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A B S T R A C T

Objective: To prospectively evaluate for changes in objective cognitive performance (attention, memory, and executive function) and psychiatric symptom severity (depression, anxiety, fatigue, and pain) in patients before, during and after interferon-alpha based therapy (IFN) for chronic hepatitis C virus infection (HCV).
Methods: 33 HCV+ adults were evaluated two months before IFN initiation (baseline), three months into IFN, and six months following IFN termination (IFN+ Group). 31 HCV+ adults who did not undergo IFN therapy were evaluated at baseline and six months later (IFN− Group). At each evaluation, participants completed the Neuropsychological Assessment Battery (NAB) Attention, Memory and Executive Functions Modules, the Beck Depression Inventory, Second Edition (BDI), Generalized Anxiety Disorder Inventory (GADI), Fatigue Severity Scale (FSS), and Brief Pain Inventory (BPI).
Results: Compared with the IFN− Group, the IFN+ Group experienced significantly ($p < 0.050$) increased symptoms of depression, anxiety, fatigue and pain during IFN therapy relative to baseline. In the IFN+ Group, psychiatric symptoms generally returned to baseline levels following IFN termination. Sustained viral response was associated with significantly lower depression and fatigue. No significant changes in cognitive performance were observed.
Conclusions: During IFN, patients with HCV evidence significantly increased psychiatric symptoms, including symptoms of depression, anxiety, fatigue and pain. These psychiatric symptoms are generally short-term and remit following IFN termination, with increased benefit if viral clearance is achieved. However, IFN is not associated with significant declines in objective cognitive performance during or following IFN.

Introduction

Approximately 2.2% of adults world-wide are chronically infected with the hepatitis C virus (HCV) [1], and approximately 10–15% of these cases progress to advanced liver disease resulting in decompensated liver cirrhosis, hepatocellular carcinoma, liver transplantation, or death [2]. Until recently, standard of care for HCV was combination therapy including both PEGylated interferon-alpha and ribavirin. For HCV genotype 1, combination therapy is typically for 48 weeks, while for genotype 2/3, treatment is typically for 24 weeks. In 2011, the Food and Drug Administration (FDA) approved two protease inhibitors, telaprevir and boceprevir, for the treatment of HCV [3]. Thus, current antiviral therapy for HCV can either entail combination therapy or triple drug therapy with pegylated interferon-alpha, ribavirin, and a protease inhibitor. Following combination therapy, sustained viral response (SVR) (i.e., viral clearance for at least six months following treatment termination) is achieved in approximately 40–50% of those with HCV genotype 1, and 75–80% of those with genotype 2/3 [4]. Recent clinical trials suggest that triple drug therapy significantly increases SVR rates among individuals with HCV genotype 1 to above 65% [5–7].

Interferon-alpha is an endogenous cytokine that can also be administered exogenously for the treatment of malignancies such as malignant

melanoma as well as chronic viral diseases including hepatitis B and HCV. Interferon-alpha based antiviral therapy for HCV (IFN) is associated with significant side effects, the most commonly reported ones including flu-like symptoms (e.g., fever, chills, myalgia, nausea, fatigue), psychiatric symptoms (e.g., depressed mood, anxiety, irritability, emotional lability, agitation, apathy, anhedonia, anorexia, psychomotor retardation, sleep disturbance, sexual dysfunction) and cognitive complaints [8].

Although cognitive complaints are frequently reported during IFN, relatively few studies have attempted to longitudinally characterize neuropsychological function before, during and after IFN using objective neuropsychological tests. Objective neuropsychological testing is important because people do not typically assess their cognitive skills accurately, and subjective cognitive complaints poorly correlate with objective neuropsychological performance [9]. Perhaps due in part to widely varying methodology, results from available cognitive studies are mixed, showing no clear pattern of whether objective cognitive performance declines during IFN, whether impairments abate following treatment termination, nor which cognitive domains are most sensitive to IFN effects [10–24]. In terms of psychiatric side effects, there is a relatively large literature documenting high rates of psychiatric symptoms during IFN administration but significantly less information regarding the possible persistence of these side effects following IFN termination. A recent community survey of 200 patients treated with IFN for HCV found that 84.5% reported psychiatric side effects during IFN, and 42.5% reported psychiatric side effects that persisted up to six months following IFN termination [25]. IFN induced depression is the most prevalent and well-studied IFN induced psychiatric side effect. The most recent meta-analysis on this topic [26] evaluated 26 prospective observational studies that reported on the incidence of IFN induced major depressive disorder in patients treated for HCV; overall cumulative incidence of depression was 25% following 24 weeks of IFN, and 28% following 48 weeks of IFN. Although the depressive symptoms associated with IFN are generally considered to be transient and remit following termination of therapy [8], a handful of case reports have described worsening depression, and at times increased suicidality, following IFN termination [27–30]. In a case series of five patients treated with IFN, suicide was attempted in four cases after IFN termination and was responsible for two deaths [30]. In another report, two attempted suicides and one successful suicide during or shortly after IFN were described [28]. The rates and time course of other IFN induced psychiatric symptoms have been less rigorously studied. However, an expert panel convened by the European Liver Patient's Organization (ELPA) recently published a consensus statement regarding treatment recommendations for the management of mental health problems among HCV infected patients [31]. Based on their review of the available literature on HCV, IFN, and mental health, this consensus statement reports prevalence rates of IFN induced psychiatric side effects ranging from 30 to 70% for depression, 39–80% for fatigue, 18–45% for sleep disturbances, 16–50% for irritability, 11–45% for anxiety, 0–3.2% for mania, 0–0.6% for psychosis, 3.5–10% for suicidal ideation, and 0–0.2% for suicidal attempts.

In light of the inconsistent findings within the cognitive literature, additional well-designed longitudinal studies are warranted to better characterize the trajectory of potential IFN induced cognitive effects both during IFN and following IFN termination. The present study, therefore, utilizes a comprehensive battery of widely used, well-validated, and adequately normed neuropsychological assessment instruments to prospectively evaluate neuropsychological functioning in patients before, during, and after IFN, and also includes a demographically similar (i.e., age, race/ethnicity, gender, education, baseline estimated IQ) control group of untreated HCV patients to control for possible confounding factors such as practice effects. This study additionally adds to the literature on the psychiatric side effects of IFN by simultaneously including well-validated symptom questionnaires to evaluate the severity and persistence of symptoms of IFN induced depression, anxiety, fatigue and pain.

