

# Assess Antiviral medication's effects on chronic hepatitis C patients' mental health

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## Abstract

**Background:** Chronic hepatitis C virus (HCV) infection is a global health issue associated with hepatic and extrahepatic complications, including psychiatric disorders that impair quality of life (QoL). Direct-acting antiviral agents (DAAs) have revolutionized HCV treatment, offering high cure rates and fewer side effects compared to interferon-based therapies. However, limited research explores the impact of DAA therapy on mental health and QoL. This study evaluates the mental health outcomes, psychiatric symptoms, coping mechanisms, and QoL in patients with HCV before and after DAA treatment.

**Methods:** A prospective observational study was conducted on 62 patients with chronic HCV infection, categorized into two groups: those with a current or past psychiatric history (Group A) and those without (Group B). Baseline and post-treatment assessments (12 weeks after DAA therapy completion) included psychiatric evaluations using the Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), and Symptom Checklist-90-Revised (SCL-90-R). Coping strategies were assessed using the Coping Orientation to Problems Experienced (COPE) Inventory, while QoL was measured with the Short Form-36 (SF-36) Health Survey. Statistical analyses examined within-group and between-group differences.

**Results:** At baseline, Group A exhibited higher levels of depression (HAM-D: 18.2 vs. 7.9;  $p < 0.01$ ), anxiety (HAM-A: 21.5 vs. 10.3;  $p < 0.01$ ), and psychological distress (SCL-90-R scores) than Group B. Following DAA therapy, both groups showed significant reductions in depression (Group A: 18.2 to 12.4,  $p < 0.05$ ; Group B: 7.9 to 4.2,  $p < 0.01$ ) and anxiety (Group A: 21.5 to 15.3,  $p < 0.05$ ; Group B: 10.3 to 6.7,  $p < 0.01$ ). Improvements in QoL were observed across most SF-36 dimensions, including mental health and vitality, with Group B experiencing more substantial gains. Coping strategies shifted toward active coping and problem-focused approaches post-treatment.

**Conclusion:** DAA therapy not only achieves virological cure but also significantly improves psychiatric symptoms, coping strategies, and QoL in patients with chronic HCV. Patients with a history of psychiatric disorders benefit from reduced psychological distress, though they continue to experience higher baseline symptomatology compared to those without such a history. These findings underscore the importance of integrating mental health assessments and support into HCV management to enhance overall patient outcomes.

## Introduction

Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease globally and can progress to cirrhosis and hepatocellular carcinoma (HCC) (1). Alongside its hepatic effects, HCV infection is often linked to various extrahepatic complications, including neurological and psychiatric disorders. These may arise from direct viral effects on the nervous system or through indirect mechanisms such as systemic inflammation, altered metabolic processes in infected cells, or disruptions in neurotransmitter systems (2,3).

Individuals with HCV infection report a significantly higher prevalence of psychiatric conditions, such as substance use disorders (36%) and mood disorders (28%), compared to the general population (4). The progression of HCV is often marked by physical symptoms like fatigue and weakness, in addition to neurological and psychiatric issues, including cognitive dysfunction, sleep disturbances, depression, anxiety, and irritability. These factors can severely diminish the patient's quality of life (QoL). Furthermore, patients' lack of awareness of the severity of the disease can further exacerbate the negative impact on health-related QoL (5,6,7). Historically, interferon-based therapies were the standard treatment but were characterized by limited effectiveness, significant toxicity, and a high incidence of psychiatric side effects (8,9,10). The advent of direct-acting antiviral (DAA) agents for treating chronic HCV has significantly improved cure rates (over 90% across all genotypes), reduced disease progression, and led to more favorable side-effect profiles (11), even among those with previous psychiatric or substance abuse issues (12). While eradicating HCV can halt liver disease progression and alleviate some extrahepatic manifestations (such as mixed cryoglobulinemia), it does not completely eliminate the risk of developing HCC (13).

However, limited research has focused on the impact of DAA treatment on the mental health and QoL of individuals with HCV. Most available data derive from patient-reported outcomes collected during observational trials examining treatment adherence and tolerance (12,13,14). A few studies (15,16,17) have observed psychiatric symptoms post-DAA therapy in individuals with a history of psychiatric disorders. What remains uncertain is whether DAA therapy worsens mood disorders in patients with a history of psychiatric conditions or induces new psychiatric symptoms in patients who have no prior history. To address this gap, we evaluated mental health disturbances in a subgroup of chronic HCV patients, categorized based on the presence or absence of past or current psychiatric conditions, both before and 12 weeks following DAA treatment. Additionally, we explored whether DAA therapy affected the intensity of psychiatric symptoms, coping mechanisms, and QoL.

### **Materials and Methods**

This was a prospective observational study conducted. Participants were consecutively recruited from the outpatient department of the Internal Medicine unit. Prior to inclusion, written informed consent was obtained from all patients after they were fully informed about the study.

