Interferon-Induced Depression in Chronic Hepatitis C: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: To carry out a systematic review of the risk factors for, and incidence of, major depressive episode (MDE) related to antiviral therapy for chronic hepatitis C.

Data Sources: The MEDLINE, PsycINFO, and Cochrane databases were searched to locate articles published from the earliest available online year until June 2011 using the keywords *hepatitis C, interferon-alpha, peginterferon, pegylated interferon, depression,* and *mood* and Boolean operators. Articles written in English, Spanish, and French were included.

Study Selection: Prospective studies reporting incidence of interferon-alpha–induced MDE were included. At baseline, patients did not present a *DSM-IV/ICD* depressive episode, and evaluation was performed by a trained clinician. Twenty-six observational studies met the inclusion criteria.

Data Extraction: Extracted data included authors, year of publication, design, characteristics of the population, viral coinfection, adjunctive psychopharmacology, instruments to assess depression, dose and type of interferon-alpha, adjunctive ribavirin treatment, and follow-up time. Outcome of incidence of MDE (primary outcome measure) was abstracted, as were potential predictive variables.

Data Synthesis: A full review was performed. Meta-analysis of the cumulative incidence of induced MDE as a function of time was carried out. Odds ratios (ORs) and mean differences were used to estimate the strength of association of variables.

Results: Overall cumulative incidence of depression was 0.25 (95% CI, 0.16 to 0.35) and 0.28 (95% CI, 0.17 to 0.42) at 24 and 48 weeks of treatment, respectively. According to our analysis, high baseline levels of interleukin 6 (mean difference = 1.81; 95% CI, 1.09 to 2.52), female gender (OR = 1.40; 95% CI, 1.02 to 1.91), history of MDE (OR = 3.96; 95% CI, 2.52 to 6.21), history of psychiatric disorder (OR = 3.18; 95% CI, 1.60 to 6.32), subthreshold depressive symptoms (mean difference = 0.96; 95% CI, 0.31 to 1.61), and low educational level (mean difference = –0.99; 95% CI, –1.59 to –0.39) were predictive variables of MDE during antiviral treatment.

Conclusions: One in 4 chronic hepatitis C patients who start interferon and ribavirin treatment will develop an induced major depressive episode. Clinicians should attempt a full evaluation of patients before starting antiviral treatment in order to identify those at risk of developing interferon-induced depression.

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Hepatitis C virus infection represents a public health problem that affects 130–170 million people worldwide.[1] Its prevalence is between 1% and 3% in the European population and is as high as 15% in some countries, such as Egypt.[2,3]

Although the infection may take decades to progress, a significant proportion of patients may develop liver cirrhosis or hepatocellular carcinoma.[4] Today, hepatitis C virus infection is the main cause of cirrhosis and the main indication for liver transplant worldwide.[5]

Currently, the approved treatment for chronic hepatitis C is the combination of pegylated interferon-alpha and antiviral ribavirin.[6] Interferon-alpha is an endogenous cytokine that modulates the immunologic system and is involved in many antiviral functions. Ribavirin is an oral nucleoside analog with a broad activity against viral pathogens.[7] Since the introduction of the combined treatment in the late 1990s, and with the use of pegylated interferon-alpha, the sustained virologic response has increased above 50%,[8–10] though it varies considerably depending on the virus genotype and other factors.[11,12] Recently, studies that added a protease inhibitor drug like telaprevir or boceprevir to the standard treatment in patients with viral genotype 1 showed significantly higher sustained virologic response rates of up to 75%.[13,14]

Antiviral treatment has a high profile of side effects including fatigue, insomnia, irritability, and low mood, and a full major depressive episode (MDE) is often observed. Depression associated with antiviral treatment is usually called *interferon-induced depression*.[15] Detecting and properly treating interferon-induced depression according to current guidelines and monitoring clinical issues[16] are essential because depressive patients often show poor quality of life,[17] suicide ideation,[18] and lack of treatment adherence.[19] Depressive symptoms are common in the early stages of treatment and reach a peak between 4 and 16 weeks.[20–22]

The exact neurobiological basis of interferon-induced depression is not known, but there is evidence that when an exogenous cytokine like interferon-alpha is administered certain proinflammatory cytokines are activated, causing alterations in brain apoptotic mechanisms and in neurotransmission.[23,24] Similar neurobiological alterations have been observed in noninduced major depression and may account for the presence of clinical depression in patients treated with interferon-alpha and ribavirin.[25,26]

Some patients may be more "vulnerable" to depression than others. In recent years, many studies have tried to detect different risk factors associated to the development

of neuropsychiatric side effects during antiviral treatment.[27] The identification of risk factors for depression may help to detect "high-risk" patients who may benefit from additional psychological support[28] or from the prophylactic administration of selective serotonin reuptake inhibitors to reduce the likelihood of depressive symptoms during antiviral treatment.[29] Several studies identified clinical variables, such as presence of depressive symptoms at baseline, that were risk factors for development of depression during antiviral treatment.[43,54,55] However, risk factors reported vary widely from study to study.[20,22] Reported rates of interferon-induced depression ranged from 0% to 90%.[21,30] The large variability in the reported depression and risk factors may be due in part to the different characteristics of the samples, but may also be due to inadequate study design or the use of different methodological approaches.[31] Several studies[69,70] of risk factors for interferon-induced depression did not use validated methods to measure depressive symptoms, and others[71] reported an MDE diagnosis using depression scales without further clinical confirmation based on *DSM*/*ICD* criteria. Depression scales are very useful for screening depression, measuring depression severity, and reporting individual symptoms and changes over time, but clinical confirmation of the condition is needed for diagnosis of a full MDE. Some authors argue that studies that report depression based on *DSM* criteria may underestimate depression rates because they miss patients with clinical depressive symptoms who do not fulfill criteria for a *DSM* major depressive episode.[31] However, studies that establish the diagnosis of depression via a clinical interview and apply strict *DSM*/*ICD* criteria may be more likely to identify a more homogeneous group of patients, particularly those with more severe depression, who require specific clinical supervision or antidepressant treatment.

