Hepatitis C infection, antiviral treatment and mental health: A European expert consensus statement

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Summary

Mental health problems frequently occur in chronic infection with the hepatitis C virus (HCV) and during antiviral treatment with pegylated interferon-alpha (PegIFNα) and ribavirin. Depression is one of the most important complications during antiviral treatment of chronic hepatitis C infection. However, an increased prevalence of depression, fatigue, and cognitive disturbances has also been reported in untreated HCV-positive patients. Patients with psychiatric disorders or drug addiction also have an increased risk of HCV infection. Furthermore, because of possible drug–drug interactions, new antivirals administered together with PegIFNα and ribavirin may complicate psychiatric side effect management, even if no specific psychiatric adverse events are known so far for these new drugs.

The European liver patient’s organization (ELPA) organised a European expert conference to review the literature and develop expert recommendations for the management of mental health problems in HCV infected patients.

This paper results from the output of the 2011 EASL meeting and subsequent dialogue with patient groups and relevant experts in Europe. It summarises the current knowledge of HCV infection and the brain; prevalence, course, and neurobiology of IFN-α associated psychiatric side effects; possible risk factors for IFN-α associated depression and suicide attempts; psychiatric management of HCV infected patients before and during antiviral treatment; prevention of IFN- α associated psychiatric side effects; and psychiatric aspects of the new antivirals.

Introduction

An estimated 170 million people are infected with the hepatitis C virus (HCV) worldwide. HCV infection is the most frequent cause of chronic hepatitis and an important risk factor for liver cirrhosis and hepatocellular carcinoma. There is an increased prevalence of psychiatric co-morbidity in patients with chronic HCV infection and emerging evidence suggests that mental health problems may be associated with the infection itself, possibly mediated by an effect on the central nervous system (CNS). In addition, antiviral combination therapy with PegIFNα and ribavirin is often associated with significant psychiatric side effects, such as depression, fatigue, insomnia, anxiety, cognitive disturbances [1,2] or suicide attempts, which represent the worst possible complication of severe depressive syndromes [3]. Mental health problems during antiviral treatment have a strong impact on quality of life, may reduce treatment compliance and are risk factors for treatment failure [4–6]. Research over recent years has sought to increase knowledge about the frequency, course, and pathophysiology of mental health problems during chronic HCV infection and antiviral therapy with PegIFNα and ribavirin. Different management strategies for the acute treatment or for the prevention of psychiatric problems have been developed to avoid dose reduction or treatment discontinuation. However, to date there has not been an international, interdisciplinary consensus regarding the current knowledge of mental health problems during HCV infection and treatment-related psychiatric problems. At the 2011 EASL meeting, the European liver patient’s organization (ELPA) initiated a European expert consensus conference to review the current available scientific data on HCV and treatment-related psychiatric effects, in order to produce recommendations for the psychiatric management of patients before, during and after hepatitis C treatment.
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Table 1. Evidence grading (adapted from the GRADE system) [7].

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Notes</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>High quality</td>
<td>Further research is very unlikely to change our confidence in the estimate of effect</td>
<td>A</td>
</tr>
<tr>
<td>Moderate quality</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate</td>
<td>B</td>
</tr>
<tr>
<td>Low quality</td>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain</td>
<td>C</td>
</tr>
<tr>
<td>Recommendation</td>
<td>Notes</td>
<td></td>
</tr>
<tr>
<td>Strong</td>
<td>Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost</td>
<td>1</td>
</tr>
<tr>
<td>Weak</td>
<td>Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption</td>
<td>2</td>
</tr>
</tbody>
</table>

Methods

The European expert consensus group consisted of four hepatologists, five clinical psychiatrists and/or neurobiologists, from Europe, and a member of ELPA. Consensus was based on current available clinical trials and other evidence published in the English language to March 2011, and the clinical experience of the consensus group. The following questions were discussed: (1) Does a chronic HCV infection affect the brain? (2) What is known about the prevalence, course, and neurobiology of IFN-α associated psychiatric side effects? (3) What are the risk factors for IFN-α associated depression and suicide attempts? (4) What should be done with HCV infected patients before antiviral treatment is started? (5) What is known about possible management of psychiatric problems during antiviral treatment? Can IFN-α -associated psychiatric side effects be prevented? (6) How will new antivirals influence psychiatric side effects of IFN-α and patients management? The Delphi-technique, requiring agreement of at least 80% of the group was employed. The level of evidence and recommendations follows the EASL system adapted from the GRADE system [7] (Table 1). Results from the consensus meeting were additionally presented in two international symposia (EASL conference, Berlin, 2011 and INHSU, Brussels, 2011) and further discussed together with professionals and patients. Subsequent important publications that significantly influenced the recommendations were further discussed in the group and included in this final version of the paper.

