Criteria Grid
Hepatitis C Research Studies, Tools, and Surveillance Systems

Best Practice/Intervention:	Quelhas R. et al. (2009) Psychiatric problems in patients infected with hepatitis C before and during antiviral treatment with interferon-alpha: a review. *Journal of Psychiatric Practice*, 15(4):262-281
Date of Review:	March 22, 2015
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☒
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☐ **Other:** **psychiatric disorders** **Level:** **Group** ☒ **Individual** ☐ **Other:** **Target Population:** **HCV infected patients with neuropsychiatric symptoms** **Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** **Country of Origin:** **Portugal** **Language:** **English** ☒ **French** ☐ **Other:**

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☐	☐	☐	Review of studies to summarize the etiology, course and management of neuropsychiatric symptoms in patients with chronic hepatitis C treated with interferon-alpha
Has the data/information been used for decision-making (e.g. program funding developments, policies, treatment guidelines, defining research priorities and funding)?	☐	☒	☐	Recommendations for treating neuropsychiatric symptoms in patients receiving interferon-alpha treatment are inconsistent. Decisions for treatments require clinical judgment.
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☒	☐	☐	

Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	Findings can be extended to patients worldwide who do develop interferon-alpha induced depression.
	YES	**NO**	**N/A**	**COMMENTS**
Are the best practices/methodology/results described applicable in developing countries?	☒	☐	☐	
The research study/tool/data dictionary is easily accessed/available electronically	☐	☒	☐	Journal subscription required for access at http://journals.lww.com/
Is there evidence of cost effective analysis with regard to interventions, diagnosis, treatment, or surveillance methodologies? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	
Are there increased costs (infrastructure, manpower, skills/training, analysis of data) to using the research study/tool/data dictionary?	☐	☒	☐	
How is the research study/tool funded? ***Please got to Comments section***	☐	☒	☐	No funding stated
Is the best practice/intervention dependent on external funds?	☐	☒	☐	
Other relevant criteria: _____	☐	☐	☐	- Interferon-alpha plus ribavirin is associated with significant neuropsychiatric adverse effects
WITHIN THE SURVEILLANCE SYSTEM FOR REVIEW				
Are these data regularly collected?	☐	☐	☒	Unclear
Are these data regularly collected at and/or below a national level?	☐	☐	☒	
Are these data collected manually or electronically?	☐	☐	☐	Electronically: search of Medline
RESEARCH REPORTS				
Has this research been published in a juried journal?	☒	☐	☐	*Journal of Psychiatric Practice*
Does the evidence utilize the existing data/surveillance information or has it generated new data and/or information?	☐	☐	☐	Existing data

Psychiatric Problems in Patients Infected with Hepatitis C Before and During Antiviral Treatment with Interferon-Alpha: A Review

ROSA QUELHAS, MD
ALICE LOPES, MD

Objective. **Neuropsychiatric symptoms are common in patients with chronic hepatitis C (CHC) and can potentially be exacerbated by interferon-alpha treatment. Such symptoms can contribute to problems with treatment adherence, which can significantly compromise epidemiological virus control. This review summarizes current knowledge about the etiology, course, and management of neuropsychiatric symptoms in patients with CHC.** ***Method.*** **Studies were identified using computerized searches, with further references obtained from the bibliographies of the reviewed articles.** ***Results.*** **Psychopathological syndromes that occur during interferon-alpha treatment frequently have atypical features that may complicate their recognition using standard diagnostic criteria. In addition, prospective studies in this area often exclude patients with psychiatric disorders and have methodological disparities that make it difficult to develop guidelines for management of psychiatric side effects induced by interferon-alpha. Despite the high prevalence of chronic hepatitis C virus (HCV) infection in patients with psychiatric and substance use disorders, neuropsychiatric concerns often lead to the exclusion of such patients from interferon-alpha treatment, inappropriately depriving them of the potential benefits of this therapy.** ***Conclusion.*** **Consultation-liaison psychiatrists should become familiar with the clinical spectrum of presentations associated with HCV infection as well as with related neuropsychiatric symptoms in order to promote the creation of multidisciplinary teams who specialize in the care of patients with HCV infections. More studies are needed to define neuropsychiatric syndromes that can be induced by interferon-alpha and to clarify best assessment and treatment procedures for these syndromes. It is also important to create and evaluate psychoeducational programs for all patients with chronic HCV infections, even those with low risk of complications, in order to promote adherence to therapy and optimize patients' quality of life.** *(Journal of Psychiatric Practice* **2009;15:262–281**)

KEY WORDS: hepatitis C, interferon-alpha, consultation-liaison psychiatry, neuropsychiatric syndromes, depression, psychiatric disorders, substance use disorders

Hepatitis C infection is a major public health problem.[1] It has been estimated that there are approximately 5 million carriers of hepatitis C virus (HCV) in Europe, 70% to 80% of whom are likely to develop a chronic infection. According to United States Centers for Disease Control and Prevention, approximately 3.2 million persons were chronically infected with HCV in 2006, with a peak prevalence among persons 40–49 years of age.[2] Although the number of new cases of acute hepatitis C has declined, a substantial burden of disease as a result of chronic infection still persists.[2] Cirrhosis will develop in 10%–20% of those with chronic HCV infection over a period of 20 to 30 years, making chronic hepatitis C (CHC) the most common cause of liver transplants in the developed world.[1]

The efficacy of antiviral treatment has significantly increased in recent years. Although treatment has up to now mainly been reserved for CHC with active viral replication, it is likely that treatment will be broadened in the future to attempt to eradicate HCV infection.

QUELHAS: Pedro Hispano General Hospital, Matosinhos' Local Health Unit (ULSM), Portugal; LOPES: Santo António General Hospital, Oporto Hospital Center, Portugal.

Please send correspondence and reprint requests to: Rosa Quelhas, MD, Pedro Hispano General Hospital, Matosinhos' Local Health Unit (ULSM), Rua Dr. Eduardo Torres, 4454-509 Matosinhos, Portugal. rosaquelhas@gmail.com

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Complex issues arise in the management of patients with psychiatric disorders who are infected with HCV. While HCV infection is very prevalent among patients with psychiatric disorders, patients with such disorders are often excluded from antiviral treatment. Antiviral treatment also has the potential to induce neuropsychiatric side effects and/or exacerbate previous psychiatric problems, which frequently have a negative impact on treatment adherence. The consultation-liaison psychiatrist is in a unique position to address problems related to the treatment of patients with CHC.

In this article, we review research findings concerning neuropsychiatric syndromes that occur in association with CHC and interferon-alpha (IFA) treatment, from the viewpoint of consultation-liaison psychiatry, including clinical features, possible underlying mechanisms, risk factors, and recommended management.

METHODS

The electronic database Medline® was searched for English language articles using the key terms "hepatitis C" and "interferon," crossed with the terms "psychiatric," "depression," "psychosis," "mania," and "anxiety," in the title field. The abstracts that were located were examined to identify articles that provided data concerning psychiatric side effects of IFA treatment in patients with CHC who did not have other comorbid infectious conditions. The reference lists of the selected articles were also searched for relevant citations. Our goal was to identify information relevant to psychiatric liaison care.

