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REVIEW

Psychiatric and substance use disorders co-morbidities and hepatitis C: Diagnostic and treatment implications

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Abstract

Chronic hepatitis C virus (HCV) viral infection is the most common blood-borne viral infection and approximately 2%-3% of the world's population or 170-200 million people are infected. In the United States as many as 3-5 million people may have HCV. Psychiatric and substance use disorders (SUDs) are common co-morbid conditions found in people with HCV and are factors in predisposing people to HCV infection. Also, these co-morbidities are reasons that clinicians exclude people from antiviral therapy in spite of evidence that people with HCV and co-morbid psychiatric and SUD can be safely and effectively treated. Furthermore, the neuropsychiatric side effects of interferon (IFN), until recently the mainstay of antiviral therapy, have necessitated an appreciation and assessment of psychiatric co-morbidities present in people with HCV. The availability of new medications and IFN-free antiviral therapy medication combinations will shorten the duration of treatment and exposure to IFN and thus decrease the risk of neuropsychiatric side effects. This will have the consequence of dramatically altering the clinical landscape of HCV care and will increase the number of eligible treatment candidates as treatment of people with HCV and co-morbid psychiatric and SUDs will become increasingly viable. While economically developed countries will rely on expensive IFN-free antiviral therapy, less developed countries will likely continue to use IFN-based therapies at least until such time as IFN-free antiviral medications become generic. The current manuscript discusses the efficacy and viability of treating HCV in people with psychiatric and SUDs comorbidities, the treatment of the neuropsychiatric side effects of IFN -based therapies and the impact of new medications and new treatment options for HCV that offer the promise of increasing the availability of antiviral therapy in this vulnerable population.

Key words: Hepatitis C; Psychiatric disorders; Substance use disorders; Antiviral treatment

Core tip: Hepatitis C viral (HCV) is among the most

common blood-borne viral infections in the world. Although disease management strategies are often complicated by the high rate of psychiatric and substance use disorders (SUDs) within this population, studies now indicate that neuropsychiatric side effects can be effectively managed during antiviral therapy and that individuals with pre-existing psychiatric and SUDs can be treated successfully and achieve sustained virologic response. Furthermore, the development of new medication options for the treatment of HCV has provided additional opportunities for treatment of people with HCV who have - or are at risk for - psychiatric illness.

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HEPATITIS C: AN OVERVIEW

Prevalence

Hepatitis C virus (HCV) is among the most common blood-borne viral infections in the world. Approximately 3% of the world's population or 170-200 million people are infected, and an estimated 35 million people are infected in the United States[1-3]. HCV is often asymptomatic for a decade or longer after initial infection, and if undiagnosed and untreated, increases the risk of liver fibrosis, cirrhosis, liver cancer, liver failure, and ultimately, death[1].

A study that assessed mortality rates between 1999 and 2004 found that there were a total of 56409 HCV related deaths in the United States during this 5 year period[4]. Over this same time period, mortality rates increased by 123% with a steady increase for those between ages 55 to 64. In the year 2004 alone, 7427 deaths accounted for 148611 years of potential life lost[4]. Furthermore, a subsequent study of 34480 HCV infected individuals and non HCV infected controls showed that HCV infected individuals who initiated or completed treatment, had a significantly reduced risk of mortality[5]. For these reasons, early detection of HCV and prompt antiviral treatment are of the utmost importance. Psychiatric and substance use disorders (SUDs) are common co-morbidities among individuals with HCV and are often barriers to antiviral treatment.

Sources of infection

Among the most common routes of HCV transmission, intravenous drug use (IVDU) in particular continues to be the most common and contemporary source of infection[6-8]. While much less frequent, HCV can be transmitted through sexual contact, or to infants born from an HCV infected mother[2]. Other routes of transmission are no longer common including blood transfusion, needle stick injuries or non-professionally applied tattoos[9].

HCV AND HEALTH RELATED QUALITY OF LIFE

Individuals with gastrointestinal disease in general and HCV in particular have a lower health related quality of life (HRQOL) than the general population[10,11]. Factors such as poorer work and social adjustment, lower acceptance of illness, higher illness stigma, poorer reported neurocognitive functioning and concentration, and higher levels of subjective physical symptoms are associated with lower HRQOL and are highly correlated with depressive symptomatology in these individuals[12]. Several studies suggest that patients with chronic liver disease (and HCV in particular) also have disproportionately high rates of pain-related diagnoses which may impair their functioning[13-17]. HCV is associated with several medical comorbidities including peripheral neuropathy, arthritis, and fibromyalgia. In one retrospective chart review study of 8224, Veterans with HCV, 67% had co-occurring pain- related diagnoses including arthropathy, low back pain, and/or arthritis and 56% had past or present SUD diagnoses[13]. Additional studies indicate that biopsychosocial factors are significantly related to pain severity and interference, where emotional distress, mood symptoms (such as depression) and sleep disturbance predicted pain severity[14,15,18] (Table 1).

Individuals with HCV have higher rates of depression than those without HCV and also have higher rates of depression when compared to those with other gastrointestinal diseases such as irritable bowel disease and irritable bowel syndrome[10], non-alcoholic fatty liver disease and hepatitis B virus[11]. Individuals with HCV are most likely to have comorbid psychiatric conditions; depression is the most common psychiatric diagnosis among these individuals and is directly related to lower HRQOL[19-22]. One study of 881 Veterans with HCV found that 37% were prescribed an antidepressant medication[22] (Table 2).

Overall, HCV has a negative impact on quality of life and overall functioning[23]. The stigma associated with known infection has a demonstrated effect on HRQOL and is often related to a lack of adequate education on HCV and antiviral treatment[1]. Further efforts to educate both individuals with HCV and treatment providers on the viability of treating those with comorbid psychiatric conditions, and in particular, depression may be of benefit.

PSYCHIATRIC AND SUD COMORBIDITIES AND TREATMENT

Treatment issues and disease management strategies are complicated by the extremely high rate of psychiatric and SUD in those who have HCV[19,22,24-29].

