Drug and Alcohol Dependence 182 (2018) 27–32

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Review

# Cannabinoid hyperemesis syndrome: Review of the literature and of cases reported to the French addictovigilance network

Benoît Schreck[a], Nicolas Wagneur[a], Pascal Caillet[a], Marie Gérardin[a], Jennyfer Cholet[c], Michel Spadari[d], Nicolas Authier[e], Juliana Tournebize[f], Marion Gaillard[g], Anais Serre[h], Louise Carton[i], Stéphanie Pain[j], Pascale Jolliet[a,b], Caroline Victorri-Vigneau[a,b,*]

[a] Addictovigilance des Pays de la Loire, Service de pharmacologie clinique, Institut de biologie, CHU de Nantes, 44093 Nantes Cedex 1, France
[b] INSERM UMR U1246 SPHERE, Institut de Recherche en Santé 2, 22 Boulevard Benoni-Goullin, 44200 Nantes, France
[c] Service universitaire de psychiatrie et d'addictologie de liaison, CHU de Nantes, 44093 Nantes Cedex 1, France
[d] Addictovigilance Marseille, Laboratoire de pharmacologie médicale et clinique, Groupe Hospitalier La Timone, 13385 Marseille Cedex 5, France
[e] Addictovigilance Auvergne, Hôpital G. Montpied, Service de Pharmacologie Médicale, CHU de Clermont-Ferrand, 63000 Clermont-Ferrand Cedex, France
[f] Addictovigilance Nancy, Hôpital Central, Pavillon Bruillatre Balbatre, CHU de Nancy, 54035 Nancy Cedex, France
[g] Addictovigilance Bordeaux, Service de pharmacologie médicale, Hôpital Pellegrin, CHU de Bordeaux, 33076 Bordeaux Cedex, France
[h] Addictovigilance Montpellier, Service de pharmacologie médicale et toxicologie, Hôpital Lapeyronie, CHU de Montpellier, 34294 Montpellier Cedex 5, France
[i] Addictovigilance du Nord-Pas-de-Calais, Service de pharmacologie médicale, CHRU de Lille, 59045 Lille Cedex, France
[j] Addictovigilance Poitiers, Service de pharmacologie clinique et vigilances, CHU de Poitiers, 86021 Poitiers Cedex, France

ARTICLE INFO

*Keywords:*
Cannabinoid hyperemesis syndrome
Addictovigilance
Cannabis
Side effects
Vomiting
Hot shower

ABSTRACT

*Background:* Cannabinoid hyperemesis syndrome is a variant of cyclical vomiting syndrome in a context of chronic cannabis usage. Our aim was to compare French cases to those identified in the international literature in order to further our knowledge of the clinical criteria, pathophysiology and treatments for cannabinoid hyperemesis syndrome.

*Methods:* We analysed cases reported in the international literature up to 30 June 2017, obtained from the MEDLINE, PsycINFO and The Cochrane Library databases; we selected relevant articles based on title and abstract. We also analysed cases of cannabinoid hyperemesis syndrome reported to the French addictovigilance network.

*Results:* A systematic search through the three databases enabled us to identify 137 articles. Finally, 55 articles were selected as they involved reported cases. In total, 113 cases were reported in these 55 articles. We were thus able to analyse 29 reported French cases of cannabinoid hyperemesis syndrome. Cannabinoid hyperemesis syndrome mainly affects young male subjects who have been smoking cannabis daily for several years. Taking hot baths or showers is the most effective means of relieving the symptoms, while antiemetics and dopamine antagonists do not appear to effective for relieving nausea and vomiting.

*Conclusions:* French cases display the same characteristics as the cases identified in the international literature. The pathophysiology of cannabinoid hyperemesis syndrome is unclear and several hypotheses have been put forward in the literature. We have only begun to characterise the syndrome, though there is an outbreak of cannabinoid hyperemesis syndrome in France.