RESULTS

Psychopathology in Patients with Chronic Hepatitis C

Yovtcheva et al. reported a high prevalence of addictive disorders (86% alcoholism, 60% polysubstance abuse), anxiety-depressive and/or personality disorders (26%–34%), and psychotic disorders (17%) in a sample of 306 subjects with HCV infection.[3] In this study, 95% of patients were diagnosed with psychiatric disorders long before HCV infection was discovered. Even given that the asymptomatic course of CHC often leads to a delay of several years before diagnosis, these results suggest that patients with psychiatric disorders are more vulnerable to behaviors that put them at risk for acquiring HCV.[4]

Extrahepatic manifestations of HCV infection are also common, including neuropsychological symptoms such as disabling chronic fatigue, depression, lack of mental clarity ("brain fog"), and a perceived inability to function effectively. These manifestations seem to be more closely related to the severity of depression than of the hepatic disease.[5] There is growing evidence concerning the relationship between these types of neuropsychological symptoms and brain injury due to HCV.[3,4,6] Weissenborn et al. reported changes in both the midbrain serotoninergic and striatal dopaminergic systems in patients with HCV who had alterations of mood (increased anxiety and depression) and cognition, irrespective of viremia and normal liver function.[7] Several studies have also reported deficits in attention, higher executive function (working memory, mental flexibility), and verbal learning, in the absence of cirrhosis and/or lifetime substance use disorder (SUD).[6–9] Laskus et al. suggested that HCV crosses the blood brain barrier and produces a secondary infection in microglia and subsequent neuronal dysfunction.[7,8] Findings in the literature increasingly agree about the effect of HCV on the modulation of inflammatory cytokines, namely, increased production of interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF) and subsequent microglia activation. This mechanism has been repeatedly found in patients with the "sickness behavior" syndrome, which includes non-specific depressive symptoms such as fatigue, anhedonia, apathy, emotional lability, irritability, agitation, anorexia, psychomotor retardation, sleep disturbance, social withdrawal, hyperalgesia, decreased libido, and cognitive impairment.[8,10] Research has also examined the effect of HCV on the release of corticotrophin-releasing hormone (CRH), and consequent hypothalamic-pituitary-adrenal axis dysregulation.[8]

Our review of the literature indicated that there is a significantly higher prevalence of depression in patients infected with HCV (21%–59%) than in the general population.[11–16] However, the etiology of depressive symptoms in patients with CHC must be carefully assessed to distinguish among a primary psychiatric disorder, an adjustment disorder related to the CHC diagnosis or somatic symptoms, and an adverse biological effect of HCV.

Studies have also found that quality of life in patients with CHC is not associated with the histologic severity of their liver disease. Constant et al. noted the importance of psychosocial factors (e.g., coping styles, sources of information) in how patients perceive the severity of their HCV illness; they found that actively searching for information (monitoring), suggesting higher stress levels and/or a pessimistic view about the future, was the strongest predictor of perceived severity.[17] Patients who have had a longer interval since initial diagnosis and have failed to respond to previous therapy have also been found to have higher scores for depression and anxiety, suggesting the effects of a perception of lack of control over the progression of the disease.[18]

These findings and the high seroprevalence of HCV in patients with psychiatric disorders[19] reinforce the need for systematic screening for HCV in psychiatric populations and the importance of including a consultation-liaison psychiatrist in the multidisciplinary team providing care to patients with HCV infections. They also highlight the crucial role of communication between patients and physicians and providing adequate, accessible information to patients to help them cope with their illness and optimize their psychological well being and physical functioning.[17,20]

Treatment for Chronic Hepatitis C

Recombinant IFA was among the first agents studied in the mid-1980s for the treatment of what was then called non-A, non-B hepatitis. The treatment of hepatitis C has evolved rapidly in recent years with the use of the combination of IFA and the oral nucleoside analogue ribavirin (RBV). The most recent advance has been the introduction of long-acting pegylated IFA (pegIFA), produced by a process known as pegylation in which polyethylene glycol is added to conventional interferon. This process alters the antiviral and pharmacokinetic properties of the drug, with the important advantage of making dosing easier (dosed once weekly instead of three times weekly for conventional IFA), and increasing exposure of the virus to the drug (detectable blood levels of IFA before the next dose). At present, the first-line treatment for CHC consists of a combination of pegIFA and RBV, which can produce sustained viral eradication in 45%–95% of treatment-naïve patients, depending on viral genotype, viral load, and treatment adherence.[21] Available data indicate that the current standard of care will continue to play a critical role in the treatment of HCV, despite the development of new therapies, such as HCV protease inhibitors and/or polymerase inhibitors.[22] The guidelines of the American Association for the Study of Liver Diseases (AASDL) recommend IFA plus RBV treatment for 48 weeks for HCV genotype 1, the most common type in the United States, and for 24 weeks for HCV genotype 2 or 3.[23] In the past, it was believed that treatment was more likely to produce sustained virological response (SVR) in genotypes 2 and 3 (approximately 80% response rate) than in genotype 1b (approximately 45% response rate). However, recent studies have found that the probability of achieving SVR in patients with HCV genotype 1 varies from 7% to 97%, depending on pretreatment and treatment characteristics.[24] The most reliable predictor of success with combination treatment involving pegIFA plus RBV, even among difficult-to-treat patients, is the actual virological response after 4 weeks (rapid virological response) or 12 weeks (early virological response) of treatment, regardless of baseline characteristics.[24–26] Thus, some experts suggest that all patients infected with HCV be started on a therapeutic trial of pegIFA plus RBV, with the decision to discontinue the trial made on an individual basis based on treatment tolerability and virological response.[22] New evidence also suggests that it may be beneficial to extend treatment for difficult-to-treat patients, possibly justifying extending treatment to 72 weeks for genotype 1 and 48 weeks for genotype 2 or 3.[27–29]

In summary, it is critical to maximize the effectiveness of pegIFA plus RBV therapy, using systematic strategies to address modifiable pretreatment factors (e.g., obesity, depression, unhealthy lifestyle) and tolerability and adherence problems. Because the side effects of IFA can have a negative effect on adherence to treatment and optimization of dose and duration of treatment, a multidisciplinary approach to the care of patients infected with HCV is needed to improve the outcome of therapy.[30–34]

Clinical Features of Neuropsychiatric Toxicity Associated with Interferon-Alpha

Episodes of delirium (particularly with higher doses), depressive syndromes, and manic episodes,

sometimes with extreme irritability and psychomotor agitation, have been reported in association with IFA therapy.[35] Patients who develop neuropsychiatric toxicity while being treated with IFA usually present with multidimensional emotional distress,[11] without meeting strict DSM-IV-TR criteria for specific disorders. Our review of the literature on IFA-induced psychiatric side effects found disparities among studies in definitions of psychiatric symptoms, sensitivities and specificities of assessment instruments, exclusion criteria, and other methodological issues. Prospective studies that excluded patients with a lifetime history of psychiatric disorders reported an incidence of IFA-induced neuropsychiatric symptoms of 12%–41%,[36–39] while studies without this exclusion criterion reported an incidence of 17%–58%.[11,33,40–52] The incidence of major depressive episodes (MDEs), diagnosed according to DSM-IV-TR criteria, generally ranged from 12% to 42%.[33,37,38,41,46,49,53] Nonpsychiatric trials usually report a lower incidence of depression (20%–30%) during IFA treatment, possibly because only severe depressive episodes that compromised continuation of antiviral therapy were recorded.[15,54]