Results and recommendations

HCV and the brain

Psychiatric co-morbidity has been reported to occur frequently in patients with chronic HCV infection, with a higher incidence of depressive symptoms, bipolar symptoms, anxiety, fatigue, psychotic symptoms, alcoholism, and drug abuse (Fig. 1). Cognitive disturbances have also been frequently reported [8–12]. The higher rate of psychiatric disorders in HCV infected populations may be related to a higher risk of HCV infection in psychiatric patients but may also be the consequence of a direct or indirect effect of HCV on the central nervous system (CNS). Whilst the prevalence of HCV infection in the European general population is approximately 2%, the prevalence in psychiatric populations has been found to be between 6.7% and 8.5%; patients with intravenous drug abuse have the highest risk, with a prevalence between 30% and 98% [13–17]. This is related to increased high risk behaviour, such as intravenous drug abuse, but also to other risk factors such as long-term hospitalisation [14,18,19].

There is also evidence that HCV infection itself may be directly associated with psychiatric symptoms, independent of pre-existing psychiatric disorders. Stigmatisation and the fact that patients have to cope with a chronic infectious disorder increase the risk of depression and anxiety [20]. A relationship between duration of HCV infection and severity of depressive symptoms or anxiety has been reported [21]. Furthermore, major depression has been reported to occur more frequently in HCV than in HBV infected patients, independent of drug or alcohol abuse, suggesting a specific association between HCV infection and the development of depression [22]. Fatigue, which is the commonest symptom in HCV infection, is unrelated to the severity of liver disease and occurs more frequently in HCV than in HBV infected patients; it also improves after successful antiviral treatment [23–28]. Fatigue may be the greatest determinant of reduced health-related quality of life in HCV infection [25,29]. Cognitive impairment has been reported in HCV infected patients with only minimal liver disease, independent of psychiatric co-morbidity or addiction disorder [8,11,30]. A small study showed that patients who were successfully treated for HCV had less cognitive impairment than HCV-positive patients [30].

A number of studies now support the hypothesis that HCV directly or indirectly induces biological changes in the CNS, which may result in psychiatric symptoms. Studies using proton magnetic resonance spectroscopy showed changes in the cerebral choline/creatinine ratio [30,31], in the N-acetylaspartate/creatine ratio [12], in the Myo-inositol/creatine ratio [32], and in choline, creatine, N-acetylaspartate, and N-acetyl-aspartyl-glutamate concentrations...
[8], suggesting an altered metabolism consistent with cerebral immune activation. Reduced dopamine transporter and serotonin transporter binding has also been reported in HCV patients, that was associated with cognitive dysfunction [33]. Moreover, a recent PET study using PK11195, a peripheral benzodiazepine receptor ligand, has shown increased caudate nucleus binding in HCV patients, consistent with microglial activation [34]. The mechanism and significance of these findings have not been defined but there is accumulating virological data to suggest that HCV may penetrate into the CNS and replicate, possibly at a very low level [35–39]. Putative biological pathways have been proposed by which hepatitis C might lead to psychiatric symptoms but causality has not been clearly demonstrated and more data are needed, particularly to evaluate reversibility with successful antiviral treatment.