At baseline, we compiled an ad hoc clinical history form to record participants' sociodemographic and clinical details, including age, gender, marital and employment status, educational level, source of infection, duration of liver disease, prior unsuccessful treatments with interferon (IFN) or ribavirin, family and personal history of psychiatric disorders, previous or current psychiatric diagnoses, ongoing psychiatric treatment, history of psychiatric hospitalization, and substance abuse history.

All patients with chronic hepatitis C (CHC) were given DAA therapy for the first time, in line with the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines and local treatment standards. Details of the administered DAA treatments are provided in Table 1. Experienced psychiatrists conducted interviews with the participants. If a psychiatric diagnosis was made, it was based on the criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and confirmed using the Structured Clinical Interviews for DSM-IV, Axis I (SCID-I) and Axis II (SCID-II) [18].

Sixty-two patients agreed to undergo both hepatic and psychiatric evaluations before beginning DAA treatment. Seven patients declined to participate.

The diagnosis of CHC was confirmed through clinical examination, ultrasound, liver function tests, and the detection of serum anti-HCV antibodies and HCV RNA. A comprehensive physical examination was performed for all patients, along with measurements of body mass index (BMI), liver function tests, glycemia, hemoglobin A1c, lipid profile (total cholesterol, HDL, LDL, triglycerides), HCV genotype, and co-infection status for HBV and HIV.

Liver fibrosis and steatosis were assessed using transient elastography (TE) (FibroScan®, EchoSens, Paris, France), as recommended by the EASL Clinical Practice Guidelines.

Biochemical testing for anti-HCV and HCV RNA levels was carried out using standard laboratory kits, and HCV genotype was determined via the HCV genotype 2.0 assay (LiPA) (Bayer HealthCare, Eragny, France). A sustained virological response (SVR12) was defined as undetectable HCV RNA in serum at least 12 weeks after completing treatment [19]. For the purposes of this study, “post-treatment” refers to the 12-week period following the completion of DAA therapy. Patients were monitored according to the EASL Clinical Practice Guidelines [20].

The following instruments were administered to assess psychiatric symptoms in all participants: the Hamilton Depression Rating Scale (HAM-D), the Hamilton Anxiety Rating Scale (HAM-A), and the Symptom Checklist-90-Revised (SCL-90-R).

The HAM-D contains 21 items designed to evaluate somatic, cognitive, and emotional symptoms of depression. Scores range from 0 to 52, with the following classification: 0–7 (no depression), 8–17 (mild depression), 18–29 (moderate depression), and 30–52 (severe depression) [21].

The HAM-A includes 14 items to assess both psychic (mental agitation, psychological distress) and somatic (physical complaints) aspects of anxiety. Scores are rated on a 5-point scale from 0 (none) to 4 (severe), with total scores ranging from 0 to 56. Anxiety levels are classified as follows:  $\leq 17$  (mild), 18–24 (mild to moderate), and 25–30 (moderate to severe) [22].

The SCL-90-R is a self-reported inventory that measures a range of psychological symptoms. It consists of 90 items rated on a 5-point scale (1 = no problem, 5 = very serious). Symptoms are grouped into nine subscales: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, anger/hostility, phobic anxiety, paranoid ideation, and psychoticism. Higher scores indicate greater psychological distress [23]. The Coping Orientation to Problems Experienced (COPE) Inventory [24] is a 60-item tool with 15 subscales, designed to assess various coping strategies in response to stress. These include problem-focused strategies (e.g., active coping, planning, restraint, seeking social support) and emotion-focused strategies (e.g., positive reinterpretation, acceptance, denial, emotional support, turning to religion). It also includes strategies such as emotional venting, behavioral disengagement, mental disengagement, substance use, and humor.

The Short Form 36 (SF-36) Health Survey consists of 36 items measuring eight dimensions of health: (i) vitality, (ii) physical functioning, (iii) bodily pain, (iv) general health perceptions, (v) physical role functioning, (vi) emotional role functioning, (vii) social role functioning, and (viii) mental health [25,26].

### **2.3. Statistical Analysis**

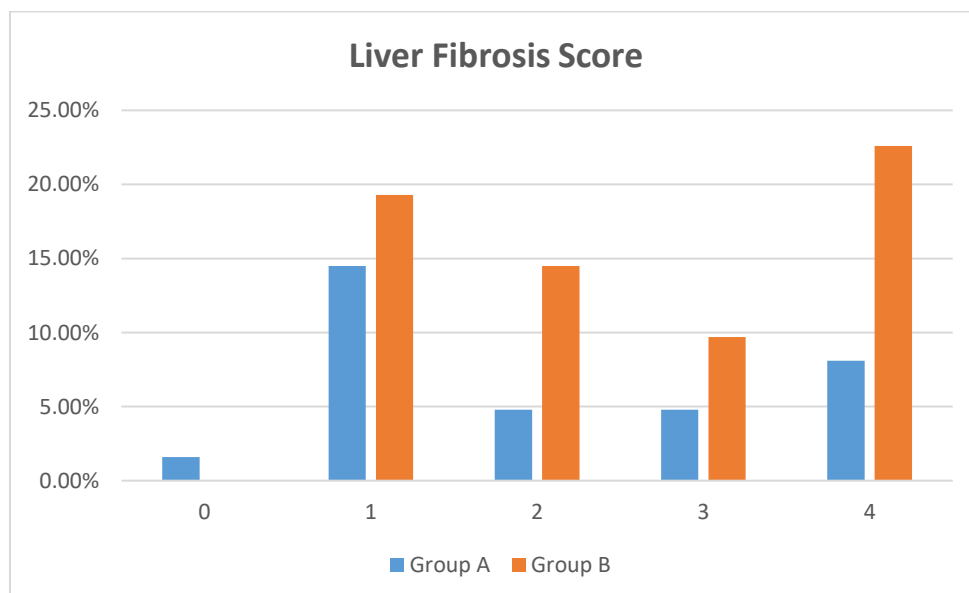
The sociodemographic and clinical data were analyzed using frequency counts, means, and standard deviations, as appropriate. Due to the small sample size and non-parametric nature of the continuous variables, non-parametric tests were applied.