Several studies have suggested that IFA-induced depression is composed of two syndromes: a depression-specific syndrome characterized by depressed mood, melancholia, anhedonia, anxiety, subjective cognitive disturbance, and sometimes suicidal ideation, and a neurovegetative syndrome, characterized by fatigue, insomnia, anorexia, pain, and/or psychomotor slowness, which develops early and persists during IFA treatment.[34,35,38,43] IFA-induced depression is associated with a substantial risk of suicidal ideation, particularly associated with anxiety and insomnia; however, with adequate support, most patients can successfully complete a full course of antiviral treatment.[45,55] Although IFA-induced depression is not usually associated with a high risk of suicide, the increased risk of suicidal ideation must be of particular concern in patients who have a history of previous suicide attempts.[33,55]

In a sample of 93 patients with no active psychiatric illness at baseline, Constant et al. found that, of the 30 individuals (32%) who developed IFA-induced mood disorders, 60% had irritable manic-hypomanic episodes associated with fatigue, while 40% had major depression associated with hypomanic symptoms and fatigue (depressive mixed state).[43] They concluded that, aside from fatigue and anhedonia, which are possibly related to nonspecific stress triggered by IFA, most cases of IFA-induced mood disorders involve mixed states.[43] Similarly, in a sample of 98 patients receiving pegIFA plus RBV for CHC, Castera et al. found that, of the 38 patients (39%) who developed psychiatric side effects, 45% had mixed depressive states (MDE with hypomanic symptoms), while 55% had hypomanic episodes; irritability was the most common isolated symptom in this sample.[44]

Although the incidence of mania during IFA treatment is unknown, several cases have been reported, including cases of mania emerging spontaneously after an IFA-induced depression and/or after withdrawal of IFA, and reports of "switches" from depression to mania during antidepressant therapy.[4,56] In discussing these reports, researchers have suggested the possibility of an IFA-induced bipolar disorder, the triggering of a "latent" bipolar disorder, or the behavioral expression of neuropharmacological effects of IFA discontinuation.[4,56] Some reports have also suggested that the risk is dependent on the dose of IFA and that there may be a higher incidence of manic symptoms in patients with subclinical neurological abnormalities.[56,57] The mechanism responsible for the development of manic symptoms remains a matter of speculation, with several lines of evidence pointing to neuroendocrine, neurotransmitter, and cytokine pathways. Clinicians should be aware of the challenge of diagnosing a manic episode in the context of predominant irritability, especially with pre-existing fatigue or dysphoric depression.[31,35,43]

Cognitive side effects have been reported in 10%–20% of patients receiving IFA-based treatment, with the risk of cognitive decline possibly higher with a higher cumulative dose of IFA[58,59] and longer duration of treatment.[60] Growing evidence suggests that mood changes and cognitive symptoms associated with IFA treatment involve separate physiological mechanisms.[34,58,61–64]

Patients with IFA neurotoxicity have been reported to exhibit mild to moderate symptoms of frontal-subcortical brain dysfunction,[59,60] including cognitive and behavioral slowing, apathy, impaired executive functioning, and decreased memory. Lieb et al. found compromises in short-term memory, working memory, and word fluency after 3 months of IFA treatment, which were mainly related to dys-

function in the prefrontal cortex and hippocampus and were independent of depressive or anxious symptoms.[61]

Clinical trials suggest that neuropsychological deficits generally remit within 2–3 weeks of discontinuation of IFA treatment.[65] Nevertheless, clinical experience indicates that patients sometimes continue to complain of cognitive difficulties 12–24 months after discontinuation of IFA treatment, especially if they have received pegIFA.[61] As early as 1991, Meyers et al. suggested that at least some cases of IFA neurotoxicity may not be completely reversible.[59] Persistent cognitive impairment does not appear to be associated with HCV clearance.[61]

Recent studies suggest that the tolerability of pegylated and conventional IFA is similar; however, the psychiatric toxicity of pegIFA seems to be more insidious and persistent than that of conventional IFA therapy.[30,66] Studies have also suggested that IFA-induced psychiatric side effects with onset late in the course of treatment are more severe.[32,49,57]

Physiopathology of Neuropsychiatric Toxicity Associated with Interferon-Alpha

The literature suggests several mechanisms to explain neuropsychiatric toxicity associated with IFA:

1. ***Induction of peripheral pro-inflammatory cytokines*, *with subsequent 2,3-indoleamine dioxygenase enzyme (IDO) activation, plasma triptophan depletion, and diminished levels of serotonin.***[67] The diminished serotonin levels result in a "sickness behavior" syndrome that includes the nonspecific depressive symptoms described above.[12,68–70] However, there is no evidence that IFA-induced reductions in *plasma* serotonin levels translate to clinically significant reductions in *brain* serotonin (5-HT). Raison et al. assessed concentrations of several inflammatory mediators, monoamine neurotransmitter metabolites, and CRH in the cerebrospinal fluid (CSF) and plasma of patients with CHC being treated with pegIFA plus RBV. They found that IFA is capable of accessing the brain in humans and is associated with an inflammatory response in the CNS, which, in turn, interacts with monoamine (serotonin) metabolism and is correlated with depression.[71]
2. ***Neurotoxicity associated with kynurenine***, a metabolite produced as a result of the degradation of tryptophan by indoleamine-pyrrole 2,3-dioxygenase (IDO).[67,68,70]
3. ***Functional variations in the serotonin transporter[72–74] and serotonin 5-HT1A receptor.[75]*** Polymorphism in the serotonin transporter-linked promoter region (5-HTTLPR) has been found to be related to the biology of and risk for depression and anxiety-related temperamental traits, through a high frequency of 5-HTTLPR s-alleles that may lead to reduced serotonin transporter levels and 5-HT1A receptor-binding potential in the brain, resulting in dysfunction of the serotoninergic responses in the limbic system.[74,76,77] Lotrich et al. reported that 5-HTTLPR had a role in influencing resiliency in the face of a depressogenic trigger (e.g., an inflammatory cytokine such as IFA) and suggested that this effect may be mediated by effects on sleep quality.[74] Kraus et al. suggested that genotyping for functional variations in the 5-HT1A receptor can identify patients genetically at risk for IFA-induced depression, which might provide guidance concerning use of antidepressant prophylaxis.[75]
4. ***Decreased turnover of dopamine in the striatum and increased release of dopamine in cortical areas,*** which may partially explain the occurrence of parkinsonian and/or psychotic symptoms. The mechanism by which IFA alters dopamine metabolism is unclear; one possibility is that it may influence dopamine neurotransmission via direct actions on opioid receptors in basal ganglia circuits.[78,79]
5. ***Effects of opioid systems***. Opioid systems may play a key role in IFA-induced neuropsychiatric side effects. This may involve regulation of pro-inflammatory cytokine secretion from peripheral immune cells via mu-opioid receptor-dependent mechanisms. However, research data concerning involvement of opioid receptors in depression are still unclear.[80]
6. ***Neurotoxicity related to glutamatergic overproduction, impaired re-uptake, and metabolic conversion.*** Peripheral inflammation may activate microglia, leading to changes in gluta-

matergic neurotransmission. Imbalance in astrocytes/microglia may disrupt the delicate balance of neuroprotective versus neurotoxic effects in the brain, potentially leading to depression.[81]

7. ***Activation of the hypothalamo-pituitary-adrenocortical (HPA) axis in the context of cytokine-induced release of CRH.***[79] Growing evidence suggests that cortisol levels do not correlate with IFA-induced depression.[82,83] Wichers et al. suggested that cortisol levels may reflect pretreatment characteristics (e.g. personality, which affects both HPA axis functioning and vulnerability to depressive symptoms) and that changes in cortisol awakening response may be related to IFA-induced fatigue.[83]

8. ***Hypo- or hyperthyroidism*** (found in 8%–20% of patients), caused by hypothalamic-pituitary-thyroid axis dysfunction, although the relationship with IFA-induced depression is doubtful.[84]

The pathological mechanisms described in items 2 and 6 above are strongly related to the cognitive impairment associated with IFA treatment, in the context of functional change in glutamatergic transmission and/or neurotoxicity of hippocampal neurons that play a major role in learning and memory.[61] Studies have also reported toxic encephalopathy with an effect on fronto-subcortical connections,[10,44,59,63] as shown by frontal slowness on electroencephalogram[63] and diminished blood flow in cerebral areas that regulate memory and language,[64] findings that merit further investigation. Other indirect mechanisms that may be related to cognitive dysfunction include neuroendocrine systems, neurotransmitter function, and/or secondary cytokines.[78]

The extent of possible hormonal changes during IFA treatment is not clear. Kraus et al. reported functional androgen deficiency and increased depression in men with sexual dysfunction during IFA treatment.[85] Since these researchers found no significant correlation between androgen levels and depression, they concluded that IFA-induced decrease in sexual function is associated with, but not causally related to, both androgen reduction and increased depressive symptoms.

