications cited, the percentage of suspect prescriptions of tramadol (on its own or in association with paracetamol) increased markedly from 2007, rising from 0.65% (3/467) in 2007 to 6.5% (46/708) in 2012 and 6.82% (53/763) in 2013 (figure 1). In 2013, tramadol (on its own or with paracetamol in equal proportions) ranked seventh among the substances most frequently cited (after zolpidem [30.7%], bromazepam [10.7%], alprazolam [9.7%], zopiclone [8.9%] buprenorphine [8.4%] and the association paracetamol-codeine [7.3%]). Of the 98 prescriptions noted in 2012 and 2013 where tramadol was mentioned, 61% involved women, and the average age of patients was 46.1 ± 17.1 [18-89].

2.2.2. The OPPIDUM survey

The observatory for illegal psychotropic substances or substances diverted from their medicinal use survey (*observation des produits psychotropes illicites ou détournés de leur utilisation médicamenteuse*, OPPIDUM) is an observational programme conducted in centres specialised in catering for substance-dependent individuals. In this surveillance system that is specific to abuse and dependence towards psychoactive medications, the subjects included present pharmacodependence and/or are receiving opiate substitution treatment. They are questioned on the substances they have used in the week preceding the survey, and the mode of use. The method, and its application to the field of addiction monitoring for the purpose of responding to different issues have been widely described in the literature.[10-12]

In the OPPIDUM survey conducted in 2013, tramadol accounted for only 0.17% of the reports overall (cited 18 times by 18 individuals out of a total of 10727 reports for substances as a whole). The proportion however doubled between 2010 and 2013. Among all the medications quoted (except for buprenorphine and methadone) the proportion of reports of tramadol remained low, but

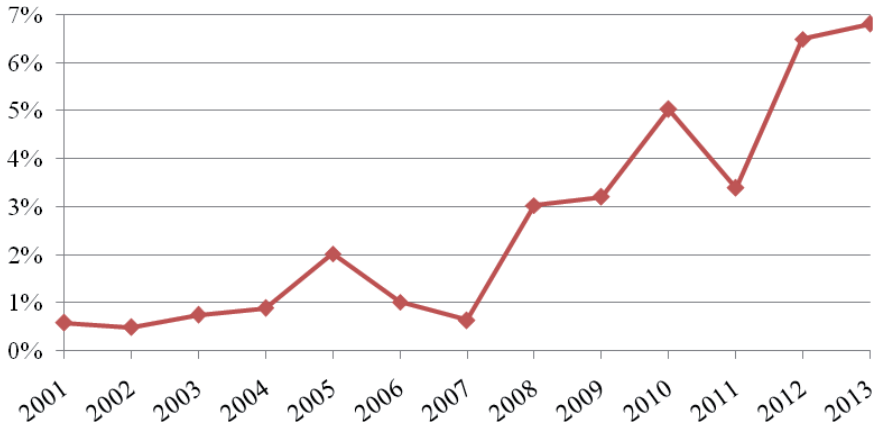

Fig. 1. Evolution of the percentage of suspect prescriptions containing tramadol between 2001 and 2013.

rose from 0.3% in 2010 (for a total of 2 757 medications) to 0.6% in 2013 (for a total of 3 210 medications).

Among tramadol users, from 2010 the proportion of men varies from 45 to 71% depending on the year considered, with an average age of between 34 and 40. All the individuals for whom tramadol was the only psychoactive substance used (more than a quarter of those included in 2013) were using it daily and exhibited signs of pharmacodependence, in the setting of therapeutic doses for the majority. Two of the ten individuals concerned in the four surveys were taking doses above the maximum recommended dose, with one case of tramadol abuse reported among these subjects taking only tramadol. Among individuals using other substances in association with tramadol, a large proportion were receiving buprenorphine or methadone treatment (half of all the subjects included in 2012 and more than a quarter in 2013).