The objectives of this study were to perform a systematic review and meta-analysis of data that could help in assessing the incidence of MDE during antiviral treatment in patients diagnosed with chronic hepatitis C and to identify the risk factors related to interferon-induced depression. These assessments may be of special interest for clinicians, allowing detection of patients at risk and improving knowledge of depression related to antiviral treatment.

METHOD

Data for this systematic review were collected with an advanced document protocol in accordance with the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines.[32] This proposal provides a checklist for reporting outcomes of reviews based on observational studies.

All steps in the literature search, study identification, study selection, quality assessment, and data extraction were performed independently by 2 investigators from different subspecialties, psychiatry and psychology (M.U. and P.C.). The interrater agreement κ statistic was 0.79.[33] Disagreements were resolved by discussion, and consensus was achieved in the selection of articles for analysis.

Clinical Points

- Incidence of depression during interferon-alpha and ribavirin treatment is substantial; 1 out of 4 patients with chronic hepatitis C who start antiviral treatment will develop an induced major depressive episode.
- Baseline levels of interleukin-6, female gender, history of depression or psychiatric disorder, subthreshold depressive symptoms, and low educational level are predictive variables of interferon-induced depression.
- Before starting antiviral treatment, clinicians should assess patients at risk of developing interferon-induced depression. During the treatment, a comprehensive assessment and management of depression must be performed.

Data Sources

A comprehensive, computerized literature search was conducted in MEDLINE, PsycINFO, and the Cochrane Library. We searched for the relevant studies published from the earliest available online year until June 2011, using the following phrase and Boolean logic algorithm: "Hepatitis and C and (Interferon-alpha or Peginterferon or (Pegylated and Interferon)) and (Depression or Mood)." We also searched for any additional studies in the reference lists of the articles identified. Only articles written in English, Spanish, and French were included.

The titles and abstracts were examined, and full-text articles of potentially relevant studies were obtained. After that, inclusion and exclusion criteria were applied, and the selected articles were included in the systematic review. See (eAppendix 1) at PSYCHIATRIST.COM for references of excluded articles.

Study Selection

Articles were reviewed using the following inclusion criteria: (1) original prospective study reporting full results of the incidence of interferon-induced MDE, (2) detailed description of methods and methodological background that evaluated MDE using a validated instrument or a semistructured interview performed by a trained clinician based on *DSM* criteria, (3) sample size > 10 subjects, (4) psychiatric evaluation before starting the treatment and a good description of subjects selected, and (5) euthymia at baseline, not fulfilling criteria for a *DSM-IV*/*ICD* depressive episode.

The following exclusion criteria were applied: (1) articles focused on a population subgroup, ie, patients in maintenance methadone treatment; (2) cross-sectional studies; (3) articles with overlapping samples; and (4) treatment-intervention studies.

Quality Assessment

To assess the studies included in this systematic review, we produced a checklist based on an instrument developed

to assess the quality of nonrandomized studies (Newcastle-Ottawa Scale)[34] and guidelines for reporting observational studies (Strengthening the Reporting of Observational Studies in Epidemiology [STROBE]).[35] We used a 10-item checklist with a total possible score of 20 points (scores ≥ 15 indicating high quality, < 15 indicating low quality) with 3 optional answers (0 = no; 1 = in part; 2 = yes). The checklist assessed the following: aims explicitly stated, representativeness of the sample, inclusion/exclusion criteria stated, reliability and validity of measures justified, rates of response and dropout specified, data adequately described, statistical significance assessed, generalizability discussed, and null findings interpreted.

Summary Measures (outcomes)

The primary outcome measure was the incidence of interferon-induced MDE based on *DSM*/*ICD* criteria throughout the follow-up period.

The secondary outcome was the evaluation of the predictive factors at baseline of interferon-induced MDE, including biological parameters, demographic and social factors, clinical issues, and treatment-related factors.

Data Extraction

Data were independently abstracted by both reviewers. We recorded author, year of publication, design, characteristics of the study population, viral coinfection, adjunctive psychopharmacology, instruments to assess depression, dose and type of interferon-alpha, adjunctive ribavirin treatment, and follow-up time. Outcome of incidence of MDE was abstracted, and potential predictive variables among those analyzed in the articles were selected for the risk factor group.

Statistical Analysis

A meta-analysis of the cumulative incidence of induced MDE as a function of time was carried out. It was estimated by means of a random effects model for treatment after weeks 4, 8, 12, 16, 24, and 48. For the sake of homogeneity, only those studies that had used ribavirin and did not exclude patients with a personal history of psychiatric disorder were considered.

The odds ratio (OR) with 95% CI was used to estimate the strength of association of dichotomous variables. For continuous variables (age and years of education), we used mean differences with 95% CI. Because depressive and anxiety symptoms at baseline were evaluated with different scales, we used the standard mean difference to assess the strength of association. Heterogeneity between trials was assessed using both the χ^2 and I^2 tests. Between-study heterogeneity was considered to be significant for $P < .10$. If there was no heterogeneity, a fixed model was used. If there was heterogeneity, a random effects model was used.[36]

Publication bias was examined in a funnel plot of log OR against its standard error using Begg's test,[37] and the degree of asymmetry was tested statistically using Egger's unweighted regression asymmetry test.[38]

Statistical analyses were performed using SPSS (version 15.0 for Windows; SPSS, Inc; Chicago, Illinois) and Review Manager (RevMan, Version 5.0; The Nordic Cochrane Centre, Copenhagen, Denmark; The Cochrane Collaboration, Oxford, United Kingdom, 2008). In addition, the meta-analysis of the cumulative incidences was carried out with R (R Foundation for Statistical Computing), version 2.12.2, specifically using the contributed package "meta."[39]

RESULTS

Characteristics and Quality of the Studies

Using keywords, 627 articles were identified and titles and abstracts were examined. At this stage, 462 articles were eliminated because they did not meet a priori the selection criteria. We further identified 10 articles through cross-referenced bibliographies and obtained 175 potentially relevant papers, which were thoroughly examined. One hundred fifty articles were rejected because inclusion criteria were not met, and 26 different articles were selected and set for at least 1 of the 2 groups of the review, 22 for the MDE incidence group[20,22,30,40–58] and 17 for the risk factor group[20,22,40–44,47,48,54–56,58–62] (Figure 1). Selected studies were published between 1999 and 2011, and all were reported in English.

