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Psychiatric disorders and hepatitis C treated with direct-acting antivirals in a French reference center

Michel Doffoel[1*], Florence Ernwein[1], Frédéric Chaffraix[1], Simona Tripon[1], Jean-Philippe Lang[1], Anais Lang[1], Lucile Haumesser[2], Robert Bader[3], Dominique Paya[4], Maude Royant[1], Aurélie Velay-Rusch[5], Martine Tebacher[6], Nicolas Meyer[2], Thomas Baumert[7], François Habersetzer[8] and Laurence Lalanne[9,10]

[1]Service expert de lutte contre les hépatites virales d'alsace (SELHVA) Pôle hépato-digestif, Nouvel hôpital civil, Hôpitaux universitaires, Strasbourg, France. [2]Groupe méthode en recherche clinique, Pôle de santé publique au travail, Hôpitaux universitaires, Strasbourg, France. [3]Service d'hépato gastroentérologie, Groupement hospitalier régional Mulhouse sud alsace, Mulhouse, France. [4]Pharmacie, Hôpitaux universitaires, Strasbourg, France. [5]Laboratoire de Virologie, Hôpitaux universitaires, Strasbourg, France. [6]Centre régional de pharmacovigilance grand est, Hôpitaux universitaires, Strasbourg, France. [7]Institut de Recherche sur Maladies Virales et Hépatiques, Inserm U1110, Université de Strasbourg, Strasbourg, Institut Universitaire de France, Paris, France [8]Service d'hépato gastroentérologie, Pôle hépato-digestif, Nouvel hôpital civil, Hôpitaux universitaires, Strasbourg, France. [9]Département de Psychiatrie et d'Addictologie et Fédération de Médecine Translationnelle de Strasbourg (FMTS), Hôpitaux universitaires, Strasbourg, France. [10]Institute for research on viral and hepatic diseases, Inserm U1110, University of Strasbourg, Strasbourg, University Institute of France, Paris, France.

ABSTRACT

HCV can cause psychiatric disorders. It is crucial to re-evaluate them with direct-acting antiviral treatment (DDAs), since the interferon-based treatments of the past were capable of causing identical psychiatric adverse effects. A system of multidisciplinary team (MDT) meetings was implemented in France in December 2014 in regional reference centers with the aim of controlling the prescription and administration of these new treatments, along with optimizing how the patients undergoing these treatments are followed up. Our study sought to compare the characteristics and type of medical care received for chronic hepatitis C in patients with (PSY+ group) and without (PSY- group) psychiatric disorders using data from MDT meetings in the Alsace area of France collected from 2015 to 2019.

All included patients were mono-infected and treated with DAAs in successive rounds between 2015 and 2019, as per recommendations from the French Hepatology Society. We compared the two groups (PSY+ and PSY-) based on 21

***Correspondence to Author:**
Michel DOFFOEL (MD)
Service expert de lutte contre les hépatites virales d'Alsace (SELHVA) Pôle hépato-digestif, Nouvel hôpital civil, Hôpitaux universitaires, Strasbourg, France.

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variables regarding the characteristics and medical care of hepatitis C.
Psychiatric disorders were observed in 15% of patients. On multivariate analysis, a positive correlation was found between them and drug use (OR: 2.35; 95%CI: 1.40-3.98; p=0.001), excessive alcohol consumption (OR: 1.92; 95%CI: 0.98-3.69; p=0.05), smoking (OR: 1.81; 95%CI: 1.09-2.98; p=0.02), and incidence of drug interactions (OR: 3.94; 95%CI: 2.15-7.17; p <0.001). The only negative correlation found was with pangenotypic DAA administration (OR: 0.55; 95%CI: 0.32-0.92; p=0.02). SVR 12 was 98.05% in the PSY+ group, not significantly different from that of the PSY- group.
All in all, the psychiatric disorders observed in patients suffering from chronic hepatitis C are primarily associated with using psycho-active substances, with no impact on SVR 12 rates.

Lay summary

The psychiatric disorders observed in patients suffering from chronic hepatitis C treated with direct-acting antivirals are primarily associated with drug use, excessive alcohol consumption and tobacco consumption. They increase the incidence of drug interactions. They have no impact on virological healing.

Highlights:

- 15% of patients with HCV monoinfection treated with direct-acting antivirals were suffering from psychiatric disorders.
- Psychiatric disorders were associated with drug use.
- They were also associated with other psycho-active substances (alcohol and tobacco).
- They increased the incidence of drug interactions.
- They have no impact on sustained virological response.

Keywords: hepatitis C, psychiatric disorders, multidisciplinary team meetings, direct-acting antivirals.