With respect to genetics, Gochee et al.[86] reported a higher risk of anxiety, irritability, and depression in CHC patients treated with IFA who were carriers of the epsilon 4 allele of the apolipoprotein E gene.

A history of fatigue in CHC patients seems to be a powerful predictor of IFA-induced depression, a finding reinforced by functional neuroimaging data showing a common neuronal circuit for fatigue and depression involving the cingulate and prefrontal cortex.[87]

The role of RBV should also be taken into account in considering the tolerability profile of CHC treatment. Studies suggest that RBV may induce depressive symptoms[39,48,86] in a dose-related manner.[39] RBV-induced anemia is also a major problem in combined therapy for CHC, which can, in turn, worsen fatigue. The literature suggests that both depressive symptoms and RBV-induced anemia are significant predictors of reduced quality of life in patients with CHC receiving combined antiviral therapy.[11,88,89]

Risk Factors for Neuropsychiatric Toxicity with Interferon-Alpha

Table 1 summarizes findings from prospective studies concerning psychiatric toxicity in patients receiving IFA therapy. The presence of a psychiatric illness has been considered a risk factor for IFA-induced psychiatric toxicity and has been an exclusion criterion in a number of studies.[31,36–39,42,44,46,66,111] Dell'Osso et al. recently found that lifetime subthreshold manic/hypomanic symptoms are a risk factor for IFA-induced depression, highlighting the need to comprehensively explore subtle mood dysregulation in patients being considered for IFA treatment.[38] Dieperink et al. reported that a family history of mood disorder and a personal history of at least two psychiatric diagnoses were predictive of IFA-induced neuropsychiatric symptoms, suggesting that greater vulnerability to stressful events may be a risk factor.[41] Martín-Santos et al. suggested that a history of major depression or alcohol dependence contributes to the risk of developing IFA-induced depressive symptoms through an association with elevated baseline depression scores.[52] However, several studies have not found a significantly higher risk of neuropsychiatric toxicity in patients with a history of psychiatric illness.[33,39,46,47,57,112–116] Some controlled studies have also found that patients without a history of psychiatric illness had significantly higher increases in depression scores and

Table 1. Reports of psychiatric toxicity in patients with chronic hepatitis C treated with interferon-alpha in prospective studies

Study	*Exclusion criteria*	*N sample (controls)*	*Assessment instruments*	*Assessment periodicity*	*Psychiatric side effects*	*PD*	*Findings*
*Hunt et al. 1997[36]	Previous IFA Past depression	28	HADS BDI SF-36	Baseline M 1, 6	21%	1 (4%)	Significant decrease in anxiety during M1; increase in depression during W6; no significant changes in health-related QOL.
*Otsubo et al. 1997[49]		85	CPI HAM-D	Baseline W 2, 4, 12, 24	MDE 37%	4 (5%)	MDEs more severe after 4Ws; MDE predictors: higher neuroticism scores; more severe depressed mood and sleep disorders.
*Miyaoka et al. 1999[50]		66	CPI HAM-D	Baseline W 4, 12, 24	44%	4 (6%)	No significant differences associated with gender or age.
*Bonaccorso et al. 2002[37]	Lifetime PI Lifetime SA	27	CPI MADRS	Baseline M 3	MDE 41%	—	Increased irritability, sadness, insomnia, anorexia, asthenia; no significant gender-related effects; no AD started; no changes in IFA dose.
Fontana et al. 2002[11]	Active PI Active SA	26	CPI BSS SF-36	Baseline Monthly M 6 after discontinuation	58%	6 (23%)	Neuropsychiatric toxicity during first 24 Ws, may require dose reductions of IFA and RBV and induces lower health-related QOL scores. Predictors of neuropsychiatric toxicity: female gender, baseline mood disorder, active medical comorbidity, no association with IFA dose. Lower SF-36 scores at W72 than baseline.
Häuser et al. 2002[33]	Active PI Active SA	39	SCID-I BDI	Baseline Weekly	MDE 33%	1 (3%)	Depression developed between W6 and 22. Rapid development of depressive symptoms related to higher baseline BDI scores; no increased risk if history of MDD or SA. 85% response to citalopram or bupropion.
Dieperink et al. 2003[41]		42 (13 controls without IFA treatment)	CPI, HAM-D, BDI, Zung SDS, IDD, PANAS +/– POMS	Baseline W 4, 8, 12, 24	48% MDE 23%	4 (10%)	Risk factors for MDE:·higher baseline BDI scores, family history of PI (7-fold increase), history ⩾ 2 psychiatric diagnoses. SVR 29%, with no effect of psychiatric history.
Gohier et al. 2003[45]	Previous IFA	71	CPI MADRS HAM-A	Baseline M 4, 12 M 6 after discontinuation	33%	7 (10%)	AD and anxiolytic treatment (baseline and during IFA). Predictors of anxiety and mood disorders: female gender, MADRS score ⩾ 15 at at M4; predictors of suicidal risk: increase in HAM-A scores between M0 and M 4; sleep disorders. High incidence of anxiety-depressive effects after end of treatment, predicted by prior AD prescription.
*Horikawa et al. 2003[47]		99	CPI HAM-D Zung SDS	Baseline, once every 4 Ws, W 12 after discontinuation	23%	1 (1%)	Depression developed during first 8 Ws in 74%. Higher rates of remission of depression with sulpiride 150 mg/day. Advanced age only risk factor for MDE.
Kraus et al. 2003[48]	Active MDE Active psychosis Active SA	84 (20 controls without IFA treatment)	HADS SCL-90-R	Baseline M 1, 3–4, 6–8 Ms 1 and 6 after discontinuation	35%	7 (8%)	Depression scores had greatest increase at W4 and peaked at Ms 6 to 8. No association among PSE, sociodemographic factors, stage of disease, or mode of acquisition. Significant increase in anger/hostility scores; RBV associated with greater emotional distress; AD therapy successful; depression scores returned to baseline after discontinuation.
Loftis et al. 2004[51]	Active PI Active SA	39	SCID-I BDI	Baseline, weekly M 6 after discontinuation	33%	2 (5%)	Managed with SSRI treatment; higher rates of end of treatment response and SVR in patients with IFA-induced depression, but no association with gender, race, or history of MDE or SA.

