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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 25$^{th}$ 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.