Introduction

The hepatitis C virus (HCV) is a neurotropic virus from the Flaviviridae family that can infect the microglia and astrocytes [1,2]. In chronic cases, HCV can cause chronic fatigue, sleep disorders, mixed anxiety-depression disorders, and less-specific cognitive disorders [3,4]. Chronic HCV is thus a disease that not only attacks the liver, potentially progressing into cirrhosis and hepatocellular carcinoma if left untreated, but also a systemic disease affecting several other organs, including the brain, by causing chronic inflammation [5,6]. Furthermore, the chronic HCV prevalence is higher in psychiatric patients than in the general population [7]. This difference is likely due, at least to some extent, to the incidence of psychiatric comorbidities in injecting drug users, either former or active, who represent the primary pool of hepatitis C [8]. Few studies examined the kind of psychiatric comorbidities in injecting drug users. Among psychiatric comorbidities, the most frequently reported are major depressive disorder, alcohol dependence, antisocial personality disorder, and borderline personality disorder [8], with a higher risk of suicide [9]. Psychological distress associated with personality disorders [10] and traumatic events exposure associated with post-traumatic disorder [11] are reported. It is difficult in differentiating these psychiatric disorders from those due to HCV infection which are depression, anxiety and fatigue [12]. In France, data on this issue remains spotty [13]. Up until 2015, chronic HCV treatment was based on a combination of interferon with ribavirin, resulting in limited efficacy with only a 50% cure rate, as well as exposing patients to

numerous adverse effects that were notably psychiatric in nature [3,4]. We thus deemed it justified to re-evaluate psychiatric disorders in the light of the emergence of direct-acting antivirals (DAAs), which truly revolutionized treatment. These drugs are remarkably effective, resulting in over 95% virological cure and offering simple, short-term administration that has proven very safe with very few psychiatric impact. This allows easily to enlarging indications of HCV treatment. Indeed, psychiatric comorbidities is not a restriction of indication and there is no necessity for the patients to be followed up by a psychiatrist during the period of treatment. With the emergence of DAAs, multidisciplinary team (MDT) meetings were implemented in France in December 2014 within regional reference centers, certified as expert services in the fight against viral hepatitis, as part of their coordinating role [14]. A treatment decision was handed down for each case presented before an MDT, according to the indications as well as DAA administration and prescription methods in practice between 2014 and 2019. In the beginning, DAAs were prescribed by hospital-based hepato-gastroenterologists, infectious diseases specialists, or internal medicine specialists, and dispensed by in-hospital pharmacies. The indications were restrictive, solely applying to chronic HCV in adults with advanced F3 or F4 fibrosis or severe F2 fibrosis (depending on clinical condition and the progression of the fibrosis) along with chronic HCV associated with HIV infection or mixed systemic and symptomatic cryoglobulinemia, or with B-cell lymphoma, irrespective of fibrosis stage [14]. In July 2016, the treatment was extended to include Stage F2 fibrosis [15]. In August 2017, the treatment was extended to all stages of fibrosis and MDTs limited to complex cases involving advanced F3-F4 fibrosis and/or comorbidities [16]. In March 2018, street pharmacies outside of hospitals were also authorized to dispense DAAs [17]. Finally, in May 2019, the prescription of pangenotypic DAAs became universal, with the notable possibility of general practitioners (GPs) being enabled to prescribe them in the context of simplified hepatitis C care, *i.e.,* in cases not involving advanced fibrosis, HIV or hepatitis B coinfection, severe kidney failure, organ transplant or poorly-managed comorbidities, such as excessive drinking, diabetes, and obesity [18]. This study sought to define the impact of age on the characteristics and medical care type of chronic hepatitis C in patients with and without psychiatric disorders based on MDT data collected from 2015 to 2019.

Patients and methods

All patients who were included in this study were residents of the Alsace area, part of the Grand-Est region of France, and presented with mono-infection of the hepatitis C virus (HCV). The files of all patients were submitted to the Alsace expert service in the fight against viral hepatitis (SELHVA) most often through a specialist practitioner, (hepatogastroenterologist or internist or addictologist) or more rarely through a general practitioner. An indication for DAA treatment over 8 to 24 weeks was approved in all patients, to be administrated in successive rounds between January 2015 and February 2019, as recommended by the French Society of Hepatology (French Association for the Study of the Liver AFEF) [19]. For some patients, this was their first DAA treatment; for the others, it was a retreatment following resistance or relapse after interferon-based treatment. The treatment's efficacy was evaluated based on sustained virological response, corresponding to absence of detectable HCV-RNA in the blood 12 weeks after treatment end (SVR 12). Patients with HCV-HIV coinfection were not included in this study, as they were treated using a different care pathway.

The patients were separated into two groups based on presence (PSY+) or absence (PSY-) of psychiatric disorders. The latter essentially consisted of depression or anxiety disorders. All the patients of the PSY+ group had consulted a psychiatrist at least once before commencing DAA treatment. In the PSY- group, the absence of psychiatric disorders was not validated by a psychiatrist. Nevertheless, all the hepatology specialists overseeing the chronic hepatitis C treatment had experience with the previous interferon-based treatments and were able to

consult a referring psychiatrist from SEHLVA if they had any concerns in regard to this.

All results were collected by the SELHVA, between January 2015 and December 2019, from computerized patient summary reports including the MDT rulings, in accordance with the AFEF model, except for data on SVR 12 rates [20]. The results of the HCV-RNA PCR were obtained at a later date by SELHVA from the prescribing specialist or the referring GP, with sensitive information kept confidential.

