Thérapie 2015 Mars-Avril; 70 (2): 123–131
DOI: 10.2515/therapie/2015011

Signal Identification in Addictovigilance: the Functioning of the French System

Emilie Jouanjus[1], *Valérie Gibaja*[2], *Jean-Pierre Kahn*[2,3,4], *Françoise Haramburu*[5] *and Amélie Daveluy*[5]

1 Centre d'Addictovigilance, Service de Pharmacologie Médicale et Clinique, CHU, Faculté de Médecine, Toulouse, France
2 Centre d'Addictovigilance, Hôpital Central, CHU de Nancy, Nancy, France
3 Service de Psychiatrie et Psychologie Clinique, Unité 6, Centre Psychothérapique de Nancy, Université de Lorraine, Laxou, France
4 Faculté de Médecine, Université Henri Poincaré Nancy 1, Nancy, France
5 Centre d'Addictovigilance, Service de Pharmacologie Médicale, CHU de Bordeaux, INSERM U657, Bordeaux, France

Text received September 11th, 2014; accepted September 23th, 2014

Keywords:
public health surveillance; pharmacoepidemiology; substance-related disorders

Abstract – The French addictovigilance network (addictovigilance: surveillance of addiction), composed of 13 Addictovigilance Centres, was set up in 1990 in order to achieve reliable surveillance and evaluation of abuse and dependence cases due to psychoactive substances (alcohol and tobacco excepted). The detection of safety signals is one of the roles of the addictovigilance centres. Signals from spontaneous reports need to be analyzed before further communication. In addictovigilance, signals may be linked to adverse effects (deaths, pathological signs), to products (new psychoactive substances with potentially dangerous effects) or to practices (new administration routes, new contexts of use). These signals are provided by numerous partners among whom the addictovigilance network has to raise awareness about information that may possibly be an alert signal. The watchful attitude of all partners will make it possible that signals will be, after analyze, considered as true alerts. The addictovigilance network collects data, assess the potential for addiction of psychoactive drugs to provide information on the risk of addiction and give opinions for public health decisions (harm reduction or prevention programs, psychoactive substances control, health alerts).

Abbreviations: see end of article.

1. Introduction

A "signal" can be generally considered as information or warning issued to indicate that something is to be done ("*signal: a gesture, action or sound that is used to convey information or instructions, typically by pre-arrangement between the parties concerned*").[1] This notion of the signal also calls on communication theories. Since the work by Shannon and Wiener, backed up by that by Weaver, there is a general theory of communication that enables an understanding of the different stages between the source of the information and the final receiver, in the course of which an element of information becomes a signal. According to this theory, the sender issues a notification on the basis of information he/she has noticed as being potentially important, and it is the receiver who analyses it and gives it meaning. Detecting and identifying signals is one of the central issues for addictovigilance agents: they need to be able, at a some stage, to label a piece of information received as a signal.[2,3] Signals suggesting a public health risk are collected and analysed in continuous manner in a surveillance process implemented by watchdog or public health structures, in a perspective of alert, anticipation and early action. In this framework, a signal is defined as a piece of information concerning a health phenomenon or exposure to a risk or hazard, which requires investigation in order to validate it and decide whether or not it should be considered as an alert.[4]

In pharmacoepidemiology, reference is made to a signal when the value of a parameter (number of cases of an event, incidence rate, etc) exceeds what is expected or allowed. A signal,

once confirmed, is an alert, which should lead to decisions or the implementation of an appropriate investigation.[5] In the area of addictovigilance, the notion of a threshold is very often lacking, and what launches a signal is generally the notification of an unusually serious event, or of an unexpected cluster of cases.

The signals observed in addictovigilance can be among the following:

- signals linked to human cases: unusual deaths, symptoms, syndromes or pathologies that are grouped in time or space, having suspected or obvious links with isolated or repeated use of a psychoactive substance or an association of such substances;
- signals linked to substances: psychoactive substances or associations thereof observed to be in circulation, found in seizures or already in use, substances that are atypical, dangerous, or liable to be life-threatening, or likely to have serious health consequences (presence of adjuvants, degree of purity, novelty of the substance or its usage, etc);
- signals linked to practices: new modes of administration, new settings of use.

The problem in addictovigilance is that there is a risk of missing a signal, since this area concerns rare or extremely rare phenomena for which there is considerable under-notification. Yet signals can be provided by many different sources, and these sources need to realise the need for awareness towards information that might provide a warning sign.

2. The sources of signals in addictovigilance

The French addictovigilance network, made up of 13 Addictovigilance Centres, was set up in 1990 under the auspices of the French Health Products Safety Agency (*Agence Française de Sécurité Sanitaire des Produits de Santé* [Afssaps]), which later became the French Medicines Agency (*Agence Nationale de Sécurité des Médicaments et des produits de santé* [ANSM]), in order to monitor serious addiction cases involving psychoactive substances, *i.e.* medicines, plantes or substances, illegal or not, with psychoactive effects, with the exception of alcohol and tobacco.[6] At the time of the creation of this network, the information available for assessing abuse, dependence and misuse of these substances was based on fairly succinct data from animal studies, clinical trials, and spontaneous reports by health professionals of addiction cases related to psychoactive substances. Notification was inadequate, and the system restricted by considerable under-reporting. This phenomenon is frequently observed in surveillance systems,[7] but it is aggravated in the area of addictovigilance by the difficulty in identifying the boundary between abuse and misuse, and in detecting misuse behaviours. In addition, the link between clinical profile and use of a psychoactive substance is rendered even more difficult to establish by the fact that the health professional, even when, he/she knows that the effect observed can be attributable to one or several substances, is not necessarily aware of the exposure of the particular patient to the substances in question.