Historically, people with HCV and comorbid psychiatric

Table 1 Hepatitis C and pain related diagnoses

Ref.	*n*	Design	Assessments	Outcome
Whitehead *et al*[13]	8224	Retrospective chart review	Clinical data, diagnoses, and medical history	Pain and SUD diagnoses were common among HCV patients, and opioids were frequently prescribed
Morasco *et al*[14]	49	Subjective assessment	Clinical interview, medical records BDI-Ⅱ, SDS, HRQOL SF-36	Psychosocial variables, particularly depression severity, account for variance in pain intensity and pain functioning
Rogal *et al*[17]	1286	Retrospective cohort study	Self-report, symptom checklist and medical record	There is a high prevalence of pain and opioid use in patients with chronic liver disease
Morasco *et al*[15]	119	Subjective assessment	TLFB, self-report; MPI, BDI-II, PCS, CPSS, CPCI, SCID	Biopsychosocial factors significantly affected pain severity and pain interference in patients with HCV

HCV: Hepatitis C virus; SUD: Substance use disorder; BDI-Ⅱ: Beck depression inventory, second edition; MPI: Multidimensional pain inventory; PCS: Pain catastrophizing scale; CPSS: Chronic pain self efficacy scale; CPCI: Chronic pain coping inventory; HRQOL SF-36: Health related quality of life short form-36 items; SCID: Structured clinical interview for The Diagnostic and Statistical Manual of Mental Disorders Ⅳ; TLFB: Time line follow back.

Table 2 Hepatitis C and psychiatric comorbidities

Ref.	*n*	Design	Assessments	Outcome
Lehman *et al*[20]	120	Subjective assessment	BDI-Ⅱ, ASI, PCL, AUDIT, medical records	Clinically significant levels of depression anxiety, PTSD and alcohol-related problems were observed in patients with HCV
Fireman *et al*[19]	293	Prospective assessment	AUDIT-C, BDI-Ⅱ	Psychiatric and substance use disorders are highly prevalent among veterans with chronic HCV
Rowan *et al*[21]	62	Subjective assessment	HRQOL SF-36	Psychosocial factors, especially depression, are strong indicators of impaired HRQOL for HCV-infected Veterans
Bini *et al*[41]	4084	Prospective cohort study	Eligibility for IFN therapy based on medical chart review of psychiatric and SUDs	The majority of veterans were not considered suitable candidates for HCV treatment because of substance use disorders, psychiatric disease, and comorbid medical disease
Mikocka-Walus *et al*[10]	139	Cross-sectional assessment	HADS, SCL-90, HRQOL SF-12, disease severity assessments	Patients with HCV had significantly higher prevalence of depression and lower HRQOL than patients with IBD and IBS, and the general population
Nelligan *et al*[22]	881	Subjective assessment	BDI-Ⅱ; medical records	Rates of depression are high among veterans with HCV and persist among those with antidepressant prescriptions
Weinstein *et al*[11]	878	Retrospective chart review	Clinical and demographic data, medical history	Individuals with HCV have a higher prevalence of depression than HBV and NAFLD patients and the general population

BDI-Ⅱ: Beck depression inventory, second edition; ASI: Anxiety severity index; PCL: Post traumatic stress disorder check-list; AUDIT: Alcohol use disorders identification test; HCV: Hepatitis C virus; HBV: Hepatitis B virus; HRQOL SF-36: Health related quality of life short form-36 items; IFN: Interferon; IBD: Irritable bowel disease; IBS: Irritable bowel syndrome; SCL-90: Symptom checklist 90; HADS: Hamilton Anxiety and Depression Scale; PTSD: Post-traumatic stress disorder.

diagnoses were not included in initial research treatment studies for various reasons including the subjective belief that individuals with co-morbid psychiatric and SUDs would be less likely to be compliant and therefore not complete treatment, more likely to develop neuro-psychiatric side effects (in particular depression), and more likely to be re-infected if they continued IVDU[30,31].

Until recently interferon-based therapies have been the standard of care for HCV treatment. However, these therapies are known to induce depression, among other neuropsychiatric problems including insomnia, irritability and mood changes[27,32-34]. Depression co-morbidity is of particular concern as interferon (IFN) precipitates depression in approximately 20%-30% of individuals who receive IFN-based antiviral therapies[24,27,35]. Those treated with IFN-α therapy often develop depressive symptoms, which can lead to reduction in medication dosage or treatment discontinuation, thus reducing the likelihood of antiviral therapy completion or achieving a sustained virologic response (SVR)[27]. IFN-based treatments are also likely to exacerbate preexisting psychiatric conditions including depression and bipolar disorder and in isolated cases, have led to suicidal ideation and suicide attempts[35-37]. The severity of depressive symptoms prior to beginning antiviral therapy but not the diagnosis of past or present major depressive disorder (if adequately treated with antidepressants - see Hauser *et al*[38], 2009) may be predictive of the onset and severity of depressive symptoms during IFN-based antiviral treatment[24,27,35,38,39] (Table 3).

Several studies suggest that individuals with psychiatric and alcohol use disorders are more likely to be considered ineligible for antiviral therapy even though other studies suggest that completion of therapy and achieving SVR among other variables is not different between people with HCV and co-morbid psychiatric disorders from those with HCV without psychiatric and SUDs[38,40-43]. One study that compared antiviral completion rates, SVR, emergency room visits and hospitalizations of HCV infected Veterans with pre-existing major depressive disorder (MDD) treated with antidepressants to those without MDD found no differences between groups[38].