## 1. Introduction

Cannabis has been known since antiquity and human usage is ancestral, particularly in traditional Chinese medicine (2727 BCE) (Brand and Zhao, 2017). It is the most widely used drug worldwide, with nearly 182.5 million users in 2014 according to the United Nations, i.e., 3.8% of the world population (United Nations Office on Drugs and Crime, 2016). According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), the French are by far Europe's leading consumers, with a lifetime prevalence for the 15–64 year age group of

* Corresponding author at: Addictovigilance des Pays de la Loire, Service de pharmacologie clinique, Institut de biologie, CHU de Nantes, 44093 Nantes Cedex 1, France.
*E-mail addresses:* benoit.schreck@chu-nantes.fr (B. Schreck), nicolas.wagneur@gmail.com (N. Wagneur), pascal.caillet@chu-nantes.fr (P. Caillet), marie.gerardin@chu-nantes.fr (M. Gérardin), jennyfer.cholet@chu-nantes.fr (J. Cholet), michel.spadari@ap-hm.fr (M. Spadari), nauthier@chu-clermontferrand.fr (N. Authier), j.tournebize@chru-nancy.fr (J. Tournebize), marion.gaillard85@gmail.com (M. Gaillard), anais-serre@chu-montpellier.fr (A. Serre), louise.carton@chru-lille.fr (L. Carton), stephanie.pain@univ-poitiers.fr (S. Pain), pascale.jolliet@univ-nantes.fr (P. Jolliet), caroline.vigneau@chu-nantes.fr (C. Victorri-Vigneau).

https://doi.org/10.1016/j.drugalcdep.2017.09.038
Received 12 June 2017; Received in revised form 12 September 2017; Accepted 12 September 2017
Available online 07 November 2017

40.9% (European Monitoring Centre for Drugs and Drug Addiction, 2017). According to the Observatoire Français des Drogues et des Toxicomanies (OFDT – French observatory of drugs and drug addictions), cannabis ranks first of the most widely used illicit substances in France. In 2014, 17 million French citizens declared having taken cannabis during their lifetime; 4.6 million during that year, 1.4 million at least 10 times during that month and 700,000 daily (Beck et al., 2015). Current cannabis usage mainly concerns younger individuals (28% of 18–25 year-olds, 34% of men and 23% of women). It then decreases with age, dropping to only 2% of 55–64 year-olds. Among 18–25 year-old men and women, respectively 11% and 6% are regular cannabis users (Beck et al., 2015). Since the 1990s, there has been an increase in usage in France, in a context of clear increase in cannabis supply, and in particular of self-growing and local weed production (Beck et al., 2015).

The properties of cannabis are still being elucidated and some of these are used to treat certain medical ailments, in particular drug-induced nausea and vomiting, anorexia and loss of appetite in HIV seropositive patients, along with relief of chronic pain and spasticity in multiple sclerosis (Whiting et al., 2015). But cannabis is also responsible for many adverse effects. Some have been extensively described: decreased attention, psychiatric disorders, cannabis use disorder (defined in the fifth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as the continued use of cannabis despite clinically significant impairment, ranging from mild to severe), etc. While one other, paradoxically, has emerged very recently: cannabinoid hyperemesis syndrome (CHS) (Allen et al., 2004). This is a variant of cyclical vomiting syndrome associated with taking hot showers, in a chronic cannabis usage context. CHS was first described in 2004 by Allen et al. (2004) and legitimacy of this syndrome was recently approved by the recent ROME IV criteria released in May 2016 for Functional Gastrointestinal Disorders (category B3c) (Stanghellini et al., 2016). Allen et al. observed that the syndrome consists of several phases. They described a prodromic phase during which patients presented with morning nausea and vomiting for one or several days. These symptoms appear several months, or even several years before the episodes of abdominal pain. During this phase, patients retain their appetite. Then, they described a hyperemetic phase during which patients would vomit abundantly, while suffering from sweating, abdominal pain and polydipsia. No effective treatments have been recommended, despite the cases reported in the literature.