2.1. On-going specific pharmacoepidemiological programmes

To counterbalance the limitations of spontaneous notification by health professionals, despite the fact that it is an essential element in detecting signals and launching alerts,[8] several pharmacoepidemiological programs were set up in France to complement the information provided by spontaneous notification, and to improve the assessment of the psychotropic medication's misuse.[9] One advantage of these programs is that they use a wide range of partners (table I) which enables the exploration of different populations liable to present a disorder related either to the use of legal substances or the use of illegal substances with addictive potential. They are thus able both to identify emergent phenomena and signals at an early stage, and to provide elements to confirm a signal, as will be seen in different examples hereafter. With the exception of the programmes "*ordonnances suspectes indicateurs d'abus possible"* (OSIAP) and "*antalgiques, stupéfiants et ordonnances sécurisées"* (ASOS), which are addressed specifically to community pharmacies and concern medications, all these programmes enable the evaluation of psychoactive substances whether or not they are medications.

These programs, which are particularly complementary in the exploration of addiction potential or different substances, follow on from year to year, so that it is possible to observe evolutions addiction risk over time, going back, depending on the programs, up to ten or twenty years.[10,11]

Thus France possesses observational surveillance programmes that are unique in Europe. While other European countries separate the surveillance of psychotropic medication (*via* national pharmacovigilance networks) from that of illegal drugs, the French addictovigilance system enables an approach that is both qualitative and quantitative to the use and abuse of psychoactive substances in general.[12]

2.2. Other data sources

To complete these on-going programs, other systems have been established. They are used in more focal manner to respond to specific questions, and they are based on consumption data or medical-administrative databases such as those of the health insurance database (*système national d'informations inter-régimes de l'Assurance maladie* [SNIIR-AM]), or the computerisation of medical information (*programme de médicalisation des systèmes d'information* [PMSI]).[13,14]

Table I. Pharmacoepidemiologic surveys in addictovigilance

Surveys	Objectives	MED	NOT MED	Collaborators	Period	Onset
NOTS	To records addiction cases spontaneously reported by health professionals	x	x	Health professionals	Continuous	1990
OPPIDUM	To monitor changes in the consumption of psychoactive products used by drug addicts and alert about the use of new products or new routes of administration	x	x	Drug dependence care centres	October	1995
OPEMA	To describe the characteristics of the population with addiction problems followed by general practitioners	x	x	General practitioners	November	2008
OSIAP	To define different profiles of forged prescriptions and describe patterns of such drug diversion	x		Sentinel community pharmacies	May and November	2001
ASOS	To describe the characteristics of the population treated with analgesic narcotics and the evolution of prescriptions over time	x		Community pharmacies	June	2001
SOUMISSION CHIMIQUE	To describe the drugs used in chemical submissions (administration of psychoactive substances without the knowledge of the victim in order to induce incapacitation and facilitate criminal or actions)	x	x	Hospital departments of medicine or forensic medicine, forensic emergencies, toxicology laboratories	Continuous	1998
DRAMES	To identify and survey deaths in relation to abuse, misuse, dependence, or accidental intake of psychoactive drugs	x	x	Toxicology laboratories	Continuous	2002

ASOS: analgesics, narcotics and secure prescriptions (*antalgiques, stupéfiants et ordonnaces sécurisées*); **DRAMES**: relationship with death and drugs or substance abuse (*décès en relation avec l'abus de médicaments et de substances*); **OPEMA**: observation of addictions on ambulatory medicine (*observation des pharmacodépendances en médecine ambulatoire*); **OPPIDUM**: observation of illicit psychotropic drugs or misuse from their drug use (*observation des produits psychotropes illicites ou détournés de leur utilisation médicamenteuse*); **MED**: drug ; **NON-MED**: non-drug; **NotS**: spontaneous reporting (*notification spontanée*); **OSIAP**: suspicious prescriptions indicators of potential abuse (*ordonnances suspectes indicateurs d'abus possible*).

2.2.1. Sales and reimbursement data

Data from the health insurance system is widely used to improve knowledge of the use of psychoactive drugs and contribute to the assessment of abuse, pharmacodependence and misuse.[15-18]

For instance, indicators have been developed to more efficiently document and estimate poly-prescription, also known as "doctor-shopping" or "medical nomadism",[17] which consists in resorting to several physicians at the same time to obtain the same medication in larger doses, outside the control of the prescribers, for the patient's own consumption, and/or for selling on. Also from this health insurance data, an original approach using multiple correspondence factor analysis and a classification method known as the "dynamic cloud" has been developed enabling a confirmation of "emerging molecules and a determination of the characteristics of exposed subjects.[19] Medical-administrative data, in particular from the "*échantillon généraliste de bénéficiaires"* (EGB), which provides a representative sample of the French population covered by compulsory health insurance, are also useful to identify populations exposed to certain medications, or using certain types of service (medical specialists, hospital departments, etc), or to describe prescription profiles, as was recently the case for baclofen in alcohol addiction.[20]

Finally, from data provided by the "*groupe pour la production et l'élaboration de statistiques*" (GERS) concerning sales figures for medication sold in community pharmacies, a programme was developed to localise geographical zones in which misuse of a medication is reported or suspected. [21]