Methods

Participants

A total of 64 adults were recruited from the Portland, Oregon area and assigned to one of two groups: 1) adults with chronic HCV (>5 years) who were about to initiate IFN (IFN+, n = 33), 2) a control group of adults with chronic HCV (>5 years) who were not planning to initiate IFN (IFN−, n = 31). Participants were recruited from Portland area hepatology clinics through referral by the hepatologists, announcements at hepatology clinic HCV education classes, mailings to patients who had previously participated in HCV research, or study advertisements posted in hepatology clinics and hospitals. *Inclusion Criteria*: 1) Able to provide informed consent, 2) HCV status confirmed by the treating hepatologist, medical record verification, and a detectable HCV viral load based on polymerase chain reaction (PCR) test at the time of study enrollment. *Exclusion Criteria*: 1) History of antiviral therapy or chemotherapy for any purpose. 2) Visual or auditory impairments that would prevent valid neuropsychological test administration. 3) History of a major medical or psychiatric condition, or currently unstable medical or psychiatric condition, that was likely to be associated with severe neurological, cognitive, or immune dysfunction at the time of enrollment or would preclude informed consent or valid testing [e.g., stroke, seizures, brain tumors, Parkinson's disease, neurodegenerative dementia, mental retardation, hepatic encephalopathy, human immunodeficiency virus (HIV), traumatic brain injury with loss of consciousness ≥30 min, schizophrenia, bipolar I disorder]. 3) Within twenty-four hours of testing, use of alcohol, illicit substances, or medications with acute cognitive effects such as sedation or intoxication (e.g., benzodiazepines, opiates, muscle relaxants, psychostimulants, steroids, anticholinergics). 4) Alcohol or drug dependence within the past three months (except nicotine or caffeine), based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria [32], confirmed with the Mini-International Neuropsychiatric Interview (MINI) [33].

Procedures

All research was conducted with permission from the Portland Veterans Affairs Medical Center (PVAMC)'s Institutional Review Board and in accordance with the Helsinki Declaration as revised in 1989. All patients were paid $75 per study visit to complete the following study procedures: clinical interview, comprehensive medical record review, a battery of cognitive assessment measures, a battery of psychiatric questionnaires to assess severity of depression, anxiety, fatigue, and pain, and blood sample collection for standard medical laboratory tests including a liver panel (serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), ammonia, bilirubin, and albumin levels), human immunodeficiency virus (HIV) antibody screening, and HCV testing (HCV antibody, followed by HCV recombinant immunoblot assay, HCV PCR Qualitative, and HCV PCR Quantitative if HCV antibody positive). Blood samples were collected by certified phlebotomists in the PVAMC medical laboratory. All other study procedures were administered by one of eight study personnel (VW, SJ, CE, MK, DK, JA, KB, HO) who were trained and supervised by a clinical neuropsychologist (MH). To ensure accuracy, all cognitive and psychiatric measures were scored and then re-scored by separate study personnel. All study data were entered into a database initially and then double-checked by separate study personnel prior to analyses.

Clinical interviews were conducted using a structured case report form, developed specifically for this study, including prompts to screen patients based on each inclusion criteria, gather relevant demographic data, assess for a full range of current and past Axis I psychiatric and substance use disorders using DSM-IV [32] criteria and the MINI [33], evaluate for history of head injuries, and record a comprehensive list of current and previous medical conditions and medications. Study

personnel additionally reviewed each participant's complete electronic medical record if treated at PVAMC, or the medical records forwarded by a treating hepatologist or primary care provider if treated elsewhere to cross-validate the psychiatric, substance use, and medical history gathered in the clinical interview.

The IFN + Group was followed longitudinally before, during, and after IFN and repeated all study visit procedures according to the following study visit schedule: 1) Visit 1 — (baseline) eligible to initiate IFN within approximately two months, 2) Visit 2 — approximately three months into IFN, 3) Visit 3 — approximately 6 months post IFN termination. The IFN − Group was followed longitudinally according to an equivalent schedule even though this group did not initiate IFN, with Visit 2 occurring approximately five to six months following baseline; however, the IFN−Group was not assessed at Visit 3.

Cognitive measures

Wechsler Test of Adult Reading (WTAR). [34]

A widely used word recognition reading test, validated for use in estimating baseline cognitive ability prior to injury or disease. Standard Index Scores are derived from age corrected norms.

Neuropsychological Assessment Battery (NAB) [35]

A well-validated, comprehensive battery of subtests assessing a range of cognitive domains. The Attention, Memory, and Executive Functions Modules were administered, each consisting of several subtests relevant to that domain. Based on demographically corrected norms (i.e., age, gender, education), standard T scores are derived for each subtest, and standard Index Scores are derived as summary measures of performance across subtests for each Module.

Psychiatric questionnaires

Depression. Beck Depression Inventory, Second Edition (BDI) [36]

A well-validated 21-item measure of depression severity. As previously described [37], we conducted a factor analysis of BDI data from a large sample of 671 HCV + patients which yielded a two-factor model and showed that HCV + adults scored significantly higher on the Somatic Factor (i.e., loss of energy, changes in sleeping pattern, irritability, changes in appetite, concentration difficulty, tiredness or fatigue, loss of interest in sex) than the Cognitive Affective Factor (i.e., sadness, pessimism, past failure, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal thoughts, crying, agitation, worthlessness). Thus, for the present study, the total BDI scores (Depression—Total) as well as the two BDI factor scores [Depression—Cognitive Affective Factor and Depression—Somatic Factor, derived according to the previously published methods [37]] are reported and analyzed.

Anxiety. Generalized Anxiety Disorder Inventory (GADI) [38]

A well-validated 18-item measure of anxiety severity.

Fatigue. Fatigue Severity Scale (FSS) [39–41]

A 9-item fatigue severity scale, previously validated for use with patients with HCV, multiple sclerosis, and other chronic illnesses.

Pain. Brief Pain Inventory, Short Form (BPI) [42–44]

A well-validated 12-item inventory assessing both the intensity of recent pain [BPI Pain Severity (BPI-PS)] as well as the level at which it interferes with daily activities [BPI Pain Interference (BPI-PI)].