After discontinuing tramadol, most subjects described states of distress that could evoke a withdrawal syndrome. It is not easy to know whether is was these symptoms that led to the continuation of tramadol, or whether the purpose was to obtain a particular effect. The analysis of the drug diversion indicators available in OPPIDUM complements the information collected: thus in 2013 seven of the sixteen subjects who indicated how they obtained tramadol stated they were given it or obtained it illegally (either by multiple prescription or by theft).

2.2.3. The OPEMA survey

Observatory for pharmacodependences in ambulatory medicine survey (*observation des pharmacodépendances en médecine ambulatoire*, OPEMA) is a national observation programme conducted among general practitioners practising in the community. In particular, it enables the description of socio-demographic characteristics, health state, and current use of psychoactive substances by subject followed in ambulatory medicine. The surveys in the OPEMA programme are conducted for one month every year.[13]

In relation to all the psychoactive substances reported, the percentage of reports for tramadol was around 1% in 2012 and 2013 (17 reports of tramadol for a total of 2064). The share of reports of tramadol in relation to medications overall (except for buprenorphine and methadone) rose from 1% in 2010 (for a total of 871 reports) to 3% in 2012 (out of 925 reports), and 2.3% in 2013 (of 746 reports in all).

While women taking tramadol were more numerous than men in the earlier surveys, in 2013 a majority of men was noted. From the first survey carried out in 2009, the mean age ranged from 38 to 50. In all the surveys, in the large majority of cases tramadol was used daily, and over several years. The proportion of tramadol-dependent subjects appears to be increasing (11 out of 17 cases in 2013), and, for increasing numbers, tramadol is the first psychoactive substance to be used having led to pharmacodependence. Tramadol abuse is noted in variable proportions depending on the year of survey (for a third of cases in 2013). No tramadol user included in 2013 was receiving buprenorphine or methadone treatment, and none reported using cannabis, cocaine or heroin.

When tramadol was discontinued, 40% of the subjects described states of distress that could evoke withdrawal syndrome. The effects sought by the use of tramadol that lead to its maintenance are not known, but the proportion of users outside the medical setting appears to be increasing, with 3/17 cases where it was obtained from another person or by theft in 2013.

2.2.4. The DRAMES survey

Deaths related to medication and substance abuse survey (*décès en relation avec l'abus de médicaments et de substances*, DRAMES) is a yearly survey using toxicological data analyses to collating cases of death linked to the abuse of psychoactive substances, whether or not they are medications, but excluding suicides.

Since 2007 the proportion of deaths registered in the DRAMES survey implicating tramadol (as the only substance or as

the main substance implicated in an association) ranged from 0.5% to 3.2%. Among the 39 deaths where tramadol was found in the blood at therapeutic levels or above since 2007, in 14 cases tramadol was the only substance implicated in the death. Between 2011 and 2012 the subjects concerned were mainly men aged between 20 and 57 (mean 39 years).

Deaths having occurred in France over this period among subjects abusing tramadol were not all recorded by the DRAMES survey. Certain cases published in the literature were not included (see for instance).[14,15]