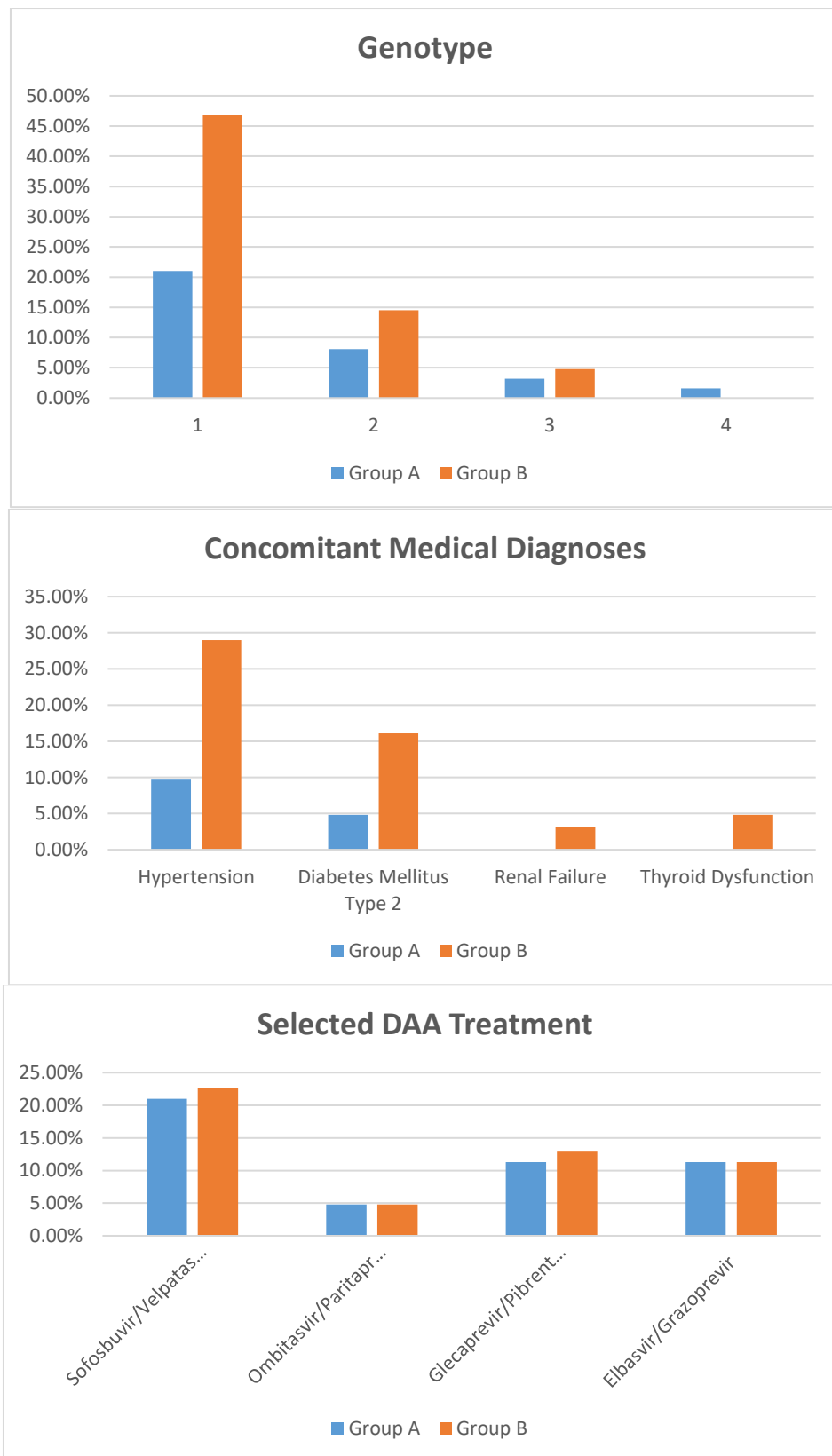
Gender differences at baseline were assessed using the Mann–Whitney test for independent samples.