Statistical analyses

Analyses were conducted using Stata v12. Results with p values < 0.05 were considered significant, unless multiple models were run and then a Bonferroni correction was employed. Primary outcome measures were the summary cognitive (NAB Attention Index, NAB Memory Index, and NAB Executive Functions Index) and psychiatric (BDI Total, BDI-Cognitive–Affective Factor, BDI-Somatic Factor, GADI, FSS, BPI-PI, BPI-PS) scores.

For Table 1, between group comparisons of baseline demographic and clinical characteristics were conducted using F tests for continuous variables; chi-square tested differences between categorical variables.

Due to the structure of the data, two sets of analyses were necessary for adequate modeling. To determine whether IFN was associated with significantly increased cognitive and psychiatric symptoms during treatment, the first analysis included all data from the first two visits (i.e., Visit 1 pre-treatment, and Visit 2 during treatment) for both the IFN + and IFN − groups. For these data, a 2 (Visit 1, Visit 2) × 2 (IFN + Group, IFN − Group) mixed-effects regression model was conducted for each of the primary outcome measures. The models assumed two levels, Participants (Level 1) nested within Visit (Level 2), in order to adjust standard errors for the longitudinal effects. GADI, BDI Total Score, FSS and both scales of the BPI used Poisson mixed-effects modeling to account for non-normal distributions. The NAB Indices and BDI Factors were analyzed with normal mixed-effects regression methods. To control for multiple comparisons, a Bonferroni correction was employed, and only omnibus tests with p values ≤ 0.005 (0.050/10 omnibus tests) were deemed significant and interpreted.

To determine whether any IFN associated cognitive or psychiatric symptoms remitted upon treatment termination, data from the IFN + group only was analyzed across all three study visits (i.e., Visit

Table 1
Between group comparisons of baseline demographic data, clinical characteristics and hepatitis C and liver biomarkers by study group.[a]

	IFN +	IFN −	p value
N	33	31	
Demographics			
Age, mean years (SD)	52 (10)	52 (8)	0.984
Male gender	64%	61%	0.846
Caucasian	94%	86%	0.323
Veteran status	33%	35%	0.891
Years of education	13 (2)	13 (2)	0.724
Estimated cognitive reserve (WTAR), mean standard score (SD)	101 (14)	105 (14)	0.309
Clinical characteristics			
Body mass index, mean (SD)	30 (5)	29 (6)	0.251
Lifetime alcohol use disorder[b]	53%	58%	0.543
Lifetime other drug use disorder[b]	64%	88%	0.022*
Lifetime medical diagnoses (any)	55%	61%	0.627
Diabetes	9%	10%	0.936
Hyperlipidemia	18%	10%	0.328
Hypertension	39%	29%	0.383
Asthma/pulmonary	9%	16%	0.395
Lifetime psychiatric diagnoses (any)[b]	41%	55%	0.618
Major depressive disorder[b]	31%	48%	0.861
Posttraumatic stress disorder[b]	16%	23%	0.482
Other anxiety disorder[b]	13%	23%	0.264
Hepatitis C and liver biomarkers			
HCV RNA ($\log_{10}$ IU/ml), mean (SD)	5.9 (0.2)	6.1 (0.2)	0.673
AST (IU/L), mean (SD)	71.0 (36.2)	46.1 (32.4)	0.754
ALT (IU/L), mean (SD)	100.9 (56.7)	63.0 (47.0)	0.915
Ammonia (μg/dL), mean (SD)	41.2 (20.0)	45.0 (29.4)	0.572
Bilirubin (mg/dL), mean (SD)	0.6 (0.3)	2.6 (11.1)	0.273
Albumin (g/dL), mean (SD)	4.2 (0.3)	4.4 (0.5)	0.019*

[a] Data expressed as n, with (%) in terms of n over total N unless otherwise stated. p values reflect comparisons between the IFN + group versus the IFN − control group. For categorical variables, chi square analysis was used. F tests were used for continuous variables.

[b] Substance use and psychiatric diagnoses were based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria verified using the Mini-International Neuropsychiatric Interview. ALT = Serum alanine aminotransferase levels. AST = Serum aspartate aminotransferase levels. HCV = Hepatitis C virus. IFN + = Adults with chronic hepatitis C virus infection who were planning to initiate antiviral treatment. IFN − = Adults with chronic hepatitis C virus infection who were not planning to initiate antiviral treatment. IU = International units. RNA = Ribonucleic acid. SD = Standard deviation. WTAR = Wechsler Test of Adult Reading.

* $p \leq 0.050$.

1: pre-treatment, Visit: 2 during treatment, and Visit 3: post-treatment). For these data, normal (NAB scores, BDI factors) or Poisson (GADI, BDI Total Score, FSS, BPI scales) regression models with clustered standard errors by participant identified differences in scores across visits for each of the primary cognitive and psychiatric outcome measures. Two models evaluated differences between two intervals: Visit 1 and Visit 2, and between Visit 2 and Visit 3. Two separate models were specified in order to avoid statistical suppression between two dummy codes. To control for multiple comparisons, a Bonferroni correction was employed, and only omnibus tests with p values ≤ 0.0025 (0.05/20 omnibus tests) were deemed significant and interpreted.

Results

Baseline characteristics

As summarized in Table 1, groups were similar in terms of age, gender, ethnicity, Veteran status, education, estimated baseline cognitive ability (i.e., WTAR scores), and body mass index, as well as rates of lifetime psychiatric disorders and medical conditions. Although rates of past alcohol use disorders were similar across groups, the IFN− group had significantly higher rates of past drug use disorders. There were no significant differences across groups in terms of HCV viral load [i.e., HCV ribonucleic acid (RNA) levels], AST, ALT, ammonia, or bilirubin levels; the IFN− had significantly higher albumin levels. Within the total sample, 70% reported contracting HCV through injection drug use, 3% through blood transfusions, 6% through tattoos, 5% through accidental work exposure, and 15% through unknown or otherwise unspecified causes.

IFN Effects during treatment and following treatment termination

Means and standard errors for each of the primary outcome measures are reported by group (IFN+, IFN−) and visit (Visit 1, Visit 2, Visit 3) in Table 2. Results from the 2 (Visit 1, Visit 2) × 2 (IFN+ Group, IFN−Group) mixed effects regression models for each of the primary outcome measures are summarized in Table 3, including Wald X^2, df, b, robust standard errors, z and p values. Results from the mixed effects regression models assessing change across visits within the IFN+ group are summarized in Table 4, including df, z and p values.