2.2.5. Other sources of data for the French CEIP-A network

Among the specific tools used in the CEIP-A network, only the data obtained from spontaneous notifications enable the analysis of the characteristics of abuse and dependence in the general population. However these data do not enable the prevalence of problematic usage to be determined for the general population, on account of a high level of under-notification.[1] To attempt to estimate these prevalence rates, *ad hoc* studies can be conducted within addiction monitoring procedures. For tramadol, the Toulouse CEIP-A conducted a specific study aimed to estimate the proportion of cases of abuse, dependence and diverted uses of tramadol for purposes other than pain management among tramadol users. This descriptive, cross-sectional study was performed over two months in 2008 in 61 pharmacies where students were in work placements in their final year in the Faculty of Pharmacy, Toulouse. It was based on responses by patients to an anonymous questionnaire. Only patients who had taken tramadol in the month preceding the survey were asked to respond to questions on the way in which they took the medication, the reasons for this usage, and any undesirable effects on their health, social or professional life. Misuse of tramadol was noted when doses above the maximum recommended dose were reported for more than 10 days, or when tramadol was used for purposes other than pain management (diverted use to obtain psychoactive effects). Tramadol abuse was defined by uses involving excessive quantities, whether continuous or intermittent, with damaging consequences on health and social or professional life.[16] Finally, the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV)[17] substance-dependence criteria (tolerance, withdrawal syndrome, tramadol taken at daily doses above those recommended, continued use despite undesirable side effects) were explored *via* questions suited to the setting of the study in pharmacies. The questionnaire was proposed to all patients over 18 presenting a prescription in a pharmacy for a pharmaceutical containing tramadol, alone or in association with paracetamol. Of the 465 questionnaires issued (participation rate 79%), 257 (55%) were completed by patients who had taken a medication containing tramadol in the previous month. The mean age was 55±17 yrs [20-88], and 66% were women.

Fourteen patients who had taken tramadol for more than 10 days were using it at doses above the maximum recommended dose, either continuously or intermittently. The highest doses were 1.2 g/d daily for 3 months and 600 mg/d for two months. In addition, three patients reported using tramadol to counteract a state of fatigue or craving, or again to obtain a stimulant effect. The misuse of tramadol (according to criteria defined for this study) concerned 6.2% of the patients.

Four patients described use that was both excessive in terms of quantities, and damaging in terms of the effects experienced. Tramadol abuse thus concerned 1.6% of the subjects.

For each of the DSM-IV criteria for dependency evaluated in this study, the proportion of patients responding positively is presented in figure 2. The criteria that were most often noted were tolerance, signs of withdrawal, and use of larger doses than recommended. Each of these criteria was reported by around 30% of the patients. In addition, 13% of the patients reported having experienced undesirable effects of tramadol on their health, and their social and/or professional life, and they were still taking tramadol despite unwanted effects.

It is however relevant to wonder what was the share of the persistence of pain in the instances of misuse, abuse and signs of pharmacodependence in this study. Indeed, several authors have underlined the fact that chronic pain can lead to behaviours that are wrongly interpreted as resulting from addiction to the medication, thus leading to an overestimation of the proportion of patients classified as substance-dependent according to DSM-IV criteria.[18-20]

3. Discussion

Addiction monitoring data on tramadol illustrate the specificity and also the complementary nature of the data obtained from the various surveillance tools used in France by the CEIP-A network for abuse and dependence towards psychoactive medication. The confrontation of data, used here in the instance of tramadol, shows the value of these tools both for assessing the characteristics of medication abuse and dependence on the scale of the country as a whole, and also for measuring any evolution in phenomena over time by way of the annual follow-up.

3.1. Evolution of prevalence data for cases of tramadol abuse and dependence in France

Although numbers of reports concerning tramadol in relation to substances cited overall have increased in recent years in spontaneous notifications and CEIP-A surveys, this progression overall does not constitute a strong signal on the scale of the French population. Indeed, from data on health cost reimbursement by the insurance system and on amounts dispensed by pharmacies, ANSM determined that between 2007 and 2012, the number of tramadol and tramadol-paracetamol users increased by 47% and 67% respectively.[21] However, in relation to the other psychoactive