2.2.2. Morbidity data

Data from hospitals *via* the PMSI are another source of potentially useful information for the identification of cases of serious abuse or pharmacodependence of psychoactive substances, liable to generate addictovigilance signals. Indeed, Article R.5132-97 of the French Code of Public Health (*Code de la Santé publique*)

defines serious pharmacodependence case as "fatal or life-threatening, causing disability or major or lasting deficit, causing or prolonging hospitalisation, or resulting in a congenital abnormality or malformation". The PMSI is a medical-administrative database which describes the activities of health facilities and records patient information, information on the receiving facility and the hospital stay, and all the diagnoses established, in the form of standard discharge sheets (*résumés de sortie standardisés* [RSS]). Thus the PMSI collects information on all hospital stays in medical, surgical and obstetric wards in all public and private health facilities in France. The processing of this data has been used by the addictovigilance network to identify cases of abuse or pharmacodependence towards substances with a potential for abuse, thus partially compensating the problem of under-notification.[22,23] The PMSI is therefore potentially a new addictovigilance tool in France. Further to this, the implementation of a capture-recapture model with three sources of data (PMSI, toxicological data, and spontaneous reports) has enabled a quantification of the frequency of complications associated with substances with a potential for abuse in the geographical area covered by Toulouse University Hospital.[24]

These various undertakings underline the fundamental role of medical-administrative databases as complementary investigation tools in the area of addictovigilance to identify or confirm a signal.

2.2.3. Data in the scientific literature and on Internet

In addition to medicoeconomic data to confirm a signal, the addictovigilance centres use data from the international scientific literature by way of active bibliographic monitoring, and they also explore data posted on the Internet. For instance, Internet is consulted to obtain official reports (by World Health Organisation [WHO], European Monitoring Centre for Drugs and Drug Addiction [EMCDDA], etc) and also to obtain information on present trends in modes of use or in the substances involved by consultation of sales websites, forums, blogs etc. This type of Internet monitoring is used elsewhere in Europe, for example in the research project Psychonaut.[25]

2.3. A dynamic network of partners

All the research work conducted by the addictovigilance centres is backed up by the strength of the local network that each centre has been able to form in its region. The networks obtain support from regular feedback of information on surveys conducted, from the diffusion of information bulletins, or from the organisation of one-day regional addictovigilance events.

Thus numerous exchanges occur among the different players who in one way or another are working in the field of addictovigilance (figure 1). In particular, drug-user risk reduction centres (*Centre d'Accueil et d'Accompagnement à la Réduction de Risques pour Usagers de Drogues* [CAARUD]) and addiction care and prevention centres (*Centre de Soins d'Accompagnement et de Prévention en Addictologie* [CSAPA]) are a particularly valuable observational setting for emergent phenomena (new substances, new behaviours) in drug abuse, pharmacodependence or misuse of medication.[26]

Hospital departments (addiction, psychiatry, emergency, or medicine) are also a setting in which signals can emerge. The personnel involved in these different structures have a fundamental role in the identification of addictovigilance signals.

These networks thus enable any signal originating from various independent sources to come to light.

3. The transition from a notification to a signal: a few examples

It is precisely the watchful attitudes of all the different partners that will enable information that might constitute a signal to circulate and be analysed by the addictovigilance centres to determine whether or not it constitutes a signal.

3.1. National mobilisation following a regional signal

In practice, when an addictovigilance centre is alerted locally of the appearance of a new effect following the use of a known or novel substance, or a particular mode of administration, the centre will launch a strictly defined process of evaluation of the signals (figure 2). A description of the initial notifications accompanied by an analysis of the literature on the subject is presented to the other addictovigilance centers. In urgent cases, the network can also be questioned by email. The decision whether to qualify and quantify the signal can then be reached. First, all the cases notified to each addictovigilance centre are collected and analysed. This information-sharing enables a first evaluation of the geographical extent of the phenomenon, and of the need for any complementary information to move on from signal to alert. As an illustration, the instance of a practice known as Slam can be considered. Slam refers to the injection of different psycho-stimulant substances in a sexual setting. In view of the notification of several cases of somatic complications from the monitoring centres in Paris and Montpellier, the decision was made to evaluate this practice at national level, and to determine whether it was specific to these two regions or whether the phenomenon extended across the national territory.

In case of absence of similar cases notified to the addictovigilance centres, a national data collection can be set up with the creation of an *ad hoc* case-form to be used should the phenomenon extend to the national level. One example of this could be the misuse of methylphenidate, identified in the PACA-Corsica region:[27] the question of whether to reiterate this survey in other regions can be raised in case of a generalisation of the phenomenon.

