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Effectiveness and safety of direct-acting antivirals in hepatitis C infected patients with mental disorders: results in real clinical practice

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Abstract
The aim of this study is to analyze the effectiveness and safety of direct-acting antivirals (DAAs) in psychiatric patients with chronic hepatitis C (CHC). Secondary objectives included adherence and drug-drug interaction (DDIs) evaluations. Prospective observational comparative study carried out during 3 years. Psychiatric patients were included and mental illness classified by a psychiatric team based on clinical records. Main effectiveness and safety variables were sustained virologic response (SVR) at posttreatment week 12 (SVR12) and rate of on-treatment serious drug-related adverse events (AEs), respectively. A total of 242 psychiatric and 900 nonpsychiatric patients were included. SVR12 by intention-to-treat (ITT) analysis of psychiatric vs nonpsychiatric patients was 92.6% (95% confidence interval [CI], 89.1-96.1) vs 96.2% (95% CI, 94.9-97.5) (P = .02). SVR12 by modified-ITT analysis was 97.8% (95% CI, 95.0-99.3) vs 98.4% (95% CI, 97.5-99.3) (P = .74). 92.2% of psychiatric patients with mental disorders secondary to multiple drug use (MDSDU) and 93.0% of psychiatric patients without MDSDU vs 96.2% of nonpsychiatric patients reached SVR12 (P = .05 and P = .20, respectively). The percentage of adherent patients to DAAs did not show differences between cohorts (P = .08). 30.2% of psychiatric patients and 27.6% of nonpsychiatric patients presented clinically relevant DDIs (P = .47). 1.7% vs 0.8% of psychiatric vs nonpsychiatric patients developed serious AEs (P = .39); no serious psychiatric AEs were present. DAAs have shown a slightly lower effectiveness in psychiatric patients with CHC, as a result of loss of follow up, which justifies the need for integrated and multidisciplinary health care teams. DAAs safety, adherence, and DDIs, however, are similar to that of nonpsychiatric patients

Keywords
Chronic hepatitis C, clinical research, comparative effectiveness research, direct-acting antivirals, drug safety, mental disorders.

1.Introduction

The worldwide prevalence of hepatitis C virus (HCV) in the general population is estimated to be around 1.6%, which means that around 115 million people are chronically infected and that there may be more than 700 000 deaths a year, secondary to terminal liver disease.[1] Several factors can affect the prevalence of HCV, such as the area of residence, age, sex, race, or comorbidities.[2-5] Several epidemiological studies have analyzed the presence of HCV in patients with psychiatric illnesses (schizophrenia, bipolar disorder, substance use disorder, etc), evidencing a higher prevalence than in the general population.[6-9] On the other hand, in parallel with liver disease, HCV can cause extrahepatic manifestations, among which are neurological and psychiatric diseases.[10-13] Therefore, the treatment of chronic HCV disease in the psychiatric population is a priority which must be addressed by multidisciplinary clinical teams promoting accessibility and continuity to antiviral treatment to guarantee the best results, in terms of safety and therapeutic effectiveness.[14-17]

Interferon (IFN) or pegylated (Peg)-IFN alone, or associated with ribavirin (RBV), was initially used to treat chronic hepatitis C (CHC). In 2011, two first-generation direct-acting antivirals (DAAs) were approved for HCV chronic infection in combination with Peg-IFN and RBV, telaprevir, and boceprevir. These IFN-based treatments were contraindicated in a great majority of psychiatric patients. So, treatment of CHC in many psychiatric patients has been deferred until the authorization of the current second-generation DAAs that, at present, constitute the gold standard of CHC treatment due to the high effectiveness and safety rates observed in clinical trials and in real-life studies.[18] Moreover, psychiatric HCV patients may present particular characteristics related to the basal pathology or pharmacological treatment (adherence to antiviral treatment, drug- medication interactions between DAAs and concomitant treatment, and increase of neurological or psychiatric adverse effects), social factors, or interaction with the health system that can condition the success of DAAs-based treatment observed in the general population.[19] Moreover, pivotal clinical trials for DAA authorization by the European or American drugs regulatory agencies pinpointed in many cases (sofosbuvir [SOF], daclatasvir [DCV], velpatasvir [VEL], ledipasvir [LDV], voxilaprevir, glecaprevir, pribentasvir, etc), the presence of current or past psychiatric illness or drug/alcohol consumption as exclusion criteria.[20-28] Likewise, real-life studies on the use of DAAs in psychiatric patients are virtually nonexistent or are limited to a very small number of antivirals or psychiatric patient subgroups.

The main objective of this study is to evaluate the effectiveness and safety in the real clinical practice of DAAs in psychiatric HCV patients. Secondary objectives include the analysis of psychiatric conditions on adherence to antiviral therapy and the assessment of the incidence of clinically significant interactions between antiviral and concomitant treatment in psychiatric HCV-infected patients.

2.Methods

2.1 Study design and patient selection

This is a unicentric observational prospective cohort study of HCV- infected patients who started DAAs-based antiviral treatment during 3 years in our institution and who had reached week 12, post end of the treatment. Adult HCV-infected patients, treatment-naïve, or treatment-experienced to peg-INF ± RBV, in all fibrosis stages (F0-F4), including patients with decompensated cirrhosis or portal hypertension, human immunodeficiency virus (HIV) coinfected patients, or liver transplant patients were included. HCV-infected patients were divided into two cohorts at baseline: psychiatric and nonpsychiatric patients. The inclusion in the cohort of psychiatric patients was established by the hospital psychiatry team, based on the baseline diagnosis of mental illness, current follow up in Outpatient Psychiatry Unit, Mental Health Unit, or Centre for Drug Addiction, hospital admissions in the Department of Psychiatry and pharmacological treatment for the psychiatric disorder. The diagnosis of mental illness was

classified based on the International Classification of Diseases-10, Classification of Mental and Behavioral Disorders.[29] Antiviral treatment selection and prescription decisions corresponded to the hospital infectologist or hepatologist, under usual clinical practice conditions valid during the study period, according to the reference treatment guidelines at the time of initiation of antiviral treatment.[30,31]

Adherence rates were made following continuous measurement of the medication acquisition method,[32] during monthly visits to the Hospital Pharmacy Service where the study was conducted, from the beginning to the end of the treatment. To compare the number of adherent patients, both cohorts have been stratified into four levels of adherence to DAAs (very high: 95%-100%; high: 90%-94%; mild: 85%-89%; and moderate: <85%); additionally, a statistical analysis comparing the integrated and stratified distribution of adherent patients in both cohorts have been carried out. Drug-drug interactions (DDIs) were identified by the clinical team (clinical pharmacists, hepatologists, and infectologists) using the Hep Drug Interactions database of the University of Liverpool,[33] recommended as a reference by the European Association for the Study of the Liver.[31] Where no information was available, Lexicomp Drug Interactions,[34] IBM Micromedex,[35] analysis of pharmacokinetic parameters available in the technical data sheet, and consultation with the DAA manufacturing laboratory were employed. Regardless of the source of information on DDIs consulted, clinically significant DDIs were considered those that required clinical or therapeutic action to achieve the therapeutic objective of antiviral treatment as well as to achieve or maintain the therapeutic objectives and safety of concomitant treatment; particularly, in the case of Hep Drug Interactions database of the University of Liverpool, interactions that contraindicated the simultaneous use of the DAAs and the concomitant drug ("contraindicated": red flag) and those that required a specific clinical action ("potential": amber flag) were included.