We found no randomized controlled trials of antiviral treatment evaluating clinical *DSM-IV* depression. All studies selected used a prospective cohort design, and 2 studies included a nonrandomized control group. Eighteen articles scored 15 or more, indicating good quality. Seven articles scored 14 or less. The older studies appeared to be of lower quality. Characteristics and quality score of the articles selected were reported (Table 1).

Incidence of Depression

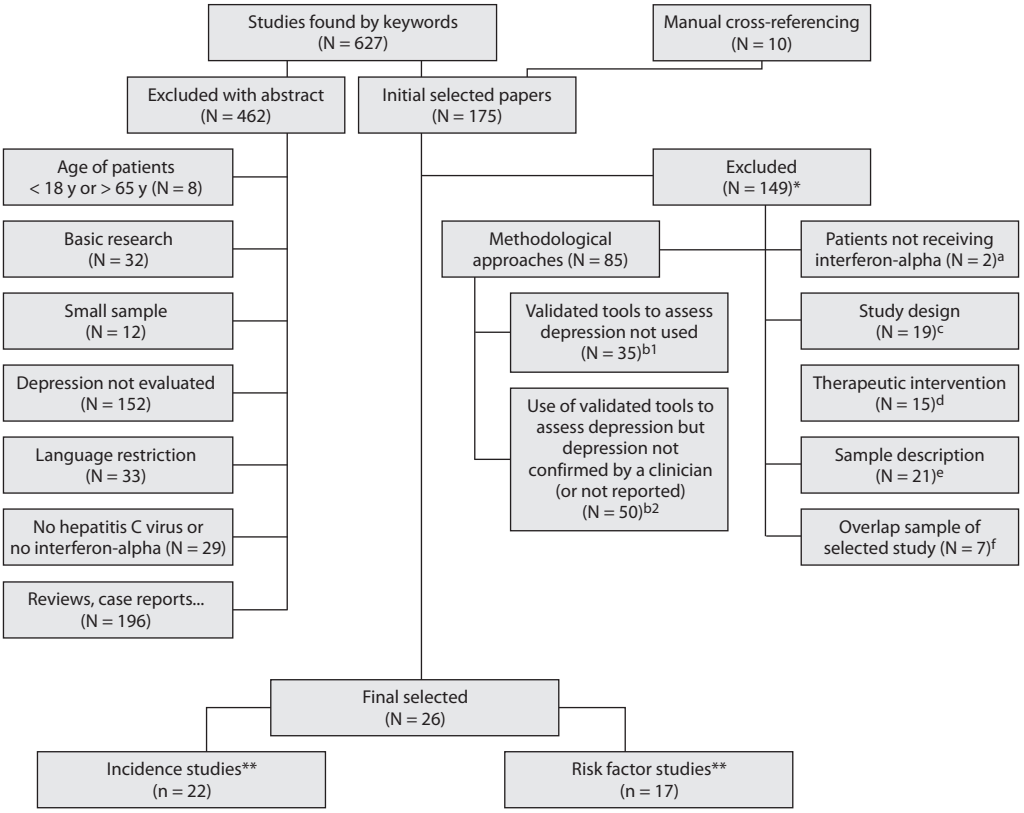
All studies established depression diagnoses using *DSM* criteria and excluded patients who presented a depressive episode before starting treatment.

The cumulative incidence of depression was reported at weeks 4, 8, 12, 16, 24, and 48 after treatment initiation (Table 2). To most closely represent common clinical practice, we estimated incidence by selecting studies that did not exclude patients who had a past psychiatric history and had used ribavirin in the therapy. Including a total of 957 patients, we estimated an overall cumulative incidence of 0.28 (95% CI, 0.167 to 0.417) at 48 weeks, observing a peak of new cases of depression between 4 and 12 weeks of treatment. Duration of treatment varied between 24 and 48 weeks depending on the patient, but cumulative incidence was slightly higher at 48 weeks, suggesting that few new cases of induced depression occur after 24 weeks of treatment (Figure 2).

Risk Factors

We performed a review using data extracted from the studies included in the risk factor group. As reported in Table 3, meta-analysis was performed in variables that were evaluated in more than 1 article and were reported using similar data.

Figure 1. Flowchart of the Studies Considered and Finally Selected for Review



*Superscripted footnotes *a* through *f* refer to the full references for excluded articles, available in eAppendix 1 at PSYCHIATRIST.COM.
**Some articles were included in both risk factor studies and incidence studies groups.

Demographic and Social Factors

Epidemiologic factors were studied in depth as predictors of interferon-induced depression. We included 8 studies[20,22,43,44,54–56,58] involving 762 patients to evaluate age as a predictive variable for MDE. The results showed that age was not a significant risk factor for developing a depressive episode during interferon treatment (mean difference = 0.31; 95% CI, −0.36 to 0.97).

Gender was a potential variable for predicting interferon-induced depression according to our analysis using 10 studies[20,22,40,43,44,48,54–56,58] with 845 patients. Female gender was a weak predictive variable for developing MDE during treatment (OR = 1.40; 95% CI, 1.02 to 1.91) (Figure 3).