HCV and brain

- Psychiatric co-morbidity is significantly more prevalent in chronic HCV patients than in the general population (Recommendation A1)
- Psychiatric morbidity is associated with an increased risk for HCV infection (Recommendation A1)
- Some psychiatric symptoms (e.g., depression, fatigue, cognitive impairment) might be specifically associated with chronic HCV infection (Recommendation B1)
- Chronic HCV leads to high degree of psychological distress (stigmatisation, anxiety, reduced quality of life) (Recommendation B1)
- There is evidence that HCV alters CNS metabolism, directly or indirectly (Recommendation B1)
- Recent studies suggest that HCV may enter and replicate within the CNS (Recommendation B1)

Prevalence, course, and neurobiology of interferon-α-induced neuropsychiatric side effects

Prevalence
Depression is a common side effect of IFN-α treatment. Overall, depression during IFN-α treatment develops in 30–70% of the treated patients. This prevalence rate depends on the methods of assessment (i.e., diagnostic interview, clinical evaluation, self-reports, observer-rated scales), the time of evaluation and the severity of depression. For instance, it is estimated that mild to moderate depression develops in 45–60% of the patients treated with IFN-α, moderate to severe depression in 15–40%, and major depression in 15–45% [2,4,40–44]. Treatment options such as standard vs. pegylated (PEG) IFN-α, types of PegIFNα2a vs. 2b and associated ribavirin do not seem to have a significant influence.

In addition to depression, IFN-α is also associated with the occurrence of a wide range of other neuropsychiatric symptoms (Table 2). Fatigue represents probably the most prominent side effect as it develops in up to 80% of the patients. Sleep alterations, irritability, anxiety, and cognitive disturbances may occur in up to 50% of the patients. In contrast, mania, and psychosis represent more rare adverse events of IFN-α treatment, developing in up to 3% of the patients. Finally, whereas suicidal thoughts have been reported in up to 10% of the patients undergoing IFN-α therapy, case reports of suicide or suicidal attempts remain only anecdotal. The incidence of depression and impaired quality of life appears greater in IFN-α treatment of HCV infection compared to treatment of chronic hepatitis B infection [45].

Time course
Dimensional analyses of symptoms developing during IFN-α treatment have revealed differential time courses for the neuro-vegetative/somatic vs. mood/cognitive symptoms. Neurovegetative and somatic symptoms, including fatigue, decreased appetite, pain, and gastrointestinal disorders, develop at early stages of treatment, usually as soon as the first weeks of therapy [46]. These symptoms appear in a majority of patients treated with IFN-α and they remain persistent during the whole duration of treatment. Mood and cognitive symptoms, including depressive symptoms, anhedonia, memory disturbances and concentration problems, develop in a smaller proportion of patients (15–50%) and at later stages of treatment, usually after week 4 of therapy, with a greater intensity of depressive symptoms after week 8 [41,46,47]. Most neuropsychiatric side effects appear between weeks 10 and 24 of IFN-α treatment and some of them may persist until the end of antiviral therapy [48,49]. Whilst most of the neuropsychiatric effects resolve with treatment cessation, cases of persistent, recurring or new developing symptoms have been described [50,51].

Neurobiology
Recent advances have been made in the identification of mechanisms leading to neuropsychiatric toxicity in patients treated with IFN-α. Whilst multiple mechanisms have been proposed, this section will focus on two major aetiological pathways, corresponding respectively to alterations in monoamine metabolism and impaired neuroendocrine function. Experimental studies have shown that IFN-α is able to alter the synthesis, transport system, and turnover of monoamines [52–55]. Moreover, recent data indicate that immune mediators, including IFN-α, induce significant alterations in enzymatic pathways involved in the metabolism of major neurotransmitters, including serotonin, dopamine, and norepinephrine [56–58]. These alterations involve the activation of the enzyme indoleamine-2,3-dioxogenase (IDO), which leads to the degradation of
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Tryptophan into neurotoxic pathways [58,59], and impairment in the metabolism of tetrahydrobiopterin (BH4), the co-factor of tyrosine hydroxylase [58,59].

Another mechanism underlying the neuropsychiatric effects of IFN-α involves changes in neuroendocrine function. In support of this notion, acute IFN-α administration in patients with malignant melanoma was found to stimulate the hypothalamic-pituitary–adrenal (HPA) axis, leading to a rapid increase in the secretion of the adrenocorticotropic hormone (ACTH) and cortisol [60]. Interestingly, this increased HPA axis reactivity to the acute administration of IFN-α was associated with the development of major depression at later stages of IFN-α treatment [60]. When IFN-α was delivered chronically, however, the activation of the HPA axis was not apparent anymore. Consistent with this data, IFN-α treatment for 12 weeks in patients with hepatitis C was found to be associated with a flattening of the diurnal ACTH and cortisol slopes [61]. This effect may be related to impairment in corticosteroid receptor signalling, as inflammatory cytokines were found to disturb glucocorticoid receptor (GR) translocation and function, likely to be associated with GR resistance in relevant cell types [62,63].