The characteristics of hepatitis C analyzed involved the following variables: a) demographics: age, gender, and country of birth, with patients born in foreign countries having lived in France for less than six months defined as migrants; b) epidemiology: with drug users defined as anyone who had injected or sniffed drugs at least once in their life, according to the criteria outlined in the French ANRS-Coquelicot study [21] and viral genotype; c) clinical and paraclinical data: fibrosis stage, evaluated in most cases using FibroScan®, with an elasticity value ≥10kP corresponding to advanced fibrosis (stages F3-F4) [20]; hepatocellular carcinoma complicated by cirrhosis, history of organ transplant (liver and/or kidney); symptomatic cryoglobulinemia; related comorbidities: obesity defined as BMI ≥30Kg/m^2, Type 2 diabetes, excessive alcohol consumption (exceeding a self-reported 10 standard drinks/week but not exceeding two standard drinks/day) [22]; other consumptions: daily tobacco and cannabis use, without any specification as for the number of cigarettes or joints per day.

The variables concerning type of care were: a) the type of care structure used: a hepato-gastroenterology department working with SELHVA and the internal medicine department of the Strasbourg university hospital center (CHU), the Alsace general hospitals, drug addiction prevention and care centers, and health networks of GPs focused on social precarity or drug addiction; b) therapeutic patient education (TPE), solely accessible to patients of the CHU, consisting of a program managed by a nurse with the support of a multidisciplinary team and aided by a patient association (*SOS Hépatites Alsace-Lorraine)*; c) first DAA treatment or retreatment following failed interferon-based treatment; d) DAA type, pangenotypic or not; e) opioid-substitution therapy (OST) for drug users; f) drug interactions with DAAs; and g) SVR 12.

All summary files saved on the Strasbourg university hospitals server were collated by SELHVA into one Excel spreadsheet, and then anonymized for statistical analysis. The ethics committee of the Strasbourg medical faculty accorded approval for the study on the December 17th 2020 (CE-2020-171). The data analysis was saved on the Strasbourg university hospitals register on January 22, 2021 (register reference: 21-009).

The statistical analysis was carried out by the clinical research analysis team (*Groupe Méthode en Recherche Clinique*) from the workplace public health service of the Strasbourg CHU. All analyses were performed using R Studio software. Continuous variables were expressed as median with first and third quartiles. Categorical variables were expressed as numbers and proportion. Regarding the analysis of variables, the first step consisted of univariate analysis, using a logistic regression model. Results were expressed by odd-ratio (OR) and 95% confidence intervals (95%CI). Each variable of the univariate analysis with a p value equal to or over 0.2 was introduced into the multivariate analysis. The multivariate analysis was a logistical regression model that was performed on the previously selected variables chosen. The criteria of information of Akaike (AIC) were applied in order to maintain only the most relevant variables so as to explain the dependent variable used.

Results

This study included 1,415 patients, 257 in the PSY+ group (15.4%) and 1,158 in the PSY- group.

All patient characteristics have been presented in *Table 1*. The median age was 54 years old (yo), with the patients being predominantly male (60.6%). More than 8/10 patients were born in France. The majority of the migrant

population were born in Eastern European countries, including Georgia, Belarus, Chechnya, Kosovo, and Bosnia. The rest were born in northern or sub-Saharan Africa or central Asia. The transmission route was related to drug use in a third of the patients. Blood transfusion or nosocomial transmission affected 12% of patients. The origin of transmission was unknown in half of the patients. Genotype 1 was predominant (57.88%). Nearly half of the patients presented with advanced fibrosis. Hepatocellular carcinoma and history of organ transplant were extremely rare. Less than 10% of patients displayed symptomatic cryoglobulinemia. The median BMI was 24.61Kg/m^2 with 13.28% of patients defined as obese. In total, 12.22% of patients were diabetic. Excessive alcohol consumption was reported in 8.27% of patients. Tobacco and cannabis uses were reported in 21.98% and 6.43% of patients, respectively. Details on where and how treatment was received for all patients are presented in *Table 2*. For over 80% of patients, this treatment was received in a hospital, either a CHU or general hospital center. Over a third of patients benefitted from TPE. Two-thirds of the patients were prescribed their first round of DAA treatment, specifically pan-genotypic DAAs in a quarter of cases. Of all the drug users, nearly 60% had been prescribed OST. Drug interactions with DAAs were reported in 12.15% of the patients. SVR 12 was observed in 97% of patients.

Table 1. Comparison of the characteristics of chronic hepatitis C between patients with (PSY+ group) and without (PSY- group) psychiatric disorders. (Abbreviations: a) BMI: body mass index; b) >10 drinks/week).