People with schizophrenia and co-morbid HCV have

Table 3 Neuropsychiatric side effects of interferon and interferon-induced depression

Ref.	*n*	Design	Treatment	Outcomes
Fried *et al*[32]	-	Retrospective literature review	PEGIFN-α-2a and 2b with RBV, IFN-α -2b/RBV	Across studies, depression occurred in 22% of those treated with PEGIFN-α-2a/RBV, 31% with PEGIFN-α-2b/RBV and 30%-34% of those treated with standard IFN treatment (PEGIFN-α-2b/RBV)
Fried *et al*[33]	1121	Randomized clinical trial	PEGIFN-α-2a/RBV, IFN-α-2b/RBV, PEGIFN-α-2a	Patients treated with PEGIFN-α-2a plus RBV or placebo had a lower incidence of depression than those treated with IFN-α-2b plus RBV (22% and 20% *vs* 30%)
Loftis *et al*[16]	-	Retrospective literature review	IFN-α, IFN-β, and IFN-γ	Symptoms of depression induced by IFN therapy is common and can limit the treatment utility, often necessitate discontinuation of IFN treatment or the use of psychopharmacologic agents. Depression is also a suspected side effect of therapy with IFN-β and IFN-γ; however, the association has not been as convincingly confirmed
Hauser *et al*[34]	-	Retrospective literature review	IFN-α	Neuropsychiatric side effects such as depression, may develop as a result of IFN therapy and lead to lower HRQOL, dose reductions or discontinuation
Raison *et al*[35]	162	Longitudinal assessment	PEGIFN-α-2b	Moderate to severe depressive symptoms occurred frequently during PEGIFN/RBV treatment and was predicted by baseline depression scores and higher doses of RBV
Inder *et al*[37]	1	Retrospective case report	IFN-α-2a/RBV	Suicide attempt occurred during IFN-α treatment, improvements were only seen with drug discontinuation. Following re-challenge with combination therapy, patient again experienced suicidal ideation
Loftis *et al*[18]	32	Prospective cohort study	PEGIFN-α-2a and 2b/RBV	IFN therapy results in a significant increase in depressive symptoms over time, with neuro-vegetative and somatic symptoms of depression increasing more than other depressive symptoms

PEGIFN: Pegylated interferon (peginterferon); RBV: Ribavirin; IFN: Interferon; HRQOL: Health related quality of life.

also been excluded from IFN-based antiviral therapy despite a higher prevalence of HCV among this group than in the general population[44,45]. However, retrospective chart review studies suggest that people with schizophrenia and co-morbid HCV can be treated safely with IFN-based antiviral therapy and achieve similar SVR rates as those without co-morbid psychiatric disorders and with no greater likelihood of adverse events or emergency room visits[43,46].

Previous studies have also indicated that individuals with SUDs, particularly intravenous drug users (IVDUer) are also underserved and undertreated for fear of decreased compliance and/or risk of reinfection[31]. Although findings are variable, more recent research indicates that treatment completion is viable when these individuals are carefully supervised, and furthermore, that risk of reinfection is minimal, even among those who continue to use intravenous (*iv*) drugs post- antiviral treatment[31,47,48] (Table 4).

While less common, IFN-based regimens can also induce muscle aches and pain which may only serve to exacerbate depressive symptoms. Neurocognitive and somatic symptoms associated with depression are known to be exacerbated with IFN regimens and, for those with preexisting pain conditions, depression severity may increase pain intensity[14,15,49]. Though somatic symptoms should not be used as a primary predictor of depression severity, pain should be assessed and monitored in relation to cognitive and affective symptoms, when monitoring patients prior to and during treatment for HCV[50].

Overall, the emergence or exacerbation of depressive symptoms is common in IFN-α therapy and can compromise the outcome of HCV treatment[30]. As such, routine screening for psychiatric disorders and early treatment intervention for psychiatric disorders not previously identified are necessary prior to initiation of antiviral therapy[19,51]. Also ongoing routine screening for new onset depression during antiviral therapy is indicated. Furthermore, treatment plans must include monitoring of comorbid psychiatric conditions throughout the course of antiviral therapy[51,52].

Untreated IFN-induced depression may lead to dose reductions and premature IFN therapy termination and in worst case scenarios risk of suicide. However, if well monitored and managed, psychiatric and SUD comorbidities do not pose a significant impediment to treatment completion and compliance[47,51,52].

DEPRESSION MANAGEMENT DURING IFN-BASED ANTIVIRAL THERAPY

As mentioned, studies suggest that preexisting psychiatric and SUDs should not be regarded as exclusionary to IFN-α therapy. Specific to depression, IFN may induce or exacerbate symptoms of depression but these symptoms can be managed during antiviral therapy and do not prevent/preclude individuals from completing treatment or achieving favorable viral clearance rates[24,36,38,52,53].

Studies suggest that the onset of depressive symptoms during IFN therapy is not predicted by age, gender, past history of MDD or substance use[24,27,35,52]. Some studies suggest that people with higher depressive symptom severity prior to antiviral therapy initiation as well as a family history of MDD are more likely to develop IFN-induced depression. However, open-label studies of antidepressants and specifically selective serotonin reuptake inhibitors (SSRIs) in people who develop IFN-induced depression during antiviral therapy, demonstrate

Table 4 Antiviral treatment response rates in patients with psychiatric and substance use disorders comorbidities

Ref.	*n*	Design	Treatment	Outcomes
Dalgard *et al*[31]	27	Longitudinal assessment	IFN-α-2a	Rate of reinfection was not significantly different among IVDUers treated for HCV as compared to non IVDUers despite reinitiation of injection drug use in 33% of IVDUers
Loftis *et al*[27]	39	Prospective cohort study	IFN-α-2b/RBV	Gender, past history of MDD, and past history of SUD were not significantly associated with response rates
Backmund *et al*[47]	18	Longitudinal assessment	IFN-α-2a, IFN-α-2a/RBV	IVDUers can be reinfected after treatment for HCV infection, but the reinfection rate is minimal and should not jeopardize the potential benefit for most patients
Chainuvati *et al*[40]	647	Retrospective database review	Eligibility/treatment rates for Interferon therapy	Therapy completion and SVR rates are similar among Veterans with and without psychiatric or SUDs, challenging the perception that adherence is worse as a result of psychiatric co-morbidities
Anand *et al*[42]	4061	Longitudinal assessment	IFN-α-2b/RBV	Patients with and without mild to moderate alcohol use had comparable completion and SVR rates to antiviral treatment
Hauser *et al*[38]	55	Retrospective chart review	PEGIFN/RBV, IFN/RBV	People with MDD had completion and SVR rates similar to those without psychiatric illness. Patients with MDD can be safely and effectively treated with antiviral therapy provided that they are on antidepressant medications during antiviral therapy
Huckans *et al*[43]	60	Retrospective chart review	PEGINF/RBV, IFN/RBV	Patients with schizophrenia experience similar rates of psychiatric symptoms on and off antiviral therapy
Grebely *et al*[48]	58	Prospective longitudinal follow up	IFN-α-2b/RBV, PEGIFN-α-2a, PEGIFN-α-2b	Rate of reinfection following treatment for HCV infection among current and former IVDUers engaged in a multidisciplinary program is low

IFN-α: Interferon alpha; IVDUer: Intravenous drug user; RBV: Ribavirin; MDD: Major depressive disorder; SUD: Substance use disorder; SVR: Sustained virologic response; PEGINF: Peglyated interferon (peginterferon); IFN: Interferon.