2.2 Effectiveness and safety variables

Pharmacological treatment adherence, DDIs, effectiveness, and safety follow up were carried out through SiMON, an artificial intelligence monitoring system for HCV-infected patients on antiviral treatment, that records effectiveness and safety events from clinical data.[36] Additional data regarding hospitalizations, admissions in the emergency room, outpatient consultations, or interconsultation to Psychiatry Department have been collected from patients' electronic clinical records.

HCV viral load (defined as the ribonucleic acid (RNA) HCV in plasma) was determined using the real-time polymerase chain reaction technique with the COBAS AmpliPrep platform from Roche. The kit is the HCV Quantitative Test, version 2.0. The limits of detection and quantification in plasma (there is no significant difference in the serum) were 11 IU/mL (10-13 IU/mL; 95% confidence interval [CI]) for the lower limit of detection (LOD) with a 95% positive result rate and 15 IU/mL for LOD with positive results. Viral load determinations were made at the baseline, end of treatment, and 12 weeks after the antiviral treatment was completed. Transient elastography was used for the staging of liver fibrosis (FibroScan), stratifying patients according to stiffness results in fibrosis F0-F1 (14.4 kPa in HCV monoinfected patients and >14.0 kPa in HIV coinfected patients).

The primary effectiveness endpoint was the sustained virologic response 12 (SVR12), defined as RNA-HCV undetectable 12-weeks post end of the treatment. Secondary efficacy variables were null response (lack of RNA-HCV undetectability during DAAs treatment) and recidivant (RNA-HCV detectable 12-weeks posttreatment in a patient with RNA- HCV undetectable at the end of treatment). The primary safety endpoint was the rate of on-treatment serious drug-related adverse events (AEs); secondary variables included on-treatment drug-related AEs, DAA or concomitant treatment withdrawal due to AEs, emergency room admission, hospitalization, or outpatient consultation secondary to drug-related AEs and death secondary to serious drug-related AEs. Specific identification of psychiatric adverse effects, potentially secondary to antiviral treatment or hospitalizations in Psychiatry Service, secondary to exacerbations of psychiatric illness in the subgroup of patients with major psychiatric disorders,

were made by comparing its incidence during two periods equal to the duration of antiviral treatment before and after the start date thereof.

The main variables related to secondary objectives of this study were the percentage of adherence to antiviral treatment and the percentage of clinically significant DDIs.

2.3 Statistical analysis

The intention-to-treat (ITT) evaluable population included all patients who took at least one dose of the prescribed treatment. Modified intention-to-treat (mITT) evaluable population included all ITT evaluable population but excluded patients without quantification of RNA-HCV 12-weeks posttreatment for reasons other than treatment failure Baseline variables (demographics, clinical, histological and laboratory values, and frequencies) were evaluated by ITT analysis. Effectiveness variables were analyzed by an mITT and ITT analysis. Safety variables were calculated by ITT analysis. Quantitative variables were expressed as mean ± standard deviation (SD) and were analyzed using Student t test or the Mann-Whitney U test, according to data distribution. Qualitative variables were expressed as count and percentage, with CI at 95%, and were compared using a χ^2 or Fisher's exact test. Primary endpoints were expressed as a percentage and an exact 95% binomial CI. To detect differences between cohorts related to psychiatric illness influence on effectiveness variables, univariate and multivariate analyses were performed. Statistically significant results were considered when $P \leq .05$. Statistical analysis (percentage, mean, median, SD, CI, univariate and multivariate analysis, Student's t test, Mann-Whitney U test, χ^2 test, and Fisher's exact test) was carried out using the Epidat 4.2 program.

2.4 Ethics approval

This study complies with the Declaration of Helsinki Good Clinical Practice. It was classified in 2015 as “Observational Post-Authorization Study with Human Medicines” by the Spanish Agency of Medicines and Health Products, and authorized by the Clinical Research Ethics Committee (CREC) of the Regional Health Service (2015). Patients signed an informed consent approved by the CREC for their participation in the study and all their data were anonymized.

3.Results

3.1 Baseline patient demographics and characteristics

A total of 1142 adult patients started antiviral treatment during the study period at our institution, of which 242 were psychiatric patients (21.2%; 95% CI, 18.8-23.6) and 900 were nonpsychiatric patients: they constitute the ITT population. Of these 1142 patients, 33 patients (13/242 psychiatric and 20/900 nonpsychiatric patients) who completed the antiviral treatment did not perform the HCV viral load determination 12 weeks after the end of treatment ($P = .02$): they constitute the mITT population (229 psychiatric and 880 nonpsychiatric patients). The psychiatric patients were mostly men under 65 years of age, with a lower percentage of patients older than 65 years ($P < .01$). The majority of psychiatric patients were HCV genotype-1 monoinfected, although they showed a higher HIV- coinfection rate vs nonpsychiatric patients (22.3% vs 11.2%; $P < .01$ Also, the psychiatric cohort had low HCV viral loads (<6.1 log IU/mL),with a homogenous distribution between the high and low degree of liver fibrosis (F3-F4: 55.4%; 95% CI, 48.9-61.9) and mostly noncirrhotics (65.3%; 95% CI, 59.1-71.5). 75.6% (95% CI, 70.0-81.2) of psychiatric patients were naïve to antiviral treatment and the majority of experienced patients had a recurrence to previous antiviral treatment based on Peg-IFN ± RBV.

Only 2.5% of cirrhotic patients had suffered hepatic decompensation before the start of antiviral treatment or had experienced a liver transplant. LDV/ SOF ± RBV and DCV + SOF ± RBV were by far the most prescribed DAAs in both cohorts; the prescription of antiviral treatments containing at least one HCV protease inhibitor (PI) was 17.8% (95% CI, 12.7-22.8) among psychiatric patients and 32.0% (95% CI, 29.9-35.1) among nonpsychiatric patients (P < .01); more psychiatric patients required antiviral treatment durations of 24 weeks vs those who ere nonpsychiatric (21.5% vs 13.8%; P < .01). Table 1 shows the main baseline characteristics and antiviral treatment of the two cohorts, as well as the statistical differences between the two subpopulations.