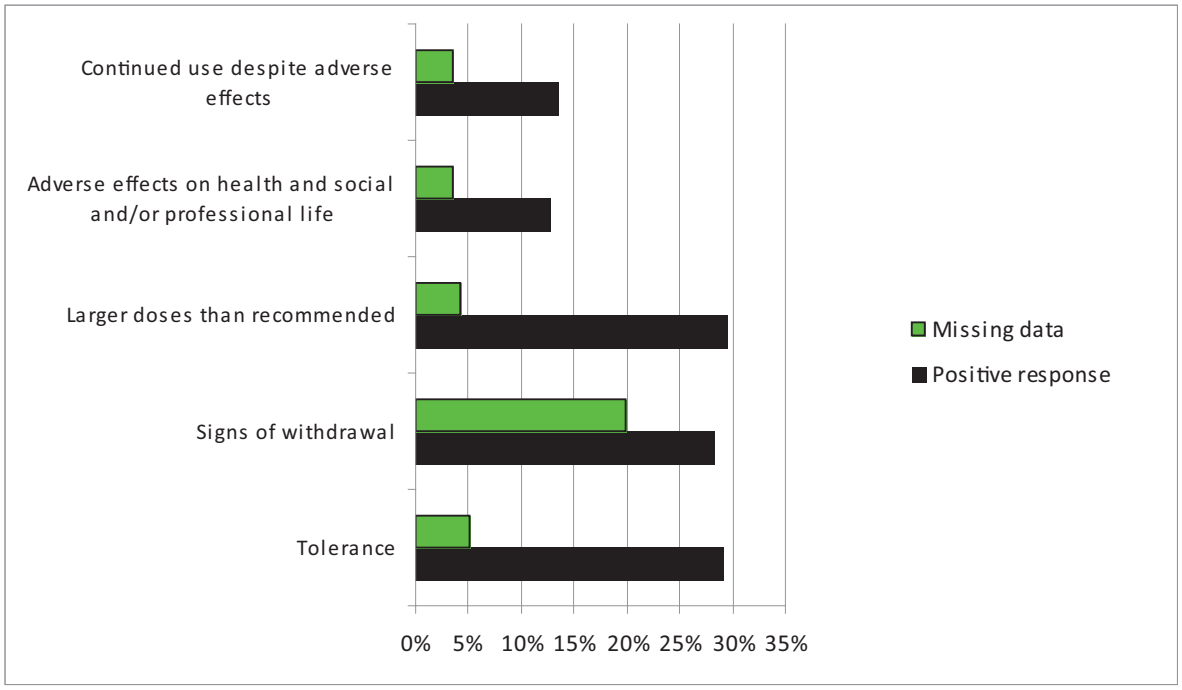

Fig. 2. Positive responses to DSM-IV criteria for dependence.
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders 4th edition.

medications involved in abuse or dependence recorded in the CEIP-A tools, the share of tramadol remains low.

3.2. Characteristics of patients presenting tramadol abuse or dependence

The analysis of spontaneous notifications and of the specific surveys by the CEIP-A network shows that problematic uses of tramadol concern both men and women. Suspect prescriptions presented in pharmacies (OSIAP) concern a majority of women, while death recorded in the DRAMES survey concern a majority of men. The mean age falls in the 37-47 age group. The data from the survey in community pharmacies show that problematic uses are also encountered among older subjects, within the setting of a medical treatment. Very few spontaneous notifications concerned under-age subjects. To our knowledge there is no published data in France in favour of an abuse and dependence signal for tramadol among adolescents. The situation appears to be different in other countries. For instance, in Iran, a survey conducted on 2 000 adolescents (mean age 16.3 yrs) showed that 4.8% had already used tramadol for purposes other than pain management.[22] Diverted use of tramadol was associated with a greater likelihood of having used other psychoactive substances (alcohol, cannabis, ecstasy, metamphetamine or opium) in the month prior to the survey. In the USA the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) system has shown that, with a frequency of 11%, tramadol ranks fifth among misused or abused medications among adolescents leading to hospitalisation between 2007 and 2009, after hydrocodone (32%), amphetamines (18%), oxycodone (15%) and methylphenidate (14%).[23]

3.3. Reasons for the diverted use of tramadol

Among the problematic uses of tramadol reported to the CEIP-A network, 27.5% concerned uses for purposes other than pain management, among which more than half the instances concerned users of other psychoactive substances. The psychoactive effects sought were stimulant, anxiolytic, hypnotic and euphoric, enhanced well-being, forgetting problems, compensating for lack of strong opioids or the desire to obtain dissociative effects. In some cases these psychoactive effects of tramadol can lead to continuing use, pharmacodependence or abuse, leading to notification, or involving patients in a follow-up for the problem in general practice or specialised centres. According to the results obtained in pharmacies, 1.2% of the subjects reported using tramadol to counteract state of fatigue or craving, or to obtain stimulant effects. The factors associated with the risk of tramadol misuse or abuse could have provided more precise information, but this could not be explored in the scope of the present study. Likewise, the existence of mental or psychiatric disturbances, or the use of psychoactive

substances alongside tramadol, would be interesting factors to explore.