Table 5 Antidepressant treatment of interferon-induced depression

Ref.	*n*	Design	Antidepressant	Outcomes
Gleason *et al*[54]	15	Open-label clinical trial	Citalopram	IFN-induced MDD in patients with HCV may be effectively and safely treated with citalopram
Hauser *et al*[24]	39	Prospective cohort study	Citalopram and buproprion	33% of patients receiving IFN therapy develop IFN-induced MDD. There were no differences in age, gender, past history of MDD, or substance use between those who became depressed and those who did not. Of those who developed IFN-induced depression most responded to antidepressant treatment allowing continuation of antiviral therapy. Also the group who developed IFN-induced depression had significantly higher baseline BDI scores than the group who did not develop IFN- induced depression
Loftis *et al*[27]	-	Various antidepressants	IFN-α, IFN-β, and IFN-γ	Depression induced by IFN therapy is common and can limit treatment utility and necessitate discontinuation of antiviral treatment. However, the use of psychopharmacologic agents allows treatment continuation
Angelino *et al*[36]	-	Various antidepressants	IFN-α	Treatment with IFN may provoke episodes of depression however, several standard treatments for depression can mediate these symptoms, suggesting that depression may not be a barrier to effective treatment
Gleason *et al*[55]	18	Open-label clinical trial	Escitalopram	IFN-induced MDD in patients with HCV may be effectively and safely treated with escitalopram

HCV: Hepatitis C virus; IFN: Interferon; RBV: Ribavirin; MDD: Major depressive disorder; BDI-Ⅱ: Beck depression inventory, second edition.

that these medications can be effective in managing depressive symptoms during IFN therapy and allow people to remain on antiviral treatment[24,54,55] (Table 5).

Antidepressant prophylaxis of patients with HCV who receive antiviral therapy

Antidepressant prophylaxis may decrease the likelihood of the development of IFN-induced depressive symptoms and MDD in HCV infected patients, particularly those with a past history of IFN-induced MDD, and may increase the rates of treatment compliance and completion[36,56].

One study of people with HCV who failed antiviral therapy due to IFN-induced depression found that citalopram is effective both before and during IFN-α therapy; used as pretreatment for these people with HCV, it helped to reduce the incidence of MDD during the first 6 mo of antiviral treatment as compared with two control groups[57]. As mentioned several studies have shown that, for those who developed MDD during IFN therapy, treatment with SSRIs led to a reduction in depressive symptoms and continuation of antiviral therapy[24,54,55].

In contrast, two double blind, placebo-controlled trials that assessed the benefit of prophylactic treatment (or pre-treatment prior to initiation of antiviral therapy) with paroxetine to prevent development of IFN-induced depression found no benefit as compared with placebo in antiviral treatment naïve people with HCV[58,59]. However, in one of these studies, of 11 patients who developed IFN-induced depression during the study and were then

Table 6 Antidepressant prophylaxis

Ref.	*n*	Design	Antidepressant	Outcomes
Angelino *et al*[36]	-	Retrospective literature review	Citalopram; fluvoxamine	Prophylactic antidepressants might be well-considered for patients with a family history of - or previous episodes of - depression
Schaefer *et al*[57]	33	Prospective clinical trial	Citalopram	Pre-treatment of psychiatric patients with citalopram significantly reduced the incidence of IFN-induced MDD during the first 6 mo of antiviral treatment
Raison *et al*[59]	61	Double-blind, placebo-controlled clinical trial	Paroxetine	Data support the use of antidepressant pre-treatment in HCV patients with elevated depressive symptoms at baseline
Morasco *et al*[58]	33	Double-blind, placebo-controlled clinical trial	Paroxetine	A prophylactic approach to reduce IFN-α-induced depression may not be indicated in patients with HCV
Galvão-de Almeida *et al*[56]	-	Retrospective literature Review	Citalopram, paroxetine, escitalopram	Antidepressant prophylaxis may blunt the magnitude of depressive symptoms in HCV patients and raise the rates of treatment completion in those with psychiatric diagnosis
Morasco *et al*[60]	39	Double-blind, placebo-controlled clinical trial	Citalopram	Citalopram is not superior to placebo in preventing IFN-induced MDD

IFN: Interferon; MDD: Major depressive disorder; HCV: Hepatitis C virus.

entered into the open - label rescue arm of the study, 10 of 11 had a significant reduction of depressive symptoms that allowed continuation of antiviral treatment[58]. In the second study, assignment to paroxetine did not decrease the likelihood of IFN-induced depression but was associated with a significantly reduced depression symptom severity score. Although sample sizes were small, these results suggest that prophylactic treatment with paroxetine is not effective in preventing the onset of IFN-induced MDD but may have benefits in reducing overall depression symptom severity[58,59].

A more recent double-blind, placebo-controlled trial that assessed the benefit of prophylactic treatment with citalopram in 39 HCV infected patients who did not have significant symptoms of depression prior to initiation of antiviral therapy reported similar results. Randomization to citalopram did not significantly reduce the likelihood of developing IFN-induced depression as compared with placebo[60] (Table 6).

Overall, there is no substantive evidence that antidepressant prophylaxis during antiviral therapy for HCV has significant benefits. Potential benefits must be weighed against the risks of antidepressant use above and beyond their common side effects. The use of SSRIs, which have been associated with an increased incidence of gastrointestinal bleeding in the general population[61], may have adverse consequences in people with HCV who are at higher risk for low platelet count, coagulopathy, and esophageal varices[62]. Furthermore, SSRIs have been associated with retinal hemorrhages in people receiving high - dose IFN therapy for malignant melanoma[63]. Other observations in the general population suggest that mirtazapine and sertraline may increase the likelihood of neutropenia[64].