Among psychiatric patients, the analysis of the diagnoses reveals that 61.6% of them (95% CI, 55.2-67.9) presented one psychiatric disorder and 32.2% (95% CI, 26.1-38.3) of them presented two baseline psychiatric disorders, namely mental and behavioral disorders due to multiple drug use (MDSDU) and use of other psychoactive substances and depressive episode or recurrent depressive disorders. 68.2% (95% CI, 62.1-74.3) of the patients were at the time of the start of antiviral treatment with at least two psychiatric medications, among which benzodiazepines, antidepressants, long-acting antipsychotics, and neuroleptics stand out. Table 2 shows the classification of mental and behavioral disorders and psychiatric drugs of the psychiatric study population and its frequency in the psychiatric cohort.

The average percentage adherence to antiviral treatment of psychiatric vs nonpsychiatric patients was 99.05% ± 1.48% vs 99.56% ± 1.27%, respectively (P < .01). Comparatively, the stratified distribution of adherent patients to antiviral treatment in psychiatric vs nonpsychiatric patients (level by level) was: very high 95.9% (232/ 242) vs 98.3% (885/900) (P = .04); high 2.9% (7/242) vs 1.3% (12/900) (P = .16); mild 0.8% (2/242) vs 0.1% (1/900) (P = .22); and moderate 0.4% (1/242) vs 0.2% (2/900) (P = .85). The integrated analysis of adherent patients (all levels) to DAAs between both cohorts did not show statistically significant differences (P = .08).

In relation to the DDIs identified, 30.2% (95% CI, 24.2-36.2) of psychiatric patients and 27.6% (95% CI, 24.6-30.5) of nonpsychiatric patients presented clinically relevant DDIs (P = .47). Among psychiatric patients, the main therapeutic group that generated clinically significant DDIs was A02 (drugs for acid-related disorders) with 11.6% of affected patients, followed by N05 (psycholeptics) with 8.3% of cases; among nonpsychiatric patients, also the therapeutic group A02 was the main one but followed by C09 (agents acting on the renin- angiotensin system) with 6.7% of affected patients. Regarding concomitants drugs, omeprazole, paliperidone, and alprazolam among psychiatric patients and omeprazole, amlodipine, and atorvastatin among nonpsychiatric patients were the main concomitants medications involved in DDIs detection. DAAs mainly involved in the development of clinically significant DDIs were paritaprevir/ombitasvir/ritonavir + RBV (PTV/OBV/RTV + RBV) and PTV/OBV/RTV + dasabuvir ± RBV among psychiatric and nonpsychiatric patients, respectively. The incidence of DDIs if antiviral treatment containing or not PIs was 40.6% vs 28.6% in psychiatric patients (P = .24) and 34.9% vs 24.1% in nonpsychiatric patients (P < .01). As a result of DDIs detection among psychiatric patients, the therapeutics interventions carried out were distributed as follows: 38.3% administration schedule adjustment, 31.5% effectiveness (eg, blood pressure) and/or safety (eg, renal function) closer clinical monitoring, 19.2% dosage regimen adjustment (with pharmacokinetic drug monitoring in 5 cases), 9.6% temporary suspension before DAA treatment (four patients with oxcarbamazepine, two metamizole, and one rosuvastatin), and one definitive substitution before DAA treatment (topiramate in one patient with oxcarbamazepine). No concomitant medication required suspension during treatment with DAAs.

A total of 33 psychiatric patients were on treatment with anticonvulsants; 10 with topiramate, 6 with sodium valproate, 5 with oxcarbamazepine, and the remaining 12 with another 6 different anticonvulsants. Of all of them, 20 were treated with LDV/SOF ± RBV, 7 with DCV + SOF ± RBV, and 3 of them with other DAAs. Five patients with clinically significant baseline DDIs between DAAs and oxcarbazepine (three treated with LDV/SOF, one with VEL/SOF, and one with DCV + SOF) were identified; as previously underlined, in four of these patients, temporary suspension of oxcarbamazepine was indicated during antiviral treatment (temporarily substituted by sodium valproate in one patient), and in one case, the indefinite replacement of oxcarbazepine

with topiramate was indicated in a patient also under concomitant treatment with lacosamide. These modifications in the antiepileptic treatment did not result in a loss of neurological control of the disease. No other clinically significant interactions were identified between DAAs and anticonvulsant treatment. No patient has been excluded from the study or analysis because of concomitant medications. Table 3 shows the therapeutic groups and concomitant drugs mainly involved in the development of clinically significant DDIs, as well as the most affected DAAs, for psychiatric and nonpsychiatric patients.

3.2 Effectiveness outcomes

The SVR12 by ITT analysis of psychiatric vs nonpsychiatric patients was 92.6% (95% CI, 89.1-96.1) vs 96.2% (95% CI, 94.9-97.5) (P = .02); SVR12 by mITT analysis was 97.8% (95% CI, 95.0-99.3) vs 98.4% (95% CI, 97.5-99.3), (P = 0.74), respectively (Figure 1). 92.2% of psychiatric patients with mental disorders secondary to MDSDU and 93.0% of psychiatric patients without MDSCU vs 96.2% of nonpsychiatric patients reached SVR12 (P = .05 and P = .20, respectively). SVR12 data were not available for the 5.4% of psychiatric vs 2.2% of nonpsychiatric patients in the ITT analysis (P = .02); more specifically, 2.2% of nonpsychiatric patients vs 7.0% of psychiatric patients with MDSDU (P < .01) and vs 3.0% of psychiatric patients without MDSDU (P = .89) did not resort to the analytical determination 12 weeks after the end of treatment. SVR12 in presence vs absence of the next diagnoses was: depressive disorders 93.4% vs 92.2% (P = .97), anxiety disorders 92.2% vs 100.0% (P = .17), and schizoaffective disorders disorders 91.8% vs 100.0% (P = .16).