<table>
<thead>
<tr>
<th>Neuropsychiatric side effects</th>
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<tbody>
<tr>
<td>• Treatment with standard and PegIFNα (2a-b) is associated with an increased incidence of mood alterations, including depression (mild to severe), fatigue, sleep disturbances, irritability, cognitive disturbances, and suicidal thoughts/ideation (Recommendation A1)</td>
</tr>
<tr>
<td>• Treatment with standard and PegIFNα (2a-b) is less frequently associated with mania/mixed states, acute confusional states, psychotic syndromes, suicide attempts, and impulsive/aggressive behavior (Recommendation B1)</td>
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<tr>
<td>• Neurovegetative symptoms (e.g., fatigue, sleep disturbances, decreased appetite) start immediately after treatment (Recommendation A1)</td>
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<tr>
<td>• Depression and cognitive disturbances develop mostly between week 4-24 (Recommendation A1) and depressive symptoms are the most intense between week 5-16 (Recommendation A1)</td>
</tr>
<tr>
<td>• Treatment with standard and PegIFNα is associated with peripheral and central immunological, hormonal and neurobiological changes (Recommendation A1)</td>
</tr>
<tr>
<td>• IFN-α induced alterations in serotonin metabolism and dopamine may play important roles in the development of depression and fatigue (Recommendation B1)</td>
</tr>
<tr>
<td>• IDO activation resulting in a serotonergic deficit and increased kynurenine synthesis may also be associated with cognitive changes by increasing potentially neurotoxic metabolites (Recommendation C1)</td>
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</table>

Risk factors for IFN-α induced depression or suicide

Predicting the occurrence of psychiatric adverse effects is an important area of clinical research, as ultimately it could lead to prophylactic interventions only in those at risk. Clinical, genetic, and biomarker predictors have all been proposed. The following chapter will focus on ‘baseline factors’ that are measurable before starting IFN-α.

Clinical risk factors

Studies have demonstrated that patients with higher levels of baseline depressive symptoms have higher depression scores during IFN-α treatment, and hence are more likely to develop clinically significant depression. This has been shown for both viral hepatitis [4,50,64] and cancer [65]. A personal history of major depression has also been found to be a risk factor, although this may be due to higher depressive baseline scores, rather than a specific effect [4]. Despite this, studies have demonstrated that patients with a pre-existing psychiatric diagnosis can have equivalent outcomes to patients without mental disorders with regard to viral response and treatment interruptions [43,44,64]. Baseline sleep disturbance is also a risk factor [50].

Genetic risk factors

Both brain- and immune-related genes have been tested in relationship to the onset of the psychopathology induced by IFN-α. The classical genetic risk factor for depression, the s allele of the short/long polymorphism in the serotonin transporter gene, has been found to be associated with depression in two studies [66,67] but not in two others [68,69]. The apolipoprotein E e4, a genetic variant also associated with neuropsychiatric disorders, has been shown to predict more depression, particularly irritability and anxiety during IFN-α [70]. A number of reports exist of an association between polymorphisms in immune genes and the occurrence of depression [66,69,70]. Interestingly, the T allele of the C/T single-nucleotide polymorphism upstream of IL28B (rs12979860), a well-known predictor of a worse antiviral response, has been shown to be associated with reduced appetite, energy, and sleep complaints, although it did not affect the risk of depression [71].

Biomarker risk factors

There is some evidence that high baseline inflammation predicts the occurrence of IFN-α-induced depression. Three studies have shown that higher baseline levels of some cytokines predict depression: interleukin-6 [72,73], soluble interleukin-2 receptor [73], interleukin-10 [73], soluble tumour necrosis factor-receptor-1 [74], and levels of soluble interleukin-6R (sIL-6R) have been found to be correlated with the risk of depression [74]. In addition, lower levels of the anti-inflammatory polyunsaturated fatty acids, docosahexaenoic acid (DHA), predict higher risks of depression [69].