Characteristics	**Total (N= 1415)**			**Group PSY + (N=257)**			**Group PSY - (N=1158)**			**P values**
	n	**median**	**CI 95%**	**n**	**median**	**CI 95%**	**n**	**median**	**CI 95%**	
Age	1405	54	31-81	257	51	32-75	1148	55	30.68-81.33	<0.001
BMI (kg/m2) (a)	1279	24.49	17.75-37.84	232	24.95	18.26-40.34	1047	24.46	17.72-37.03	NS
	n	**%**	**CI 95%**	**n**	**%**	**CI 95%**	**n**	**%**	**CI 95%**	
Sex										0.01
male	858	60.63	58.04-63.19	174	67.70	61.61-73.38	684	59.07	56.17-61.92	
female	557	39.36	36.81-41.96	83	32.30	26.62-38.39	474	40.93	38.08-43.83	
Native country										NS
France	1172	82.83	80.76-84.76	217	84.44	79.41-88.64	955	82.47	80.15-84.62	
Migrants	243	17.17	15.24-19.24	40	15.56	11.36-20.59	203	17.53	15.38-19.85	
Drug users										<0.01
yes	458	32.37	29.93-34.88	139	54.09	47.78-60.29	319	27.55	24.99-30.22	
no	957	67.63	65.12-70.07	118	45.91	39.71-52.22	839	72.45	69.78-75.01	
Genotypes										NS
1	819	57.88	55.26-60.47	139	54.09	47.78-60.29	680	58.72	55.82-61.58	
3	312	22.05	19.91-24.30	75	29.18	23.70-35.15	237	20.47	18.18-22.91	
others	241	17.03	15.11-19.09	35	13.62	9.67-18.43	206	17.79	15.63-20.12	
Advanced fibrosis										<0.05

yes	671	47.42	44.79-50.06	135	52.53	46.23-58.77	536	46.29	43.28-49.21	
no	717	50.67	48.03-53.31	115	44.75	38.57-51.05	602	51.99	49.06-54.90	
Hepatocellular carcinoma										NS
yes	46	3.25	2.39-4.31	4	1.56	0.43-3.94	42	3.63	2.63-4.87	
no	1369	96.75	95.69-97.61	253	98.44	96.06-99.57	1116	96.37	95.13-97.37	
Transplantation										NS
liver	23	1.63	1.03-2.43	5	1.95	0.63-4.48	18	1.55	0.92-2.45	
kidney	6	0.42	0.16-0.92	1	0.39	0.01-2.15	5	0.43	0.14-1.00	
none	1385	97.88	96.99-98.57	251	97.67	94.99-99.14	1134	97.93	96.93-98.67	
Cryoglobulin										NS
yes	112	7.92	6.56-9.45	20	7.78	4.82-11.76	92	7.94	6.45-9.65	
no	1281	90.53	88.88-92.01	226	87.94	83.32-91.66	1055	91.11	89.32-92.68	
BMI (kg/m2) (a)										NS
<25	715	50.53	47.89-53.17	131	50.97	44.69-57.24	584	50.43	47.51-53.35	
25-29.9	374	26.43	24.15-28.81	64	24.90	19.74-30.66	310	26.77	24.24-29.42	
≥ 30	188	13.29	11.56-15.17	37	14.40	10.34-19.29	151	13.04	11.15-15.12	
Diabetes										NS
yes	173	12.23	10.56-14.05	25	9.73	6.39-14.02	148	12.78	10.91-14.84	
no	1242	87.77	85.95-89.44	232	90.27	85.98-93.61	1010	87.22	85.16-89.09	
Excessive consumption of alcohol (b)										<0.001
yes	117	8.27	6.89-9.83	41	15.95	11.70-21.01	76	6.56	5.21-8.15	
no	1268	89.61	87.9-91.15	208	80.93	75.59-85.55	1060	91.54	89.78-93.08	
Tobacco										<0.001
yes	311	21.98	19.85-24.23	87	33.85	28.09-39.99	224	19.34	17.11-21.74	
no	663	46.86	44.23-49.49	79	30.74	25.16-36.77	584	50.43	47.51-53.35	
Cannabis										
yes	91	6.43	5.21-7.84	34	13.23	9.34-17.99	57	4.92	3.75-6.33	<0.001
no	880	62.19	59.61-64.73	131	50.97	44.69-57.24	749	64.68	61.85-67.44	

Table 2. Comparison of the therapeutic care of chronic hepatitis C between patients with (PSY+ group) and without (PSY- group) psychiatric disorders. (Abbreviations: a) TPE: therapeutic patient education; DAAs: direct acting antivirals; OST: opioid substitution treatment; SVR 12: substained virological response after 12 weeks).