Table 1 Demographic and virological characteristics of the study population

Characteristic	Psychiatric patients n = 242 (21.2%)	Nonpsychiatric patients n = 900 (78.8%)	P
Males, % (n)	69.4% (168)	62.8% (565)	.07
Age, mean (years ± SD)	52.8 ± 10.0	58.72 ± 13.1	<.01
Age ≥ 65 y, % (n)	9.9% (25)	33.2% (299)	<.01
HCV genotype			
1	60.3% (146)	73.3% (660)	<.01
2	5.0% (12)	5.7% (51)	.79
3	21.1% (51)	12.2% (110)	<.01
4	13.6% (33)	8.8% (79)	.03
HIV coinfection, % (n)	22.3% (54)	11.2% (101)	<.01
Fibrosis stage, % (n)			
F0-F1	12.4% (30)	18.1% (162)	.05
F2	32.2% (78)	31.2% (281)	.82
F3	20.7% (50)	24.3% (219)	.27
F4	34.7% (84)	26.4% (238)	.01
Previous clinical decompensation, % (n)	3.3% (8)	3.3% (30)	.86
CTP classification, % (n)			
A (5-6)	97.9% (237)	99.1% (892)	.23
B (7-9)	2.1% (5)	0.9% (8)	.06
C (>9)	0.0% (0)	0.0% (0)	.99
Hepatocellular carcinoma, % (n)	2.5% (6)	3.3% (30)	.64
Estimated glomerular filtration rate < 60 mL/min, % (n)	5.4% (13)	6.7% (60)	.56
Previous antiviral treatment. % (n)			
Naïve	75.6% (183)	73.6% (662)	.57
IFN-based treatment-experienced	24.4% (59)	26.4% (238)	.57
DAAs			
LDV/SOF ± RBV	54.1% (131)	48.1% (433)	.11
DCV + SOF ± RBV	20.2% (51)	12.2% (110)	<.01
PTV/OBV/RTV + DBV ± RBV	7.4% (18)	24.3% (219)	<.01
SMV/SOF ± RBV	6.6% (16)	2.1% (19)	<.01
ELB/GRZ	3.7% (9)	5.6% (50)	.33
VEL/SOF ± RBV	3.3% (8)	2.4% (22)	.60
PTV/OBV/RTV + RBV	2.1% (5)	2.2% (20)	.92
SOF + RBV	1.7% (4)	3.0% (27)	.37
Treatment duration, % (n)			
8 wk	7.0% (17)	10.0% (90)	.20
12 wk	70.3% (170)	76.0% (684)	.08
16 wk	1.2% (3)	0.2% (2)	.11
24 wk	21.5% (52)	13.8% (124)	<.01
RBV addition, % (n)	26.9% (65)	21.8% (196)	.11

Abbreviations: CTP, child-pugh-turcotte; DBV, dasabuvir; DCV, daclatasvir; ELB, elbasvir; GRZ, grazoprevir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; LDV, ledipasvir; OBV, ombitasvir; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SD, standard deviation; SMV, simeprevir; SOF, sofosbuvir; VEL, velpatasvir

95.6% of psychiatric patients with a single diagnosis of mental disorder reached SVR12, compared to 90.8% of psychiatric patients with at least two diagnoses of mental disorders (P = .27). 93.9% of psychiatric patients on treatment with a single psychiatric drug reached SVR12, compared to 89.6% of psychiatric patients with at least two psychiatric drugs (P = .35). No statistically significant differences were observed in SVR12 due to viral genotype (P > .15). SVR12 in cirrhotic patients was 92.2% vs 94.6% (P = .78) in psychiatric vs nonpsychiatric patients. Table 4 shows primary andsecondary effectiveness endpoints. Table5 shows the results ofmultivariate analysis on SVR12.

Table 2 Classification of mental and behavioral disorders and psychiatric drugs of the psychiatric study population

Category	% (n)
Mental and behavioral disorders	
Mental and behavioral disorders due to multiple drug use and use of other psychoactive substances	58.7%(142)
Depressive episode or recurrent depressive disorders	25.6% (62)
Phobic anxiety disorders or other anxiety disorders	15.7% (38)
Schizophrenia, schizoaffective disorders or schizotypal disorders	14.9% (36)
Disorders of adult personality and behavior	14.1% (34)
Bipolar affective disorders	3.3% (8)
Habit and impulse disorders	2.5% (6)
Others	10.3% (25)
Number of mental and behavioral disorders perper patient	
1 Mental and behavioral disorders	61.6%(149)
2 Mental and behavioral disorders	32.2% (78)
>2 Mental and behavioral disorders	6.2%% (15)
Psychiatric drugs	
Benzodiazepines	59.9% (145)
Antidepressants	51.7%(125)
Long-acting antipsychotics	37.6% (91)
Neuroleptics	35.9% (87)
Anticonvulsants	13.6% (33)
Lithium	2.1% (5)
Other psychiatric drugs	15.3% (37)
Number of psychiatric drugs per patient	
1 Psychiatric drug	31.8% (77)
2 Psychiatric drugs	34.3% (83)
3 Psychiatric drugs	21.9% (53)
>3 Psychiatric drugs	11.9% (29)

3.3 Safety outcomes

The rate of any degree AEs secondary to DAAs treatment for psy-chiatric and nonpsychiatric HCV patients was 59.1% (95% CI, 52.7%-65.5%) and 56.4% (95% CI, 53.2%-59.7%), respectively (P = .51).Meanwhile, 1.7% (95% CI, 0.5%-4.2%) vs 0.8% (95% CI, 0.2%-1.4%) ofpsychiatric vs nonpsychiatric patients developed serious AEs(P = .39); three psychiatric patients manifested severe headaches(which responded to the use of nonsteroidal analgesics) and onepatient presented constipation which required the use of a rectalenema; no serious adverse psychiatric effects were present in bothcohorts. Beyond this, 5.4% (95% CI, 2.3-8.4) vs 6.3% (95% CI,4.7-8.0I) of psychiatric vs nonpsychiatric patients developed moderate AEs (P = .69), of very similar nature between the two co-horts, highlighting fatigue/asthenia, pruritus, and headache. In relation to severe or moderate adverse effects of a psychiatric orneurological nature, one psychiatric patient developed anxiety duringantiviral treatment against nine nonpsychiatric patients who mani-fested insomnia (four), irritability (three), depressive state (one), andanxiety (one), although without statistically significant differences (P = .63). No patient from both cohorts required treatment with-drawal (antiviral or concomitant) as a consequence of the develop-ment of serious AEs. 0.8% vs 0.7% of psychiatric patients vsnonpsychiatric patients went to the emergency room as a result ofAEs to antiviral treatment (P = .87). No patient required hospitalization or died due to serious AEs. Table4 shows the main safety data.

4.Discussion

CHC treatment has undergone a radical change with the introductionof second-generation DAAs due to its very high efficacy and safetyrates that have positioned them as treatments of choice in generalpopulation HCV-infected patients.[30,31]DAAs have also provided anopportunity for virological cure in populations where the use ofinterferon-based treatments (associated with RBV and/or first-generation DAAs) was contraindicated or had to be used with cau-tion. This is the case of psychiatric HCV-infected patients, wheretreatments based on IFN caused a high rate of therapeutic with-drawal, null virological responses, or intolerance[37]; in these patients,the difficulty in antiviral treatment accessing had clinical con-sequences both to hepatic and extrahepatic level, such as the in-cidence of psychiatric symptoms due to the action of HCV on centralnervous system.[12,38]In fact, DAAs have meant greater access for thepsychiatric population to antiviral treatment against HCV.[39].