Risk of suicide

The overall risk of suicidal thoughts or suicide is elevated in patients with untreated chronic HCV infection because of the increased prevalence of intravenous drug use and psychiatric co-morbidity, as standard risk factors for suicide. However, treatment with IFN-α has been reported to be associated with suicidal thoughts and single cases of completed suicides [3]. Nevertheless because most data come from case reports, the relative risk...
associated with treatment is unknown, although there is no real evidence that a previous psychiatric history is a risk factor [3].

### Risk factors

<table>
<thead>
<tr>
<th>Risk factors for IFN-α-induced depression or suicide are:</th>
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<tr>
<td>• Depression during previous treatment with IFN-α (Recommendation C1)</td>
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<tr>
<td>• Depressive symptoms before treatment is started (recommendation A1), although this is not associated with outcome (Recommendation B1)</td>
</tr>
<tr>
<td>• Sleep disturbances before treatment (Recommendation B1)</td>
</tr>
<tr>
<td>• Early vegetative symptoms (such as sleep, loss of appetite) during treatment (Recommendation B2)</td>
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<tr>
<td>• Baseline stress and lack of social support (Recommendation B2)</td>
</tr>
<tr>
<td>• Genetic factors (Recommendation B1)</td>
</tr>
<tr>
<td>• Biomarkers of inflammation before starting treatment (Recommendation B1)</td>
</tr>
<tr>
<td>• Specific risk factors for suicide during IFN/RBV therapy are unknown – but there is no evidence that a previous psychiatric history is in general a risk factor (Recommendation C2)</td>
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</table>

### Psychosocial management of HCV infected patients before antiviral treatment

A number of psychosocial issues have been shown to influence quality of life in patients with HCV infection. Strategies to improve psychological adjustment to chronic medical illness, increase social support, reduce stigmatisation, promote lifestyle changes (alcohol use, nutrition, exercise, work) and give information about possible side effects of antiviral therapy, all significantly improve treatment adherence [75].

It is generally accepted that a patient’s psychiatric condition should be monitored during PegIFNα therapy, to detect early treatment-related changes. Practice varies from informal clinical assessment to the systematic use of rating scales to formal psychiatric assessment. A number of well validated depression rating scales are available to monitor mood changes, including self-report scales such as the BDI (Beck Depression Inventory), the Z-SDS (Zung Self-Rating Depression Scale), the CES-D (Centre for Epidemiologic Studies Depression Scale), the PHQ-9 (Patient Health Questionnaire) or the HADS (Hospital Anxiety and Depression Scale). Clinician-administered scales, performed by experienced and trained professionals, include the HAMD (Hamilton Depression Scale) and the MADRS (Montgomery-Åsberg Depression Scale). All scales can be used to monitor depressive mood changes over time and to quantify the severity of depressive symptoms. However, although cut-offs are used in scientific investigations to define depression, these scales are not diagnostic instruments and a diagnosis of depression should be confirmed by an experienced psychiatrist using the official diagnostic criteria (ICD-10, DSM-IV) [76,77].

Although depression-scales may help detect early depressive mood changes, a specific cut-off or change in total scores has not yet been defined to indicate the optimal time to initiate antidepressant treatment. A subthreshold treatment strategy has been suggested to start antidepressant treatment when scores are increasing, even at low level [78]. However, an evidence base to support this is lacking.

The arrangements for depression screening will depend on the composition, skills, and experience of each multidisciplinary team, but formal psychiatric referral is recommended in the following situations: the treating physician is unable to manage depression or initial management has failed; the psychiatric situation is complex or uncertain; there is an identified or suspected risk of suicide, alcohol or substance abuse; a complex and difficult social situation; multiple psychotropic drugs are necessary; or psychotherapeutic treatment is required [42,79]. Hospitalisation may be necessary in cases of high suicide risk, lack of response to treatment, psychotic symptoms, psychotic depression, disorientation, and symptoms of delirium. Psychiatric symptoms may improve with treatment, and the continuation of antiviral treatment because of psychiatric complications should be decided on a case by case basis [15,42,80,81].