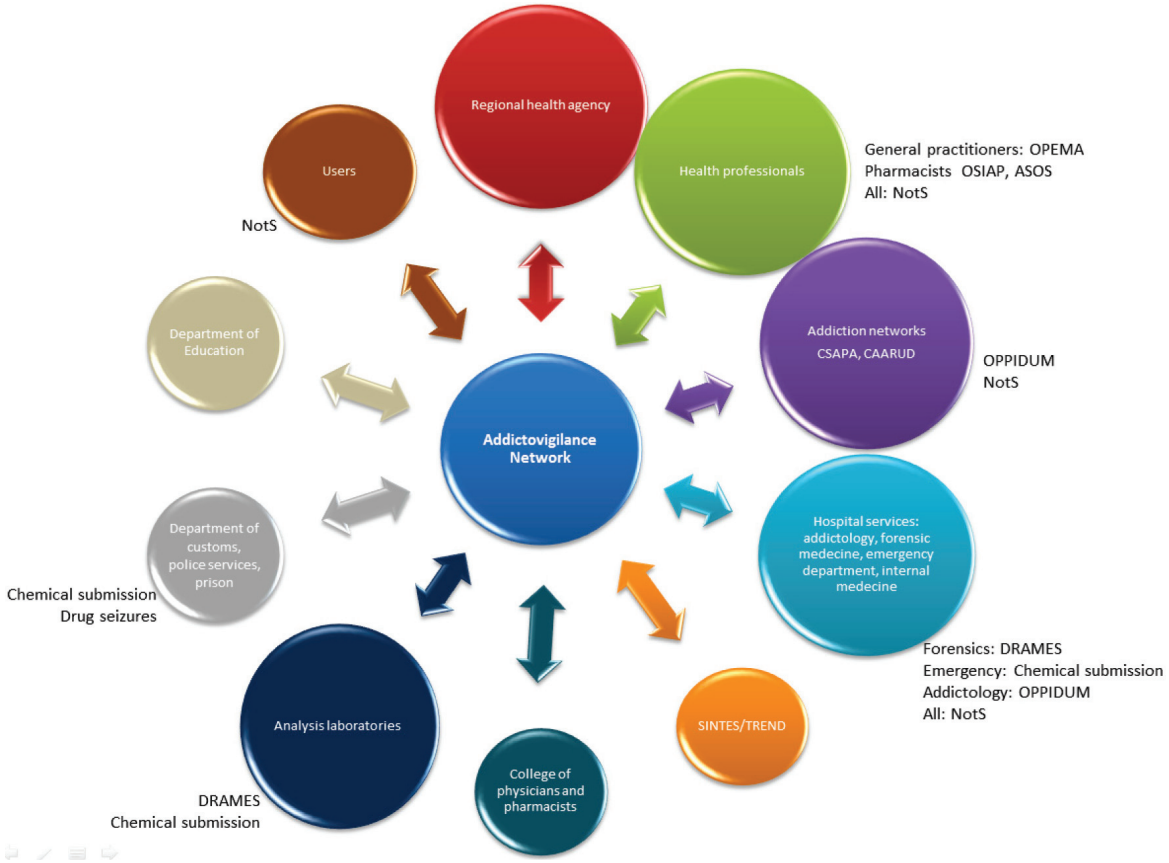

Fig. 1. Partners of the addictovigilance network.
ASOS: analgesics, narcotics and secure prescriptions (*antalgiques, stupéfiants et ordonnances sécurisées*); **CAARUD**: drug-user risk reduction centers (*Centre d'Accueil et d'Accompagnement à la Réduction de Risques pour Usagers de Drogues*); **CSAPA**: addiction care and prevention centres (*Centre de Soins d'Accompagnement et de Prévention en Addictologie*); **DRAMES**: relationship with death and drugs or substance abuse (*décès en relation avec l'abus de médicaments et de substances*); **EGB**: sample of beneficiaries (*échantillon généraliste de bénéficiaires*); **OPEMA**: observation of addictions on ambulatory medicine (*observation des pharmacodépendances en médecine ambulatoire*); **OPPIDUM**: observation of illicit psychotropic drugs or misuse from their drug use (*observation des produits psychotropes illicites ou détournés de leur utilisation médicamenteuse*); **NotS**: spontaneous reporting (*notification spontanée*); **OSIAP**: suspicious prescriptions indicators of potential abuse (*ordonnances suspectes indicateurs d'abus possible*).

3.2. Alerting dispensing chemists: dextromethorphane, pseudoephedrine (Sudafed®)

Community chemists, because they are close to patients and have a role in the dispensation of psychoactive medications, are in the front line to be informed or alerted towards deviant behaviours of the abuse or addiction type. Below we describe two instances of situations that were notified to the addictovigilance network by dispensing chemists and that were identified as signals.

Dextromethorphane

The first example concerns the misuse of dextromethorphane for recreational purposes and/or misuse, mainly among adolescents.

This substance, a morphine derivate with central action used as a cough medicine, is available in pharmacies without prescription, in liquid form (syrup), tablets or capsules. Its potential for addiction is limited compared to other opiates, but dextromethorphane presents effects close to those of ketamine, in particular hallucinogenic effects.

Towards the end of 2010, the addictovigilance network noted an increase in reports from dispensing chemists concerning recurrent demands for dextromethorphane medication, most often in the form of tablets or capsules, from adolescents and young adults. Alongside, the addictovigilance network also received reports of a few cases of hospitalisation following the concomitant use of dextromethorphane and alcohol, again involving adolescents.