3.4. Tramadol abuse and dependence among users of psychoactive substances

Tramadol abuse and dependence are noted both among individuals who were not concomitantly taking other psychoactive substances, and, to a lesser extent, among those who were. This distinction was possible by confrontation of the results of spontaneous notification with those from studies conducted among patients who were dependent or treated for an addiction, and those from the DRAMES survey. Between 2007 and 2012 tramadol was the only substance, or the substance mainly implicated in an association, in 0.5% to 3.2% of deaths recorded. This percentage seems smaller than in other countries. For example in Iran the deaths implicating tramadol increased by 32.5 between 2005 and 2008. In the majority of cases the subjects concerned were young men, with a large proportion of abusers of psychoactive substances.[24] In the UK, the number of deaths implicating tramadol rose from 83 in 2008 to 154 in 2011.[25] This information was taken into account by the Advisory Council on the Misuse of Drugs, which in 2013 recommended a reinforcement of the legislation concerning tramadol.[26] However, in the British data the share of suicides in these deaths is not know, although most of the deaths observed in the UK concerned individuals who had obtained tramadol without a medical prescription.

3.5. Tramadol withdrawal signs frequently leading to its continued use

While the French addiction monitoring data show an increase in the use of tramadol in self-medication for mental disturbances or to counteract lack of strong opioids, or for addictive reasons, the cases described mainly concern physical dependency on tramadol. The data from the pharmacy survey show that these signs are frequently described among patient treated for pain. However, the data derived from the CEIP-A tools and, in particular, from spontaneous notifications, show that early dependence on tramadol sets in in contexts of persistent use of tramadol (mainly at therapeutic doses), while the pain has gone, following failed attempts to discontinue the treatment because of withdrawal signs which are frequently psychic signs of opioid withdrawal (including craving). The durations of use are long. The resumption of use after attempts to discontinue is frequently motivated by the withdrawal signs, as a result of physical dependence. As previously observed, tramadol withdrawal syndromes are observed following discontinuation of therapeutic doses or when doses are reduced, even for short periods of exposure.[27]

The continued use of tramadol is sometimes motivated by the desire to obtain well-being, or pleasant, euphoric or stimulant effects, with or without increases in dosage.

3.6. Tramadol obtained by means other than medical prescription

One indicator of diverted use, abuse and dependence towards a medication is the determination of the rates of procurement by means other than medical prescription. With the exception of the DRAMES survey, this information is provided by each of the tools of the French CEIP-A network. Although it is not always possible to determine whether usage is linked to the existence of signs of withdrawal (on discontinuation or decrease in dose), to the desire for psychoactive effects, or to the persistence of pain that is inadequately catered for, the results show that, in a fairly large number of cases, tramadol users taking therapeutic or excessive doses sidestep the legal medical prescription requirement to obtain the substance. In 2013, in spontaneous notifications and among patients in the OPEMA survey, around one fifth obtained tramadol outside the legal framework, and this was the case for almost half of the subjects in the OPPIDUM survey. In addition, in 2013, with the proviso that the frequency of notifications needs to be set against exposure data, tramadol ranked seventh among the most frequently noted substances in suspicious prescriptions in the OSIAP survey, immediately after the codeine-paracetamol combination.