Table 1. ***continued***

Study	*Exclusion criteria*	*N sample (controls)*	*Assessment instruments*	*Assessment periodicity*	*Psychiatric side effects*	*PD*	*Findings*
*Maddock et al. 2004[40]		60	SCID-I, HAM-D, BDI, STAI-Y	Baseline Monthly	30%	1 (2%)	Treatment for psychiatric symptoms included paroxetine, amisulpride, levosulpiride, thioridazine; psychopharmacological treatment (for baseline or emergent depression) led to less severe PSE.
Constant et al. 2005[43]	Previous IFA, AD, active psychosis, active mania	93	MINI MADRS STAI-Y BFI	Baseline W 4, 12	32%	—	IFA-induced mood disorders in 30 patients (32%): mainly neurovegetative symptoms until W5, 80% developed after W24, 15 (50%) irritable hypomanic episodes; 12 (40%) MDE with hypomanic symptoms. Risk factors for IFA-induced mood-disorders: history of PI, infection through IDU, elevated MADRS and STAI-Y scores at baseline. Fatigue score likely related to flu-like symptoms.
Raison et al. 2005[39]	Previous IFA, lifetime depression or psychosis, active SA (last 6 Ms)	162	SCID-I Zung SDS (telephone)	Baseline W 4, 8, 12, 24	32%	6 (4%)	Depressive symptoms predicted by baseline scores and peaked at W24. Risk related to history of depression and RBV dosage. Mood symptoms ameliorated by ADs.
Scalori et al. 2005[42]	Active SA, active psychosis, lifetime suicide attempt	185	CPI MMPI	Baseline M 3	17%	—	89% of patients with baseline pathology developed PSE. Symptoms remitted with SSRIs, benzodiazepines, or counseling.
Schaefer et al. 2005[46]	Psychotropics Active SA	14 (22 controls: without prophylactic AD)	SCID-I MADRS	Bi-weekly until W 9, then monthly	MDE 42%	0	Group A (n = 14): psychiatric patients; prophylactic AD (citalopram) Group B (n = 11): psychiatric patients, no AD Group C (n = 11): non-psychiatric control patients Pre-treatment with AD reduced IFA-induced MDE (14%); Group B and C similar incidence of MDE (64% and 55%); when PSE developed, AD treatment (citalopram +/- mirtazapine) produced 86% response. SVR: 50%, no difference between groups.
Castera et al. 2006[44]	Previous IFA Psychotropics	97	SCID-I MADRS	Baseline W 4, 12, 24, 48 W 24 after discontinuation	39%	1 (1%)	PSE mostly between baseline and W 12 (88%); treated with SSRIs, benzodiazepines, and/or amisulpride. Dose reduction in 60% of patients. Risk factors: history of PI, higher baseline MADRS scores; younger age; infected via IDU. SVR: 68%, with no relationship to psychiatric factors.
Dell'Osso et al. 2007[38]	Previous IFA Active PI Lifetime PI Lifetime SA	49	SCID-I, MOODS-SR, BPRS, BRMMS, STAI-Y	Monthly M 6	MDE 12%	2 (4%)	Lifetime subthreshold manic/hypomanic symptoms predicted IFA-induced depression; no correlation with lifetime subthreshold depressive symptoms.

**Treatment did not include ribavirin*
AD antidepressant; BDI Beck Depression Inventory;[90] BFI Brief Fatigue Inventory;[91] BPRS Brief Psychiatric Rating Scale;[92] BRMMS Bech-Rafaelsen Mania–Melancholia Scale;[93,94] BSS Beck Scale for Suicide Ideation;[95] CPI clinical psychiatric interview; HADS Hospital Anxiety and Depression Scale;[96] HAM-A Hamilton Anxiety Rating Scale;[97] HAM-D Hamilton Rating Scale for Depression;[98] IDD Inventory to Diagnose Depression,[99] IDU intravenous drug use; IFA conventional interferon-alpha treatment; M month; MADRS: Montgomery-Asberg Depression Rating Scale;[100] MDE major depressive episode; MINI Mini International Neuropsychiatric Interview;[101] MMPI Minnesota Multiphasic Personality Inventory;[102] MOODS-SR Subthreshold Mood Spectrum Symptoms Scale;[103] PANAS+ and PANAS– Positive and Negative Affect Scale;[104] PD treatment discontinuation for psychiatric reason; PI psychiatric illness; POMS Profile of Mood States;[105] PSE psychiatric side effects; QOL quality of life; RBV ribavirin; SA substance abuse; SCID Structured Clinical Interview for DSM;[106] SCL-90-R Symptom Checklist-90–Revised;[107] SF-36 Short-Form 36-Item Health Survey;[108] SSRI Selective serotonin reuptake inhibitor; STAI-Y: State-Trait Anxiety Inventory;[109] SVR sustained viral response; W week; Zung SDS Zung Self-rating Depression Scale[110]

were more likely to require antidepressant treatment than those with such a history.[116,117] Given this lack of consensus, there does not appear to be any justification for denying IFA treatment to patients with psychiatric illness.

Other reported risk factors for IFA-induced depression include lack of social support, older age,[47] comorbid medical conditions,[11] and a history of IFA-induced depression.[32] Quarantini et al. challenged the hypothesis that patients receiving a second course of IFA treatment are at higher risk for neuropsychiatric side effects than treatment-naïve patients.[118] Dose and duration of treatment may also influence the development of IFA-induced neurotoxicity, especially cognitive dysfunction.[35,63,119] Studies have not found any significant relationship between IFA-induced depression and gender, severity of HCV infection, or type of IFA.[120]

As noted above, some studies have also reported an association, which may be dose-dependent, between RBV therapy and depressive symptoms in CHC patients.[39,48,86] This effect may be related to the anemia that is a frequent side effect of RBV and a potential aggravator of fatigue.

In summary, our review of the literature identified a number of different risk factors for IFA-induced neuropsychiatric toxicity, independent of the patient's psychiatric history, making it clear that the exclusion of psychiatric patients from antiviral treatment programs is an unreasonable procedure that targets a particularly vulnerable population. There is a growing consensus about the importance of diagnosing and treating depressive and anxious symptoms in all patients with CHC being considered for IFA treatment, even when the symptoms are subclinical, as well as the need to regularly assess for such symptoms during treatment.[11,33,38,39,41,42,44,45,52,113,116,121,122] Several studies have found that correct management of psychiatric symptoms improves adherence to CHC treatment and reduces treatment discontinuation due to psychiatric reasons.[33,39,40,44,46–48,51,52]

The Effect on Treatment Outcome of Interferon-Alpha-Induced Neuropsychiatric Toxicity

Neuropsychiatric side effects have been cited as a frequent (10%–20% of cases) cause of treatment discontinuation.[30,57] However, other prospective studies that have included psychiatric patients and evaluated the management of emergent psychopathology have reported only a 0%–10% incidence of treatment discontinuation due to psychiatric causes.[13,33,39,40–42,44-47,51,52,111,112,121]

Nonadherence, an important concern in the treatment of any chronic disorder, is influenced by individual factors such as lack of socio-familial support and psychological stress. Kraus et al. assessed several areas, including emotional status, personality factors, interpersonal problems, and sociodemographic factors, that might predict adherence to IFA treatment,[31] and found that nonadherence was correlated only with high scores on hostility, paranoid ideation, and phobic anxiety, which may reflect interpersonal problems that could interfere with socio-familial support. Recent studies have reported good treatment adherence in patients with psychiatric illness, perhaps because psychiatric support during treatment for HCV was guaranteed.[116,117,123,124]

Prospective studies have not found a consistent relationship between psychiatric side effects and antiviral response.[61] One study found an association between IFA-induced depression and lower viral response until treatment week 24.[111] Another study reported diminished SVR in patients with IFA-induced depression.[12] However, the mechanism underlying this relationship is unknown and may include bidirectional neuroimmune pathways and/or the effect of depression on treatment adherence, which is not fully understood. It is important that such studies control for use of antidepressants in order to assess the contribution of antidepressants to IFA treatment response.