Therapeutic care	Total (N=1415)			Group PSY+ (N=257)			Group PSY- (N=1158)			P values
	n	%	CI 95%	n	%	CI 95%	n	%	CI 95%	
Structures										NS
university hospital center	717	50.67	48.03-53.31	130	50.58	44.30-56.85	587	50.69	47.77-53.61	
general hospitals	437	30.88	28.48-33.36	84	32.68	26.99-38.79	353	30.48	27.84-33.23	
addictology centers	73	5.16	4.07-6.44	19	7.39	4.51-11.30	54	4.66	3.52-6.04	
general medicine networks	188	13.29	11.56-15.17	24	9.34	6.08-13.58	164	14.16	12.20-16.30	
TPE (a)										0.01
yes	241	33.61	30.16-37.20	58	44.62	35.90-53.58	183	31.18	27.45-35.10	
no	447	62.34	58.68-65.90	66	50.77	41.86-59.64	381	64.91	60.89-68.77	
Primary treatment										NS
yes	971	68.62	66.13-71.03	182	70.82	64.85-76.30	789	68.13	65.36-70.81	
no	444	31.38	28.97-33.87	75	29.18	23.70-35.15	369	31.87	29.19-34.64	
Type of DAAS										0.02
pangenotypic	351	24.81	22.57-27.14	49	19.07	14.45-24.41	302	26.08	23.57-28.71	
no pangenotypic	1064	75.19	72.86-77.43	208	80.93	75.59-85.55	856	73.92	71.29-76.43	
OST (b)										NS
yes	271	59.17	54.51-63.71	89	64.03	55.46-71.99	182	57.05	51.42-62.55	
no	187	40.83	36.29-45.49	50	35.97	28.01-44.54	137	42.95	37.45-48.58	
Drug interactions										<0.001
yes	172	12.15	10.50-13.97	52	20.23	15.50-25.67	120	10.36	8.67-12.26	
no	1243	87.85	86.03-89.50	205	79.77	74.33-84.50	1038	89.64	87.74-91.33	
SVR 12 (c)										NS
yes	1374	97.10	96.00-97.91	252	98.05	95.52-99.37	1122	96.89	95.72-97.81	
no	31	2.19	1.49-3.10	5	1.95	0.63-4.48	26	2.25	1.47-3.27	

We compared patient characteristics and hepatitis C care type between the two groups, PSY+ and PSY- by univariate analysis, with the results presented in *Tables 1 and 2*. The PSY+ patients were younger ($p < 0.001$) and more predominantly male ($p=0.01$). Drug use was twice as common in this group (54.09% *vs.* 27.55%, $p < 0.01$). Advanced fibrosis was more common (52.53% *vs.* 46.29%, $p < 0.05$), as was excessive alcohol consumption (15.95% *vs.* 6.56%, $p < 0.001$), and was tobacco (33.85% *vs.* 19.34%, $p < 0.001$) and cannabis use (13.23% *vs.* 4.92%, $p < 0.001$), as well. The proportion of migrants, distribution of genotypes, and BMI

classes, as well as the frequency of hepatocellular carcinoma, organ transplant, cryoglobulinemia, and diabetes did not differ significantly between both groups. Out of the different hepatitis C care types received, TPE was most common in the PSY+ group (44.62% *vs.* 31.18%, p=0.01), as were non-pan-genotypic DAA treatment (80.93% *vs.* 73.92%, p <0.02) and drug interactions (20.23% *vs.* 10.36%, p <0.001). The distribution in terms of type of medical center used, however, along with the incidence of this being a first DAA treatment, that of OST in drug users, and SVR 12 rate, did not significantly differ between the groups.

On multivariate analysis (*Table 3*), there was a positive correlation between the presence of psychiatric disorders on the one hand and drug use (p=0.001), excessive alcohol consumption (p=0.05), tobacco use (p=0.02), and incidence of drug interactions (p <0.001) on the other. The only negative correlation found was with pan-genotypic DAA administration (p=0.02).

Table 3. Association between psychiatric disorders and characteristics/therapeutic care of chronic hepatitis C (multivariate analysis by logistical regression model).

Variables	OR	95% CI	p-values
Drug users	2.35	1.40-3.98	0.001
Alcohol exces	1.92	0.98-3.69	0.05
Tobacco	1.81	1.09-2.98	0.02
Drug interactions	3.94	2.15-7.17	<0.001
Type of DAAs	0.55	0.32-0.92	0.02

Discussion

In total, this study on HCV mono-infections discussed in MDT meetings demonstrated that 15% of patients were suffering from psychiatric disorders. These were associated with the use of psychoactive substances (injectable and/or sniffed drugs, alcohol consumption, and tobacco use) and higher incidence of drug interactions with DAAs. Psychiatric disorders were more common in the younger patients, as in the study of Mackesy-Amiti *et al* [8], with a median age of 51 yo, and in males (2/3 of cases). Chronic hepatitis C was associated with advanced fibrosis in over half of all patients; this higher incidence could be explained by the MDTs' selection methods. Over 80% of patients received their medical care in a CHU or general hospital, 44% of whom followed TPE programs; these higher numbers could likewise be explained by the selection methods of the MDTs. The SVR 12 rate was 98%, which did not significantly differ from that of the patients without psychiatric disorders. Nevertheless, the long-term outcomes of these patients were not evaluated in our study.