The 62 CHC patients were divided into two groups: those with a current or past psychiatric history (Group A) and those without (Group B). We compared clinician-rated and self-reported psychiatric symptoms, coping strategies, and QoL before and 12 weeks after completing DAA therapy. Group differences were examined using the Mann–Whitney test, and within-group differences before and after treatment were analyzed using the Wilcoxon test for paired samples, as appropriate. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 17.0, with statistical significance set at  $p \leq 0.05$ .

**Table 1. General characteristics of enrolled chronic hepatitis C (CHC) patients with (Group A) and without (Group B) a current or lifetime psychiatric history in basal conditions.**

Variables	Group A (n = 21)	Group B (n = 41)	p
Males (n, %)	7 (11.3%)	23 (37.1%)	
Age (Mean ± SD) (Range)	65.7 ± 9.2 (51–78)	62.0 ± 12.2 (33–82)	
BMI (Mean ± SD)	26.8 ± 4.5	26.1 ± 3.3	
Liver Fibrosis Score (n, %):			
0	1 (1.6%)	0 (0.0%)	
1	9 (14.5%)	12 (19.3%)	
2	3 (4.8%)	9 (14.5%)	
3	3 (4.8%)	6 (9.7%)	
4	5 (8.1%)	14 (22.6%)	
Median HCV RNA UI/mL × 10 <sup>6</sup> (Range)	2.87 (0.009–9.0)	3.54 (0.058–14.0)	
Genotype: 1			
2	13 (21.0%)	29 (46.8%)	
3	5 (8.1%)	9 (14.5%)	
4	2 (3.2%)	3 (4.8%)	
4	1 (1.6%)	0 (0.0%)	
Previous Hepatocellular Carcinoma (HCC) (n, %)	1 (1.6%)	2 (3.2%)	
Concomitant Medical Diagnoses (n, %):			
Hypertension	6 (9.7%)	18 (29.0%)	
Diabetes Mellitus Type 2	3 (4.8%)	10 (16.1%)	
Renal Failure	0 (0.0%)	2 (3.2%)	
Thyroid Dysfunction	0 (0.0%)	3 (4.8%)	
Selected DAA Treatment (n, %):			
Sofosbuvir/Velpatasvir	13 (21.0%)	14 (22.6%)	
Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir (3D)	3 (4.8%)	3 (4.8%)	
Glecaprevir/Pibrentasvir	7 (11.3%)	8 (12.9%)	
Elbasvir/Grazoprevir	7 (11.3%)	7 (11.3%)	





## Results

### 3.1. Patient Demographics and Clinical Characteristics

Out of 69 patients initially recruited from the outpatient unit of the Internal Medicine Department, 62 agreed to participate, while six patients declined and one cited time constraints as the reason for not participating.

The sociodemographic and clinical characteristics of the enrolled chronic hepatitis C (CHC) patients are summarized in Table 1. Among the cohort, 43 patients (69.3%) had chronic hepatitis, and 19 (30.6%) had cirrhosis. Both Group A and Group B had a similar prevalence

of smokers (30.6% in both groups), individuals who were overweight (38.7% vs. 40.5%), and those who were obese (19.3% vs. 6.8%). Other common factors included a sedentary lifestyle (35.5% vs. 42.0%) and irregular dietary habits (38.7% vs. 27.9%). Furthermore, comorbidities such as hypertension (9.7% vs. 29.0%), type 2 diabetes (4.8% vs. 16.1%), renal failure (3.2%, exclusive to Group B), and thyroid dysfunctions (4.8%, exclusive to Group B) were noted. The predominant HCV genotype was Type 1 in both groups, with no co-infection with hepatitis B virus (HBV) or HIV.

In Group A, 21 patients (33.9%) had a psychiatric history, most commonly anxiety-depressive disorders (20.8%). Eleven patients (17.7%) had previously been prescribed psychotropic drugs, such as anxiolytics (n = 9, 14.5%), antidepressants (n = 5, 8.1%), and antipsychotics (n = 1, 1.6%). None of these patients required psychiatric emergency care or hospitalization during the DAA treatment period.

Seventeen patients (27.4%) had previously undergone interferon (IFN)-based therapies with or without ribavirin. All patients in the study were treatment-naïve for DAA agents. Upon assessment, they were prescribed various DAA regimens, including sofosbuvir-velpatasvir (13 patients, 21.0% in Group A; 14 patients, 22.6% in Group B), ombitasvir/paritaprevir/ritonavir + dasabuvir (3D) (3 patients, 4.8% in both groups), glecaprevir/pibrentasvir (7 patients, 11.3% in Group A; 8 patients, 12.9% in Group B), and elbasvir/grazoprevir (7 patients, 11.3% in both groups) (Table 1). Treatment commenced at the recommended dosages following baseline evaluations.

All patients completed their prescribed treatment course, achieving a sustained virological response (SVR12) rate of 98.4%, with the exception of one patient who relapsed at the end of treatment. The therapy was well-tolerated, with no significant changes in liver enzymes, bilirubin, prothrombin time, or evidence of hepatic decompensation or renal dysfunction.