In view of the emergence of this recreational use, information messages were diffused on several occasions through 2012, aiming to alert chemists to this behaviour, and reminding that the chemist

should refuse to deliver a drug when the well-being of the patient might be compromised (Article R.4235 of the *Code de la Santé publique*).[28] As notifications persisted, dextromethorphane is today one of the substances monitored by the addictovigilance network.[29]

Pseudoephedrine (Sudafed®)

The second example illustrating how dispensing chemists enabled the addictovigilance network to identify a signal is that concerning Sudafed®. This speciality contains pseudoephedrine in isolated form. Like ephedrine, it is a precursor of methamphetamine, and also like ephedrine belongs to table I of the 1988 United Nations Convention on illicit traffic in narcotic drugs and psychotropic substances. Both these molecules have an adrenergic effect by both direct and indirect action: they lead to a central stimulation of the amphetamine type, but weaker than that derived from metamfetamine. For some years, the International Narcotics Control Board (INCB) noticed an increase in the traffic of methamphetamine manufactured by clandestine laboratories from pseudoephedrine and ephedrine. In France, following reports to the addictovigilance network from dispensing chemists of demand for suspiciously large volumes of Sudafed®, ANSM on several occasions reiterated their recommendation to dispensing chemists and pharmaceutical wholesalers to be watchful regarding suspicious demands for these medications, and to pharmaceutical wholesalers regarding sales for export.[30] The forms of pseudoephedrine intended for nasal use were already listed in class II (medication requiring medical prescription). Since March 2014, oral route specialities containing only pseudoephedrine have also been listed in class II. In July and September 2013 the manufacturing laboratories decided to cease marketing these specialities, which means they are no longer available.[31,32]

Reports from dispensing chemists are very valuable in alerting the addictovigilance network so that measures of information and control can be instated.

3.3. Enhanced vigilance for novel substances

Since the end of the first decade of this century, there has been a very marked evolution in practices and substances involved in addiction. In recent years "new psychoactive substances" (NPS) or "designer drugs" have appeared, the chemical structures of which are related to those of known substances. However they are for the most part not subjected to any control, regulation or ban. These new drugs are copies, although not quite identical, of known drugs, and the clinical effects observed are therefore close to those of known substances, but they also differ, either in duration of effect, or in intensity of effect. Very little information is available today on these NPS, in particular for their specific effects, dose-effect and so forth.[33]

Clinical cases, including death, linked to the use of these substances are beginning to be reported to the French addictovigilance network. Theses substances are too often regarded by users as "reliable" and legal. However, they are yet used in fairly small circles in France. These reports have enabled the network to more particularly assess certain synthetic cannabinoids following user reports of the use of blends of plants as cannabis substitutes, as well as several synthetic stimulants after alerts as to their dangerousness and potential for abuse and addiction. These assessments led to the classification of certain cannabinoids as narcotics (JWH-018, CP 47,497 and its homologues [C6, C8 and C9], HU-210),[34,35] to the generic classification of cathinones on the list of narcotics[36] and also to the classification of 4-fluoroamfetamine on the same list.[37] More recently, methoxetamine,[38] a ketamine analogue, was classified after notification to the addictovigilance network of around ten cases, including one that was fatal, implicating this molecule.[39] Serious intoxication is possible, and it is essential that cases should be reported. Indeed, when a clinical symptom profile is available, the notification of the case enables a differential and also aetiological diagnosis to be determined. Given the large number of substances that may be involved, the clinical evaluation needs to be confirmed with pharmacological toxicology analyses. Thus, all the more because information on these novel substances is lacking, the notification of all suspected cases is essential for monitoring purposes so as to improve knowledge on the effects of these drugs and to adapt care provision.

3.4. Cannabis and cardiovascular complications

A first study aiming to identify hospitalisations linked to cannabis use in Toulouse University Hospital between 2004 and 2007 using PMSI data, evidenced several cases of serious cardiovascular complications.[23] They involved 7 myocardial infarctions, 4 strokes and 3 cases of arterial thrombosis, occurring in 11 men and 3 women. With the exception of one of the men who was aged 49, all these patients were under 40 (mean 32.6 ± 6.5 yrs). These cases particularly drew our attention because of their seriousness, and because the majority, on account of absence of any known cardiovascular risk, underwent a complete aetiological investigation. They were all regular or daily cannabis users

As several fairly similar cases of cardiovascular disturbances in association with cannabis had been reported to addictovigilance centres in the same period, all these spontaneous reports linked to cardiovascular complications in the context of cannabis use were analysed to assess the scale of these events at national level. This second analysis evidenced cardiac complications (mainly acute coronary syndromes) and extra-cardiac complications (stroke, peripheral arteriopathies).[40] These results should alert clinicians to the need to look for cannabis exposure among patients presenting for cardiovascular disorders. In addition, while Sativex®, a drug based on cannabinoid derivates, has recently obtained marketing authorisation and will soon be on the French market, the results

should recommend caution and close surveillance of patients exposed in the future to this medication.

The identification of cardiovascular complications linked to cannabis use is an excellent example of the collaborative work undertaken within the addictovigilance network. These two studies illustrate how an addictovigilance signal, first of all identified locally *via* exploitation of PMSI data, was confirmed at national level by analysis of spontaneous reports.

4. How can the process of signal identification be improved?

France is the only European country with an organised, specialised network concerned with the issues of drug addiction. This network, which possesses expertise in the area of pharmacodependence and addictovigilance, is a public decisional tool in the area of health, whether for prevention and risk reduction programmes, or for the decision whether to classify psychoactive substances and medications, or again for the launching of health alerts.

The assessment of the abuse and addiction potential of psychoactive substances is an approach combining several complementary sources of information. The data collected provide a body of evidence enabling conclusions to be reached as to the addiction potential of a substance, and the identification of a signal. This addictovigilance system can only function on the basis of circulating information among professionals in the field, in particular at local level. This valuable collaboration enables the rapid diffusion of information and alerts following the identification of a signal by one or other of the partners.