The present study analyses the effectiveness and safety in realpractice of treatments with second-generation DAAs in a large groupof patients infected with HCV and with mental illness, compared tononpsychiatric patients. A high percentage of patients of the popu-lation analyzed in this study have a psychiatric illness; a higher per-centage than that observed in European epidemiological studies,[40]although justified by the prevalence of HCV infection in the popu-lation with mental illness.[41,42]These data are probably due to thefact that the treatment of HCV in patients with mental illness hasbeen deferred for the reasons mentioned above. This may also be thereason for the higher percentage of cirrhotic patients compared tononpsychiatric patients in the analyzed population. Also, the psy-chiatric subpopulation of this study is significantly younger, probablydue to earlier diagnoses linked to contact with the health systemmotivated to psychiatric diagnosis or high-risk viral contagionbehaviors.[43]There is also a higher rate of HIV coinfection in psychiatricpatients compared to nonpsychiatric patients, already identified inprevious studies,[42]although this will not affect the effectiveness andsafety results in real clinical practice if adequate control of basal in-teractions with antiretroviral treatment is carried out.[44]In addition,although longer durations of antiviral treatment are observed in psychiatric patients, this is justified by the higher percentage of cir-rhotic patients in this study subgroup, as indicated by the currentlyvalid treatment recommendations.[30,31]

Table 3 Main therapeutic groups, concomitant drugs, and DAAs involved in clinically significant DDIs

	Psychiatric patients	Nonpsychiatric patients	P
Therapeutic group			
A02 drugs for acid-related disorders	11.6%	8.9%	.25
N05 psycholeptics	8.3%	3.7%	<.01
C09 agents acting on the Ren-An system	3.3%	6.7%	.07
N03 anticonvulsants	2.9%	0.1%	<.01
C10 lipid modifying agents	2.1%	5.2%	.06
C08 calcium channel blockers	1.7%	3.9%	.13
C07 beta-blocking agents	1.2%	3.2%	.15
Concomitant medication			
Omeprazole	8.7%	8.4%	.98
Paliperidone	3.3%	0.0%	<.01
Alprazolam	2.9%	0.8%	.04
Oxcarbamazepine	2.1%	0.0%	<.01
Amlodipine	1.7%	3.3%	.25
Atorvastatin	0.8%	2.7%	.14
Pravastatin	0.8%	0.4%	.82
DAAs			
PTV/OBV/RTV + RBV	60.0%	20.0%	.22
SOF + RBV	50.0%	22.2%	.57
PTV/OBV/RTV + DBV ± RBV	38.9%	38.8%	.81
LDV/SOF ± RBV	38.9%	26.8%	.01
VEL/SOF ± RBV	37.5%	18.8%	.65
ELB/GRZ	33.3%	24.0%	.86
SMV/SOF ± RBV	12.5%	10.5%	.73
DCV/LDV ± RBV	3.9%	17.2%	.04

Figure 1 SVR12 in psychiatric vs nonpsychiatric HCV-infected patients according to statistical analysis. HCV, hepatitis C virus; ITT, intention to treat; mITT, modified intention to treat; SVR12, sustained virologic response 12

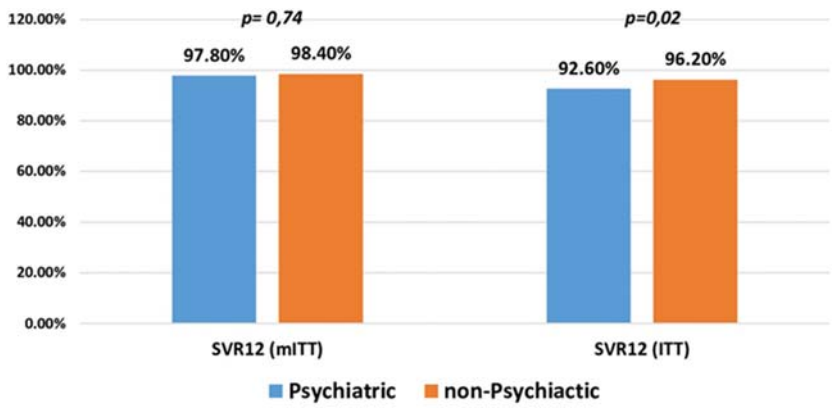

Table 4 Effectiveness and safety of direct-acting antivirals based on psychiatric disorder presence

	Psychiatric patients % (n)	Nonpsychiatric patients % (n)	P
Global virologic response (mITT analysis)			
SVR12	97.8% (224)	98.4% (866)	.74
Null responder	0.0% (0)	0.5% (4)	.69
Recidivant	2.2% (5)	1.1% (10)	.37
No data	5.7% (13)	2.3% (20)	.01
Global virologic response (ITT analysis)			
SVR12	92.6% (224)	96.2% (866)	.02
Null responder	0.0% (0)	0.4% (4)	.67
Recidivant	2.1% (5)	1.1% (10)	.40
No data	5.4% (13)	2.2% (20)	.02
Virologic response by mental (ITT analysis)			
Mental and behavioral disorders due to multiple drug use and use of other psychoactive substances	92.2% (131)	96.2% (866)	.05
Depressive episode or recurrent depressive disorders	93.5% (35)	96.2% (866)	.48
Phobic anxiety disorders or other anxiety disorders	94.7% (36)	96.2% (866)	.97
Schizophrenia, schizoaffective disorders or schizotypal disorders	97.2% (35)	96.2% (866)	.89
Disorders of adult personality and behavior	94.2% (34)	96.2% (866)	.86
Bipolar affective disorders	75% (6)	96.2% (866)	.03
Habit and impulse disorders	83.3% (5)	96.2% (866)	.57
Any grade drug-related AEs	59.1% (143)	56.4% (508)	.51
Serious drug-related AEs	1.7% (4)	0.8% (7)	.39
Emergency room admission due to serious drug-related AEs	0.8% (2)	0.7% (6)	.87
On-treatment hospitalization due to serious drug-related AEs	0.0% (0)	0.0% (0)	>.99
Death due to serious drug-related AEs	0.0% (0)	0.0% (0)	>.99
Any grade AEs with global incidence > 2.0%			
Fatigue/asthenia	40.1%	34.0%	.09
Headache	23.5%	18.6%	.10
Dizziness	4.5%	3.6%	.60
Gastrointestinal upset	3.7%	3.6%	.94
Anxiety	3.7%	1.1%	.01
Insomnia	3.3%	6.3%	.10
Drowsiness	2.9%	1.7%	.33
Nausea	3.3%	4.2%	.65
Diarrhea	3.3%	2.6%	.68
Pruritus	2.9%	7.4%	.02
Dry skin and mucous membranes	2.1%	1.7%	.89
Constipation	2.1%	1.1%	.40
Appetite disorders	2.1%	0.9%	.23
Musculoskeletal pain	1.2%	2.0%	.61

Abbreviations: AEs, adverse events; ITT, intention to treat; mITT, modified intention to treat; SVR12, sustained virologic response 12.