Race was not a predictive variable of MDE according to our meta-analysis of 3 studies[43,55,56] and 216 patients. Being Caucasian (164 of the 216 patients) was not a risk factor for developing a depressive episode during treatment (OR = 0.40; 95% CI, 0.02 to 7.07).

Education was related with depression during interferon treatment. Analysis of 3 articles[20,54,58] and 405 patients showed that low academic level was a predictive variable for developing a depressive episode (mean difference = −0.99; 95% CI, −1.59 to −0.39) (Figure 3). Marital status was not a risk factor (OR = 1.14; 95% CI, 0.53 to 2.45) according to 2 studies[20,58] involving 231 patients.

Clinical Factors

Subclinical depressive symptoms at baseline (measured with validated depression scales) were a frequently identified risk factor for developing MDE during interferon treatment. According to an analysis of 9 studies[20,40,42,43,47,54–56,58] and 777 patients, higher scores on depression scales before starting antiviral treatment predicted subsequent development of depression (mean difference = 0.96; 95% CI, 0.31 to 1.61). The analysis did not estimate the values of 1 article[40] that did not report standard deviation (Figure 3).

Higher scores on baseline anxiety scales were not associated with a higher rate of MDE (mean difference = 0.87; 95% CI, −0.45 to 2.21) according to an analysis of 2 studies[20,47] and 273 patients.

Personal MDD background was evaluated in 5 studies[43,48,54–56] involving 417 patients and was a predictive variable according to our analysis (OR = 3.96; 95% CI, 2.52 to 6.21) (Figure 3).

General psychiatric history (including MDE) was also a predictive variable of interferon-induced depression (OR = 3.18; 95% CI, 1.60 to 6.32) according to the analysis of 2 studies[22,54] and 190 patients. However, previous substance abuse disorder, evaluated in 3 studies[43,54,55] and 308 patients, was not a significant predictive variable for induced depression (OR = 0.02; 95% CI, 0.37 to 2.64) (Figure 3).

Table 1. Characteristics of the Studies Selected

Study	N	Gender	Age, y[a]	Coinfected	Psychotropic Drugs	Includes Past Psychiatric Disorder	Instrument Used (*DSM* diagnoses)	Incidence of MDE (%)	Interferon Type (weekly dose)	Ribavirin (daily dose)	Follow-Up (wk)	Quality Score (0–20)
Miyaoka et al,[40] 1999	60	37 M 23 F	49.9 ± NR	NR	NR	NR	Interview	48.3	Subtypes of IFN-α (NR)	No	24	10
Bonaccorso et al,[41] 2002	30	24 M 6 F	56.2 ± 10.1	No	NR	No	Interview	40.7	IFN-α (9 MU)	No	12	11
Castéra et al,[42] 2002	33	17 M 16 F	44.0 ± 2.2	NR	NR	No	SADS-L	12	IFN-α (9 MU)	No	12	10
Hauser et al,[43] 2002	39	26 M 13 F	44.9 ± 6.9	NR	No	Yes	SCID	33	IFN-α2b (9 MU)	Yes (0.6 g)	24–48	17
Kraus et al,[44] 2002	121	72 M 49 F	41.2 ± 8.9	No	No	No	ADIS-R	11.6	IFN-α2b (15 MU), PegIFN-α (80–150 μg)	80/121 (0.8–1.2 g)	24–48	15
Horikawa et al,[20] 2003	99	54 M 45 F	48.3 ± 12.2	NR	NR	Yes	Interview	23.2	IFN-α, IFN-α2b (18–30 MU)	No	24	13
Amodio et al,[30] 2005	20	NR	Range, 18–60	No	No	Yes	MINI	0	IFN-α (9–18 MU)	Yes (15 mg/kg)	24	12
Russo et al,[45] 2005	18	13 M 5 F	Range, 24–55	NR	No	No	Interview	17	IFN-α, PegIFN-α (100–125 μg)	Yes (1–1.2 g)	8	11
Wichers et al,[22] 2005[b]	16	12 M 4 F	42.0 ± 6.9	No	No	Yes	MINI	31	IFN-α (variable dose), PegIFN-α (variable dose)	Yes (1–1.2 g)	24	16
Castéra et al,[46] 2006	98	51 M 47 F	46.0 ± 12.0	No	Yes	Yes	MINI	17	PegIFN-α2b (1.5 μg/kg)	Yes (0.8–1.2 g)	24	17
Dell'Osso et al,[47] 2007	49	29 M 20 F	49.5 ± NR	No	NR	No	SCID	12	IFN-α, IFN-α2b (9 MU)	Yes (1–1.2 g)	24	15
Lotrich et al,[48] 2007	23	12 M 11 F	45.0 ± NR	No	No	Yes	SCID	39	PegIFN-α2 (NR)	Yes (NR)	12	14
Quarantini et al,[49] 2007[c]	30	25 M 5 F	49.0 ± 7.7	No	NR	No	MINI	10	IFN-α (9–18 MU)	Yes (0.9–1.2 g)	24	15
Robaeys et al,[50] 2007	49	38 M 11 F	37.0 ± NR	No	NR	Yes	Interview	38	PegIFN-α2b (1.5 μg/kg), PegIFN-α2a (9 MU)	Yes (1–1.2 g)	24–48	17
Schäfer et al,[51] 2007	101	53 M 48 F	39.9 ± 10.0	No	No	No	Interview	11.9	IFN-α2b (80–150 μg)	Yes (1–1.2 g)	24	16
Fontana et al,[52] 2008[c]	150	112 M 38 F	50.15 ± 8.0	NR	Yes	Yes	CIDI	21	PegIFN-α2a (180 μg)	Yes (0.8–1.2 g)	24	18
Pawelczyk et al,[53] 2008	Cases n = 26	19 M 7 F	42.8 ± 10.8	NR	No	Yes	MINI	30	PegIFN-α2b (80–150 μg), PegIFN-α2a (90–180 μg)	Yes (0.8–1.2 g)	12	16
	Controls n = 21	12 M 9 F	44.1 ± 12.0					0				
Castellví et al,[54] 2009	174	103 M 71 F	44.4 ± 10.6	No n = 130 HIV n = 44	Yes	Yes	SCID	42	PegIFN-α2a (180 μg), PegIFN-α2b (80 μg)	Yes (0.8–1.2 g)	24–48	19
Prather et al,[55] 2009	95	64 M 31 F	47.3 ± 1.5	No	No	Yes	SCID	22	PegIFN-α2b, PegIFN-α2a (120–150 μg)	Yes (NR)	16	18
Franzen et al,[56] 2010[b]	86	57 M 29 F	47.4 ± 12.4	No	Yes	Yes	SCID	19	PegIFN-α2 (NS dose)	Yes (NR)	16	17
Raison et al,[57] 2010	Cases n = 20	12 M 8 F	47.6 ± 6.3	NR	No	No	SCID	20	PegIFN-α2a, PegIFN-α2b (NR)	Yes (NR)	12	17
	Controls n = 13	6 M 7 F	46.8 ± 6.6					0				
Su et al,[58] 2010	132	82 M 50 F	49 ± 12.0	NR	No	Yes	MINI	28	PegIFN-α2b (1.5 μg/kg)	Yes (0.8–1.2 g)	24	18