In summary, the wide-spread use of antidepressants to prevent IFN-induced depression in people receiving IFN-based therapy for HCV is not warranted. A more conservative approach involves screening all patients prior to initiation of antiviral therapy for depression, treating depression prior to beginning antiviral therapy, and proactively monitoring depressive symptomatology at regular intervals during the course of treatment.

Interdisciplinary team/integrated care

Optimal care for HCV is best provided by an interdisciplinary team approach that involves mental health care providers. Individuals with psychosocial comorbidities are able to successfully complete treatment, when an interdisciplinary team with both medical and mental health support is applied[65]. The early identification of depression during HCV treatment can be achieved using an integrated model of care and can also assist individuals who have both mild or severe psychiatric illness in initiating and completing antiviral treatment[66]. Individuals who receive care from an interdisciplinary team are more likely to complete the evaluation for HCV treatment and start antiviral treatment[67].

NEW MEDICATION TREATMENT OPTIONS FOR HCV

The use of new Food and Drug Administration (FDA)-approved medications for the treatment of HCV has distinct advantages when considering antiviral therapy in people with HCV and co-morbid psychiatric and SUDs, in large part, because the duration of antiviral therapy and therefore the period of risk for IFN-induced depression as well as other common neuropsychiatric side effects has been shortened. Moreover, medications in development to treat HCV will eliminate the need for IFN altogether. A review of new FDA-approved medications as well as medications under development and their neuropsychiatric side effects are reviewed briefly-below.

Telaprevir

Telaprevir used in combination with peginterferon α (PEGIFN-α) and ribavirin (RBV) has been shown to improve response rates in the treatment of HCV, genotype 1[68,69]. It can be used for those with compensated liver disease, including cirrhosis, who are treatment-naïve or who have been previously treated with IFN-based therapies, including prior non- responders, partial

Table 7 Telaprevir

Ref.	*n*	Design	Treatment	Population	Outcome
Hézode *et al*[73]	334	Phase 2 randomized clinical trial	Telaprevir PEGIFN/RBV	HCV genotype 1 - treatment naïve	Telaprevir groups had significantly higher rates of SVR than PEGIFN/RBV alone. Depression occurred in 20%-23% of patients and was not significantly different across groups
McHutchison *et al*[68]	115	Randomized clinical trial	Telaprevir	HCV genotype 1 - previous non-responders to PEGINF/RBV	Re-treatment with telaprevir was more effective than PEGIFN-α/RBV alone. Depression occurred in 11%-17% of participants
Zeuzem *et al*[69]	663	Phase III randomized clinical trial	Telaprevir, PEGIFN-α-2a/ RBV	HCV genotype 1 - previous non responders, partial responders and relapsers	Telaprevir in combination with PEGIFN/RBV significantly improved rates of SVR and, as compared with PEGIFN/RBV alone showed no increase in neuropsychiatric side effects
Kumada *et al*[72]	1126	Multicenter randomized clinical trial	Telaprevir, PEGIFN-α-2b/RBV	HCV genotype 1 - treatment naive	Triple therapy with telaprevir-based regimen resulted in higher SVR with shorter duration. Depression was not listed as an adverse event
Sherman *et al*[74]	540	Randomized clinical trial	Telaprevir PEGIFN-α-2a/RBV	HCV genotype 1 - treatment naïve	Combination therapy with telaprevir for 24 wk was non inferior to standard therapy for 48 wk. Fifty-three percent of patients experienced psychiatric symptoms

PEGIFN: Pegylated interferon (peginterferon); RBV: Ribavirin; HCV: Hepatitis C virus; SVR: Sustained virologic response.

responders, and relapsers[70].

Despite several known side effects associated with telaprevir, including fatigue, rash, nausea, anemia and influenza like symptoms, changes in mood or depression are not known to be direct side effects of this medication[69]. While depressive symptoms have been noted in some clinical trials, they have not been considered primary adverse events nor have they led to drop out or discontinuation of treatment[68,69,71,72].

Telaprevir in combination with PEGIFN/RBV is superior to PEGIFN/RBV alone and has higher SVR (approximately 72% *vs* 50%-60%); it is also known to increase response time[68,69,72,73].

Overall, telaprevir may increase the ability to achieve SVR, without a drastic influence on the side effects profile[68]. The risk of depression is not noted to be increased when using telaprevir in combination with PEGIFN/RBV (Table 7).

Boceprevir

Boceprevir, a medication that is similar to telaprevir, is a potent oral HCV-protease inhibitor that is also used in conjunction with PEGIFN/RBV for the treatment of patients infected with HCV genotype 1. Studies indicate that rates of SVR are improved significantly when boceprevir is used in combination with PEGIFN/RBV as compared with PEGIFN/RBV alone[75,76].

While some side effects (such as anemia) commonly associated with PEGIFN/RBV may be more likely to occur with the addition of boceprevir, side effects associated with PEGIFN/RBV treatment regimens including dysgeusia, rash, dry skin, headache and flu-like symptoms are no more likely to occur with addition of boceprevir[75-77].

Based on the results of the above studies as well as prescribing information published by the FDA, common psychiatric side effects associated with PEGIFN/RBV are not more likely to occur in patients with the addition of boceprevir[78] (Table 8).

Simeprevir

Several studies have assessed the efficacy of simeprevir in combination with PEGIFN/RBV for the treatment of hepatitis C. Simeprevir is a HCV NS3/4A protease inhibitor indicated as a component of a combination antiviral treatment for the treatment of HCV[78].

Studies suggest that simeprevir in combination with PEGIFN/RBV significantly improves rates of SVR as compared with PEGIFN/RBV alone. Studies also suggest that the addition of simeprevir can shorten the duration of antiviral therapy to 24 wk (instead of 48 wk with PEGIFN/RBV alone) without a change in SVR or the side effects profile[79-83].

The most common adverse events found with the use of simeprevir in combination with PEGIFN/RBV include fatigue, headache, pruritus, influenza like illness, nausea and neutropenia[79-81]. However, in these studies there were non-significant differences in frequency of adverse events between groups on simeprevir in combination with PEGIFN/RBV *vs* PEGIFN/RBV, suggesting the side effects may be attributable to the PEGIFN/RBV[79-82].