Regarding IFN effects on cognition, following a Bonferroni correction for multiple comparisons, the 2 (Visit 1, Visit 2) × 2 (IFN+ Group, IFN− Group) mixed effects regression model (Table 3) remained significant and was therefore interpreted for NAB Attention (but not for NAB Memory nor NAB Executive Function). Although there was a significant Visit effect for NAB Attention, the IFN and interaction effects were non-significant. Results from the mixed-effects regression model evaluating changes across visits before, during and after IFN in the IFN+ group (Table 4) were largely consistent with the results in Table 3. Following a Bonferroni correction for multiple comparisons, NAB Memory showed a significant increase between treatment and post-treatment. However, given the small magnitude of this increase (and the non-significant effects in Table 3), this change is most consistent with a modest practice effect rather than a robust IFN effect. No other effects were significant in these models. Overall, these results indicate there was no statistically robust or clinically significant effect of IFN on objective cognitive performance during treatment or following treatment termination.

Regarding IFN effects on psychiatric symptoms, following a Bonferroni correction for multiple comparisons, the 2 (Visit 1, Visit 2) × 2(IFN+ Group, IFN− Group) mixed effects regression models (Table 3) remained significant and were therefore interpreted for BDI Total Score, BDI Somatic Factor, GADI, FSS, and BPI-PI (but not for BDI Cognitive Affective Factor or BPI-PS). Significant interaction effects were observed for the BDI Total Score and the BDI Somatic Factor, suggesting that IFN is associated with significantly increased somatic but not cognitive–affective symptoms of depression during treatment. Significant interaction effects were also observed on the GADI and FSS (but not on the BPI-PI), suggesting that IFN is also associated with increased anxiety and fatigue during treatment. Results from the mixed effects regression model evaluating changes across visits before, during and after IFN in the IFN+ group (Table 4) were largely consistent with the results in Table 3. Following Bonferroni corrections for multiple comparisons, BDI Total Score, BDI Cognitive Affective Factor, GADI, FSS and BPI-PI showed significant increases between baseline and mid-treatment. BDI Total Score, BDI Somatic Factor, BDI Cognitive Affective Factor, GADI, and FSS showed significant decreases between treatment and post-treatment (see means across visits in Table 2). Psychiatric rating scales with scores that had significant between visit effects are also shown in Fig. 1. Overall, these results indicate that IFN is associated with significant increases in psychiatric symptoms (depression, anxiety, fatigue, pain) during treatment which decrease or remit following treatment termination.

Post-hoc analyses

Post-hoc exploratory regression models were constructed to determine whether HCV disease variables [AST, ALT, ammonia, bilirubin, and albumin levels] significantly mediated changes in cognitive or psychiatric outcomes across visits. This was accomplished by a series of mixed effects regression analyses (with adjusted standard errors for participant) with appropriate distributional assumptions, with the primary outcome measures entered as the dependent variables, visit number entered as an independent variable, and the HCV disease variables entered as simultaneous covariates. When ALT and AST were included in the FSS regression, the increase in FSS from Visit 1 to Visit 2 became non-significant (but the decrease from Visit 2 to Visit 3 remained significant) showing that ALT and AST in part mediated the effect between FSS and IFN. None of the other HCV disease variables were significant in the FSS model. Otherwise, results were consistent with those shown in Table 4, with none of the other outcomes being mediated by any of the HCV diseases variables.

Additional post-hoc exploratory analyses were conducted to determine whether SVR contributed to cognitive and psychiatric outcomes within the IFN+ group. Normal and Poisson regressions compared the psychiatric and cognitive outcomes as dependent variables and SVR at Visit 3 as an independent variable. SVR was significantly associated with the BDI Total Score ($z = -2.07$, $p = 0.038$), indicating that those with a SVR were less depressed ($M = 8.05$, $SD = 10.92$) than those who did not achieve a SVR ($M = 17.0$, $SD = 10.8$) (Fig. 1). SVR was significantly associated with the BDI Somatic factor ($z = -2.19$, $p = 0.028$), similarly showing lower scores for those attaining a SVR ($M = 0.55$, $SD = 0.60$) than those who did not ($M = 1.12$, $SD = 0.49$) (Fig. 1). FSS scores were also significantly lower for those who attained a SVR ($z = -2.38$, $p = 0.017$) ($M = 3.14$, $SD = 1.39$) than those who did not ($M = 5.44$, $SD = 3.15$) (Fig. 1). SVR was not significant for the NAB indices, BDI Cognitive Affective Factor, GADI or the BPI scales.

Lastly, rates of clinically significant depressive episodes, defined as a BDI score >18, were explored post-hoc across groups, and based on SVR in the IFN+ group using chi square analysis. At Visit 1, rates of clinically significant depressive episodes were comparable across groups (IFN− group = 10%, IFN+ = 9%). At Visit 2, rates were significantly higher in the IFN+ group (IFN− = 6%, IFN+ = 24%). At Visit 3, individuals in the IFN+ group who achieved a SVR had a much lower rate of clinically significant depressive episodes (15%) compared with those who did not achieve a SVR (50%), but this was a non-significant trend ($p = 0.087$).

Table 2
Means and standard errors on primary cognitive and psychiatric outcome measures by study group and visit.[a]

	IFN+ (n = 33)			IFN− (n = 31)	
Outcome Measure	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2
NAB Attention	94.85 (2.51)	98.00 (2.59)	100.96 (3.03)	97.87 (2.59)	101.87 (2.63)
NAB Memory	97.55 (2.59)	96.36 (2.59)	102.37 (3.09)	93.00 (2.67)	96.42 (2.67)
NAB Executive Functions	103.31 (2.80)	104.09 (2.76)	107.48 (3.14)	99.68 (2.84)	105.74 (2.84)
BDI Total (Depression)	7.64 (1.29)	14.34 (1.31)	9.85 (1.66)	7.26 (1.33)	7.35 (0.33)
Somatic Factor	0.60 (0.08)	1.16 (0.08)	0.67 (0.10)	0.53 (0.08)	0.49 (0.09)
Cognitive Affective Factor	0.21 (0.06)	0.39 (0.06)	0.34 (0.08)	0.23 (0.06)	0.20 (0.06)
GADI (Anxiety)	11.73 (1.87)	21.50 (1.89)	15.85 (2.25)	11.94 (1.93)	12.81 (1.93)
FSS (Fatigue)	3.36 (0.86)	7.31 (0.88)	3.60 (1.14)	3.67 (0.89)	3.41 (0.89)
BPI-PI (Pain Interference)	1.80 (0.43)	3.54 (0.44)	2.35 (0.49)	2.09 (0.45)	2.78 (0.44)
BPI-PS (Pain Severity)	2.17 (0.40)	2.69 (0.40)	2.18 (0.46)	2.26 (0.41)	2.86 (0.41)