Table 5 Multivariate analysis on SVR12

Variable	OR	95% CI		P
Naïve	0.99	0.51	1.91	.98
Genotype 2	1.22	0.28	5.23	.79
Genotype 3	0.53	0.26	1.08	.08
Genotype 4	1.44	0.43	4.83	.56
Cirrhosis	0.72	0.39	1.32	.29
Psychiatric	0.51	0.27	0.96	.04

Abbreviations: CI, confidence interval; OR, odds ratio; SVR12, sustained virologic response 12.

In relation to the antiviral treatment used, a lower prescription of DAAs based on PIs is observed in the psychiatric population, because the PIs are the drugs with the highest degree of clinically significant interactions with the psychiatric treatment, as we have confirmed in the results of this study. The adequacy of the baseline antiviral treatment in psychiatric and nonpsychiatric patients in this study has allowed no statistically significant differences to be observed in the percentage of clinically significant interactions between both subgroups. Regarding to therapeutic groups and concomitant medication, most frequently involved in clinically significant DDIs, it is observed that although antacids are the most affected medications (as in the nonpsychiatric population), specific therapeutic groups widely used in psychiatric patients (psycholeptics or anticonvulsants) stand out for their high degree of interaction with DAAs. This fact is confirmed at the level of concomitant medication, since it is observed that paliperidone or alprazolam have more clinically significant DDIs in the group of psychiatric patients when compared to nonpsychiatric patients. In relation to DAAs involved in the development of DDIs, it is important to note that in the group of psychiatric patients LDV/SOF ± RBV and DCV + SOF ± RBV generate more DDIs than in the cohort of nonpsychiatric patients; in parallel, the presence of PIs among antiviral treatment in psychiatric patients does not affect the development of DDIs, unlike what happens among nonpsychiatric patients; these differences can be explained on the basis that SOF (polymerase inhibitor antiviral, not PI) generates more interactions with psycholeptics and anticonvulsants, which are therapeutic groups more prescribed in the cohort of patients with mental disorders in this study. It is also noteworthy that a very significant number (almost one-third) of psychiatric patients required the suspension or dose adjustment of concomitant treatment in the presence of a clinically significant DDI with the antiviral treatment. In this sense, of particular interest is the management of psychiatric patients treated with anticonvulsants, since certainly this is one of the most difficult groups to treat with DAAs given the magnitude of DDIs with all the older anticonvulsants; in this study, only oxcarbamazepine presented clinically significant DDIs at baseline, that were resolved, without neurological consequences, by temporary or definitive replacement of this antiepileptic.

The importance of adherence to antiviral treatment based on DAAs is an aspect that international treatment guidelines recommend to maximize the effectiveness of the treatment.[30,31] However, there

is no clearly established consensus on the percentage of adherence above which a patient can be considered "adherent." In this study, as had already been evaluated in previous studies,[45,46] no clinically significant differences were observed in relation to the global adherence to antiviral treatment between psychiatric and nonpsychiatric patients (rates higher than 99%, in both cases). Moreover, although the number of patients with very high adherence (≥95%) is greater in the cohort of nonpsychiatric patients, when statistically analyzing the overall distribution of the four levels of DAAs adherence, no significant differences were observed.

The ITT results of this study reveal a lower DAAs effectiveness in real clinical practice in psychiatric vs nonpsychiatric patients; less effective than that observed in mITT analysis. This is because more psychiatric patients quit clinical follow up after the completion of antiviral treatment and, therefore, it is not possible to determine SVR12. The results of our study show that these follow up losses in the group of psychiatric vs nonpsychiatric patients must be attributed to MDSDU-patients and not to patients with other psychiatric disorders. These results reinforce the importance of care in integrated multidisciplinary health systems for the treatment of psychiatric patients, as is currently recommended, since they promote clinical adherence and improve the likelihood of achieving SVR in this subgroup of patients.[47-49] The results of our study are in line with those reported in similar studies, in which the SVR12 reached with DAAs in patients with psychosocial comorbid conditions, substance use, mental health disorders, psychiatric disease or illicit drug use, was found among the 90%-96%.[50-54] Of particular interest are the results observed by Back et al[55] in an integrated analysis of the use of glecaprevir/ pibrentasvir in psychiatric vs nonpsychiatric patients; they found that SVR12 by ITT was equal in both subgroups of patients, 97.3% and 97.5%, respectively. This confirmed the importance of a highly controlled environment on the clinical follow up of patients, such as clinical trials, to obtain the best results in the use of DAAs in HCV patients. In our study, no significant differences were observed in the effectiveness in relation to baseline mental disorder compared to nonpsychiatric patients, except in patients with bipolar disorder, although it is important to note that only 8 patients had this psychiatric diagnosis in the analyzed population. Within the subgroup of psychiatric patients, no differences have been observed in the DAAs effectiveness based on the baseline psychiatric diagnosis, a number of psychiatric diagnoses or number of psychiatric medications per patient. Other baseline variables of psychiatric patients, such as the presence of cirrhosis, previous treatments or viral genotype, have not influenced the effectiveness of antiviral treatment (multivariate analysis).

A high and very similar global therapeutic safety has been observed in the group of psychiatric patients vs nonpsychiatric patients, with very similar incidence rates of mild, moderate, or severe adverse effects reported by the patients, as well as visits to the emergency room or treatment withdrawals secondary to the development of serious adverse effects. These results are in line with those reported but limited to the use of glecaprevir/pibrentasvir in psychiatric patients.[55] It is also important to highlight the results of DAAs neuropsychiatric safety in this study, with a very low incidence in psychiatric patients and because of the parallelism of the symptoms in the two subgroups of patients analyzed. Only a higher incidence of mild anxiety has been observed in

psychiatric vs nonpsychiatric patients, although the difference was not considered clinically significant. These safety results of the psychiatric symptomatology corroborate those observed in previous studies, at the level of the evaluation on anxiety or depression, fatigue and mood, cognitive state, or sleep disturbances.[56-60] In addition, patients with psychiatric disorders, in this study, have not developed decompensation of their mental illness during DAAs treatment, as other authors have also evaluated but limited to DAAs treatments based on ribavirin.[61]

Although this study presents the strengths of being prospectiveand includes a large number of patients in both treatment subgroups,we would like to emphasize that patients have not undergone anevaluation through validated scales on psychiatric symptoms before,during, or after antiviral treatment.

