

## LETTER TO EDITOR

# 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

Emilie Jouanjus<sup>o</sup>, Joëlle Micallef<sup>o</sup>, Michel Mallaret<sup>o</sup>, Maryse Lapeyre-Mestre<sup>o</sup>

CEIP-Addictovigilance, Service de Pharmacologie Médicale et Clinique, CHU Toulouse, Toulouse, France (Dr Jouanjus); CEIP-Addictovigilance, Service de Pharmacologie Clinique, CHU Timone, Marseille, France (Dr Micallef); CEIP-Addictovigilance, Service de Pharmacologie Clinique, CHU Grenoble, Grenoble, France (Dr Mallaret); CEIP-Addictovigilance, Service de Pharmacologie Médicale et Clinique, CHU Toulouse, Toulouse, France (Dr Lapeyre-Mestre); the French Addictovigilance Network (Drs Jouanjus, Micallef, Mallaret, and Lapeyre-Mestre).

Correspondence: Emilie Jouanjus, PharmD, PhD, Pharmacoepidemiology, INSERM UMR 1027, University of Toulouse and CEIP-Addictovigilance, Service de Pharmacologie Médicale et Clinique, CHU Toulouse, 37, Allées Jules Guesde, 31000 Toulouse, France ([emilie.jouanjus@univ-tlse3.fr](mailto:emilie.jouanjus@univ-tlse3.fr)).

## Abstract

After the publication of an article discussing the methodological options to detect the diversion potential of prescription drugs, this letter presents the multidimensional functioning of the French Addictovigilance System. This system aims at monitoring all substances with abuse potential, relying on a network of experts specialized in clinical and fundamental pharmacology. For more than 25 years, we have created collaborations with partners at the interface with field data related to substance use and the potential related disorders. When relevant depending on the context, these data sources are explored and crossed to analyze the abuse potential of one given substance. This organizational approach is useful to detect early Addictovigilance warning signals and to take appropriate measures. Generalizing such a multidimensional approach outside France appears an appealing option to move towards more effective Addictovigilance systems at the international level.

Dear Editor,

The research article published by Schifano and colleagues in the *International Journal of Neuropsychopharmacology* illustrates the ins and outs of detecting the diversion potential of prescription drugs by developing the example of Z-drugs (Schifano et al., 2019). They analyzed the adverse drug reports recorded in the Eudravigilance database with the aim of confirming the abuse, dependence, and withdrawal issues linked to zaleplon,

zolpidem, and zopiclone. They conclude by encouraging proactive postmarketing surveillance activities to detect, understand, and prevent any possible misuse potential of prescribed medications better.

Previously in 2018, Throckmorton and colleagues on behalf of the Food and Drug Administration (FDA) proposed applying a strategy in line with Schifano's article to detect drug abuse (Throckmorton et al., 2018). Against the backdrop of the

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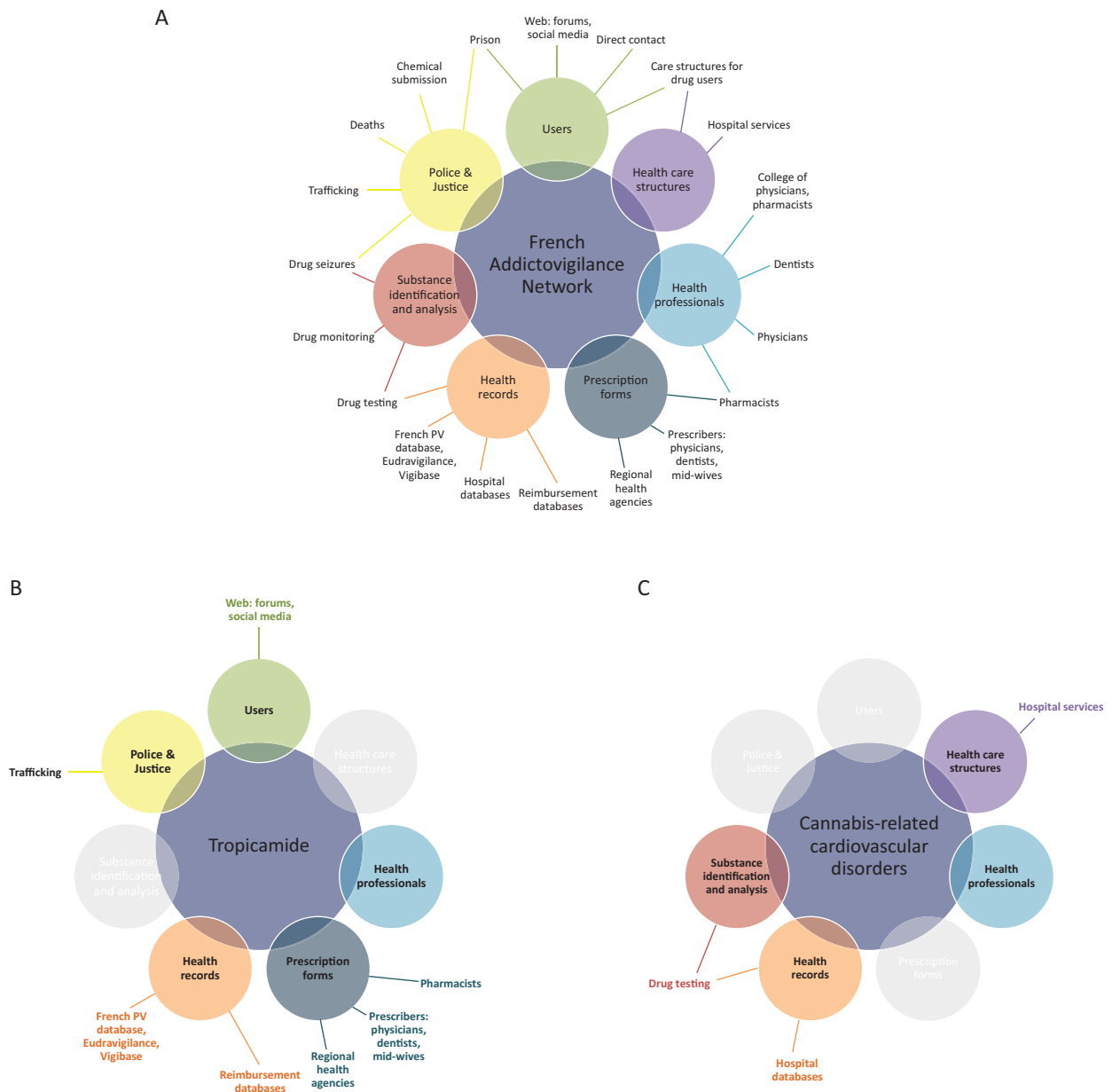
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US opioid crisis, they recommended a multicomponent approach to comprehend these matters. They namely pointed out the usefulness of monitoring drug utilization, tracking users' posts on social media, and exploring health care databases. This, they explained, enables performing proactive and effective Pharmacovigilance. They relied on the examples of diversion of several prescription drugs with abuse potential (gabapentinoids and loperamide) and "kratom," a preparation with psychoactive properties made from leaves of the *Mitragyna speciosa* tree.