[a] Data expressed as mean (standard error). NAB Attention, Memory and Executive Functions Module scores are reported as demographically corrected standard index scores. Psychiatric symptom severity scores are reported as total scale scores (BDI Total, GADI, FSS, BPI-PI, BPI-PS) or factor scores (BDI Somatic Factor, BDI Cognitive Affective Factor). BDI = Beck Depression Inventory, Second Edition. BPI-PI = Brief Pain Inventory-Pain Interference. BPI-PS = Brief Pain Inventory-Pain Severity. FSS = Fatigue Severity Scale. GADI = Generalized Anxiety Disorder Inventory. IFN+ = Adults with chronic hepatitis C virus infection who were planning to initiate interferon-alpha based antiviral treatment. IFN− = Adults with chronic hepatitis C virus infection who were not planning to initiate interferon-alpha based antiviral treatment. NAB = Neuropsychological Assessment Battery.

Table 3
Results from a 2 (Visit 1, Visit 2) × 2 (IFN+ Group, IFN− Group) mixed effects model to evaluate the effect of interferon-alpha based antiviral therapy (IFN) for hepatitis C on primary cognitive and psychiatric outcome measures during treatment.[a]

Neuropsychological Assessment Battery — Attention (Normal) Wald $X^2 = 13.86$, df = 3, p = 0.0031*

Effect	b (robust SE)	z	p
Intercept	97.87 (2.27)	43.02	<0.000
Visit	4.56 (1.51)	3.02	0.002
Group	−3.02 (3.49)	−0.87	0.386
Visit × group	−1.70 (2.06)	−0.83	0.409

Neuropsychological Assessment Battery — Memory (Normal) Wald $X^2 = 5.45$, df = 3, p = 0.1415

Effect	b (robust SE)	z	p
Intercept	93.00 (2.35)	39.58	<0.000
Visit	3.42 (1.58)	2.16	0.031
Group	4.54 (3.78)	1.20	0.230
Visit × group	−4.60 (2.33)	−1.97	0.048

Neuropsychological Assessment Battery — Executive Functions (Normal) Wald $X^2 = 11.38$, df = 3, p = 0.0098

Effect	b (robust SE)	z	p
Intercept	99.67 (2.98)	33.46	<0.000
Visit	6.06 (1.85)	3.29	0.001
Group	3.28 (4.16)	0.79	0.430
Visit × group	−4.93 (2.51)	−1.96	0.050

Beck Depression Inventory — Total Score (Poisson) Wald $X^2 = 40.37$, df = 3, p < 0.0000*

Effect	b (robust SE)	z	p
Intercept	1.62 (.17)	9.65	<0.000
Visit	−0.0007 (0.14)	−0.01	0.996
Group	0.14 (0.23)	0.61	0.542
Visit × group	0.72 (.19)	3.85	<0.000

Beck Depression Inventory — Somatic Factor (Normal) Wald $X^2 = 54.99$, df = 3, p < 0.0000*

Effect	b (robust SE)	z	p
Intercept	0.52 (0.073)	7.14	<0.000
Visit	−0.019 (0.082)	−0.23	0.816
Group	0.072 (0.11)	0.69	0.493
Visit × group	0.57 (0.11)	5.00	<0.000

Beck Depression Inventory — Cognitive Affective Factor (Normal) Wald $X^2 = 11.84$, df = 3, p = 0.0079

Effect	b (robust SE)	z	P
Intercept	0.23 (.061)	3.69	<0.000
Visit	−0.011 (.035)	−0.33	0.745
Group	−0.014 (0.081)	−0.17	0.865
Visit × group	0.18 (0.061)	2.95	0.003

Generalized Anxiety Disorder Inventory (Poisson) Wald $X^2 = 45.28$, df = 3, p < 0.0000*

Effect	b (robust SE)	z	P
Intercept	2.12 (0.17)	12.77	<0.000
Visit	0.037 (0.12)	0.30	0.761
Group	0.027 (0.23)	0.12	0.908
Visit × group	0.69 (0.17)	4.15	<0.000

Fatigue Severity Scale (Poisson) Wald $X^2 = 24.39$, df = 3, p < 0.0000*

Effect	b (robust SE)	z	p
Intercept	1.23 (0.12)	9.95	<0.000
Visit	−0.075 (0.17)	−0.45	0.653
Group	−0.089 (0.17)	−0.51	0.608
Visit × group	0.71 (0.23)	3.17	0.002

Table 3 (*continued*)

Brief Pain Inventory-Pain Interference (Poisson) Wald $X^2 = 18.48$, df = 3, p = 0.0003*

Effect	b (robust SE)	z	P
Intercept	0.39 (0.22)	1.76	<0.078
Visit	0.26 (0.17)	1.56	0.119
Group	−0.15 (0.30)	−0.50	0.614
Visit × group	0.38 (0.23)	1.65	0.099

Brief Pain Inventory-Pain Severity (Poisson) Wald $X^2 = 8.78$, df = 3, p = 0.0323

Effect	b (robust SE)	z	p
Intercept	0.52 (0.20)	2.55	<0.011
Visit	0.24 (0.16)	1.48	0.138
Group	−0.063 (0.28)	−0.23	0.821
Visit × group	−0.010 (0.23)	−0.05	0.963

[a] Data reflect results from a 2 within (Visit 1, Visit 2) × 2 between (IFN+ Group, IFN− Group) groups design to assess the effects of IFN on patients with HCV+ during treatment. Models are classified as either normal or Poisson mixed-effect regression models depending on the shape of the distribution of the outcome variable. IFN+ = Adults with chronic hepatitis C virus infection who were planning to initiate interferon-alpha based antiviral treatment. IFN− = Adults with chronic hepatitis C virus infection who were not planning to initiate interferon-alpha based antiviral treatment. Visit 1 = Baseline (two months before treatment.) Visit 2 = Three months into IFN treatment, or approximately six months following baseline for the IFN− group.