The incidence of psychiatric disorders in HCV-infected patients is higher than that of the general population [3]. Among the different psychiatric disorders, depression is the most common, with an incidence approaching 40% according to the 2011 report by the European expert consensus group, in other words 3.5 times that of the general population [3]. The incidence of anxiety disorders is over 20%, *i.e*., 1.5 times that of the general population [3]. Bipolar disorders and schizophrenia are less common, with an incidence below 10%. Yet fatigue, often classed as a psychiatric comorbidity, is present in over 50%. These numbers are higher than those we found in our studies, except for fatigue, which was not assessed. They were reported, however, back when chronic hepatitis C treatment was based on a combination of interferon and ribavirin, which also exposes patients to psychiatric undesirable effects. These include episodes of

depression that can be severe, and even delirium or hallucinations [3,4]. The incidence of psychiatric disorders reported by the European expert consensus group could thus be overestimated. Furthermore, they are averages from the results of six to 10 cumulative studies, but not from a meta-analysis. These limitations do not throw into doubt the brain tropism associated with HCV, particularly within mic- roglial cells, the cells involved in brain inflammation, which could correlate with the manifestation or aggravation of mixed anxiety-depressive disorders and cognitive disorders [1,2]. Moreover, the incidence of chronic hepatitis C is higher in the psychiatric population than in the general population. Hence, in a 2016 international meta-analysis, the incidence in Europe was estimated at 0.5%, *i.e.,* 5 to 10 times that of the general population [7].

This increase is probably linked to the frequency with which psychiatric comorbidities manifest in drug users, both former and active, who still constitute the primary pool of hepatitis C sufferers, despite the preventative measures and risk-reduction action that have been put in motion [23]. In our study, there consequently was a significant positive correlation found on multivariate analysis between the presence of psychiatric disorders and drug use. Such drugs included not only injected substances but also sniffed drugs, confirming the particular risk of transmission via straw-sharing. In the meta-analysis by Goldner *et al.* [24] analyzing north-American users of non-prescription opiates, 43% displayed psychiatric disorders. In the 2011 report by the European expert consensus group, the incidence of psychiatric disorders even exceeded 50% among drug users infected with HCV [3]. Drug use does not, however, fully explain this increased prevalence. In an American epidemiological study conducted among a psychiatric population, only 2/3 of the patients testing positive for HCV reported a history of substance abuse [25]. In our study, we also discovered a significant positive correlation on multivariate analysis between presence of psychiatric disorders and excessive alcohol consumption. In the 2011 report by the European expert consensus group, the incidence of psychiatric disorder exceeded 50% in HCV-infected patients reporting excessive alcohol consumption [3]. Nevertheless, the studies have primarily included institutionalized populations that probably indulge in multi-risk behaviors [8]. In our study, alcohol consumption was solely self-reported, which represents a limitation. The significant correlation between psychiatric disorders and smoking, revealed on multi-variate analysis in our study, is a well-known correlation even outside of the chronic HCV population. The incidence of smoking is 2 to 3 times higher in patients with psychiatric disorders than in the general population [26]. This increase is largely due to how difficult it is for psychiatric patients to quit smoking. Conversely, the incidence of psychiatric disorders is higher in smokers than in non-smokers [27]. Hence, in the Lasser *et al* investigation [28], the incidence of smokers rose to 36.6% and 59% in the month preceding the investigation and in the whole life-time, respectively, among patients with depression. The numbers were even higher, 46

% and 68.4%, respectively, in patients with generalized anxiety disorder. In our study, cannabis use was 2.7 times higher in the PSY+ group than in the PSY- patients on univariate analysis, yet the correlation between cannabis use and psychiatric disorders was not significant on multivariate analysis,yet there was a significant amount of missing data in both groups. The last significant positive correlation revealed involved psychiatric disorders and drug interactions with DAAs. While the exact prescription drugs causing these interactions were not recorded in this study, the majority of these involved central nervous system activity. Among them, potential interactions were observed with anti-psychotics, such as aripiprazole, clozapine, paliperidone, and quetiapine [29]. These interactions may require a dosage adjustment, altered timing of administration, or additional monitoring. They mainly concern glecaprevir/pibrentasvir and grazoprevir/elbasvir [29].

The only significant negative correlation discovered in our study concerned pan-genotypic

DAAs, as revealed on multivariate analysis. This correlation is likely related to how MDTs have evolved, since they were no longer obligatory from August 2017 onwards, hence at a time before all pan-genotypic DAAs were available [17]. Our study was unable to define the quantities of pan-genotypic DAAs that were prescribed outside of MDT rulings, particularly in the context of simplified hepatitis C care [18].

In conclusion, psychiatric disorders no longer represent a barrier to chronic hepatitis C treatment. Our study confirms the efficacy of DAAs, with a virological cure rate close to 100%. Further studies are now necessary in order to assess the long-term outcomes of these patients, both in terms of their liver and psychiatric health, as well as their reinfection risk.