At baseline (T0), patients in Group A exhibited significantly higher scores on the Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A) ( $p < 0.05$ ) compared to Group B (Table 2). In addition, Group A had notably higher total scores on the SCL-90-R, as well as on specific subscales such as somatization ( $p < 0.05$ ), depression ( $p < 0.05$ ), anxiety ( $p < 0.05$ ), paranoid ideation ( $p < 0.01$ ), and psychoticism ( $p < 0.01$ ) (Table 2). No significant differences were found between the two groups in terms of coping strategies used prior to DAA treatment (Table 3), nor in quality of life scores, except for the mental health subscale, which was lower in Group A ( $p < 0.012$ ). Gender analysis revealed that male patients in both groups had higher subscale scores on somatization, obsessive-compulsive symptoms, depression, sensitivity, and psychoticism. Additionally, male patients less frequently employed coping strategies like denial, turning to religion, or humor. Baseline HCV RNA levels did not show significant differences between the groups, nor did they vary significantly between patients with or without cirrhosis.

In Group A, treatment with DAA resulted in significant reductions in both HAM-A and HAM-D scores ( $p < 0.05$ ). However, no changes were observed in the total or subscale scores of the SCL-90-R or coping strategies, although there was a marked decline in the general health perception subscale of the SF-36 ( $p < 0.05$ ).

In contrast, patients in Group B showed a substantial decrease in both HAM-A and HAM-D scores ( $p < 0.0001$ ), and the depression subscale of the SCL-90-R also significantly decreased ( $p < 0.05$ ). However, the somatization subscale score increased markedly ( $p < 0.001$ ). Changes in coping strategies indicated that problem-focused coping significantly increased in the suppression of competing activities ( $p < 0.01$ ), while instrumental social support ( $p < 0.01$ ), emotion-focused acceptance ( $p < 0.001$ ), and mental disengagement ( $p < 0.05$ ) decreased. In terms of quality of life, Group B patients experienced significant improvements in vitality ( $p < 0.01$ ), physical role functioning ( $p < 0.05$ ), and social role functioning ( $p < 0.05$ ). Additionally, emotional ( $p < 0.037$ ) and social ( $p < 0.007$ ) role functioning, along with mental health ( $p < 0.037$ ), were significantly better in Group B compared to Group A after treatment (T1).

## Discussion

This study sought to investigate whether treatment with direct-acting antivirals (DAAs) influences mood symptoms in individuals with a history of psychiatric conditions or triggers new psychiatric symptoms in DAA-naïve chronic hepatitis C (CHC) patients. Mental health changes were assessed in CHC patients before and 12 weeks after completing DAA therapy. Additionally, the study examined how patients managed the disease and its challenges and how treatment impacted their quality of life (QoL).

The patient cohort achieved a sustained virological response at 12 weeks post-treatment (SVR12) rate of 98.4%, aligning with findings in previous studies (27,28). Baseline comparisons showed no notable differences in HCV RNA levels between those with or without psychiatric histories or between cirrhotic and non-cirrhotic patients.

Psychiatric issues, including depression, are prevalent in CHC patients, irrespective of treatment status (2,28,29). Among the study participants, the majority were diagnosed with mixed anxiety-depressive disorder and were treatment-naïve. Only 27.4% had prior exposure to interferon-alpha (IFN- $\alpha$ ) therapy, either alone or combined with ribavirin.

These findings mirror those of other research into the prevalence of anxiety and depression in CHC patients. However, variations in study methodologies, sample characteristics, symptom definitions, and diagnostic tools account for differences across studies (29-34). While some research indicates DAA therapy does not worsen psychiatric symptoms in patients with mental health histories (12,35-38), others suggest the therapy could provoke mood disturbances in this population (15-17).

In this study, DAA therapy neither aggravated pre-existing mood symptoms nor caused new psychiatric symptoms in DAA-naïve patients, irrespective of their psychiatric history. This contrasts with earlier reports linking antiviral treatments to increased psychiatric complications (13,31,33). Consistent with Sakamari et al. (2019) (16), only patients without prior psychiatric histories exhibited an increase in somatization symptoms post-treatment, as measured by SCL-90-R. Conversely, these patients reported a significant improvement in self-rated depressive symptoms ( $p < 0.02$ ).

The findings suggest that while some patients may be vulnerable to psychiatric side effects during DAA therapy, targeted psychotherapeutic interventions could enhance treatment outcomes.

Using the COPE Inventory, this study assessed coping mechanisms in CHC patients before and after therapy. No significant changes were observed in patients with psychiatric histories. However, patients without such histories demonstrated increased use of problem-focused coping strategies, such as suppressing competing activities ( $p < 0.01$ ), while reducing reliance on instrumental social support ( $p < 0.01$ ). Emotion-focused strategies, such as acceptance ( $p < 0.001$ ) and mental disengagement ( $p < 0.05$ ), also decreased. This suggests that patients without psychiatric histories are more adaptable to the challenges posed by treatment. In contrast, psychological distress in patients with mental health issues remained unchanged, highlighting the need for therapeutic interventions. Supporting this, other research has demonstrated the effectiveness of psychiatric counseling in alleviating mental health symptoms during antiviral therapy (39).