* $p \leq 0.005$, indicates the overall model remained significant after a Bonferroni correction for multiple comparisons ($p \leq 0.050/10$ tests).

Discussion

Overall, our results indicate that adults undergoing IFN treatment for HCV report significantly increased psychiatric symptoms, including depression, anxiety, fatigue and pain that interferes with daily life during treatment, but that these symptoms remit or are markedly reduced six months following treatment termination. Although many studies have documented increased rates of depression during IFN therapy [8,26], our data reveals that while the somatic symptoms of depression, including loss of energy, fatigue, changes in sleep patterns, changes in appetite, loss of interest in sex, irritability, and concentration difficulties, are significantly increased during treatment, the changes are not as robust for many other classic symptoms of depression, namely cognitive and affective symptoms including sadness, pessimism, feelings of failure, feeling guilty, feeling punished, self-dislike, self-criticism, suicidal ideation, crying, agitation, or worthlessness. These findings extend our previous work demonstrating that somatic, but not cognitive and affective, symptoms of depression are increased in untreated HCV+ adults [37,45].

Moreover, we found evidence that individuals who achieved a SVR following IFN termination reported significantly less depression and fatigue following IFN than those who did not achieve a SVR. This latter finding is consistent with our recent work demonstrating that peripheral immune activation, particularly as indicated by altered levels of immunoregulatory factors such as inflammatory cytokines, is significantly associated with increased psychiatric symptoms in individuals with and without HCV [46]. Similarly, an expanding literature demonstrates that elevations of pro-inflammatory cytokines and chemokines are evidenced in patients diagnosed with a range of chronic psychiatric disorders including depression [47,48], anxiety [49,50], chronic fatigue syndrome [51], and pain disorders [52–55]. Although the present study design prevents definitive confirmation of mechanism, results support the hypothesis that, upon HCV viral clearance in individuals treated with IFN, cytokines and other immune factors return to normal homeostatic levels, reversing a pattern of extended peripheral immune activation and inflammation, and contributing toward improved mood and psychiatric function.

In contrast, we found no evidence of significant decline in terms of objective cognitive performance on neuropsychological tests during or following IFN treatment for HCV. Nor did we find evidence that SVR or other HCV disease variables were associated with improved cognitive

Table 4
Results from mixed-effects regression models evaluating change across visits on primary cognitive and psychiatric measures in patients with hepatitis C two months before (Visit 1), three months into (Visit 2), and six months after (Visit 3) interferon-alpha based antiviral treatment, n = 33.[a]

Test between visits	1 and 2	2 and 3
Degrees of freedom = 2	z (p)	z (p)
NAB Attention	1.81 (0.071)	2.21 (0.027)
NAB Memory	−0.65 (0.515)	3.25 (0.001)*
NAB Executive Functions	0.48 (0.631)	1.98 (0.047)
BDI Total (depression)	7.93 (<0.000)*	−5.22 (<0.000)*
Somatic Factor	2.35 (0.019)	−0.07 (<0.000)*
Cognitive Affective Factor	5.79 (<0.000)*	−4.42 (<0.000)*
GADI (Anxiety)	9.55 (<0.000)*	−5.26 (<0.000)*
FSS (Fatigue)	7.04 (<0.000)*	−6.74 (<0.000)*
BPI-PI (Pain Interference)	4.15 (<0.000)*	−2.83 (0.005)
BPI-PS (Pain Severity)	1.58 (0.113)	−1.61 (0.107)

[a] Data reflect results from a mixed-effects regression model (with adjusted standard errors for participant) based on the distribution of the outcome variable (Poisson or Normal). Two models are displayed: one for the difference between Visit 1 and Visit 2, and another independent model for the difference between Visit 2 and Visit 3 to evaluate change on measures of cognitive and psychiatric function across visits in patients with hepatitis C. All models had 2 degrees of freedom. BDI = Beck Depression Inventory, Second Edition. BPI-PI = Brief Pain Inventory-Pain Interference. BPI-PS = Brief Pain Inventory-Pain Severity. FSS = Fatigue Severity Scale. GADI = Generalized Anxiety Disorder Inventory. NAB = Neuropsychological Assessment Battery.

* $p \leq 0.005$, indicates the overall model remained significant after a Bonferroni correction for multiple comparisons ($p \leq 0.0025/20$ tests).

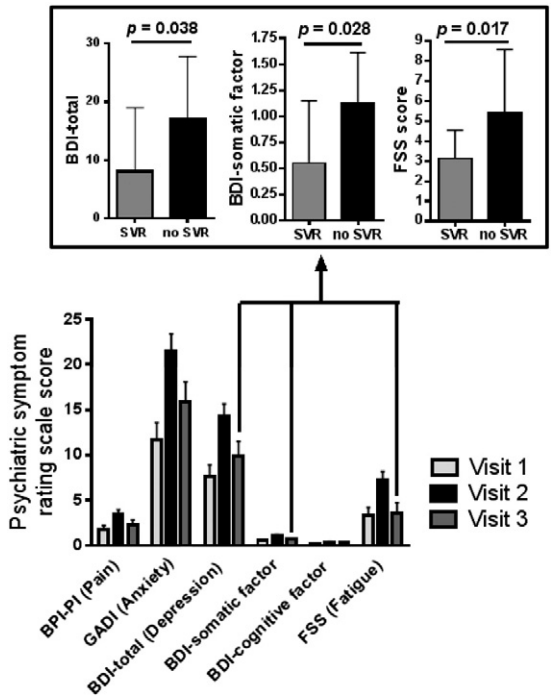

Fig. 1. Psychiatric symptom rating scale scores before, during and after interferon alpha-based antiviral therapy (IFN) for hepatitis C virus (HCV) infection (IFN+ Group, n = 33). Significant ($p < 0.05$) changes across visits were observed on the Beck Depression Inventory, Second Edition (BDI) Total, BDI Somatic Factor, BDI Cognitive Affective Factor, Generalized Anxiety Disorder Inventory (GADI), Fatigue Severity Scale (FSS), and Brief Pain Inventory-Pain Interference (BPI-PI); specifically, psychiatric symptoms increased at Visit 2 during IFN and then returned to near baseline levels at Visit 3 following IFN termination. Inset box illustrates that for individuals undergoing IFN for HCV (IFN+ Group), there were significant effects of sustained viral response (SVR) on fatigue (FSS), overall depression (BDI Total), and somatic depression (BDI Somatic Factor) scores. Participants who achieved an SVR (n = 19) reported less fatigue ($p = 0.017$), less overall depression ($p = 0.038$), and fewer somatic depressive symptoms ($p = 0.028$), as compared with those who did not achieve an SVR (n = 6).