Studies that have employed multivariate analyses to evaluate factors predictive of SVR have found a significant relationship between SVR and IFA-induced depression,[12] HCV genotype,[44,111,116,125] viral load,[44] gender,[125] and RBV dose.[111] Other studies have found no significant association between psychiatric risk factors (baseline depression scores, change in depression scores over time, antidepressant treatment) and efficacy of IFA treatment in CHC.[44,116,125] Wichers et al. suggested that an IFA-induced increase in concentration of cytokines will produce a better response to antiviral treatment and increased depression ratings.[53] Similarly, Loftis et al. reported significantly higher SVRs in patients with IFA-induced MDEs.[51]

Interferon-Alpha Treatment of Chronic Hepatitis C in Patients with Drug or Alcohol Dependence

There is a high prevalence of past and current injection drug use among individuals with CHC, since injection drug use is a primary risk factor for contracting HCV. The consensus in both Europe and the United States has been not to treat injection drug users (IDUs) until injection drug use has been discontinued for at least 6 months.[126] The literature discusses the following reasons for excluding addicted patients from IFA treatment:

1. ***Risk of HCV reinfection if the patient resumes injection drug use.*** Nevertheless, the literature reports a low incidence of HCV reinfection during 5 year follow-up of former IDUs who achieved SVR with antiviral treatment.[126,127] Dalgard et al. also reported low risk of reinfection in former IDUs who resumed injection drug use, with an incidence of reinfection of 2.5/100 person-years in this group compared with incidence rates as high as 15–40/100 person-years of primary infection in IDUs.[126] The low incidence of reinfection may be explained by safer injection routines in experienced IDUs, highlighting the need to integrate psychoeducational programs and address issues such as a supply of sterile syringes in the multidisciplinary care of IDUs being treated with IFA. It may also be useful to distinguish sporadic versus frequent injectors in assessing the risk that patients will resume drug injection.[126]

2. ***Risk of diminished SVR.*** This has been contradicted by several studies.[115,123,126–130] Reports in the literature also do not indicate a significant reduction in SVR rates in former IDUs who resume drug injection during IFA treatment[127] or in patients receiving methadone maintenance treatment.[123,131,132] Neri et al. reported faster viral response and higher SVRs in addicted patients treated soon after the end of detoxification; they hypothesized that the absence of narcotics in chronic opiate abusers resulted in hyperactive CD 11 macrophages, which may have induced an abnormal response with elevated cytokine production and accelerated viral clearance.[130]

3. ***Risk of nonadherence.*** Mauss et al. found that, during the first 8 weeks of IFA treatment, rates of treatment discontinuation among patients with HCV in methadone maintenance treatment were significantly higher than among patients with HCV who had no history of injection drug use.[131]

4. ***Higher risk of neuropsychiatric toxicity.*** This has been contradicted by several studies.[11,33,35,39,48,115,120,133,134] Available data generally do not support a significantly increased risk of IFA-induced psychiatric side effects and dropouts in addicted patients, especially if they are in methadone treatment[115] and/or if interdisciplinary care and psychopathological management are available.[129,135,136]

The literature provides evidence that antiviral treatment for CHC can be provided to IDUs safely and effectively, that rates of re-infection in IDUs may not necessarily be higher than in the non-IDU population, and that IDUs can adhere to medical protocols in the same manner as non-IDUs.[135]

The National Institutes of Health Consensus Development Conference Statement concerning HCV management indicates that hepatitis C treatment is possible in the setting of ongoing drug use.[137] In treating these patients, clinicians should adhere to up-to-date structured high-quality guidelines in this area.[138,139]

Alcohol abuse is also prevalent among individuals who are HCV positive, justifying use of the Alcohol Use Disorders Identification Test (AUDIT) to screen for alcohol abuse. Because alcohol users are often categorically excluded from clinical trials, few large-scale studies have examined the effect of current alcohol use on HCV treatment outcomes. Tabone et al. reported that lifetime alcohol consumption, in particular heavy drinking, had a strong negative effect on IFA treatment outcomes, indicating the need for further studies to determine the advisable period of abstinence before treatment starts.[140] In a multicenter study, Anand et al. found that recent alcohol use resulted in higher rates of treatment discontinuation and lower rates of SVR; however, when patients who discontinued treatment were excluded from the analysis, the trend in favor of nondrinkers achieving SVR disappeared.[141] Given these findings, alcohol users need not be excluded from HCV therapy. However, abstinence from alcohol is strongly rec-

ommended both before and during antiviral therapy to maximize chances of SVR, given that no clear relationship between level of alcohol and adverse treatment outcomes has been established.[142]

Assessment of Neuropsychiatric Toxicity Induced by Interferon-Alpha

There is some disparity in time periods reported before onset of psychiatric toxicity during IFA treatment. Castera et al. reported that, of 38 patients (39% of their sample) who developed psychiatric side effects, 87% developed those symptoms in the first 12 weeks of treatment.[44] Hauser et al. reported that, of 13 patients (33% of their sample) who developed IFA-induced MDD, more than 50% developed those depressive symptoms between treatment weeks 12 and 22.[33] Other studies have reported that 100% of patients who developed psychiatric side effects did so by week 20[143] or 24,[11,39] with a higher incidence of psychiatric symptoms by week 24.[39] Hauser et al.[33] reported that mean time of onset for depressive symptoms with conventional IFA therapy was 12 weeks (range 1–32 weeks), and that symptoms developed rapidly, reaching maximum intensity in 2–3 weeks. It should be noted, however, that pegIFA, especially pegIFA-2a, has slower absorption, resulting in a higher incidence of psychiatric adverse effects after 12 weeks of therapy.[144]

These results highlight the need for regular psychiatric assessment during the first 6 months of IFA treatment. It is recommended that a clinical evaluation be done just before as well as during IFA treatment, to guarantee early intervention for emergent psychopathology. Studies suggest that patients be screened for depression biweekly or monthly, particularly between the second and fifth months of IFA therapy, including the administration of a scale for assessing depressive symptoms.[120] Studies have used a variety of assessment instruments, including the Montgomery-Asberg Depression Rating Scale (MADRS),[37,43–46,53,100] the Beck Depression Inventory (BDI),[13,33,36,40,41,51,90] the Zung Self-Rating Depression Scale (Zung SDS),[39,41,47,110,111] the Hamilton Rating Scale for Depression (HAM-D),[13,40,41,47,50,98] the Hospital Anxiety and Depression Scale (HADS),[36,48,61,66,96] and the Center for Epidemiologic Studies Depression Scale (CES-D),[143,145] but there is not yet any consensus about the most appropriate scale for assessing depressive symptoms in patients being treated for HCV. Because the potential loss of libido associated with IFA therapy may be related to depression and/or hormonal changes,[85] it may also be helpful to perform baseline hormone screening before initiating IFA therapy to guarantee comprehensive management of any sexual dysfunction that may occur.