[a]Age data expressed as mean ± SD unless otherwise indicated. [b]Four articles were selected to study risk factors but not to study incidence due to overlapping samples.[59–62] Characteristics of these articles were similar to the studies of Wichers et al[22] or Franzen et al.[56] [c]Sample based in previous antiviral treatment nonresponders.

Abbreviations: ADIS-R = Anxiety Disorders Interview Schedule Revised, CIDI = Composite International Diagnostic Interview, *DSM* = *Diagnostic and Statistical Manual of Mental Disorders*, F = female, HIV = human immunodeficiency virus, IFN-α = interferon-alpha, Interview = semistructured clinical interview, M = male, MDE = major depressive episode, MINI = Mini-International Neuropsychiatric Interview, MU = million units, NR = not reported, PegIFN-α = pegylated interferon-alpha, SADS-L = Schedule for Affective Disorders and Schizophrenia-Lifetime, SCID = Structured Clinical Interview for *DSM-IV*.

Table 2. Cumulative Incidence of Interferon-Induced Depression in the Studies Selected

Study	N	Cumulative Incidence [95% CI] 4 Weeks	8 Weeks	12 Weeks	16 Weeks	24 Weeks	48 Weeks
Studies that do not specify patients with past psychiatric history and use monotherapy with interferon-alpha							
Miyaoka et al,[40] 1999	60					0.48 [0.35–0.62]	
Studies that exclude patients with past psychiatric history and use combined treatment with interferon-alpha and ribavirin							
Bonaccorso et al,[41] 2002	30			0.4 [0.23–0.59]			
Castéra et al,[42] 2002	33			0.12 [0.03–0.28]			
Kraus et al,[44] 2002	121						0.12 [0.07–0.20]
Russo et al,[45] 2005	18		0.17 [0.04–0.41]				
Quarantini et al,[49] 2007	30					0.10 [0.02–0.26]	
Schäfer et al,[51] 2007	23					0.13 [0.03–0.34]	
Raison et al,[57] 2010	20			0.20 [0.06–0.44]			
Overall cumulative incidence				*0.24 [0.1–0.42]*		*0.13 [0.05–0.23]*	
Studies that do not exclude patients with past psychiatric history and use monotherapy with interferon-alpha							
Horikawa et al,[20] 2003	99	0.06 [0.02–0.13]	0.17 [0.04–0.41]	0.19 [0.12–0.28]	0.21 [0.14–0.30]	0.23 [0.15–0.33]	
Studies that do not exclude patients with past psychiatric history and use the combination treatment of interferon-alpha and ribavirin							
Hauser et al,[43] 2002	39	0.03 [0.01–0.13]	0.15 [0.05–0.30]	0.23 [0.11–0.39]	0.26 [0.13–0.42]	0.31 [0.17–0.48]	0.33 [0.19–0.50]
Amodio et al,[30] 2005	20	0.0 [0–0.17]	0.0 [0–0.17]	0.0 [0–0.17]	0.0 [0–0.17]	0.0 [0–0.17]	
Wichers et al,[22] 2005	16					0.31 [0.11–0.59]	
Castéra et al,[46] 2006	98						0.17 [0.10–0.26]
Dell'Osso et al,[47] 2007	49						0.12 [0.05–0.25]
Lotrich et al,[48] 2007	23			0.39 [0.20–0.61]			
Robaeys et al,[50] 2007	49						0.38 [0.25–0.54]
Fontana et al,[52] 2008	150	0.02 [0–0.06]		0.07 [0.04–0.12]		0.21 [0.15–0.29]	
Pawelczyk et al,[53] 2008	26			0.30 [0.14–0.52]			
Castellví et al,[54] 2009	174	0.20 [0.14–0.27]		0.31 [0.24–0.38]		0.38 [0.31–0.45]	0.42 [0.34–0.50]
Prather et al,[55] 2009	95				0.22 [0.14–0.32]		
Franzen et al,[56] 2010	86				0.19 [0.11–0.28]		
Su et al,[58] 2010	132					0.28 [0.21–0.36]	
Overall cumulative incidence		*0.06 [0–0.18]*	*0.07 [0–0.29]*	*0.20 [0.09–0.34]*	*0.17 [0.08–0.28]*	*0.25 [0.16–0.35]*	*0.28 [0.17–0.42]*

History of subclinical manic symptoms was evaluated in only 1 article[47] and may be a predictive variable of MDE. In that study, patients with subthreshold lifetime manic symptoms (higher scores on the self-report version of the Structured Clinical Interview for Mood Spectrum) were more likely to develop MDE during interferon treatment.