Addictovigilance clearly concerns the detection of particular effects linked to the use of psychoactive substances, relying especially on collecting indicators (such as forged prescriptions). It however also has a watchdog function towards unusual phenomena that might be linked to a health risk (in particular from spontaneous notifications) in a perspective of anticipation and alert.[9,41] It can be noted that in addictovigilance the measure of exposure to a medication or a psychoactive substance in the setting of recreational or addictive behaviours to obtain psychoactive effect is no easy task. The behaviour of addiction is often hidden, and it generally involves a fairly small number of individuals. It is therefore important to do all possible to ensure that the notification of situations of interest to the addiction watchdog bodies is as exhaustive as possible, so as not to miss data that could amount to a signal.

The existence of this network dedicated to addictovigilance, unique in Europe, has several strengths. The first is that it has a field of competence that is extremely well-defined, with a restricted number of molecules to monitor in comparison with other systems (*i.e.* psychoactive substances excluding alcohol and tobacco). This enables the identification of clinical situations that are similarly restricted in scope. The second strength resides in the constant interactions within the addictovigilance network, which enable a signal identified at local level to be ascertained at national level. A single national database specifically dedicated to addictovigilance would be a valuable tool to improve signal detection. Finally, the third strength, and not the least, is that the regional partners are now clearly identified, and that numerous examples, some of which have been detailed here, demonstrate the efficiency of the part they play in identifying signals. In order to promote exhaustive notifications of clinical pharmacodependence situations, feedback to the different partners is required. This will "educate" agents in the field and reinforce their watchfulness, essential for the proper functioning of health surveillance in addiction (figure 2). Indeed, underreporting means there is underestimation of the risk, all the more so because certain phenomena of interest for addictovigilance may be rare. Constant monitoring by the addiction watchdog system is designed to reduce the risk of missing a signal. This requires the network and its partners to be on the receiving end for information that might be useful for risk evaluation. In addition, to complement the improvement of notifications, surveillance of the Internet appears as another requirement, since Internet provides considerable data on the use of psychoactive substances. Surveillance systems are becoming organised for the report of potential undesirable events by users themselves, while alongside the users in question are fairly willing to share their experiences on forums and blogs frequented by initiates. Critical clinical situations may be described on these media, and should be collected. Finally, alongside the complementarity of the members of the addictovigilance system, in particular for expert analysis, specific clinical trials or certain animal studies, it appears useful today to envisage the creation of new tools, for instance to explore psychoactive substance use in private settings. Parallel to the development of new approaches to the study of practices and usage, it also seems necessary to strengthen links with other watchdog systems also working on a local-regional grid (for instance *Agence Régionale de Santé* [ARS], *Cellule de l'Institut de Veille Sanitaire en Région* [CIRE], etc). The quantity and quality of information collected condition the identification and evaluation of signals, and the quality of the measures adopted as a result.

What are the main points to be retained? For surveillance to be efficient, a set of data needs to be collected, identified, sorted and given meaning, and its status as significant information or as a signal needs to be established. This is the function of a network like the French addictovigilance network, which collects, analyses and transfers relevant information to the hierarchy, but also provides feedback to its partners. This makes it able to have an impact on practice and behaviours. Addictovigilance is therefore of fundamental importance for our medical system to move on towards preventive medicine and a public health system where each player, from substance users to field professionals and decision-makers, has a part to play.

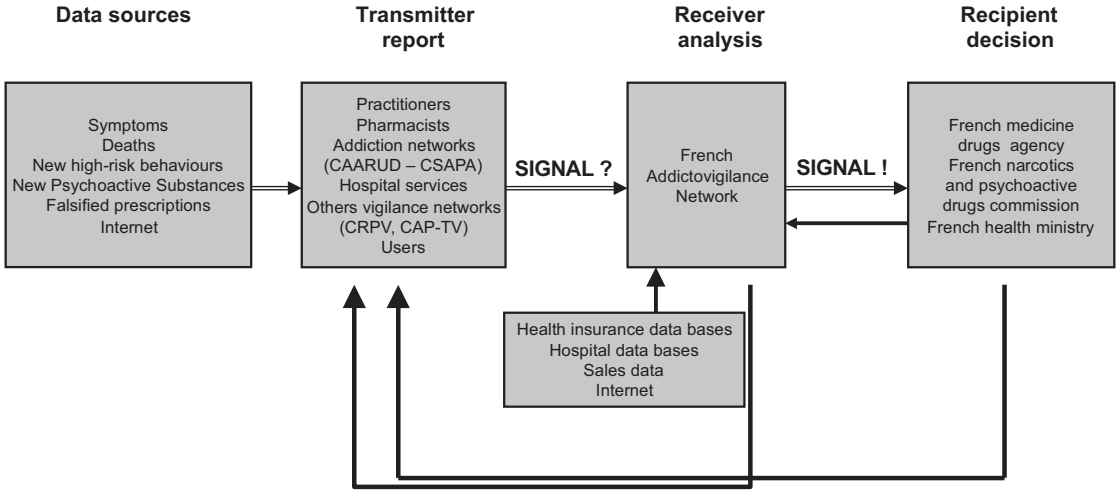

Fig. 2. From alert to signal. From Shannon et Weaver.[2]
ANSM: French Medicines Agency (*Agence Nationale de Sécurité du Médicament et des Produits de Santé*); **CAARUD**: drug-user risk reduction centers (*Centre d'Accueil et d'Accompagnement à la Réduction des Risques pour les Usagers de Drogue*s); **CAP-TV**: Antipoison and Toxicovigilance Centres; **CRPV**: Regional Pharmacovigilance Center; **CSAPA**: addiction care and prevention centres (*Centre de Soins d'Accompagnement et de Prévention en Addictologie*); **GERS**: *groupe pour la production et l'élaboration de statistiques*; **PMSI**: computerisation of medical information (*programme de médicalisation des systèmes d'information*).