Some studies report that neuropsychiatric symptoms persist after cessation of IFA treatment,[32,34,45] suggesting the need for follow-up maintenance treatment, especially in patients with a history of psychiatric illness. Because psychiatric symptoms induced by pegIFA may persist for several months,[21,46] vigilance is justified until 6–12 months after treatment discontinuation.[61]

Treatment for Neuropsychiatric Toxicity Induced by Interferon-Alpha

Neuropsychiatric symptoms seem to improve 3 to 4 days after the dose of conventional IFA therapy is reduced.[57] However, such a reduction compromises optimal dosing and efficacy. Therefore, current evidence supports managing the patient without changing the IFA dose in order to optimize treatment outcome.[13,44,46,111,115,128,146] In selecting treatments for managing neuropsychiatric symptoms related to IFA treatment, it is important to consider possible drug interactions due to IFA's ability to reduce hepatic cytochrome P450 (CYP450)-mediated metabolism.

Two antidepressant treatment strategies are supported by studies in this area:[4,9,15,21,35,147–149] 1) prophylactic treatment for patients with risk factors for developing anxious and/or depressive disorders,[45,115] and 2) symptomatic treatment for emergent symptoms identified through regular psychiatric assessments.[115,146,149,150] Studies have found a high rate of response to antidepressant treatment for mild to moderately severe depression associated with the effects of IFA on the central nervous system.[151] Approximately 80% of patients have been shown to respond within 4 weeks of beginning antidepressant treatment,[146,150] with complete remission achieved after 9 weeks in about 85% of cases.[33]

Selective serotonin reuptake inhibitors (SSRIs) are the antidepressants for which there is the most support for treating cytokine-induced depressive symptoms. A large number of studies have reported the efficacy and safety of SSRIs in treating IFA-

induced depression, with positive outcomes reported for citalopram,[33,150,152] paroxetine,[40,146,149] sertraline,[153] fluoxetine,[33,154] and escitalopram.[155] Escitalopram may be a good choice, since it has the advantage of minimal cytochrome P450 enzyme activity, few drug-drug interactions, linear pharmacokinetics, and no known hepatotoxicity.[155]

If neurovegetative symptoms persist despite SSRI treatment, serotonin norepinephrine reuptake inhibitors (SNRIs)[4,68] (e.g., venlafaxine, duloxetine, milnacipran) or other agents with noradrenergic/dopaminergic action (e.g., mirtazapine, bupropion) may be helpful. Several case reports and studies have reported successful treatment with mirtazapine,[46] bupropion,[33] amisulpride,[40] and sulpiride[47] (the last two are not available in the United States). However, there are some safety concerns with non-SSRI antidepressants. Buproprion has an additive pharmacodynamic effect on risk of seizures, and mirtazapine may increases the risk of bone marrow suppression and agranulocytosis.[156,157] Nefazodone has been shown to induce hepatotoxicity and is contraindicated in patients with liver disease.[158]

A diagnosis of mania indicates the need to discontinue any antidepressant that is being used and begin treatment with a mood stabilizer. Recommendations in the literature for treating IFA-induced mania are consistent with the usual guidelines for the treatment of mania, except that caution should be used in employing divalproex (valproate) because of possible hepatotoxic risk. Some investigators advocate discontinuing IFA therapy during a manic episode and then reintroducing antiviral treatment after symptoms stabilize, highlighting the need to make treatment decisions on an individual basis, depending on symptom severity.

Treatment of IFA-induced psychotic symptoms should also follow the usual guidelines for treatment of psychosis. However, clinicians should be aware that there is a high risk of a drug-drug interaction between IFA and clozapine, in the context of additive pharmacodynamic effects on risk of hematologic toxicity,[157] as well as a moderate risk of a drug-drug interaction with pimozide, related to potentiation of its pharmacological effects by IFA inhibition of the CYP450 1A2 isoenzyme and subsequent higher risk of QT interval prolongation.[157]

Some findings suggest that clinicians might also consider using alternative treatment strategies, such as psychostimulants (e.g., methylphenidate, modafinil) for fatigue and opioid antagonists (e.g., naltrexone) for cognitive impairment. Note, however, that psychostimulants are contraindicated in patients with addictive disorders, while opioid antagonists have significant hepatotoxic risk.

DISCUSSION

In this article, we have reviewed reports that indicate a higher prevalence of psychiatric disorders in patients with HCV than in the general population. Discussions concerning the etiology of psychopathological symptoms in patients with CHC have focused on the possibility that psychiatric patients may have a greater predisposition for HCV infection as well as on the causal relationship with pathophysiological and psychological effects of the disease. The controversy and lack of consensus about these issues appears to justify undertaking an antidepressant trial to determine whether improvement in depressive symptoms will lead to reduction in fatigue and improvement in functioning.[5]

Therapy with IFA plus RBV, the gold standard for antiviral treatment of CHC, is associated with significant neuropsychiatric adverse effects.[15,41] IFA-induced depression is widely reported, and it can be aggravated by anemia, a frequent adverse effect of RBV.[11,101,143] Depression is a consistent predictor of decreased quality of life in patients with CHC.

Numerous host- and viral-related factors can contribute to lack of virological response to IFA plus RBV, with only limited treatment options available for nonresponders. Recent data also suggest that IFA-based therapy results in some degree of histological improvement even in patients who do not achieve SVR,[142,159–161] and several clinical trials are evaluating whether maintenance monotherapy with pegIFA can provide therapeutic benefits such as prevention of fibrosis progression and reduction in hepatic decompensation, hepatocellular carcinoma, and need for liver transplantation, despite incomplete virologic suppression.[142] Until new evidence-based recommendations become available, findings from currently available studies highlight the need to avoid inadequate treatment, whether due to treatment type, side effects, or nonadherence, which can result in inadequate antiviral pressure and reduced likelihood of response.[162] It is therefore very important to manage neuropsychiatric toxicity that occurs in association with IFA therapy in order

to promote treatment adherence and optimize dosage.[134]

In determining a patient's eligibility for IFA treatment, clinicians should undertake a risk-benefit assessment. Findings from the literature show that the presence of a severe psychiatric disorder is not an exclusion criterion for participating in an IFA treatment program, as long as the patient presents with stabilized psychopathology, and psychiatric vigilance is assured.[35,46,112,116–117,163,164]

A growing and consistent body of data is available concerning premorbid, patient-related risk factors for IFA-induced mood disorders.[38] It is important for clinicians to assess for previous depressive episodes, subtle dysregulations of mood (even if not previously recognized), family history of psychiatric disorder, adverse social factors, persistent HCV disease, or previous failed antiviral trials. Clinicians should, however, keep in mind that effects of potential risk factors are still being debated, since such factors can be mediated by baseline mental state or a greater vulnerability to stress.

Recommendations for psychiatric assessment during IFA treatment are unfortunately still largely based on findings from studies limited by small sample size, lack of control groups, and methodological disparities related to exclusion criteria, psychopathological assessment methods, and diagnostic criteria. Nevertheless, the available results are consistent in supporting psychiatric interventions to improve treatment tolerability and adherence, which can have a beneficial effect both on general quality of life and antiviral efficacy.[40–42,44–46,51]

Constant et al.[43] reported that a key component of IFA-induced mood disorders was irritability, which can be related to dysphoric depression or mania or hypomania. It is critically important to distinguish between (hypo)manic and depressive mixed states in selecting a first-line treatment. Clinicians should take a detailed psychiatric history and evaluate for signs and symptoms of a possible manic/hypomanic episode, including lack of insight for irritable behavior, excessive energy, accelerated speech, unusual sexual behavior, grandiose plans, or psychotic symptoms.