As final conclusions, we can highlight the high effectiveness andsafety of DAAs in psychiatric HCV-infected patients. However, ef-fectiveness is slightly lower in psychiatric patients as a result oftracking losses in the subgroup of patients with mental disorderssecondary to multiple drug use. This fact supports the need for in-tegrated and multidisciplinary health care teams that guarantee theclinical follow up of patients throughout the health care process. Norelevant rates of psychiatric hospital admission or urgent psychiatricattention were observed during antiviral treatment, so it is deducedthat DAAs do not significantly influence the symptomatology of thepsychiatric disorder. Furthermore, no clinically significant differenceshave been observed in relation to adherence to antiviral treatment orincidence of clinically significant interactions

Conflict of interest

Luis Margusino-Framiñán—Honoraria for speaking at symposia: GileadSciences, Inc, Janssen, AbbVie Inc, and Merck Sharp & Dohme; financialsupport for attending symposia: Gilead Sciences, Inc, Janssen, AbbVie Inc,and Merck Sharp & Dohme; and position on advisory board: BristolMyers-Squibb. Manuel Delgado-Blanco—Honorari a for speaking at sym-posia: Gilead Sciences, Inc, AbbVie Inc, Merck Sharp & Dohme, andBristol Myers-Squibb . Isabel Martín -Herranz—Honoraria for speaking atsymposia: Gilead Sciences, Inc and Janssen; and financial support forattending symposia and educational programs: Janssen. Ánge les Castro-Iglesias—Honoraria for speaking at symposia: Gilead Sciences, Inc andAbbvie Inc; financial support for attending symposia: Gilead Sciences, Inc,AbbVie Inc, and Merck Sharp & Dohme; and position on advisory board:Gilead Sciences, Inc. Other authors declare that there are no confli ct ofinterests

References

1. World Health Organization. Hepatitis C Fact Sheet N°164. https:// www.who.int/news-room/fact-sheets/detail/hepatitis-c. Accessed 24 December 2019.
2. GBD Mortality and Causes of Death Collaborators. Global, regional,and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385:117-171.
3. Spradling PR, Rupp L, Moorman AC, et al. Hepatitis B and C virus infection among 1.2 million persons with access to care: factors associated with testing and infection prevalence. Clin Infect Dis. 2012;55:1047-1055.
4. Falla AM, Hofstraat SHI, Duffell E, Hahné SJM, Tavoschi L, Veldhuijzen IK. Hepatitis B/C in the countries of the EU/EEA: a systematic review of the prevalence among at-risk groups. BMC Infect Dis. 2018;18:79.
5. Hofstraat SHI, Falla AM, Duffell EF, et al. Current prevalence ofchronic hepatitis B and C virus infection in the general population, blood donors and pregnant women in the EU/EEA: a systematic review. Epidemiol Infect. 2017;145:2873-2885.
6. Chiu Y-L, Lin H-C, Kao N-W, Kao S, Lee H-C. Increased risk of concurrent hepatitis C among male patients with schizophrenia. Psychiatry Res. 2017;258:217-220.
7. Martin-Subero M, Diez-Quevedo C. Mental disorders in HIV/HCV coinfected patients under antiviral treatment for hepatitis C. Psychiatry Res. 2016;246:173-181.
8. Kilbourne AM, Cornelius JR, Han X, et al. Burden of general medicalconditions among individuals with bipolar disorder. Bipolar Disord.
   2004;6:368-373.
9. Hauser P, Kern S. Psychiatric and substance use disorders comorbidities and hepatitis C: diagnostic and treatment implications.
   World J Hepatol. 2015;7:1921-1935.
10. Iriana S, Curry MP, Afdhal NH. Neurologic manifestations of hepatitisC virus infection. Clin Liver Dis. 2017;21:535-542.
11. Yarlott L, Heald E, Forton D. Hepatitis C virus infection, and neurological and psychiatric disorders—a review. J Adv Res. 2017;8:139-148.
12. Adinolfi LE, Nevola R, Lus G, et al. Chronic hepatitis C virus infectionand neurological and psychiatric disorders: an overview. World J Gastroenterol. 2015;21:2269-2280.
13. Michel L, Lions C, Winnock M, et al. Psychiatric and substance usedisorders in HIV/hepatitis C virus (HCV)-coinfected patients: does HCV clearance matter? HIV Med. 2016;17:758-765.
14. Lin M, Kramer J, White D, et al. Barriers to hepatitis C treatment inthe era of direct-acting anti-viral agents. Aliment Pharmacol Ther.
   2017;46:992-1000.
15. Belperio PS, Chartier M, Ross DB, Alaigh P, Shulkin D. Curing hepatitis C virus infection: best practices from the U.S. Department of Veterans Affairs. Ann Intern Med. 2017;167:499-504.
16. Ho SB, Bräu N, Cheung R, et al. Integrated care increases treatmentand improves outcomes of patients with chronic hepatitis C virus infection and psychiatric illness or substance abuse. Clin Gastroenterol Hepatol. 2015;13(11):2005-2014.e3.
17. Zhou K, Fitzpatrick T, Walsh N, et al. Interventions to optimise thecare continuum for chronic viral hepatitis: a systematic review and meta-analyses. Lancet Infect Dis. 2016;16:1409-1422.
18. Jakobsen JC, Nielsen EE, Feinberg J, et al. Direct-acting antivirals for chronic hepatitis C. Cochrane Database Syst Rev. 2017;6:CD012143.

19. Chasser Y, Kim AY, Freudenreich O. Hepatitis C treatment: clinicalissues for psychiatrists in the post-interferon era. Psychosomatics. 2017; 58:1-10.
20. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014;370:1889-1898.
21. Bourlière M, Gordon SC, Flamm SL, et al. Sofosbuvir, velpatasvir, andvoxilaprevir for previously treated HCV infection. N Engl J Med. 2017; 376:2134-2146.
22. Feld JJ, Jacobson IM, Hézode C, et al. Sofosbuvir and velpatasvir forHCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med. 2015;373:2599-2607
23. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014; 370:1594-1603.
24. Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med. 2014;370:1983-1992.
25. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis Cgenotype 2 or 3 in patients without treatment options. N Engl J Med.2013;368:1867-1877.
26. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreatedchronic hepatitis C infection. N Engl J Med. 2013;368:1878-1887.
27. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. 2014;370:211-221.
28. Zeuzem S, Foster GR, Wang S, et al. Glecaprevir-pibrentasvir for 8 or 12 weeks in HCV genotype 1 or 3 infection. N Engl J Med. 2018;378:354-369.
29. World Health Organization. ICD-10 Classification Of Mental And Behavioural Disorders. https://www.who.int/substance_abuse/terminology/ icd_10/en/. Accessed 24 December 2019.
30. AASLD-IDSA HCV Guidance Panel. Hepatitis C guidance 2018 update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection. Clin Infect Dis. 2018;67:1477-1492.
31. Pawlotsky JM, Negro F, Aghemo A, et al. EASL recommendations ontreatment of hepatitis C 2018. J Hepatol. 2018;69:461-511.
32. Hess L, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. Ann Pharmacother. 2006;40:1280-1288.
33. University of Liverpool. Hep Drug Interactions. https://www.hepdruginteractions.org/. Accessed 24 December 2019.
34. Lexicomp Drug Interactions. https://www.uptodate.com/home/drugsdrug-interaction. Accessed 24 December 2019.
35. IBM Micromedex. http://www.micromedexsolutions.com/micromede x2/librarian. Accessed 24 December 2019.
36. Margusino-Framiñán L, Cid-Silva P, Mena-de-Cea Á, et al. Intelligent MONitoring system for antiviral pharmacotherapy in patients with chronic hepatitis C (SiMON-VC). Farm Hosp. 2017;41:68-88.
37. Nordstrom EM, Keniston A, Baouchi F, Martinez-Camacho A. Interferon-based hepatitis C therapy in a safety net hospital: access, efficacy, and safety. Eur J Gastroenterol Hepatol. 2017;29:10-16.