Depression was not assessed with symptom rating instruments and noted only by self-report in these studies; overall the rates of self-reported depression were not different between the group that received simeprevir in combination with PEGIFN/RBV *vs* the group that received PEGIFN/ RBV alone and there were very few subjects who experienced depression as a major contributing factor for discontinuation[79,80].

In summary simeprevir does not increase the risk of side effects attributable to PEGIFN/RBV and can shorten the duration of antiviral therapy and thus the length of exposure to PEGIFN and presumably side effects associated with peginterferon treatment[81] (Table 9).

Sofosbuvir

Sofosbuvir is a HCV nucleotide analog NS5B polymerase inhibitor indicated for the treatment of HCV infection as a component of a combination antiviral treatment

Table 8 Boceprevir

Ref.	*n*	Design	Treatment	Population	Outcome
Kwo *et al*[77]	520	Two part randomized clinical trial	Boceprevir	chronic HCV genotype 1 - treatment naïve	Boceprevir has the potential to double the SVR rate compared with standard treatment alone. Insomnia was the only psychiatric illness documented
Bacon *et al*[75]	403	Placebo controlled, randomized clinical trial	PEGIFN-α-2b/RBV boceprevir, PEGIFN-α-2b/RBV	Retreatment of patients with chronic HCV genotype 1 infection	Boceprevir resulted in significantly higher rates of SVR. Significant onset of depression was not indicated
Poordad *et al*[76]	1097	Double blind, placebo controlled randomized clinical trial	Boceprevir PEGIFN-α-2b/RBV	Chronic HCV genotype 1 - treatment naïve	Boceprevir significantly increased the rates of SVR. Insomnia was the only psychiatric condition identified as an adverse event

PEGIFN: Pegylated interferon (peginterferon); RBV: Ribavirin; HCV: Hepatitis C virus; SVR: Sustained virologic response.

Table 9 Simeprevir

Ref.	*n*	Design	Treatment	Population	Outcome
Fried *et al*[80]	338	Phase 2b double blind, placebo controlled randomized clinical trial	Simeprevir PEGIFN-α-2a/RBV	Treatment-naıve patients with HCV genotype 1 infection.	Simeprevir in combination with PEGIFN/RBV significantly improved SVR rates and shortened therapy duration. Depression occurred in 10.4% of patients on simeprevir and 18.2% on standard treatment
Zeuzem *et al*[79]	396	Placebo controlled, randomized clinical trial	Simeprevir, PEGIFN-α-2a/RBV	patients with HCV genotype-1 infection previously treated with PEGIFN/RBV	12, 24, or 48 wk simeprevir with 48 wk PEGIFN/RBV significantly increased rates of SVR and was generally well tolerated. Depression occurred in 2/396 simeprevir patients
Jacobson *et al*[81]	394	Phase 3, randomized, double blind, placebo controlled multicenter clinical trial	Simeprevir, PEGIFN-α-2a/RBV	Treatment naïve patients with HCV genotype 1	Simeprevir with PEGIFN-α-2a/RBV shortens therapy without worsening the adverse event profiles associated with PEGIFN
Manns *et al*[82]	257	Phase 3 multicenter randomized, placebo controlled clinical trial	Simeprevir PEGIFN-α-2a or 2b/RBV	Treatment-naive patients with HCV genotype 1 infection	Addition of simeprevir to PEGIFN-α-2a or PEGIFN-α-2b plus RBV improved SVR without worsening the known adverse events associated with peginterferon
Kumada *et al*[83]	79	Open label non comparative multicenter trial	Simeprevir PEGIFN-α-2b/RBV	HCV genotype 1 - treatment-naïve or had previously received IFN-based therapy	Simeprevir combined with PEGIFN-α-2b/RBV was effective across both groups. One patient in the control group receiving standard therapy alone discontinued due to grade 2 depression

PEGIFN: Pegylated interferon (peginterferon); RBV: Ribavirin; HCV: Hepatitis C virus; SVR: Sustained virologic response; IFN: Interferon.

regimen; it is recommended to be used with PEGIFN-α/RBV or with RBV alone thus excluding the need for IFN altogether[78].

The most common adverse events when used with PEGIFN/RBV combination therapy are fatigue, headache, nausea, insomnia and anemia (similar to those found in other combination therapies with PEGIFN). The most common adverse events (≥ 20%) for sofosbuvir and RBV combination therapy are fatigue and headache[84,85].

Overall results indicate that psychiatric issues, including depression, are not significant side effects and are rarely the reason for study drop out or discontinuation[85-87]. However the rates of depression in these studies, when reported, are below the generally accepted rate of IFN-induced depression, which is 20%-30%. While this may reflect the decreased duration of IFN exposure, these lower rates of depression may also be due to relying on patient report of side effects.

In summary, results indicate the sofosbuvir in combination with other medications can lead to an early viral response as well as SVR with a shorter duration of treatment, with and without the use of PEGIFN. Furthermore, sofosbuvir provides an effective treatment with little evidence of psychiatric side effects and overall, is well tolerated. Authors suggest that for most, there is no additional benefit to prolonging treatment beyond 12 wk when using a sofosbuvir based medication regimen[86].

Previous studies have indicated that the majority of people who develop IFN-induced depression have an onset between 6 and 12 wk after antiviral therapy initiation but approximately one third develop IFN-induced depression after 12 wk of antiviral therapy[38]. Thus it's possible that the use of sofosbuvir in combination with other therapies or alone, may reduce the risk of onset of depressive symptoms by decreasing or eliminating exposure to PEGIFN (Table 10).