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**Table 3. Strategies for the management of IFN-associated acute adverse events.**

<table>
<thead>
<tr>
<th>Education, monitoring, and support</th>
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<tbody>
<tr>
<td>Information and psychoeducation before and during treatment</td>
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<tr>
<td>Monitoring of patients and psychiatric issues</td>
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<tr>
<td>Psychosocial interventions</td>
</tr>
<tr>
<td>Supportive psychotherapy</td>
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<thead>
<tr>
<th>Pharmacological strategies</th>
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<tbody>
<tr>
<td>Treatment of sleep disturbances</td>
</tr>
<tr>
<td>Antidepressant treatment (acute or preventive)</td>
</tr>
<tr>
<td>Treatment options: antipsychotics, benzodiazepines (mood stabilisers, amphetamines, naltrexone, tryptophan, etc)</td>
</tr>
<tr>
<td>Antiviral therapy dose reduction, discontinuation</td>
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</tbody>
</table>
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The experience of the last 10 years has clearly shown that patients with psychiatric co-morbidity should not necessarily be excluded from IFN-α-based antiviral therapy [44,64,81-84]. A multidisciplinary approach is recommended with immediate access to specialist management in cases of severe psychiatric symptoms. For patients with drug addiction, treatment in an opiate substitution programme has been reported as the best setting to start antiviral therapy [84–87]. The decision to offer antiviral therapy should be individualised in current users of illicit drugs or alcohol who are willing to participate in a substance use programme (such as a methadone programme or alcohol support programme) [81,84,88]. Antiviral therapy is not recommended for patients with major uncontrolled psychiatric illness [88].

Management, acute treatment, and prevention of IFN-α associated psychiatric problems

Acute psychiatric problems due to IFN-α have a high impact on access to treatment, adherence, and response rates. Between 10% and 14% of the patients discontinue therapy due to a psychiatric adverse event such as fatigue, depression, irritability, and insomnia [89,90]. Specific psychopharmacological management can successfully treat psychiatric symptoms in patients on IFN-α [42,81,91]. However, approximately only one third of patients who develop depression during antiviral treatment are correctly diagnosed [6]. Increased education of both treating nurses/physicians and patients is necessary to allow improved early detection of psychiatric symptoms. An ability to distinguish pre-existing mental health issues from IFN-α related effects is important in correctly guiding treatment [81]. A concomitant and continuous psychotherapeutic support programme has recently been shown to be able to reduce acute psychiatric complications and the need for pharmacological interventions during antiviral therapy [92]. In general, psychoeducational programmes, supportive treatment, behavioural or cognitive therapy, may all increase adherence to antiviral therapy, but so far trials are lacking. However, if psychiatric complications are associated with IFN-α treatment, acute pharmacological intervention becomes necessary and psychotherapy should not be offered alone [42,81,93].

The pharmacological management of side effects depends on a degree when they occur during treatment (Table 3). Management of sleep disturbance appears important because it is a risk factor for the development of depressive symptoms [3]. In addition to short-term (zolpidem) or long-term hypnotics (zopiclone), some patients might also require benzodiazepines, although the risk of drug dependence must be taken into account. Alternative strategies include the use of sedative antidepressants such as mirtazapine or trimipramine [81]. Early antidepressant treatment is recommended to prevent the development of severe depression. Uncontrolled studies have shown that different classes of antidepressants are highly effective, especially the selective serotonin reuptake inhibitors (SSRI) (response rates >80%, defined as >40% reduction of depression scale scores) [94–97]. In the only prospective, randomised, placebo-controlled trial, citalopram 20 mg od was significantly superior to placebo in reducing depressive symptoms after 2 and 4 weeks [98]. The frequency and severity of adverse events due to SSRIs are comparable to those in patients not infected with HCV [99]. Currently available data do not indicate negative long-term effects on virological response or an increase of treatment discontinuation because of side effects of antidepressants [43,81,100,101]. If patients...
respond to acute pharmacological treatment of IFN-α associated depression, the antidepressant should be continued through antiviral therapy and for 6–12 weeks after discontinuation because persistence or recurrence of depression, suicidal thoughts or cognitive disturbances have been reported after the end of antiviral treatment [29,49–51,102]. For other IFN-α associated psychiatric complications, no specific trial data are available and symptomatic treatment should be individualised. Fatigue might be ameliorated by antidepressant treatment especially if there are also depressive symptoms [46]. One prospective and controlled trial showed a positive effect of ondansetron, but data have not been confirmed so far [103]. Single case reports also indicate positive effects of tryptophan or stimulating agents [104–107]. Because cognitive disturbances might be related to depressive symptoms, antidepressants treatment should be initiated as first line treatment. However, no specific treatment is known for acute or long-lasting cognitive disturbances unrelated to depression. Irritability as symptom of depression and sleep disturbance might respond to antidepressant treatment. However, if irritability is related to mania, antidepressants may exacerbate symptoms, and a case series has suggested that a small dose of antipsychotic medication may help with this symptom [91]. In any case of manic or psychotic symptoms, confusional state, or suicidal thoughts, patients should immediately be evaluated by an experienced psychiatrist. The decision to dose reduce or discontinue IFN-α treatment should be made by the multidisciplinary team [3,42,81].