performance following IFN termination. As the results of previous longitudinal studies evaluating change on objective neuropsychological measures across IFN for HCV have been largely mixed, our results can neither be deemed consistent nor inconsistent with the available literature. Table 5 provides a summary of results from selected published studies prospectively following the neuropsychological performance of adults with HCV across IFN. Of the published studies that measured neuropsychological performance both at baseline (i.e., prior to treatment) as well as during IFN, 9/14 reported a significant IFN associated decline in at least one cognitive domain [11,15–19,21,22,24], while 5/14 did not [10,12–14,23]. Across the nine studies that detected cognitive decline, there was little consistency with regard to which domains were significantly affected. The discrepant study results are likely due to large variations in study design including selection of neuropsychological measures and sample characteristics. For example, only 6/14 of these studies included a non-treated control group [12,13,15,19,21,22] (4/6 detecting significant decline), six primarily utilized computerized batteries [17–19,22–24] (5/6 detecting significant decline), three were designed primarily as neuroimaging studies [one was an electroencephalogram (EEG) study [10], one a magnetic resonance spectroscopy (MRS) study [12], and another a positron emission tomography (PET) study [16]] (1/3 detecting decline), three report only on one global cognitive score (1/3 finding a decline), two report on only one cognitive domain [15,22] (both finding decline), and two include only previous non-responders to IFN undergoing repeat IFN rather than treatment naïve adults [13,14] (neither finding a decline).

The results of the six published studies that compared neuropsychological performance at baseline with performance several months following IFN termination are also mixed (Table 5). These types of studies are particularly important because patients and clinicians want to know whether potential IFN associated cognitive effects are permanent (i.e., persist long-term) versus temporary (i.e., subside once IFN is terminated). One study found significant decreases in cognitive performance during IFN, which appeared to abate following treatment termination regardless of depression [11]. Another study [17] found no significant differences in cognitive performance between baseline and 6–8 months post IFN termination, regardless of antiviral response. Since these two studies had found significant declines during IFN, these results might suggest that IFN induced cognitive effects are temporary and return to baseline following IFN termination. However, another study [20] measured cognitive performance at baseline and 6 months post IFN termination and found no differences across time points except that a subgroup of individuals who did not achieve an SVR significantly declined between baseline and IFN termination in Speeded Visual Processing but no other cognitive domains; this study did not measure performance during IFN. In contrast, the remaining 3/5 studies [12,14,23] found that the subgroup of IFN treated individuals who maintained an SVR following IFN termination (but not those who did not achieve an SVR) improved in at least one cognitive domain compared with baseline. The cognitive domains that improved were not consistent across these latter three studies, and none of these three studies detected significant cognitive decline during IFN in their samples.

In light of the inconsistencies across available neuropsychological studies, it is worth highlighting important strengths that increase the validity of our study demonstrating non-significant effects of IFN on cognition. We evaluated participants before, during, and after IFN therapy, and our IFN treated group was compared with an untreated control group that was similar in terms of key demographic, psychiatric and medical characteristics (Table 1). This design allowed us to rule out confounds such as practice effects or medical factors that might otherwise explain improvement or decline across time in a study without a control group. The neuropsychological assessment measures we selected, namely the NAB Attention, Memory, and Executive Functions Modules, are from a widely-used, well-validated, and clinically relevant instrument yielding demographically corrected standard summary index

Table 5
Summary of results from published studies prospectively evaluating objective cognitive performance across interferon-alpha based treatment (IFN) in adults with chronic hepatitis C virus (HCV) infection.