Another factor to take into account was the role of personality traits in the development of interferon-induced depression. Three studies[48,54,60] associated personality traits with induced depression, suggesting that individuals with higher neuroticism, lower agreeableness, or lower self-directedness may be more likely to suffer depression.

Finally, 2 recent studies[48,55] showed that sleep alterations (bad sleep quality measured with the Pittsburgh Sleep Quality Index) may be an important predictor of depression.

Biological Factors

Two[55,59] of the selected articles studied pretreatment levels of circulating cytokines as a predictor for developing MDE during interferon-alpha treatment and were included in the meta-analysis. Considering a total of 116 patients, those with higher serum levels of interleukin 6 (IL-6) were more likely to present a depressive episode (mean difference = 1.81; 95% CI, 1.09 to 2.52) (Figure 3).

One study[59] also evaluated baseline levels of IL-10 and soluble interleukin-2 receptor (sIL-2R), which were higher in patients who developed MDE during treatment.

Genetic findings were reported in individual studies, and meta-analyses were not performed. One recent study[58] showed that polymorphisms of phospholipase A (PLA2) and cyclooxygenase 2 (COX2) may increase the risk of interferon-induced depression, specifically in those with the AG polymorphism of COX2 (rs4648308) and those with the GG polymorphism of PLA2 (rs10798052), both of which presented lower levels of polyunsaturated fatty acids. Two studies showed no association between depression and

Figure 2. Cumulative Incidence of Depression: Studies That Included Patients With a Psychiatric History and Treated With Interferon and Ribavirin

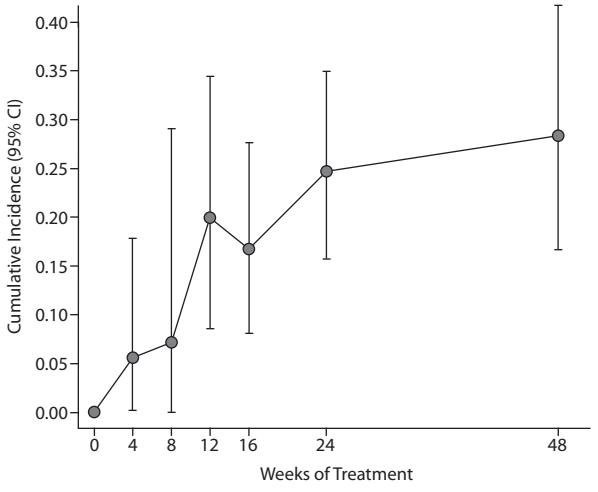


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Table 3. Risk Factors for Interferon-Induced Depression Evaluated

Risk Factor	Evidence For	Evidence Against	Evidence According to This Meta-Analysis[a]		
			Risk for Depression	OR/Mean Difference	95%CI
Advanced age	Horikawa et al,[20] 2003	Miyaoka et al,[40] 1999; Hauser et al,[43] 2002; Kraus et al,[44] 2002; Wichers et al,[22] 2005; Castellví et al,[54] 2009; Prather et al,[55] 2009; Franzen et al,[56] 2010; Su et al,[58] 2010	No	0.31	−0.36 to 0.97
Female gender		Miyaoka et al,[40] 1999; Hauser et al,[43] 2002; Kraus et al,[44] 2002; Horikawa et al,[20] 2003; Wichers et al,[22] 2005; Lotrich et al,[48] 2007; Prather et al,[55] 2009; Castellví et al,[54] 2009; Su et al,[58] 2010; Franzen et al,[56] 2010	**Yes**	**1.40**	**1.02 to 1.91**
Race (Caucasian)	Hauser et al,[43] 2002	Prather et al,[55] 2009; Franzen et al,[56] 2010	No	0.40	0.02 to 7.07
Low education	Castellví et al,[54] 2009	Horikawa et al,[20] 2003; Su et al,[58] 2010	**Yes**	**−0.99**	**−1.59 to −0.39**
Marital status (single)		Horikawa et al,[20] 2003; Su et al,[58] 2010	No	1.14	0.53 to 2.45
Depressive symptoms at baseline	Miyaoka et al,[40] 1999; Castéra et al,[42] 2002; Hauser et al,[43] 2002; Castellví et al,[54] 2009; Prather et al,[55] 2009; Franzen et al,[56] 2010	Horikawa et al,[20] 2003; Dell'Osso et al,[47] 2007; Su et al,[58] 2010	**Yes**	**0.96**	**0.31 to 1.61**
Anxiety symptoms at baseline		Horikawa et al,[20] 2003; Dell'Osso et al,[47] 2007	No	0.87	−0.45 to 2.21
Personal MDE history	Prather et al,[55] 2009; Castellví et al,[54] 2009; Franzen et al,[56] 2010	Hauser et al,[43] 2002; Lotrich et al,[48] 2007	**Yes**	**3.96**	**2.52 to 6.21**
General psychiatric history	Castellví et al,[54] 2009	Wichers et al,[22] 2005	**Yes**	**3.18**	**1.60 to 6.32**
History of subclinical manic symptoms	Dell'Osso et al,[47] 2007		…	…	…
Personality traits	Lotrich et al,[48] 2007; Castellví et al,[54] 2009; Lotrich et al,[60] 2009		…	…	…
Sleep alterations	Lotrich et al,[48] 2007; Prather et al,[55] 2009		…	…	…
High baseline cytokine levels	Wichers et al,[59] 2006; Prather et al,[55] 2009		**IL-6: Yes** IL-10, sIL-2R: NP[a]	**1.81**	**1.09 to 2.52**
Genetic polymorphisms	*PLA2* gene: Su et al,[58] 2010 *COX2* gene: Su et al [58] 2010 *5HTTLPR* gene: Lotrich et al,[60] 2009	*IL-28* gene: Lotrich et al,[62] 2010 *TNF-α* gene: Lotrich et al,[61] 2010	NP[a]	…	…
Interferon dose		Horikawa et al,[20] 2003	NP[a]	…	…