HCV ANTIVIRAL MEDICATIONS IN DEVELOPMENT

ABT-450/r-Ombitasvir and dasabuvir with RBV

A new medication combination of ABT-450/r-Ombitasvir

Table 10 Sofosbuvir

Ref.	*n*	Design	Treatment	Population	Outcome
Kowdley *et al*[86]	316	Multicenter, open label, phase 2 clinical trial	Sofosbuvir-2a PEGIFN-α-2a/ RBV	HCV genotype 1 - non-cirrhotic treatment-naive, patients	SVR occurred in 90% of patients treated with sofosbuvir and PEGIFN/RBV for 12 wk. Depression occurred in 8%-16% of patients across all groups but was not a primary reason for discontinuation
Lawitz *et al*[87]	147	Two-cohort, phase 2, placebo controlled, clinical trial	Sofosbuvir PEGIFN/RBV	Treatment-naive patients with genotype 1-3 HCV infection	SVR occurred in 90% of patients treated with sofosbuvir and PEGIFN/RBV and the side effects profile was similar to that of PEGIFN/RBV and did not include depression. Depression was not a significant adverse event in this study
Jacobson *et al*[85]	240	Phase 3 randomized placebo controlled clinical trials	Sofosbuvir RBV	Chronic HCV genotype 2 or 3 previously unable to be treated with IFN, or previously treated with IFN-based therapies	Sofosbuvir and RBV was effective at 12 wk for genotype 2 and 16 wk for genotype 3. Premature discontinuation of the study drug due to adverse events was uncommon in all groups. Depression was not a significant adverse event in this study
Gane *et al*[84]	75	Open label randomized clinical trial	Sofosbuvir, RBV	HCV genotype 2 or 3 infection. with no response to prior treatment or with no prior treatment	Sofosbuvir plus RBV for 12 wk was effective for patients with genotype 1, 2, or 3 infections. Insomnia occurred in 30%-67% of participants across groups and was the only significant psychiatric symptom to develop during treatment

PEGIFN: Pegylated interferon (peginterferon); RBV: Ribavirin; HCV: Hepatitis C virus; SVR: Sustained virologic response; IFN: Interferon.

with dasabuvir has also been assessed both with and without the addition of RBV. Though not yet FDA approved, this combination has yielded promising results; 95% of previously treated individuals with HCV genotype 1 had SVR after 12 wk of treatment[88].

The most commonly reported adverse events of this combination include headache and fatigue, with secondary effects of pruritus (> 10% of participants) anemia, vomiting, constipation, erythema, neck pain, neutropenia and a decrease in hemoglobin (< 10% of participants). Signs and symptoms of depression are not a significant side effect for this combination treatment and does not contribute to discontinuation or drop out[88].

ABT-450/Ombitasvir and dasabuvir has also been assessed with the addition of ritonavir, either with RBV or placebo. Those treated with this regimen (both with and without RBV) have SVR rates of between 96.6% and 100% after 12 wk of treatment[89].

The most common adverse events were fatigue and headache, along with nausea and decreased hemoglobin. Participants in the RBV group also experienced insomnia, anemia, rash and increased bilirubin levels (all known to be side effects of RBV). Serious adverse events included cellulitis, nephrolithiasis and osteoarthritis, though none were judged to be study drug related or led to discontinuation. Outside of insomnia (noted above) no other psychiatric symptoms were reported for either group, both with and without RBV[89].

Overall, it appears this combination with and without ritonavir and/or RBV, is useful in treating HCV without the use of IFN.

Daclatasvir

Daclatasvir is a potent NS5A replication complex inhibitor, and is generally well tolerated in phase 1 and phase 2 trials[90]. It has been used successfully in various HCV genotypes, and in both treatment naïve and non-responder/relapser populations[90,91]. Daclatasvir has been used in combination with several other medications including PEGIFN/RBV, asunaprevir and sofosbuvir, all of which show varying levels of treatment success, as measured by SVR after 12 and 24 wk of treatment, and in some studies, SVR was obtained after 8 wk treatment duration[91-93]. In certain combinations, daclatasvir allows the use of IFN-free combinations for those unable to tolerate IFN and have been shown effective in those who previously failed telaprevir/boceprevir regimens[93,94].

Across studies, the most frequently reported adverse events are diarrhea, headache and nasopharyngitis, all of which were reported to be mild. Less common adverse events include abdominal discomfort, malaise, constipation and back pain. No studies reported psychiatric symptoms or adverse events[91,93,94].

Ledipasvir

Ledipasvir, another NS5A inhibitor has also resulted in high rates of SVR among both previously treated as well as treatment naïve patients with HCV[95,96]. The rates of SVR ranged from 97%-99% across groups given combination therapy of ledipasvir and sofosbuvir, with and without RBV at 12 and 24 wk. Additional assessments indicate that ledipasvir-sofosbuvir regimens given for 8 wk is associated with a high rate of SVR among both previously treated and treatment naïve patients with HCV genotype 1 including those with cirrhosis. No additional benefit was associated with the addition of RBV to this combination or with extension of the duration of treatment to 12 wk[97,98] (Table 10).

The most common adverse events across studies were fatigue, headache, insomnia, and nausea[95]. The incidence of adverse events was lower among patients