Conflicts of interests. None.

Abbreviations. Afssaps: French Health Products Safety Agency (*Agence Française de Sécurité Sanitaire des Produits de Santé*); ANSM: French Medicines Agency (*Agence Nationale de Sécurité des Médicaments et des produits de santé*); ARS: *Agence Régionale de Santé*; ASOS: analgesics, narcotics and secure prescriptions (*antalgiques, stupéfiants et ordonnaces sécurisées)*; CAARUD: drug-user risk reduction centers (*Centre d'Accueil et d'Accompagnement à la Réduction de Risques pour Usagers de Drogues*); CIRE: *Cellule de l'Institut de Veille Sanitaire en Région*; CSAPA: addiction care and prevention centres (*Centre de Soins d'Accompagnement et de Prévention en Addictologie*); EGB: *échantillon généraliste de bénéficiaires*; EMCDDA: *European Monitoring Centre for Drugs and Drug Addiction*; GERS: *groupe pour la production et l'élaboration de statistiques*; NPS: new psychoactive substances; OSIAP: *ordonnances suspectes indicateurs d'abus possible*; PMSI: computerisation of medical information (*programme de médicalisation des systèmes d'information*); SNIIR-AM: health insurance database (*système national d'informations inter-régimes de l'Assurance maladie*); WHO: World Health Organisation.

References

1. Centre National de Ressources Textuelles et Lexicales (CNRTL) http://www.cnrtl.fr/lexicographie/signal Accessed December 29th, 2014
2. Shannon CE, Weaver W. La théorie mathématique de la communication (trad) Paris: Retz, CEPL, 1975
3. Wiener N. Cybernetics or control and communication in the animal and the machine. The MIT Press, London, 1965
4. Weber F. Veille, alerte, surveillance. Application au champ du médicament. Les assises du médicament, 2011
5. Bégaud B. Dictionnaire de pharmacoépidémiologie. 3e ed. Bordeaux: ARME-Pharmacovigilance, 1998
6. Baumevieille M, Miremont G, Haramburu F, *et al.* Le système français d'évaluation de la pharmacodépendance et de l'abus : consécration juridique. Therapie 2001; 56: 15-22
7. Begaud B, Martin K, Haramburu F, *et al.* Rates of spontaneous reporting of adverse drug reactions in France. JAMA 2002; 288: 1588
8. Baumevieille M, Daveluy A, Maurain C, *et al.* Medicines submitted to narcotics regulations in France, 1992-2007. Fundam Clin Pharmacol 2009; 23: 345-9
9. Micaleff J, Jolliet P, Victorri-Vigneau C, *et al.* Premières journées nationales de pharmacodépendance (CEIP). Place de la pharmacodépendance dans l'évaluation du médicament. Therapie 2008; 63: 55-65
10. Boeuf O, Lapeyre-Mestre M, French Network of CEIP. Survey of forged prescriptions to investigate risk of psychoactive medications abuse in France: results of OSIAP survey. Drug Saf 2007; 30: 265-76
11. Frauger E, Moracchini C, Le Boisselier R, *et al.* OPPIDUM surveillance program: 20 years of information on drug abuse in France. Fund Clin Pharmacol 2013; 27: 672-82
12. Rhodes T, Hedrich D. Harm reduction: evidence, impacts and challenges. Avril 2010 http://www.emcdda.europa.eu/publications/monographs/harm-reduction Accessed December 29th, 2014
13. CSP. Arrêté du 30 juin 2011 relatif au recueil et au traitement des données d'activité médicale des établissements de santé publics ou privés ayant une activité en soins de suite et de réadaptation et à la transmission d'informations

issues de ce traitement, dans les conditions définies aux articles L. 6113-7 et L. 6113-8 du code de la santé publique.
http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000024290191&dateTexte=&categorieLien=id
Accessed December 29th, 2014