Study	Sample. Evaluation time points across IFN.	Cognitive domains tested during IFN (Was there a significant IFN related decline in this domain during IFN relative to baseline?)	Cognitive domains tested following IFN termination (Was there a significant IFN related change in this domain post IFN relative to baseline?)
Amodio et al., 2005 [10]	HCV+ adults: 1) IFN+ (n = 20). Evaluated at baseline; during IFN (2 m, 6 m)	Auditory Attention/Working Memory (N); Speeded Visual Processing (N); Visuoconstruction (N); Verbal Learning (N); Verbal Fluency (N); Executive-Inhibition/Switching (N)	None
Baranyi et al., 2013 [11]	HCV+ adults: 1) IFN+ (n = 41). Evaluated at baseline; during IFN (1 m, 3 m, 6 m, 9 m); post IFN	Global Score of Memory and Attention (Y)	Global Score of Memory and Attention (N)
Byrnes et al., 2012 [12]	Non cirrhotic HCV+ adults: 1) IFN+ (n = 15), 2) IFN− (n = 7). Evaluated at baseline; during IFN (12w); post IFN (12w)	Verbal Learning (N); Verbal Recall (N); Visual–Spatial Learning (N); Visual–Spatial Recall (N); Visuoconstruction (N); Speeded Visual Processing (N); Auditory Attention/ Working Memory (N); Verbal Fluency (N); Motor Speed (N); Executive-Inhibition/ Switching (N)	Individuals with an SVR, but not those without an SVR, significantly improved on the following domains: Verbal Learning (Y); Verbal Recall (T); Visual–Spatial Learning (Y); Visual–Spatial Recall (N); Visuoconstruction (N); Speeded Visual Processing (T); Auditory Attention/Working Memory (N); Verbal Fluency (N); Motor Speed (N); Executive-Inhibition/Switching (N)
Fontana et al., 2007 [14]	HCV+ adults with advanced fibrosis who were previous non-responders to IFN: 1) retreated with IFN for 24w (n = 177), 2) had an SVR at 24w and continued IFN for 48w (n = 57). Evaluated at baseline; during IFN (24w, 48w); post IFN (24w)	Visual–Spatial Learning (N); Auditory Attention/Working Memory (N); Speeded Visual Processing (N); Motor Speed (N); Executive-Problem Solving/Mental Flexibility (N); Verbal Fluency (N); Reaction Time (N)	Adults in Group 2 showed significant improvements at 24w post IFN on the following: Visual-Spatial Learning (Y); Auditory Attention/Working Memory (N); Speeded Visual Processing (Y); Motor Speed (N); Executive-Problem Solving/Mental Flexibility (Y); Verbal Fluency (Y); Reaction Time (N)
Fontana et al., 2010 [13]	HCV+ adults with advanced fibrosis who were previous non-responders to IFN, randomized to: 1) IFN+ for 3.5 years (n = 66), 2) IFN− (n = 63). Evaluated at baseline; during IFN (12 m, 24 m, 36 m, and 48 m)	Global Deficit Score (N)	None
Hilsabeck et al., 2005 [15]	HCV+ adults: 1) IFN+ (n = 11), 2) IFN− (n = 19). Evaluated at baseline; during IFN (6 m).	Speeded Visual Processing (Y)	None
Juengling et al., 2000 [16]	HCV+ adults: 1) IFN+ (n = 11). Evaluated at baseline; during IFN (12w)	Verbal Learning (Y); Verbal Fluency (N); Speeded Visual Processing (N)	None
Kraus et al., 2005 [17]	HCV+ adults: 1) IFN+ (n = 70). Evaluated at baseline; during IFN (4w, 3–4 m, 6–8 m); post IFN (6–8 m)	Reaction Time/Motor Speed (Y); Divided Attention (N); Sustained Visual Attention (N); Visual Attention/Working Memory (Y)	Reaction Time/Motor Speed (N); Divided Attention (N); Sustained Visual Attention (N); Visual Attention/Working Memory (N)
Lieb et al., 2006 [18]	33 HCV+, 4 HBV+, and 1 HBV+/HCV+ adults: 1) IFN+ (n = 38). Evaluated at baseline; during IFN (12w)	Verbal Learning (Y); Speeded Visual Processing (N); Verbal Fluency (Y)	None
Majer et al., 2008 [19]	HCV+ adults: 1) IFN+ (n = 20); 2) IFN− (n = 12). Evaluated at baseline; during IFN (12w)	Reaction Time/Motor Speed (Y); Speeded Visual Processing (N); Executive-Inhibition/ Switching (N); Executive-Problem Solving/Mental Flexibility (N)	None
Pattullo et al., 2011 [20]	HCV+ adults with no other cognitive risk factors: 1) IFN+ with SVR (n = 31), 2) IFN+ without SVR (n = 9), 3) IFN− (n = 39). Evaluated at baseline; post IFN (6 m)	None	Verbal Learning (N); Visual Learning (N); Speeded Visual Processing (Y — Group 2 only declined); Auditory Attention/Working Memory (N); Motor Speed (N); Executive-Inhibition/Switching (N); Executive-Problem Solving/Mental Flexibility (N)
Pawelczyk et al., 2008 [21]	HCV+ adults: 1) IFN+ (n = 26), 2) IFN− (n = 21). Evaluated at baseline; during IFN (12w)	Executive-Inhibition/Switching (Y); Speeded Visual Processing (Y)	None
Raison et al., 2010 [22]	HCV+ adults: 1) IFN+ (n = 19), 2) IFN− (n = 12). Evaluated at baseline; during IFN (12w)	Reaction Time/Motor Speed (Y)	None
Thein et al., 2007 [23]	IFN+ (n = 34): 1) HCV+ Monoinfected (n = 19), 2) HIV+/HCV+ Coinfected (n = 15). Evaluated at baseline; during IFN (18w, 42w); post IFN (24w)	Global Cognitive Performance (Subtests measured Speeded Visual Processing and Reaction Times/ Motor Speed) (N)	At 24w post IFN, Group 2 only significantly improved in terms of Global Cognitive Performance related to Speeded Visual Processing. In the Total Sample, those who achieved an SVR, but not those who did not, performed significantly better following IFN termination on tests of Reaction Time/Motor Speed.
Wobrock et al., 2009 [24]	HCV+ adults: 1) IFN +(n = 17). Evaluated at baseline; during IFN (12w)	Attention (N); Speeded Visual Processing (Y); Motor Speed (N); Reaction Time/Motor Speed (N)	None

HCV = Hepatitis C virus. HCV+ = Infected with the hepatitis C virus. HIV+ = Infected with the human immunodeficiency virus. IFN = Interferon-alpha based antiviral therapy. IFN+ = Undergoing interferon-alpha based antiviral therapy. m = Month. N = No, there were no significant effects in this cognitive domain. SVR = Sustained viral response. T = There was a non-significant trend suggesting a possible effect in this cognitive domain. w = Week. Y = Yes, there was a significant effect in this cognitive domain.

scores based on a very large normative sample; the structure of the NAB allowed us to focus our primary analyses on a small number of robust index scores that were each derived from multiple individual subtests within a cognitive domain. We also used a mixed effects model that accounted for repeated measures and individual baseline scores, and we controlled for multiple comparisons. This analysis plan minimized our risk of over-interpreting weak effects of limited clinical significance.

Despite strengths, several limitations should be discussed. Our control group was assessed at two rather than three time points, requiring us to conduct two separate analyses to effectively assess for IFN effects during and following treatment. Our sample size was adequate for the present analyses, but not large, potentially increasing the risk of sample specific findings. For example, our sample was 63% male and 91% Caucasian, potentially limiting its generalizability to more diverse populations.

It is worth noting that in the very near future there will likely be new and improved treatments for HCV that do not use IFN, and, fortunately, these new treatment options are not anticipated to cause cognitive or psychiatric side effects [56–58]. Until these new treatments are available, healthcare providers should continue to screen for and treat depression and other psychiatric symptoms in patients who are considering IFN for HCV [59–62]. Further, it is well-documented that the development of depression during IFN therapy can be effectively treated using pharmacotherapeutic interventions (e.g., selective serotonin reuptake inhibitor antidepressants) or even prevented (in subsets of patients) by the use of prophylactic antidepressant treatment [60,63–66].

In summary, our study adds to the literature by using both well-validated objective neuropsychological measures as well as psychiatric symptom questionnaires to longitudinally characterize symptom course in patients with HCV who were either initiating or not initiating IFN for HCV. Our results indicate that patients report significant increases in psychiatric symptoms, including symptoms of depression, anxiety, fatigue and pain, during IFN treatment, which remit following treatment termination, with added benefit if viral clearance is achieved. However, IFN treatment for HCV was not associated with significant declines in objective cognitive performance on tests of attention, memory, or executive functions during IFN treatment or following IFN treatment termination.

Conflict of interest statement

The authors have no competing interests to declare.

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