Although they offer different perspectives, both articles hence converge, advocating the generalization of proactive activities to improve the effectiveness of postmarketing surveillance. Postmarketing activities not only refer to Pharmacovigilance but also includes Addictovigilance, the monitoring of health consequences related to the use of substances with abuse potential within the real-life context. The World Health Organization

(WHO) has recommended that countries should develop vigilance systems specifically dedicated to the survey of substance use disorders; however, many of the existing postmarketing surveillance systems around the world rely on spontaneous reporting of adverse events related to prescription drugs.

France has long been developing a specific national Addictovigilance system aside from the other postmarketing activities. This system is devoted to the monitoring of prescription drugs and other legal or illegal substances with abuse potential. It is organized in a network of regional offices covering the entire country with a membership of experts specialized in clinical and fundamental pharmacology. For more than 25 years, this French Addictovigilance Network (FAN) has gradually developed interconnections with partners hovering around substance use and the potential related disorders. These partners constitute an interface with field data (Figure 1). Besides, the FAN has designed



**Figure 1.** The multidimensional French Addictovigilance Network: Partners and datasources involved in early warning signals of substance use disorders (A) and the examples of tropicamide (B) and cannabis-related cardiovascular disorders (C) illustrate the crossing of several relevant datasources.

and implemented several original monitoring tools that complement the more traditional spontaneous reporting (Jouanjus et al., 2015). Each of these tools and, more generally, each type of field data uses a specific approach to evaluate the issues of drug abuse. Crossing their results beside the pharmacological expertise enables to address the abuse potential of drugs in all its dimensions. Such a multidimensional organization has enabled to detect early Addictovigilance warning signals leading health authorities to launch alerts, raise health professionals' awareness, and implement regulatory measures. As a first example of an Addictovigilance warning signal, the diversion of tropicamide, a mydriatic eye-drop, was first reported by community pharmacists (Ponté et al., 2017). The analysis of several data sources, including falsified medical prescriptions, confirmed the diversion practice consisting of preparing solutions for i.v. injection in search of central atropinic effects (Figure 1). This signal led to withdraw the highly divertible 10-mL packaging from the market and maintain only the single-dose pack. A second illustration of this multidimensional approach is the survey of gabapentinoids (Bossard et al., 2016; Driot et al., 2019). The abuse potential of pregabalin and gabapentin, described outside France since the beginning of the 2010s, has been carefully surveyed through the analysis of complementary data sources including Pharmacovigilance data and reimbursement data from the health insurance databases. Patients who abused these drugs were thereby identified; their profiles could be defined along with their trajectories in the healthcare system. In parallel, experimental studies were conducted to assess the underlying mechanisms (Coutens et al., 2019). The FAN's data were shown to be also contributory to apprehend the misuse of prescription drugs at the European level (Casati et al., 2012). At the US level, the authors of an article reviewing the cardiovascular effects of cannabis promote the FAN's experience and emphasize the relevance of implementing a similar strategy in the United States (Rezkalla and Kloner, 2018). Indeed, the multisource analysis identified and characterized an early signal of cardiovascular disorders including myocardial infarction and ischemic stroke in young cannabis users with neither cardiovascular history nor identified risk factors (Figure 1) (Jouanjus et al., 2014). In conclusion, the French Addictovigilance system illustrates well the multifaceted system supported by Schifano, Throckmorton, and their colleagues. The multidimensional approach is an appealing complement to the necessary pharmacological analysis. It is adaptive depending on the substance considered and the related context of use. It allows defining profiles of users as in the example of gabapentinoids, understanding the ways of obtaining drugs as in that of tropicamide, or detecting and characterizing somatic disorders related to the use of psychoactive drugs as in the example of cannabis-related cardiovascular complications. Relying on long experience, the French system has monitored and anticipated drug safety issues related to abuse of drugs, whether illicit or available under medical prescription. The choice of a broad strategy, applied to all substances with an abuse potential regardless of their regulatory status (i.e., prescription drugs or illicit substances), provides the benefit of allowing continuous monitoring even if changes occur. With reason, Schifano and colleagues encourage

investing in proactive vigilance systems enabling to detect early Addictovigilance signals: this has already been proven to be a relevant, efficient, and accurate strategy in France. Generalizing such a multidimensional approach outside France could be a helpful option to move towards effective Addictovigilance at the international level.

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## Statement of Interest

None.

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