HCV infection detrimentally affects patients' quality of life, social interactions, and emotional well-being, exacerbated by concerns about disease progression and transmission (40). SF-36 scores indicated poor QoL in both patient groups prior to treatment.

In line with previous studies, psychiatric complications and antiviral treatments can negatively impact QoL, daily activities, and social functioning (4,27,31,41). However, patients without psychiatric histories experienced improvements in physical vitality, role functioning, and social role functioning 12 weeks after completing DAA therapy. Conversely, patients with psychiatric histories showed no significant improvement in SF-36 subscales, except for general health perception scores, which declined significantly post-treatment.

While the study confirmed the safety of DAAs in avoiding QoL deterioration compared to IFN- $\alpha$  and ribavirin therapies (13,42), several limitations must be acknowledged. These include the

short follow-up duration of 12 weeks post-treatment, the focus on neuropsychiatric side effects over more common ones like fatigue and gastrointestinal disturbances, and the lack of data on drug interactions with comorbid conditions. Moreover, the small sample size, absence of a control group, and overrepresentation of patients without psychiatric histories limit the generalizability of the findings.

### Conclusions

The latest clinical guidelines emphasize that HCV treatment goals should extend beyond viral eradication to include QoL enhancement and psychosocial support (20). Research has shown that psychiatric symptoms in CHC patients can impair physical, emotional, and cognitive functioning, further diminishing QoL.

This study demonstrated that DAA therapy is generally safe, with no significant adverse psychiatric or hepatic effects in either patient group. However, lingering psychological distress in some patients suggests the importance of integrating psychological interventions with medical treatment. Collaborative efforts between hepatologists and mental health professionals are essential for optimizing outcomes and improving QoL in CHC patients.

### References

1. Lavanchy D. Evolving epidemiology of hepatitis C virus. *Clin. Microbiol. Infect.* 2011;17:107–115. doi: 10.1111/j.1469-0691.2010.03432.x.
2. Adinolfi L.E., Nevola R., Lus G., Restivo L., Guerrera B., Romano C., Zampino R., Rinaldi L., Sellitto A., Giordano M., et al. Chronic hepatitis C virus infection and neurological and psychiatric disorders: An overview. *World J. Gastroenterol.* 2015;21:2269–2280. doi: 10.3748/wjg.v21.i8.2269.
3. Forton D.M., Allsop J.M., Main J., Foster G.R., Thomas H.C., Taylor-Robinson S.D. Evidence for a cerebral effect of the hepatitis C virus. *Lancet.* 2001;358:38–39. doi: 10.1016/S0140-6736(00)05270-3.
4. Carithers R.L., Sugano D., Bayliss M. Health assessment for chronic HCV infection: Results of quality of life. *Dig. Dis. Sci.* 1996;41:75S–80S. doi: 10.1007/BF02087879.
5. Amodio P., Salari L., Montagnese S., Schiff S., Neri D., Bianco T., Minazzato L. Hepatitis C virus infection and health-related quality of life. *World J. Gastroenterol.* 2012;18:2295–2299. doi: 10.3748/wjg.v18.i19.2295.
6. Miller E.R., McNally S., Wallace J., Schlichthorst M. The ongoing impacts of hepatitis C—A systematic narrative review of the literature. *BMC Public Health.* 2012;12:2–13. doi: 10.1186/1471-2458-12-672.
7. Manns M.P., Wedemeyer H., Cornberg M. Treating viral hepatitis C: Efficacy, side effects, and complications. *Gut.* 2006;55:1350–1359. doi: 10.1136/gut.2005.076646.
8. Udina M., Castellví P., Moreno-España J., Navinés R., Valdés M., Fornés X., Langohr K., Solà R., Vieta E., Martín-Santos R. Interferon-induced depression in chronic hepatitis C: A systematic review and meta-analysis. *J. Clin. Psychiatry.* 2012;73:1128–1138. doi: 10.4088/JCP.12r07694.
9. Evon D.M., Esserman D.E., Howell M.A., Ruffin R.A. Pegylated interferon pharmacokinetics and self-report depressive symptoms during antiviral treatment for chronic hepatitis C. *Pharmacopsychiatry.* 2014;47:195–201. doi: 10.1055/s-0034-1385929.
10. Hepatitis C guidance: AASLD-IDS recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology.* 2015;62:932–954. doi: 10.1002/hep.27950.
11. Sundberg I., Lannergård A., Ramklint M., Cunningham J.L. Direct-acting antiviral treatment in real world patients with hepatitis C not associated with psychiatric side effects: A prospective observational study. *BMC Psychiatry.* 2018;16:157. doi: 10.1186/s12888-018-1735-6.
12. Marcellin P., Chousterman M., Fontanges T., Ouzan D., Rotily M., Varastet M., Lang J.P., Melin P., Cacoub P. Adherence to treatment and quality of life during hepatitis C therapy: A prospective, real-life, observational study. *Liver Int.* 2011;31:516–524. doi: 10.1111/j.1478-3231.2011.02461.x.
13. Rowan P.J., Bhulani N. Psychosocial assessment and monitoring in the new era of non-interferon-alpha hepatitis C virus treatments. *World J. Hepatol.* 2015;7:2209–2213. doi: 10.4254/wjh.v7.i19.2209.
14. Ho S.B., Monto A., Peyton A., Kaplan D.E., Byrne S., Moon S., Copans A., Rossaro L., Roy A., Le H., et al. Efficacy of Sofosbuvir plus ribavirin in veterans with hepatitis C virus genotype 2 infection, compensated cirrhosis, and multiple comorbidities. *Clin. Gastroenterol. Hepatol.* 2017;15:282–288. doi: 10.1016/j.cgh.2016.05.024.