3.7. Contributions of the specific pharmacoepidemiological tools used in addiction monitoring

A synthesis of the data on tramadol abuse and dependence in France was performed on the basis of the combined analysis of spontaneous notifications and the results specifically related to tramadol derived from the CEIP-A network surveys on these themes (OSIAP, OPPIDUM, OPEMA and DRAMES). This work illustrates the value of reiterating this addiction monitoring data analysis on a yearly basis so as to follow the evolution of trends in abuse and dependence towards psychoactive substances on national level, and to determine whether the information derived constitutes a signal. In this respect, for medications, it is important to compare data on abuse and dependence with exposure data in the general population, and also in specific populations (adolescents, the elderly, psychoactive substance users etc). This is the reason why other pharmaco-epidemiological tools have been developed by the CEIP-A network, making use in particular of health cost reimbursement databases.[1] These specific methods adapted to the assessment of abuse and dependency have been used on different occasions, for instance to assess overlap of prescriptions by several physicians for a given patient.[28-29] Thus in 2008, the share of tramadol obtained by "doctor shopping" in the whole amount dispensed was 1.3% in the PACA region, 0.9% in the Rhône-Alpes region and 1% in the Midi-Pyrénées region (three administrative regions in southern France).

Internationally, different countries have developed surveillance systems for medications with abuse and dependence potential.

These are presented according to their methodologies by Nordmann *et al*. in a review published in 2011.[30] The reiteration of these surveillance programmes is particularly important to assess the impact of regulatory measures on psychoactive substance abuse and dependence. For instance, in France, the instatement of "care contracts" with patients engaging in doctor shopping for buprenorphine (as determined by health insurance reimbursement data) had a positive effect observed via a decrease in the doctor-shopping indicator.[31] The impact of the regulatory measures of 2010 and 2011 on the abuse and diversion of opioid medications was evaluated in Florida by the RADARS® system, which uses several sources.[32] Between January 2009 and September 2012 a significant drop in diverted usages was observed for oxycodone, morphine and methadone. However the rates for diversion of tramadol remained stable (as was likewise the case for fentanyl, hydromorphone and buprenorphine).

4. Conclusion

This work illustrates the usefulness of comparing results obtained from different addiction monitoring data sources for the evaluation of the abuse and dependence potential in humans of substances where the pharmacokinetic and pharmacodynamic characteristics are not enough to enable its assessment, or for estimations of the frequency of problematic uses

To date, addiction monitoring for tramadol in France does not conclude to a major public health problem of abuse and dependence. Nevertheless, the confrontation of data derived from spontaneous notifications with that from specific observation programmes developed by the CEIP-A network shows that the abuse and dependence observed for this substance have clinically significant consequences. It is therefore important to inform health professionals of the abuse and dependence potential of tramadol, so that its prescription does nor become too routine. Thus the analysis of the evolution of addiction monitoring data on a national level has practical consequences, providing assistance in decision-making on suitable measures by the health authorities.

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Conflicts of interests. None.

Abbreviations. Afssaps: *Agence Française de Sécurité Sanitaire des Produits de Santé*; ANSM: *Agence Nationale de Sécurité du Médicament et des produits de santé*; CEIP-A: Centre of Evaluation and Information on Pharmacodependance-Addictovigilance (*Centre d'Évaluation et d'Information sur la Pharmacodépendance-Addictovigilance*); DRAMES: deaths related to medication and substance abuse survey (*décès en relation avec l'abus de médicaments et de substances*); DSM-IV: Diagnostic and Statistical Manual of Mental Disorders 4th edition; EMA: European Medicines Agency; OPEMA: observatory for pharmaco-dependency in ambulatory medicine survey (*observation des pharmacodépendances en médecine ambulatoire*); OPPIDUM: observatory of illegal psychotropic substances or delivered substances diverted from their medicinal use survey (*observation des produits psychotropes illicites ou détournés de leur utilisation médicamenteuse*); OSIAP: suspicious prescriptions suggesting possible abuse (*ordonnances suspectes, indicateur d'abus possibles*); RADARS®: Research Abuse, Diversion, and Addiction-Related Surveillance.

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