[a]Meta-analysis was not performed in case of heterogeneity of data extracted or in variables reported by a single study. Bold indicates significant predictor of MDE during antiviral treatment. Ellipses indicate no test performed.
Abbreviations: IL = interleukin, MDE = major depressive episode, OR = odds ratio, sIL-2R = soluble interleukin-2 receptor.

polymorphisms of tumor necrosis factor-α[61] and IL-28[62] genes. Furthermore, polymorphisms of the functional 5′ promoter of the serotonin transporter gene (*5-HTTLPR*) were also studied, and results showed that patients with a long allele (*L*) in the *5-HTTLPR* gene were less likely to present MDE than those with the short allele (*S*).[60]

Treatment-Related Factors

As regards types of interferon, there was little evidence regarding their roles, and no meta-analysis was performed. One selected study[20] involving 99 patients found no differences in depression incidence in patients treated with higher doses of interferon (6 MU/d [million units/d] vs 10 MU/d) or in those treated with different kinds of interferon (natural interferon-alpha vs recombinant interferon-alpha 2b).

Heterogeneity and Publication Bias

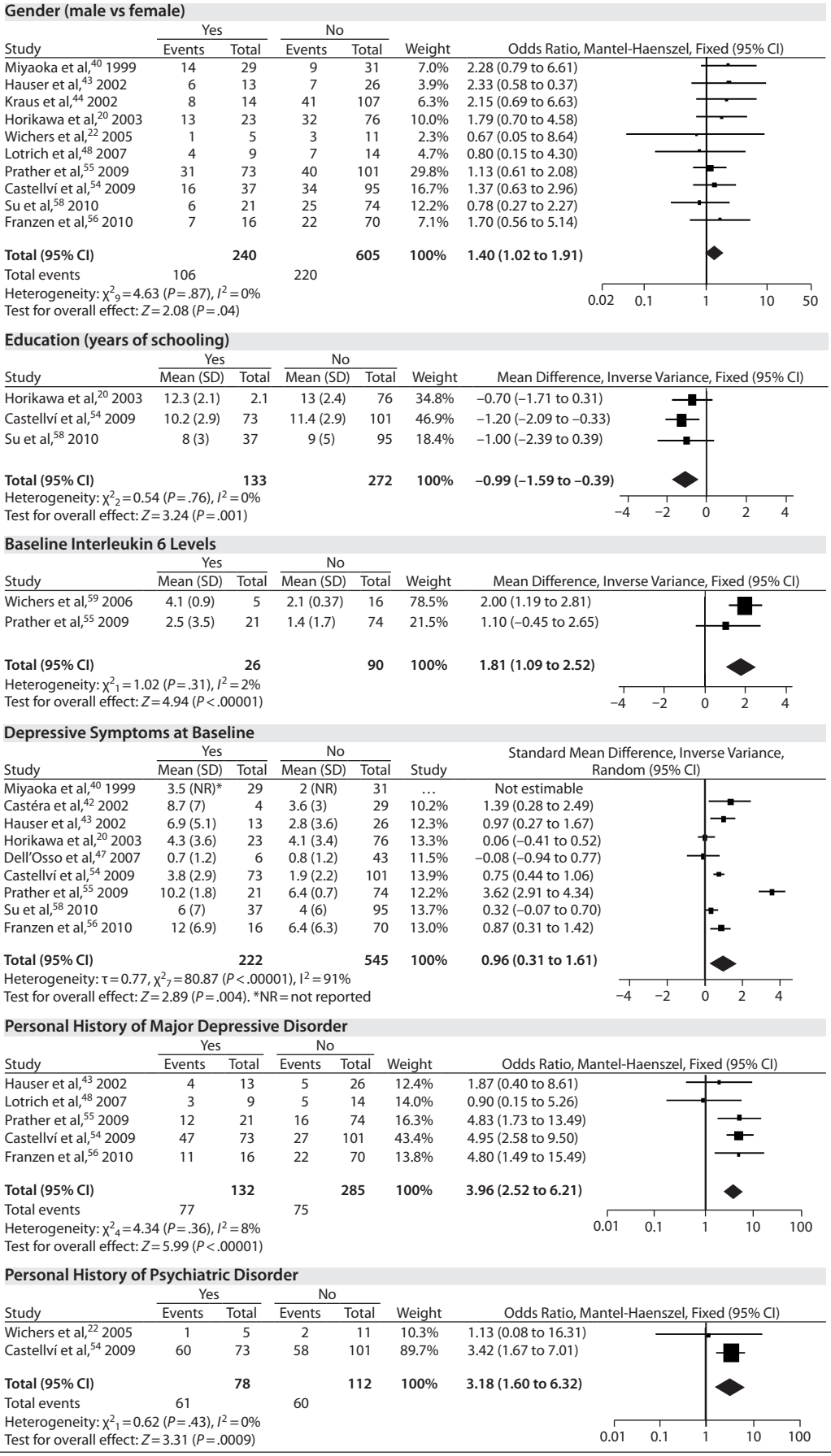
Heterogeneity in the reported incidence of depression was observed between studies. Significant heterogeneity was identified only in comparisons of baseline depressive score ($\chi^2 = 16.02$, $P < .001$) and race variables ($\chi^2 = 16.02$, $P < .001$), justifying the use of random effects models. We did not find significant heterogeneity between studies with respect to the other variables evaluated.

Publication bias was not identified among the studies, as demonstrated by funnel plots.

DISCUSSION

In this systematic review and meta-analysis, we report a cumulative incidence of MDE during interferon treatment of 25% at 24 weeks after initiation and 28% after 48 weeks. No patients were depressed before starting treatment. The results suggest that 1 out of 4 patients starting combined treatment with interferon-alpha and ribavirin may develop a full major depressive episode. Most of the new cases of depression were observed during the first 12 weeks of treatment, suggesting that the beginning of treatment is a period that may require comprehensive monitoring and clinical supervision. The confidence interval of incidence values is

Figure 3. Risk Factors for Interferon-Alpha–Induced Depression



quite wide due to the heterogeneity in the reported cumulative incidence between studies.