15. Sakamaki A., Kamimura K., Fukui N., Watanabe H., Sakai N., Tominaga K., Mizuno K., Takamura M., Kawai H., Takuro Sugai T., et al. A case report of psychiatric symptoms following direct-acting antiviral and ribavirin combination therapy for chronic hepatitis C in a patient with innate anxiety. *BMC Gastroenterol.* 2019;19:85. doi: 10.1186/s12876-019-1013-1.
16. Volpato S., Montagnese S., Zanetto A., Turco M., De Rui M., Ferrarese A., Amodio P., Germani G., Senzolo M., Gambato M., et al. Neuropsychiatric performance and treatment of hepatitis C with direct-acting antivirals: A prospective study. *BMJ Open Gastroenterol.* 2017;4:e000183. doi: 10.1136/bmjgast-2017-000183.
17. Nemeroff C.B., Weinberger D., Rutter M., MacMillan H.L., Bryant R.A., Wessely S., Stein D.J., Pariante C.M., Seemüller F., Berk M., et al. DSM-5: A collection of psychiatrist views on the changes, controversies, and future directions. *BMC Med.* 2013;11:202. doi: 10.1186/1741-7015-11-202.
18. Yoshida E.M., Sulkowski M.S., Gane E.J., Herring R.W., Jr., Ratziu V., Ding X., Wang J., Chuang S.M., Ma J., McNally J., et al. Concordance of sustained virological response 4, 12, and 24 weeks post-treatment with sofosbuvir-containing regimens for hepatitis C virus. *Hepatology.* 2015;61:41–45. doi: 10.1002/hep.27366.
19. Pawlotsky J.M., Negro F., Aghemo A., Berenguer M., Dalgard O., Dusheiko G., Marra F., Puoti M., Wedemeyer H. EASL Recommendations on Treatment of Hepatitis C 2018. *J. Hepatol.* 2018;69:461–511. doi: 10.1016/j.jhep.2018.03.026.
20. Williams J.B. A structured interview guide for the Hamilton Depression Rating Scale. *Arch. Gen. Psychiatry.* 1988;45:742–747. doi: 10.1001/archpsyc.1988.01800320058007.
21. Shear M.K., Vander Bilt J., Rucci P., Endicott J., Lydiard B., Otto M.W., Pollack M.H., Chandler L., Williams J., Ali A., et al. Reliability and validity of a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH--A). *Depress. Anxiety.* 2001;13:166–178. doi: 10.1002/da.1033.
22. Derogatis L.R., Cleary P.A. Confirmation of the dimensional structure of the SCL--90: A study in construct validation. *J. Clin. Psychol.* 1977;33:981–989. doi: 10.1002/1097-4679(197710)33:4<#x0003c;981::AID-JCLP2270330412&#x0003e;3.0.CO;2-0.
23. Carver C.S., Scheier M.F., Weintraub J.K. Assessing coping strategies: A theoretically based approach. *J. Pers. Soc. Psychol.* 1989;56:267–283. doi: 10.1037/0022-3514.56.2.267.
24. Ware J.E., Jr., Sherbourne C.D. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med. Care.* 1992;30:473–483. doi: 10.1097/00005650-199206000-00002.
25. Apolone G., Mosconi P. The Italian SF-36 Health Survey: Translation, validation, and norming. *J. Clin. Epidemiol.* 1998;51:1025–1036. doi: 10.1016/S0895-4356(98)00094-8.
26. Ware J.E., Bayliss M.S., Mannocchia M., Davis G.L. Health related quality of life in chronic hepatitis C: Impact of disease and treatment response. *Hepatology.* 1999;30:550–555. doi: 10.1002/hep.510300203.
27. Younossi Z., Kallman J., Kincaid J. The effects of HCV infection and management on health-related quality of life. *Hepatology.* 2007;45:806–816. doi: 10.1002/hep.21565.
28. Roche B., Coilly A., Duclos-Vallee J.C., Samuel D. The impact of treatment of hepatitis C with DAAs on the occurrence of HCC. *Liver Int.* 2018;38:139–145. doi: 10.1111/liv.13659.
29. Grebely J., Dalgard O., Conway B., Cunningham E.B., Bruggmann P., Hajarizadeh B., Amin J., Bruneau J., Hellard M., Litwin A.H., et al. Sofosbuvir and velpatasvir for hepatitis C virus infection in people with recent injection drug use (SIMPLIFY): An open-label, single-arm, phase 4, multicentre trial. *Lancet Gastroenterol. Hepatol.* 2018;3:153–161. doi: 10.1016/S2468-1253(17)30404-1.
30. Schaefer M., Capuron L., Friebe A., Diez-Quevedo C., Robaey G., Neri S., Foster G.R., Kautz A., Forton D., Pariante C.M. Hepatitis C infection, antiviral treatment and mental health: A European expert consensus statement. *J. Hepatol.* 2012;57:1379–1390. doi: 10.1016/j.jhep.2012.07.037.
31. Fontana R.J., Hussain K.B., Schwartz S.M., Moyer C.A., Su G.L., Lok A.S.F. Emotional distress in chronic hepatitis C patients not receiving antiviral therapy. *J. Hepatol.* 2002;36:401–407. doi: 10.1016/S0168-8278(01)00280-X.
32. Golden J., O'Dwyer A.M., Conroy R.M. Depression and anxiety in patients with hepatitis C: Prevalence, detection rates and risk factors. *Gen. Hosp. Psychiatry.* 2005;27:431–438. doi: 10.1016/j.genhosppsy.2005.06.006.
33. Navines R., Castellvi P., Moreno-Espana J., Gimenez D., Udina M., Cañizares S., Diez-Quevedo C., Valdésab M., Solà R., Martín-Santos R. Depressive and anxiety disorders in chronic hepatitis C