Use of psychiatric assessment scales can help clinicians, especially nonpsychiatric practitioners, detect reversible psychiatric toxicity early in treatment. Because depressive and somatic symptoms (e.g., sleep disturbance, changes in appetite, reduced libido, fatigue) overlap, studies need to validate specific instruments for use in the psychiatric assessment of CHC patients.[151] Such assessments should place particular emphasis on identifying subsyndromal psychopathology, which can have a significant impact on treatment adherence, tolerability, outcome, and quality of life.[46]

Patients who are *currently* being treated for psychiatric disorders should continue their current psychopharmacologic treatment when they begin IFA therapy, as long as the psychopharmacologic agent is not associated with additional hepatotoxic risk.

With regard to prophylactic treatment, IFA treatment does not induce major depressive symptoms in at least 50% of patients,[128] and no formal guidelines regarding prophylactic use of antidepressants in the treatment of HCV have been developed. Kraus et al.[165] suggested that prophylactic antidepressant treatment is appropriate for patients with depressive or anxiety symptoms during pretreatment screening, even if the symptoms are mild; for patients who developed psychiatric symptoms during previous IFA treatment; or if the patient requests such treatment. In any case, a careful risk/benefit assessment is needed in deciding to use a prophylactic antidepressant.

Findings in the research literature provide growing evidence concerning the usefulness of antidepressants in the treatment of patients who do develop IFA-induced depression. In evaluating any psychotropic treatment for patients being treated for HCV, clinicians need to consider potential pharmacokinetic interactions and side effects.[35] Treatment for emergent psychiatric syndromes should be selected based on usual treatment guidelines, except that it is important to avoid substances with higher hepatotoxic risk (e.g., divalproex). SSRI antidepressants are widely used, primarily due to their relatively mild side effect profile and ease of administration. Nevertheless, there is a significant risk associated with use of these antidepressants in patients with CHC because of the anticoagulant effects of SSRIs (e.g., risk of retinal hemorrhages and gastric bleeding).[155] Antidepressants that affect both the serotonin and noradrenergic systems may be advantageous for neurovegetative symptoms, and milnacipran might be a good choice because of its minimal hepatic metabolism; however, to date milnacipran has only been approved in the United States for the treatment of fibromyalgia, and there

are no controlled studies concerning its use in IFA-induced depression. Little is known about issues relevant to IFA treatment of psychiatric patients who are being maintained on antipsychotic medications or about use of antipsychotics in the treatment of IFA-induced psychotic symptoms. However, IFA-associated agranulocytosis during clozapine treatment has been reported, so that it makes good clinical sense to combine IFA with less "toxic" antipsychotics if possible.[166]

Treatment with IFA has been reported to be associated with suicidal thoughts and attempts as well as completed suicides; however, robust estimates of suicide rates in this population are lacking. Clinicians should ask about suicidal ideation and advise patients to alert their healthcare providers if such ideation develops during therapy. Clinicians should consider discontinuing IFA therapy in patients who have consistent suicidal ideation or who have a severe mood or psychotic disorder that compromises their family or social life. Once these psychiatric symptoms have been successfully treated, IFA therapy can be restarted.

Studies suggest that neuropsychiatric toxicity does not hinder patients from achieving SVR; however, more controlled studies are needed to evaluate relevant neuroendocrinological and immunological variables that may affect neuropsychiatric toxicity and its management as well as response to antiviral therapy.[128,167] It is possible that a more persistent virus may aggravate fatigue and depression by inducing effects in the inflammatory and immune systems, and that neuropsychiatric toxicity of IFA treatment may be related to a greater antiviral effect. Thus, further research is needed to assess the impact of psychopharmacological treatment on immunotherapy outcomes.[167]

Patients who use drugs or alcohol should be evaluated for treatment on an individual basis. Although clinical trials have shown that patients who are current IDUs may have high rates of IFA discontinuation, there is evidence that, when adherence is achieved, success rates are not significantly different than in non-IDUs.[137] Evidence also suggests that patients with recent alcohol use may achieve SVR rates equal to those of nondrinkers, when patients who discontinue treatment are excluded from analysis.[141] Patients who are currently using injection drugs or who are heavy alcohol users (> 14 drinks/week or > 4 drinks/day for men, > 7 drinks/week or > 3 drinks/day for women) should be referred to an addiction specialist before HCV treatment is initiated. Patients with stabilized substance use disorders who initiate IFA treatment require close monitoring and should be strongly encouraged to participate in drug and/or alcohol treatment programs, and in methadone clinics when appropriate, to increase opportunities for successful HCV therapy.[142] To provide effective treatment for HCV infection in this population, it is essential that patients and providers develop a therapeutic relationship that allows for active communication.

Nonpharmacological strategies for managing fatigue, cognitive impairment, and depressive symptoms and to optimize quality of life appear promising.[4,9,120,147] Psychoeducation can be useful for all patients with CHC, even those at low risk of developing cirrhosis, in order to alleviate anxiety and fear and improve treatment adherence.[36,168] Psychoeducational programs for patients with multiple sclerosis receiving IFA-beta treatment have demonstrated benefits in improving treatment adherence and general quality of life. Psychoeducation for patients with CHC should include guidance on strategies for improving general health (e.g., importance of regular exercise, proper diet, good sleep habits, avoiding alcohol and smoking, and behavioral interventions focused on occupational and leisure time)[128] as well as specific information about therapeutic options for CHC.[17,128,168] Such treatment-specific information should include potential side effects of IFA therapy, strategies for improving tolerability, and warning signs of developing psychiatric toxicity. This counseling could include information on how to administer injections, daily activity planning, stress reduction techniques, and medications available to manage iatrogenic symptoms. In addition, medical personnel who work with patients with CHC, such as physician assistants and nurse practitioners, can play an influential role in enhancing treatment adherence by closely monitoring patients, taking steps to minimize adverse effects of treatment, and offering support.[20] A robust psychosocial support network that includes medical providers as well as friends and family is critical for the successful completion of HCV treatment. More research is needed to assess the effect of nonpharmacological strategies on the outcome of IFA treatment for CHC.

CONCLUSION

Although uncontrolled psychiatric disorders are a contraindication to treatment for HCV, patients with a psychiatric disorder that has been stabilized or is in remission are eligible for therapy. Nevertheless, the presence of depression, irritability, anxiety, psychosis, and/or suicidal ideation can greatly complicate HCV treatment and can compromise treatment efficacy if not optimally managed. All patients should therefore be carefully evaluated before and during treatment to identify and manage any neuropsychiatric conditions to ensure the best opportunity for treatment success.

Patients receiving IFA treatment should be monitored for emergence of psychopathology and treatment adherence problems and receive psychoeducation aimed at early detection and reduction of these problems. Recommendations for treating neuropsychiatric symptoms in these patients are inconsistent, and robust findings concerning the impact of psychopharmacology on antiviral outcomes are lacking. Thus, clinical judgment remains the ultimate "gold standard" in making these treatment decisions. Clinicians may decide to use preventive antidepressant treatment even for subclinical levels of depression or might instead prefer to employ a nonpharmacological intervention for mild depression. The decision should be based on availability of resources (access to a care team, regularity of psychopathological assessment, psychoeducational tools, support groups) and the patient's social and clinical characteristics (level of treatment adherence, self-monitoring knowledge, social support, and treatment preference).

Finally, available empirical data highlight the need to involve a multidisciplinary treatment team in the management of CHC. Such a treatment team should include a consultation-liaison psychiatrist in order to guarantee that patients with psychiatric disorders have access to IFA treatment when indicated, promote treatment adherence, minimize dropouts, efficiently manage psychiatric adverse events, and optimize virological efficacy.

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