Abbreviations:

AFEF: French Association for the Study of the Liver (Association française pour l'étude du foie).
BMI: body mass index.
CHU: university hospital center (Centre hospitalo-universitaire).
GPs: general practitioners.
MDT: multidisciplinary team.
SELHVA: Alsace expert service in the fight against viral hepatitis (Service expert contre les hépatites virales Alsace).
OST: opioid-substitution treatment.
PSY: psychiatric.
TPE: therapeutic patient education.
yo: years old.

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Michel DOFFOEL: originated the study conception and design and drafted the manuscript.
Florence ERNWEIN: contributed to the study conception and manuscript preparation.
Frederic CHAFFRAIX: contributed to the study conception and design, drafted and reviewed the manuscript.
Simona TRIPON: originated the study, contributed to interpretation of findings and reviewed the manuscript.
Jean-Philippe LANG: contributed to the study and reviewed the manuscript.
Anais LANG: contributed to the study and reviewed the manuscript.
Lucile HAUMESSER: conducted the statistical analyses.
Robert BADER: contributed to the study and interpretation of findings.
Maude ROYANT: contributed to the study and interpretation of findings.
Aurélie VELAY-RUSCH: contributed to the study and interpretation of findings.
Martine TEBACHER: contributed to the study and interpretation of findings.
Nicolas MEYER: advised on the statistical analysis and interpretation of findings.
Thomas BAUMERT: contributed to interpretation of findings and reviewed the manuscript.
François HABERSETZER: contributed to the study and interpretation of findings.
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References

[1] Wilkinson J, Radkowski M, Laskus T. Hepatitis C virus neuroinvasion: identification of infected cells. J Virol 2009; 83: 1312–1319. https://doi.org/10.1128/JVI.01890-08

[2] Pflugrad H, Meyer GJ, Dirks M, Raab P, Tryc AB, Goldbecker A, et al. (2016). Cerebral microglia activation in hepatitis C virus infection correlates to cognitive dysfunction. J Viral Hepat 2016; 23: 348–357. https://doi.org/10.1111/jvh.12496

[3] Schaefer M, Capuron L, Friebe A, Diez-Quevedo C, Robaeys G, Neri S, et al. Hepatitis C infection, antiviral treatment and mental health: a European expert consensus statement. J Hepatol 2012; 57: 1379–1390.

https://doi.org/10.1016/j.jhep.2012.07.037

[4] Negro F, Forton D, Craxì A, Sulkowski MS, Feld JJ, Manns MP (2015). Extrahepatic morbidity and mortality of chronic hepatitis C. Gastroenterology 2015; 149: 1345–1360. https://doi.org/10.1053/j.gastro.2015.08.035

[5] Sène D, Limal N, Cacoub P. (2004). Hepatitis C virus-associated extrahepatic manifestations: a review. Metab Brain Dis 2004, 19: 357–381. https://doi.org/10.1023/b:mebr.0000043982.17294.9b

[6] Pol S, Vallet-Pichard A, Hermine O (2018). Extrahepatic cancers and chronic HCV infection. Nat Rev Gastroenterol Hepatol 2018;15: 283–290. https://doi.org/10.1038/nrgastro.2017.172

[7] 7. Hughes E, Bassi S, Gilbody S, Bland M, Martin F. (2016). Prevalence of HIV, hepatitis B, and hepatitis C in people with severe mental illness: a systematic review and meta-analysis. Lancet Psychiatry 2016; 3: 40–48. https://doi.org/10.1016/S2215-0366(15)00357-0

[8] 8. Mackesy-Amiti ME, Donenberg GR, Ouellet LJ. Prevalence of psychiatric disorders among young injection drug users. Alcohol Depend 2012; 124: 70-78. doi:10.1016/j.drugalcdep.2011.12.012

[9] Dinwiddie SH, Reich T, Cloninger CR. Psychiatric comorbidity and suicidality among intravenous drug users. J Clin Psychiatry 1992; 53 : 364-369.

[10] Gibbie TM, Hides LM, Cotton SM, Lubman DI, Aitken C, Hellard M. The relationship between personality disorders and mental health substance use severity and quality of life among injecting drug users. Med J Aust 2011; 195: S16-21. https://doi.org/10.5694/j.1326-5377.2011.tb03260.x

[11] Peirce JM, Kolodner K, Brooner RK, Kidorf MS. Traumatic event re-exposure in injecting drug users. J Urban Health 2012; 89: 117-128. https://doi.org/10.1007/s11524-011-9619-9

[12] Adinolfi LE, Nevola R, Lus G, Restivo L, Guerrera B, Romano C, et al. Chronic hepatitis C virus infection and neurological and psychiatric disorders: An overview. World J Gastroenterol 2015; 21: 2269-80. https://doi.org/10.3748/wjg.v21.i8.2269

[13] Rolland B, Bailly F, Cutarella C, Drevon O, Carrieri P, Darque A, et al. Hépatite C en milieu psychiatrique: un réservoir oublié? L'Encephale 2021; 47: 181–184. https://doi.org/10.1016/j.encep.2020.03.003