38. Fuller BE, Loftis JM, Rodriguez VL, McQuesten MJ, Hauser P. Psychiatricand substance use disorders comorbidities in veterans with hepatitis C virus and HIV coinfection. Curr Opin Psychiatry. 2009;22:401-408.
39. Jain MK, Thamer M, Therapondos G, et al. Has access to hepatitis Cvirus therapy changed for patients with mental health or substance use disorders in the direct-acting-antiviral period? Hepatology. 2019; 69:51-63.
40. Alonso J, Angermeyer MC, Bernert S, et al. Prevalence of mentaldisorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand Suppl. 2004;109(420):21-27.
41. Ramachandran J, Budd S, Slattery H, et al. Hepatitis C virus infectionin Australian psychiatric inpatients: a multicenter study of seroprevalence, risk factors and treatment experience. J Viral Hepat.2019;26:609-612.
42. De Hert M, Wampers M, Van Eyck D, et al. Prevalence of HIV andhepatitis C infection among patients with schizophrenia. Schizophr Res.2009;108:307-308.
43. Rifai MA, Gleason OC, Sabouni D. Psychiatric care of the patient withhepatitis C: a review of the literature. Prim Care Companion J Clin Psychiatry. 2010;12(6):e1-e13.
44. Sockalingam S, Tseng A, Giguere P, Wong D. Psychiatric treatmentconsiderations with direct acting antivirals in hepatitis C. BMC Gastroenterol. 2013;13:86.
45. Petersen T, Townsend K, Gordon LA, et al. High adherence to all-oral directly acting antiviral HCV therapy among an inner-city patient population in a phase 2a study. Hepatol Int. 2016;10:310-319.
46. Slevin AR, Hart MJ, Van Horn C, et al. Hepatitis C virus direct-acting antiviral nonadherence: relationship to sustained virologic response and identification of at-risk patients. J Am Pharm Assoc. 2003;2019(59):51-56.
47. Akiyama MJ, Agyemang L, Arnsten JH, et al. Rationale, design, andmethodology of a trial evaluating three models of care for HCV treatment among injection drug users on opioid agonist therapy. BMC Infect Dis. 2018;18:74.
48. Bajis S, Dore GJ, Hajarizadeh B, Cunningham EB, Maher L, Grebely J.Interventions to enhance testing, linkage to care and treatment uptake for hepatitis C virus infection among people who inject drugs: a systematic review. Int J Drug Policy. 2017;47:34-46.
49. Cachay ER, Mena A, Morano L, et al. Predictors of hepatitis C treatmentfailure after using direct-acting antivirals in people living with human immunodeficiency virus. Open Forum Infect Dis. 2019;6(3):ofz070.
50. Benhammou JN, Dong TS, May FP, et al. Race affects SVR12 in a largeand ethnically diverse hepatitis C-infected patient population following treatment with direct-acting antivirals: analysis of a single-center Department of Veterans Affairs Cohort. Pharmacol Res Perspect. 2018;6: e00379.
51. Falade-Nwulia O, Sutcliffe C, Moon J, et al. High hepatitis C cure rates among black and nonblack human immunodeficiency virus-infected adults in an urban center. Hepatology. 2017;66:1402-1412.
52. Kim HN, Nance RM, Williams-Nguyen JS, et al. Effectiveness of directacting antiviral therapy in patients with human immunodeficiency virus-hepatitis C virus coinfection in routine clinical care: a multicenter study. Open Forum Infect Dis. 2019;6(4):ofz100.
53. Trabut J-B, Barrault C, Charlot H, et al. Integrated care for the use of direct-acting antivirals in patients with chronic hepatitis C and substance use disorder. J Addict Med. 2018;12:346-352.

54. Yek C, de la Flor C, Marshall J, et al. Effectiveness of direct-acting antiviral therapy for hepatitis C in difficult-to-treat patients in a safety-net health system: a retrospective cohort study. BMC Med. 2017;15:204.
55. Back D, Belperio P, Bondin M, et al. Efficacy and safety of glecaprevir/pibrentasvir in patients with chronic HCV infection and psychiatric disorders: an integrated analysis. J Viral Hepat. 2019;26:951-960.
56. Gallach M, Vergara M, da Costa JP, et al. Impact of treatment withdirect-acting antivirals on anxiety and depression in chronic hepatitis C. PLoS One. 2018;13:e0208112.
57. Tang LSY, Masur J, Sims Z, et al. Safe and effective sofosbuvir-based therapy in patients with mental health disease on hepatitis C virus treatment. World J Hepatol. 2016;8:1318-1326.
58. Hahn D, Stokes CS, Kaiser R, Meyer MR, Lammert F, Gruenhage F.Antidepressant effects of direct-acting antivirals against hepatitis C virus—results from a pilot study. Eur J Clin Invest. 2018;48: e13024.
59. Kleefeld F, Heller S, Ingiliz P, et al. Interferon-free therapy in hepatitis C virus (HCV) monoinfected and HCV/HIV coinfected patients: effect on cognitive function, fatigue, and mental health. J Neurovirol. 2018; 24:557-569.
60. Sundberg I, Lannergård A, Ramklint M, Cunningham JL. Direct-acting antiviral treatment in real world patients with hepatitis C not associated with psychiatric side effects: a prospective observational study.BMC Psychiatry. 2018;18:157.
61. Sackey B, Shults JG, Moore TA, Rogers R, Mehvar M, King JG. Evaluating psychiatric outcomes associated with direct-acting antiviral treatment in veterans with hepatitis C infection. Ment Health Clin.2018;8:116-121