Table 11 Newer medications and interferon free therapies

Ref.	*n*	Design	Treatment	Population	Outcome
Pol *et al*[92]	48	Double blind parallel group, dose finding phase 2a randomized, placebo controlled clinical trial	Daclatasvir PEGIFN-α-2a/RBV	HCV genotype 1 - treatment-naive (without cirrhosis)	Daclatasvir increases the antiviral potency of PEGIFN/RBV without increasing the side effects profile. Psychiatric adverse events were not significant in this study
Chayama *et al*[91]	10	Open label phase 2a clinical trial	Daclatasvir asunaprevir	Chronic HCV genotype 1b - previous null responders to PEGINF/RBV	Dual therapy with daclatasvir and asunaprevir alone can achieve high rates of SVR in difficult-to-treat patients and has minimal side effects
Herbst *et al*[90]	-	Retrospective literature review of phase 1 to phase 3 clinical trials	Daclatasvir	All genotypes; treatment naive and experienced cohorts	Daclatasvir has a potent antiviral effect and clinical efficacy across genotypes and in both treatment naive and experienced cohorts with no evidence of psychiatric adverse events
Suzuki *et al*[94]	43	Open label phase 2a clinical trial	Daclatasvir asunaprevir	HCV genotype 1b for patients with limited treatment options including those with complications of depression	Dual therapy with daclatasvir and asunaprevir was well tolerated and achieved high SVR rates. The adverse event profile was favorable; no psychiatric abnormalities were reported
Zeuzem *et al*[88]	394	Phase 3 placebo controlled randomized clinical trial	ABT-450 ritonavir (ABT-450/r), ombitasvir (ABT-267) dasabuvir (ABT-333) RBV	Retreatment of HCV in patients who were previously treated with peginterferon-ribavirin	Rates of response to a 12-wk IFN-free combination regimen were more than 95%. Psychiatric adverse events were not reported
Andreone *et al*[89]	179	Phase 3 open label randomized clinical trial	ABT-450, ritonavir, ombitasvir, dasabuvir RBV	HCV genotype 1b - treatment experienced patients	ABT-450, ritonavir, ombitasvir, and dasabuvir, with or without RBV, produced a high rate of SVR. Both regimens were well tolerated with minimal adverse events
Sulkowski *et al*[93]	167	Two part, open label clinical trial	Daclatasvir sofosbuvir	HCV genotype 1, 2, or 3	Daclatasvir plus sofosbuvir was associated with high rates of SVR. Psychiatric problems were not listed as significant adverse events
Afdhal *et al*[96]	865	Phase 3, open-label randomized clinical trial	Ledipasvir sofosbuvir RBV	HCV genotype 1 - treatment naive	Ledipasvir–sofosbuvir with or without RBV for 12 or 24 wk was highly effective. The most common adverse events were fatigue, headache, Insomnia, and nausea
Lawitz *et al*[98]	100	Open label randomized clinical trial	Sofosbuvir ledipasvir RBV	HCV genotype 1 - treatment-naive or previously treated with a protease-inhibitor regimen	Sofosbuvir-ledipasvir alone or with RBV has the potential to cure most patients with genotype-1. Psychiatric symptoms were not a listed as significant adverse events
Afdhal *et al*[95]	440	Phase 3, randomized, open-label clinical trial	Ledipasvir sofosbuvir RBV	HCV genotype 1 - previously treated	Treatment with ledipasvir and sofosbuvir resulted in high rates of SVR. Neuropsychiatric side effects were minimal, but were observed more frequently among groups with the RBV-containing regimen than ledipasvir sofosbuvir alone
Kowdley *et al*[97]	647	Phase 3, open label clinical trial	Sofosbuvir ledipasvir	HCV genotype 1 - treatment naive	Ledipasvir-sofosbuvir was associated with a high rate of SVR. Adverse events were more common in the group that received RBV. No additional benefit was associated with the inclusion of RBV

PEGIFN: Pegylated interferon (peginterferon); RBV: Ribavirin; HCV: Hepatitis C virus; SVR: Sustained virologic response; IFN: Interferon.

receiving ledipasvir-sofosbuvir alone than among those receiving ledipasvir-sofosbuvir plus RBV[95-98]. Patients in the groups that received ledipasvir - sofosbuvir plus RBV for 12 or 24 wk had higher rates of events known to be associated with RBV therapy-fatigue, insomnia, asthenia, rash, cough, pruritus, and anemia-than did those in the corresponding groups that received ledipasvir-sofosbuvir without RBV[95,96]. Few to no patients dropped out of the study or discontinued due to adverse events, and in some cases, even those who discontinued still achieved a SVR[96]. Overall, no psychiatric adverse events were reported across studies and none led to discontinuation[95-98] (Table 11).

In summary, these new medications will shorten the duration of treatment and also allow IFN-free combination therapy, thus reducing dramatically the risk of neuropsychiatric symptoms and, in particular, depression.

SUMMARY

HCV infection is known to decrease HRQOL, an issue only exacerbated by various psychosocial factors and psychiatric illness. Antiviral therapy with HCV is often

complicated by pre-existing depression as well as other psychiatric illnesses including schizophrenia, bipolar disorder and SUD. The common neuropsychiatric side effects - in particular depression - associated with IFN-based therapies made antiviral therapy problematic and often resulted in exclusion of people who had pre-existing depression or other psychiatric illnesses. However, various studies have shown that neuropsychiatric side effects can be successfully managed during IFN-based antiviral therapy and that people with pre-existing psychiatric illness can be treated successfully and achieve SVR within interdisciplinary care models that involve mental health care providers. The use of interdisciplinary teams has been shown to increase the likelihood of treatment completion for patients with psychiatric illnesses. This approach must be fostered because IFN-free antiviral therapy will not be immediately available due to the prohibitively high cost of these medications. Furthermore, the cost will likely impact treatment viability in developing countries.

The development of new medication options for the treatment of HCV has provided additional opportunities for treatment of people with HCV who have - or are at risk for - psychiatric illness. For those who can tolerate the side effects of IFN and are compliant with treatment, the addition of telaprevir or simeprevir can significantly decrease treatment duration, and thereby decrease the likelihood of developing depressive and other psychiatric symptomatology. Moreover, sofosbuvir based regimens remain the most viable FDA approved drug at this time. New medications under development will allow IFN-free medication combinations and higher rates of SVR, with little to no risk of developing or exacerbating preexisting depressive symptoms.

LIMITATIONS

Despite new treatment options, there are several factors that should be considered. One consideration is that the use of newer direct acting antiviral (DAA) medications such as telaprevir, boceprevir, simeprevir, sofosbuvir, ombitasvir and dasabuvir may be limited by drug to drug interactions. While studies identify minimal neuropsychiatric risks directly associated with the use of various DAAs, they can potentially interact with a variety of psychotropic agents causing unwanted adverse effects which may alternatively and indirectly affect treatment outcomes[99,100]. Triazolam, oral midazolam, St. John's Wort, carbamazepine, phenytoin, phenobarbital, oxcarbazepine and pimozide, are among psychotropic medications known to be contraindicated with DAAs[99,100].

A second consideration is that medications under development may not be options for all genotypes of HCV or for those with severe liver disease. Furthermore, these medications are costly, with some estimated to be $1000/pill, and thus, may not be a viable option in less developed countries and/or families with low SES or lack of insurance for whom this cost is too great.

A final limitation of this review is that the vast majority of studies related to medications under development may have excluded patients with preexisting psychiatric diagnoses or those in historical underserved health disparity populations. So called "real world" clinical trials are necessary in order to assess the viability of these new medications in underserved populations. However, the shorter duration of antiviral therapy and the availability of IFN-free therapies hold great promise for the future of HCV treatment.

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