14. De Roquefeuil L, Studer A, Neumann A, *et al.* L'échantillon généraliste de bénéficiaires : représentativité, portée et limites. Prat Organ Soins 2009; 40: 213-23
http://www.iresp.net/iresp/files/2013/04/091020182511_pos093_echantillon_g.pdf
Accessed December 29th, 2014
15. Boczek C, Frauger E, Micallef J, *et al.* National and regional market penetration rates of generic's high dosage buprenorphine: its evolution from 2006 to 2008, using reimbursed drug database. Therapie 2012; 67: 129-36
16. Nordmann S, Pradel V, Lapeyre-Mestre M, *et al.* Doctor shopping reveals geographical variations in opioid abuse. Pain physician 2013; 16: 89-100
17. Pradel V, Thirion X, Ronfle E, *et al.* Assessment of doctor-shopping for high dosage buprenorphine maintenance treatment in a French region: development of a new method for prescription database. Pharmacoepidemiol Drug Saf 2004; 13: 473-81
18. Victorri-Vigneau C, Feuillet F, Wainstein L, *et al.* Pharmacoepidemiological characterisation of zolpidem and zopiclone usage. Eur J Clin Pharmacol 2013; 69: 1965-72
19. Frauger E, Pradel V, Natali F, *et al.* Détournement d'usage du clonazépam (Rivotril®) : tendances récentes. Therapie 2006; 61: 49-55
20. Dupouy J, Fournier JP, Jouanjus E, *et al.* Baclofen for alcohol dependence in France: incidence of treated patients and prescription patterns--a cohort study. Eur Neuropsychopharmacol 2014; 24: 192-9
21. Blayac JP, Pinzani V, Hillaire-Buys D, *et al.* An original method for estimating a possible geographic abuse or misuse of a drug: application to morphine sulfate (Skenan®). 21è journées de Pharmacovigilance. Rouen, 2000
22. Daveluy A, Miremont-Salame G, Kostrzewa A, *et al.* Identification of abuse and dependence cases through a hospital database. Pharmacoepidemiol Drug Saf 2012; 21: 1344-9
23. Jouanjus E, Leymarie F, Tubery M, *et al.* Cannabis-related hospitalizations: unexpected serious events identified through hospital databases. Br J Clin Pharmacol 2011; 71: 758-65
24. Jouanjus E, Pourcel L, Saivin S, *et al.* Use of multiple sources and capture-recapture method to estimate the frequency of hospitalizations related to drug abuse. Pharmacoepidemiol Drug Saf 2012 Jul; 21(7): 733-41
25. Schifano F, D'Offizi S, Piccione M, *et al.* Is there a recreational misuse potential for pregabalin? Analysis of anecdotal online reports in comparison with related gabapentin and clonazepam data. Psychother Psychosom 2011; 80: 118-22
26. Moracchini C, Frauger E, Pauly V, *et al.* Harm reduction centers ("CAARUD"): privileged places for warning signal detection in addictovigilance. Therapie 2012; 67: 437-45
27. Micallef J, Frauger E, Palmaro A, *et al*. Exemple of an investigation of an "emergent" phenomenon in addictovigilance: the case of methylphenidate. Therapie 2015 DOI: 10.2515/therapie/2015013
28. Ordre National des pharmaciens. Dextrométhorphane : alerte face aux usages détournés. La lettre n°18. Avril 2012
http://lalettre.ordre.pharmacien.fr/accueil-lettre-18/C-est-utile-pour-votre-pratique-professionnelle
Accessed December 29th, 2014
29. ANSM. Comité technique des CEIP. Compte-rendu de la séance du 19 décembre 2013.
http://ansm.sante.fr/var/ansm_site/storage/original/application/240cb0ac457dbf87b4143de46d8b22b4.pdf
Accessed December 29th, 2014 (14 pages)
30. Ordre National des Pharmaciens. Sudafed® : l'ANSM appelle à la surveillance des ventes à l'exportation. La lettre n°31.
http://lalettre.ordre.pharmacien.fr/accueil-lettre-13/Ce-qu-il-faut-savoir-ce-mois-ci-pour-vos-dispensations
Accessed December 29th, 2014
31. Arrêté du 6 février 2014 portant classement sur la liste des substances vénéneuses. JORF du 14 février 2014.
http://www.legifrance.gouv.fr/
Accessed December 29th, 2014
32. Ministère des Affaires Sociales, de la Santé et des Droits des Femmes.
http://base-donnees-publique.medicaments.gouv.fr
Accessed December 29th, 2014
33. Papaseit E, Farre M, Schifano F, *et al.* Emerging drugs in Europe. Curr Opin Psychiatry 2014; 27: 243-50
34. Arrêté du 24 février 2009 portant classement sur la liste des substances vénéneuses. JORF du 27 février 2009.
http://www.legifrance.gouv.fr/
Accessed December 29th, 2014
35. ANSM. Commission Nationale des Stupéfiants et des Psychotropes. Compte-rendu de la 82è réunion du 19 février 2009.
http://ansm.sante.fr/var/ansm_site/storage/original/application/cd1d2f893a221733e629d0109256798a.pdf
Accessed December 29th, 2014 (16 pages)
36. Arrêté du 27 juillet 2012 portant classement sur la liste des substances vénéneuses. JORF du 2 août 2012
http://www.legifrance.gouv.fr/
Accessed December 29th, 2014
37. Arrêté du 7 mars 2011 portant classement sur la liste des substances vénéneuses. JORF du 16 mars 2011
http://www.legifrance.gouv.fr/
Accessed December 29th, 2014
38. Arrêté du 5 août 2013 portant classement sur la liste des substances vénéneuses. JORF du 9 août 20014
http://www.legifrance.gouv.fr/
Accessed December 29th, 2014
39. ANSM. Commission Nationale des Stupéfiants et des Psychotropes n°1. Evaluation du potentiel d'abus et de dépendance de la methoxetamine en vue du classement comme stupéfiant. 21 mars 2013
http://ansm.sante.fr/var/ansm_site/storage/original/application/c8dc712e050f9aa116e3466a202d18b4.pdf
Accessed December 29th, 2014 (22 pages)
40. Jouanjus E, Lapeyre-Mestre M, Micallef J. Cannabis use: signal of increasing risk of serious cardiovascular disorders. J Am Heart Assoc 2014; 3: e000638
41. Lapeyre-Mestre M. Addiction médicamenteuse : quelles données pour évaluer et prévenir ? Psychotropes 2013; 19: 65-80

Correspondence and offprints: *Amélie Daveluy*, Centre d'Addictovigilance, Service de Pharmacologie Médicale, Hôpital Pellegrin, CHU, 33076 Bordeaux cedex, France.
E-mail: amelie.daveluy@u-bordeaux.fr