[14] Direction générale de la Santé. Lettre d'instruction relative à l'organisation de la prise en charge de l'hépatite C par les nouveaux antiviraux d'action directe (NAAD). Paris: DGS; 2014. 5 p. http://www.chru-strasbourg.fr/sites/default/files/u122/Lettre_d_instruction_hepatite_C_NAAD_29_dec_2014.pdf

[15] Ministère des Affaires sociales et de la Santé. Instruction N° DGOS/PF2/DGS/SP2/PP2/DSS/1C/2016/246 du 28 juillet 2016 relative à l'organisation de la prise en charge de l'hépatite C par les nouveaux antiviraux d'action directe (NAAD). 2016. 14 p. http://www.chru-strasbourg.fr/sites/default/files/u122/Circulaire_du_28_juillet_2016_pec_des_AAD.pdf

[16] Ministère des Solidarités et de la Santé. InstructionN° DGOS/PF2/DGS/SP2/DSS/1C/2017/246 du 3 août 2017 relative à l'élargissement de la prise en charge par l'assurance maladie du traitement de l'hépatite C par les nouveaux agents antiviraux d'action directe (AAD) à tous les stades de fibrose hépatique pour les indications prévues par l'autorisation de mise sur le marché et à la limitation de la tenue d'une réunion de concertation pluridisciplinaire pour les initiations de traitement à des situations particulières listées. 2017. 9 p. https://solidarites-sante.gouv.fr/fichiers/bo/2017/17-08/ste_20170008_0000_0046.pdf

[17] Thelliez B. La révolution passe (enfin) par l'officine. Le Pharmacien de France 2018; 1330 http://www.lepharmaciendefrance.fr/actualite-web/la-revolution-passe-enfin-par-lofficine

[18] Haute Autorité de Santé. Hépatite C : prise en charge simplifiée chez l'adulte. Recomman- dations de bonne pratique. [Internet]. Saint Denis La Plaine: HAS; 2019. https://www.has-sante.fr/jcms/c_2911891/fr/hepatite-c-prise-en-charge-simplifiee-chez-l-adulte

[19] Société Française d'Hépatologie. Recommandations AFEF sur la prise en charge des hépatites virales C. 2015, 2016, 2017 et 2019. Paris: AFEF. https://afef.asso.fr/recommandations/recommandations-afef/

[20] Société Française d'Hépatologie. Recommandations AFEF sur la prise en charge des hépatites virales C. Fiche RCP hépatites virales C. Paris : AFEF 2017. https://afef.asso.fr/wp-content/uploads/2018/06/Fiche-RCP-juillet-2017-afef.pdf

[21] Jauffret-Roustide M, Pillonel J, Weill-Barillet L, Léon L, Le Strat Y, Brunet S, et al. Estimation de la séroprévalence du VIH et de l'hépatite C chez les usagers de drogues en France. Premiers

résultats de l'enquête ANRS-Coquelicot 2011. Bull Epidémiol Hebd. 2013 ; 39-40: 504-509. http://beh.santepubliquefrance.fr/beh/2013/39-40/2013_39-40_2.html

[22] Drinking guidelines: General population. International Alliance for Responsable Drinking (IARD); 2019 https://iard.org/science-resources/detail/Drinking-Guidelines-General-Population

[23] Organisation de la prise en charge thérapeutique et du suivi des personnes usagères de drogues infectées par le virus de l'hépatite C. In : Prise en charge thérapeutique et suivi de l'ensemble des personnes infectées par le virus de l'hépatite C. Rapport de recommandations 2016. EDP Sciences, Paris, 2016, p 13-30.

[24] Goldner EM, Lusted A, Roerecke M, Rehm J, F. B. Prevalence of Axis-1 psychiatric (with focus on depression and anxiety) disorder and symptomatology among non-medical prescription opioid users in substance use treatment: systematic review and meta-analyses. Addict Behav 2014; 39: 520–531. https://doi.org/10.1016/j.addbeh.2013.11.022

[25] Dinwiddie SH, Shicker L, Newman T. Prevalence of hepatitis C among psychiatric patients in the public sector. Am J Psychiatry 2003; 160: 172–174. https://doi.org/10.1176/appi.ajp.160.1.172

[26] Dervaux A, Laqueille X. Comorbidités psychiatriques du tabagisme. In : Traité d'Addictologie, Reynaud M Ed. Cachan, France : Lavoisier Médecine, 2016 ; p 585-589. https://www.cairn.info/traite-d-addictologie--9782257206503-page-585.htm

[27] Luger T M, Suls J, Van der Weg MW. How robust is the association between smoking and depression in adults? A meta-analysis using linear mixed-effects models. Addict Behav 2014; 39: 1418–1429. https://doi.org/10.1016/j.addbeh.2014.05.011

[28] Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. (2000). Smoking and mental illness: A population-based prevalence study. JAMA 2000; 284:2606–2610. https://doi.org/10.1001/jama.284.20.2606

[29] Pawlotsky JM, Negro F, Aghemo A, Berenguer M, Dalgard O, Dusheiko G, et al. EASL recommendations on treatment of hepatitis C: Final update of the series. J Hepatol 2020;73: 1170-1218.