In this study, several potential predictive variables of interferon-induced depression were reviewed. Age was not a risk factor according to our analysis, but female gender and low education were associated with interferon-induced depression. Clinical factors such as baseline subthreshold depressive symptoms were also associated with a higher incidence of MDE during treatment together with the presence of a past depressive or psychiatric disorder. Although some variables such as personality traits, sleep disturbances, or subthreshold manic symptoms were not included in the meta-analysis, they have been reported as risk factors for induced depression in some studies, emphasizing the fact that more research is needed to replicate and increase the evidence on data of this kind. Finally, it must be said that the risk factors reported are similar to those found in non-induced MDE.[63–65] The incidence of common depression is higher in females[63] and in patients with personality traits of neuroticism or lower self-directedness.[64,65] Furthermore, subthreshold depressive symptoms and depression background increase the risk of developing a new depressive episode, as observed in large epidemiologic studies.[66]

Biological parameters may play an important role in the development of MDE during treatment. An increased baseline IL-6 level was a predictive variable for depression in our analysis, and individual studies also showed that other cytokines (IL-10, sIL-2R) or polymorphisms related with the immunologic system such as COX2 and PLA2 may be linked with MDE. These findings support the hypothesis that alterations of the immune system may be linked with depression. Changes in inflammatory modulation and enhancement of proinflammatory markers (such as IL-6) may cause numerous changes in neuroplasticity and neurotransmitter pathways, which may culminate in a depressive episode.[23] Similarly, a recent meta-analysis of cytokines in MDE showed that depressive patients presented higher levels of IL-6 compared with control subjects.[67] However, considering the lack of replicated results and the small sample of patients included in our analysis, more studies designed to study cytokines and other biological parameters are needed.

Before starting treatment with interferon and ribavirin, clinicians should conduct a full clinical evaluation of patients, addressing sociodemographic data, exploring clinical and psychiatric history, and evaluating baseline depressive symptoms with validated scales. Considering the high incidence of depression, a comprehensive evaluation of all patients should be performed. Detecting and individualizing follow-up in high-risk patients may be useful, involving teamwork between different specialists[28] and even prophylactic antidepressant treatment in some cases.[29,68] The results clearly emphasize that patients with a psychiatric history or baseline depressive symptoms are more likely to develop interferon-induced depression. At present, the evidence for recommending screening of biological parameters such as serum IL-6 levels or certain polymorphisms in all patients starting interferon and ribavirin therapy is probably insufficient, but it may become a valid option soon depending on the results of future research.

CONCLUSIONS

One in 4 chronic hepatitis C patients who start interferon and ribavirin treatment will develop an induced major depressive episode. Before starting antiviral treatment, clinicians should assess patients at risk of developing interferon-induced depression. During the treatment, a comprehensive assessment and management of depression must be performed.

Future research should focus on the study of potential predictive variables of depression that have not been assessed in depth in the literature and take the emergence of new treatment regimens into account. New studies on identifying biological factors related with depression may focus on evaluation of cytokines such IL-6 or IL-10 or on genetic markers related to inflammation pathways and serotonin neurotransmission. The evaluation of biological variables is especially urgent, considering the small sample sizes in the studies carried out to date and the lack of conclusive results.

Limitations

This study has several limitations. Observational studies have limited methodological quality. However, performing a systematic review and meta-analysis of observational studies can help to increase scientific evidence. The MOOSE methodology has been accepted as an alternative when few RCTs have been performed and observational studies with a similar design are available.[32] Another limitation of the analysis is the introduction of a measurement bias. All selected studies performed clinical diagnosis of depression based on *DSM* criteria, but the diagnostic instruments (structured interview, Mini-International Neuropsychiatric Interview, Schedule for Affective Disorders and Schizophrenia-Lifetime, Structured Clinical Interview for *DSM-IV*, or Anxiety Disorders Interview Schedule Revised) were slightly different.

Moreover, we observed heterogeneity with respect to characteristics of the samples between studies. We tried to minimize this problem by reporting potential confounding variables like age, gender, coinfection, use of psychopharmacology before treatment, exclusion of patients with psychiatric history, interferon dose and type, and cotreatment with ribavirin. To increase homogeneity and maximize the focus on current clinical practice, we estimated the incidence of depression using studies that did not exclude patients with past psychiatric history and that used combination therapy with interferon and ribavirin. Lastly, observational studies are likely to present significant publication bias. It is possible that susceptive predictive variables of depression were not published when the variable was not related to depression. However, we assessed this potential publication bias using the Begg-Egger funnel plots.

Drug names: boceprevir (Victrelis), methadone (Methadose and others), ribavirin (Rebetol, Copegus, and others), telaprevir (Incivek).

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Supplementary material: eAppendix 1 is available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Interferon-Induced Depression in Chronic Hepatitis C: A Systematic Review and Meta-Analysis

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DOI Number: 10.4088/JCP.12r07694

List of Supplementary Material for the article

1. eAppendix 1 References of excluded articles

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

eAppendix 1. References of excluded articles

A) Not VHC or not IFN

1. Maddock C, Baita A, Orrù MG, et al. Psychopharmacological treatment of depression, anxiety, irritability and insomnia in patients receiving interferon-alpha: a prospective case series and a discussion of biological mechanisms. *J Psychopharmacol*. 2004;18(1):41-46.
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B) Methodological

B1. Validated tools to assess depression not used

3. Renault PF, Hoofnagle JH, Park Y, et al. Psychiatric complications of long-term interferon alfa therapy. *Arch Intern Med.* 1987 Sep;147(9):1577-1580.
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C) Study design

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D) Therapeutic intervention

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E) Sample description

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F) Overlap sample

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