Since the detection of early IFN-α-related depressive symptoms relies on close observation and may be missed, preventive strategies using antidepressants as a pre-treatment may offer the chance to protect patients from the development of clinically relevant depression. The first prophylactic study was conducted in melanoma patients [41]. Paroxetine pre-treatment was able to reduce the incidence of major depression and the likelihood of IFN-α withdrawal in patients receiving high-dose therapy with IFN-α. Three open label trials focused on patients with psychiatric risk factors: previous history of IFN-α-induced depression [108], major depressive disorder in remission [109], or pre-existing depression and drug addiction [97]. In all three studies, antidepressants were able to reduce the incidence of IFN-α-induced depression. Six prospective, randomised, placebo-controlled trials have been published up to date [100,101,110–113]. In four

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**Management of acute treatment and prevention**

- Symptoms of depression are highly responsive to serotonergic antidepressants (Recommendation A1)
- When selecting an agent, consideration should be given to drug-drug interactions, underlying hepatic function, the possibility of drug-induced hepatotoxicity and other adverse side effects (Recommendation C1). The first line antidepressant for acute antidepressant treatment is citalopram (Recommendation A1)
- Second line antidepressant treatments include escitalopram (Recommendation C1), paroxetine (Recommendation C1), mirtazapine (Recommendation C1), sertraline (Recommendation C2), other antidepressants (Recommendation C2)
- Antidepressant treatment should be continued for at least 12 weeks after the end of antiviral therapy (Recommendation C1)
- Early treatment of sleep disturbances is recommended (Recommendation B1)
- Antidepressant pretreatment reduce the incidence and severity of IFN-α associated depression independent from pre-existing psychiatric risk factors (Recommendation A1)
- Prophylactic treatment with antidepressants is recommended for HCV patients with a previous history of IFN-α induced depression (Recommendation B1)
- HCV patients with symptoms of depression at baseline should also receive antidepressant pre-treatment before starting antiviral therapy (Recommendation B1)