- patients: Reliability and validity of the Patient Health Questionnaire. *J. Affect. Disord.* 2012;138:343–351. doi: 10.1016/j.jad.2012.01.018.
34. Back D., Belperio P., Bondin M., Talal A.H., Park C., Zhang Z.Z., Pinsky B., Crown E., Mensa F.J., Marra F. 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. doi: 10.1111/jvh.13110.
35. Sackey B., Shults J.G., Moore T.A., Rogers R., Mehvar M., King J.G. Evaluating psychiatric outcomes associated with direct-acting antiviral treatment in veterans with hepatitis C infection. *Ment. Health Clin.* 2018;8:116–121. doi: 10.9740/mhc.2018.05.116.
36. Egmond E., Marinõ Z., Navines R., Oriolo G., Pla A., Bartres C., Lens S., Fornis X., Martin-Santos R. Incidence of depression in patients with hepatitis C treated with direct-acting antivirals. *Braz. J. Psychiatry.* 2020;42:72–76. doi: 10.1590/1516-4446-2018-0336.
37. Durcan E., Hatemi I., Sonsuz A., Canbakan B., Ozdemir S., Tuncer M. The effect of direct antiviral treatment on the depression, anxiety, fatigue and quality-of-life in chronic hepatitis C patients. *Eur. J. Gastroenterol. Hepatol.* 2020;32:246–250. doi: 10.1097/MEG.0000000000001501.
38. Neri S., Bertino G., Petralia A., Crisafulli G., Rizzotto A., Calvagno G.S., Mauceri B., Abate G., Boemi P., Di Pino A., et al. A multidisciplinary therapeutic approach for reducing the risk of psychiatric side effects in patients with chronic hepatitis C treated with pegylated interferon  $\alpha$  and ribavirin. *J. Clin. Gastroenterol.* 2010;44:e210–e217. doi: 10.1097/MCG.0b013e3181d88af5.
39. Hussain K.B., Fontana R.J., Moyer C.A., Su G.L., Sneed-Pee N., Lok A.S.F. Comorbid illness is an important determinant of health-related quality of life in patients with chronic hepatitis C. *Am. J. Gastroenterol.* 2001;96:2737–2744. doi: 10.1111/j.1572-0241.2001.04133.x.
40. Martin L., Younossi Z. Health-related quality of life (HRQOL) in chronic liver disease. *Dig. Liver Dis.* 2005;37:819–820. doi: 10.1016/j.dld.2005.04.022.
41. Conversano C., Carmassi C., Carlini M., Casu G., Gremigni P., Dell’Osso L. Interferon  $\alpha$  Therapy in Patients with Chronic Hepatitis C Infection: Quality of Life and Depression. *Hematol. Rep.* 2018;7:e5632. doi: 10.4081/hr.2015.5632.
42. Musselman D.L., Lawson D.H., Gumnick J.F., Manatunga A.K., Penna S., Goodkin R.S., Greiner K., Nemeroff C.B., Miller A.H. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N. Engl. J. Med.* 2001;344:961–966. doi: 10.1056/NEJM200103293441303.
43. Capuron L., Miller A.H. Immune system to brain signaling: Neuropsychopharmacological implications. *Pharm. Ther.* 2011;130:226–238. doi: 10.1016/j.pharmthera.2011.01.014.
44. Reichenberg A., Gorman J.M., Dieterich D.T. Interferon-induced depression and cognitive impairment in hepatitis C virus patients: A 72-week prospective study. *AIDS.* 2005;19:S174–S178. doi: 10.1097/01.aids.0000192087.64432.ae.