France is the only European country with a national system dedicated to observing and evaluating psychoactive products, medicines and drug abuse and potential addiction. The addictovigilance centres are in charge of collating cases of drug dependence, abuse and misuse related to the use of psychoactive substances, reported by healthcare professionals. There are thirteen of these French centres, organized in a network. The duties of the addictovigilance centres are laid out in the French Public Health Code (*Code de la santé publique – Article R5132-112,* n.d.). The three main duties of the CEIP-A (Centre d'Evaluation et d'Information sur la Pharmacodépendance – Addictovigilance – Centre for drug dependence evaluation and information) are: i) to collect data and evaluate the dependence potential of identified psychoactive medicines; French regulations require that all cases of severe abuse and severe drug dependence associated with the usage of substances or plants with psychoactive effects, along with all other medicines or products be reported (*Code de la santé publique – Article R5132-113,* n.d.; *Code de la santé publique- Article R5132-114,* n.d.), ii) to provide information concerning the risk of psychoactive substance abuse or dependence, and iii) to conduct scientific research.

The prevalence of cannabis usage in France is one of the highest worldwide (United Nations Office on Drugs and Crime, 2016) and France possesses a dedicated monitoring system. A study of this new clinical entity was thus considered necessary. The purpose of this work was to analyse French cases of CHS reported to the French addictovigilance network; our aim was to compare these French cases to those identified in the international literature in order to further our knowledge of the clinical criteria, pathophysiology and treatments for CHS.

## 2. Material and methods

We submitted a query to the addictovigilance network in June 2016. We analysed the notification files for cases of CHS reported to the French addictovigilance centres without time limitation.

For the retrospective analysis, we selected those patients presenting with cyclical symptoms of nausea, vomiting and abdominal pain, in a context of chronic cannabis or synthetic cannabinoid usage. We analysed the data derived from their "drug dependence case notification files". In this context of scientific research, which is one of main duties of the French addictovigilance centres, no permission to use database was required (*Code de la santé publique -Article R5132-112,* n.d.). Indeed, all healthcare professionals (regardless of their field of expertise) are required to anonymously report cases of serious drug abuse and dependence associated with the use of substances or plants with psychoactive effects (*Code de la santé publique- Article R5132-97,* n.d.; *Code de la santé publique- Article R5132-116,* n.d.). These spontaneous notification reports (Nots) by healthcare professionals are key for determining "real life" drug misuse and abuse and for identifying new non-medicinal drugs that present a risk to public health.

The following characteristics, when available, were used for the analysis: gender, age, daily usage, duration of cannabis usage, time from start of usage to onset of the first crisis periods, desired effects of usage, other substances consumed, duration of crisis periods, patient complaints (in addition to abdominal, nausea and vomiting), clinical examination anomalies, biological test anomalies, weight loss during the crisis periods, improvement of symptoms by taking hot showers, existence of similar episodes, associated diseases and medical and surgical history. Finally, we analysed the efficacy of the various symptomatic treatments prescribed to these patients.

Moreover, we performed a literature review, with no time limit, on the MEDLINE, PsycINFO and The Cochrane Library databases. For this, we used the following keywords: "cannabinoid"; "hyperemesis". Our search equation was as follows: ("cannabinoids"[MeSH Terms] OR "cannabinoids"[All Fields] OR "cannabinoid"[All Fields]) AND ("hyperemesis"[All Fields]). We limited out literature search to those articles indexed in the database up to 30 June 2017. We analysed those articles pertaining to CHS; no language restriction was imposed. We selected relevant articles from their title and abstract. Articles not reporting any cases were excluded. The full text of the articles was then downloaded to analyse the characteristics of these reported cases; when available; they were collected; they were the same as those used to analyse the cases reported to the French addictovigilance network. Case report or case series were rejected if details about CHS were not enough provided.

A statistical analysis has been performed to compare the following two groups: French cases and literature cases. The Fisher's exact test was used to compare proportions between independent two groups. The Wilcoxon – Mann – Whitney's test was utilized to compare mean scores among two groups. A P-value of $< 0.05$ was considered statistically significant.

## 3. Results

### 3.1. Study of cases reported to the addictovigilance network

In total, the addictovigilance network collected 29 notifications of CHS cases. The characteristics of these cases are given as a Supplementary Material.

The first notifications of CHS were reported only recently. Before 2013, this syndrome had never been reported to the addictovigilance centres; notifications increased markedly from 2015 onwards (Fig. 1).

All of these cases had a similar clinical presentation. Patients