- HCV patients with subthreshold depressive symptoms at baseline, or with a previous history of depression or substance abuse currently in remission, should be informed about the possibility of antidepressant pre-treatment to reduce the risk of developing depression. Individualised decisions should be taken together within the multidisciplinary team (Recommendation A1)
- Antidepressant pretreatment is so far not generally recommended for all HCV patients during antiviral therapy and should be based on a case by case decision and patients view (Recommendation A1)
- If adequate monitoring of psychiatric symptoms is provided, it is safe and efficacious to start antidepressant medication after the onset of depressive episodes (Recommendation B1)
- Pre-treatment with antidepressants is well tolerated by HCV patients on antiviral therapy (Recommendation A1) and does not affect virological outcomes (Recommendation A1)
- The above recommendations apply only to the use of escitalopram, citalopram and paroxetine (Recommendation A1). Escitalopram should be used as first-line treatment based on the evidence and the low risk of drug-drug interactions (Recommendation A1)
- Pre-treatment with antidepressants should be continued for the whole course of antiviral therapy, and up to 12 weeks after it has been stopped (Recommendation D1)
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of them, antidepressant pre-treatment with paroxetine, citalopram or escitalopram, did not reduce the incidence of IFN-α-induced major depressive episodes or the overall severity of depressive symptoms [100,101,111,112]. However, the largest trial to date by Schaefer et al. demonstrated a positive effect of escitalopram on the incidence and severity of depression defined by MADRS-score and major depression during treatment in patients without prior psychiatric disorders [113]. A further study by de Knegt et al. found similar positive results, but only investigated single items on depression scales [110]. In the trial by Raison and colleagues, paroxetine pre-treatment showed a positive prophylactic effect only in the subgroup of patients with mildly elevated baseline depression scores [101]. There were no safety issues or negative effects on virological outcome in any of the studies [100,101,112,113]. The heterogeneous results in the studies published to date are related to methodological concerns. There were small sample sizes in three studies [101,111,112], one trial only evaluated depression during the first 3 treatment months and there were low rates of major depression in placebo-treated patients [100], thus reducing the power of the trial to detect differences between groups. The populations studied were also different, with various rates of previous history of psychiatric and addiction disorders. Moreover, future trials should enlarge the pool of symptoms to be targeted (pain, irritability, fatigue, insomnia, and cognitive dysfunction), define the study populations carefully and try to identify subgroups that show real benefit from antidepressant pre-treatment. Beside specific psychotherapeutic interventions [114], the protective effect of intensive, multidisciplinary management should also be taken into account.

New antivirals and IFN-α: Psychiatric side effects and possible interactions

New antivirals have been developed that directly inhibit HCV. The first substances for clinical use in combination with PegIFNα (2a or 2b) are telaprevir and boceprevir [115–118]. Triple therapy with new antivirals together with PegIFNα and ribavirin may be associated with an increase of neuropsychiatric side effects or drug–drug interactions. However, currently available data shows that both new antivirals do not have specific neuropsychiatric side effects. For telaprevir, the most common "psychiatric" adverse events are fatigue and insomnia. The most common other adverse events (AEs) are rash, pruritus, headache, nausea, anemia, diarrhoea, flu-like symptoms, and pyrexia, with the majority being mild or moderate in severity [123,124]. However, depression was only evaluated in the trial by Hézode et al. [119], with an incidence of 20–22% in all groups. Regarding boceprevir, this treatment appears to be associated with anaemia and dysgeusia [120]. No specific additional psychiatric side effects could be observed. Although 2 patients from different groups committed suicide, no specific information about depression was given in this trial. Other AEs include headache, fatigue, and were observed at similar rates across all groups.

The treatment of IFN-α-induced AEs during combination triple therapy may be complicated by possible drug–drug interactions. Telaprevir is primarily metabolised by the cytochrome P450 system (CYP3A) whilst boceprevir is catalysed by cytochrome P450-mediated oxidation (strong inhibitor of CYP3A4/5) and ketone reduction. Benzodiazepines such as midazolam, alprazolam or triazolam should not be combined with either of the two new antivirals because of increased blood levels and sedative effects. Carbamazepine and St. John’s wort as strong inducers of the CYP3A4 and should not be combined with telaprevir or boceprev (reduced blood levels, reduced effects). Citalopram and escitalopram can be combined with the new antivirals, but a lowered blood concentration around 35% was reported for escitalopram with telaprevir. During treatment of sleep disturbances with zolpidem, blood levels can be reduced up to 50%. For antipsychotic treatment, olanzapine, and for antiepileptic therapy, levetiracetam, gabapentine, and pregabalin, are recommended based on the low rate of interactions. Up to date information about possible drug–drug interactions should be considered for in the management of IFN-α side effects (e.g., www.hep-druginteractions.org).

New antivirals and IFN-α

- The new drugs do not reduce the side-effect profile of PegIFNα and ribavirin (Recommendation A2)
- The new antivirals may shorten treatment to 24 weeks, reducing the duration of IFN-α-associated side effects (Recommendation A2)
- Although many important antidepressants do not interact with CYP3A, pharmacological management of depression will be more difficult (Recommendation C2)
- There are many possible drug-drug interactions with common psychiatric medications (hypnotics, antidepressants, antipsychotics, methadone, buprenorphine, antiepileptics) and more specific data are required (Recommendation C1)

Conflict of interest

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Meeting Report


