Estudi de la incidència, factors de risc (sociodemogràfics, clínics i genètics), i resposta al tractament profilàctic amb antidepressius de la depressió induïda per interferó alfa en la hepatitis C crònica

Marc Udina i Bonet

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Presentació de la tesi

L'estudi dels símptomes neuropsiquiàtrics relacionats amb altres malalties mèdiques o amb tractaments farmacològics pot ser d'interés per a comprendre millor els mecanismes fisiopatològics subjacents als trastorns mentals i per a millorar el maneig clínic dels pacients que ho pateixen. En aquest projecte ens hem centrat en l'estudi de la simptomatologia depressiva relacionada amb l'administració exògena d'una citocina proinflamatòria, l'interferó alfa, en els pacients amb hepatitis C crònica.

Aquesta tesi doctoral es presenta en forma de compendi d'articles, segons la normativa de la Universitat de Barcelona. El treball inclou, per aquest ordre: un resum del projecte en llengua catalana, castellana i anglesa, una introducció, un apartat amb la hipòtesi de l'estudi, un resum dels tres treballs inclosos i el seu corresponent article original, un apartat de discussió, unes conclusions, un llistat de la bibliografia utilitzada i uns annexes.

Els **tres** articles inclosos en aquesta tesi (*) són producte d'una línia d'investigació centrada en l'estudi de les alteracions psiquiàtriques que apareixen amb l'administració exògena de citocines i en l'estudi de les alteracions immunològiques relacionades amb els trastorns afectius, que ha donat lloc a una sèrie de publicacions científiques:

- ✓ **(*)** Prophylactic antidepressant treatment of interferon-induced depression in chronic hepatitis C: A systematic review and meta-analysis. M. Udina, D. Hidalgo, R. Navinés, X. Forns, R. Solà, M. Farré, L. Capuron, E. Vieta, R. Martín-Santos. 2013, en revisió externa (Annals of Internal Medicine)
- ✓ **(*)** Serotonin and interleukin-6: The role of genetic polymorphisms in IFN-induced neuropsychiatric symptoms. M. Udina, J. Moreno-España, R. Navines, D. Giménez, K. Langohr, M. Gratacòs, L. Capuron, R. de la Torre, R. Solà, R. Martín-Santos. Psychoneuroendocrinology, 2013, http://dx.doi.org/10.1016/j.psyneuen.2013.03.007.
- ✓ Cytokine-induced depression: current status and novel targets for depression therapy. M. Udina, J. Moreno-España, L. Capuron, R. Navinés, M. Farré, E. Vieta, R. Martín-Santos. 2013, en revisió externa.

- ✓ Inflammatory markers in chronic hepatitis C patients treated with interferon-alpha. J. Moreno-España, M. Udina, S. Lens, R. Navinés, X. Forns, X. Filella, L. Capuron, R. Martín-Santos. 2013, en revisió externa.
- ✓ A multidisciplinary support program increases the efficiency of pegylated interferon alfa-2a and ribavirin in hepatitis C. J. Carrión, E. González-Colominas, M. García-Retortillo, N. Cañete, I. Cirera, S. Coll, D. Giménez, C. Márquez, V. Martin-Escudero, P. Castellví, R. Navinés, JR. Castaño, JA. Galeras, E. Salas, F. Bory, R. Martín-Santos, R. Solà. 2013, en revisió externa.
- ✓ **(*)** Interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. M. Udina, P. Castellví, J. Moreno-España, R. Navinés, M. Valdés, X. Forns, K. Langohr, R. Solà, E. Vieta, R. Martín-Santos. Journal of Clinical Psychiatry, 2012; 73:1128-38.
- ✓ Depressive and anxiety disorders in chronic hepatitis C patients: Reliability and validity of the Patient Health Questionnaire. R. Navinés, P. Castellví, J. Moreno-España, D. Giménez, M. Udina, S. Cañizares, C. Diez-Quevedo, M. Valdés, R. Solà, R. Martín-Santos R. Journal of Affective Disorders, 2012; 138:343-51.
- ✓ Prophylactic treatment with escitalopram of pegylated interferon alfa-2a-induced depression in hepatitis C: a 12-week, randomized, double-blind, placebo-controlled trial. C. Diez-Quevedo, H. Masnou, R. Planas, P. Castellví, D. Giménez, R. Morillas, R. Martín-Santos, R. Navinés, R. Solà, P. Giner, M. Ardèvol, J. Costa, M. Diago, J. Pretel. Journal of Clinical Psychiatry, 2011; 72:522-8.
- ✓ Depression in hospitalized patients with malignant melanoma treated with interferon-alpha-2b: primary to induced disorders. R. Navinés, E. Gómez-Gil E, S. Puig, I. Baeza, J. De Pablo, R. Martín-Santos. European Journal of Dermatology, 2009; 19:611-5.
- ✓ Pegylated interferon and ribavirin-induced depression in chronic hepatitis C: role of personality. P. Castellvi, R. Navinés, F. Gutierrez, D. Jiménez, C. Márquez, S. Subirà, R. Solà, R. Martín-Santos. Journal of Clinical Psychiatry, 2009; 70:817-28.

- ✓ Peginterferon and ribavirin induced bipolar episode successfully treated with lamotrigine without discontinuation of antiviral therapy. R. Navinés, P. Castellví, R. Solà, R. Martín-Santos. General Hospital Psychiatry, 2008; 30:387-9.
- ✓ De novo depression and anxiety disorders and influence on adherence during peginterferon-alpha-2a and ribavirin treatment in patients with hepatitis C. R. Martín-Santos, C. Díez-Quevedo, P. Castellví, R. Navinés, M. Miquel, H. Masnou, A. Soler, M. Ardevol, F. García, J. Galeras, R. Planas, R. Solà. Alimentary Pharmacology Therapeutics, 2008; 27:257-65.

Els resultats preliminars i parcials del treball s'han presentat a diverses congressos Nacionals i Internacionals:

- ✓ Genetic risk factors for Interferon-induced anxiety. M. Udina, J Moreno-España, R Navinés, K Langohr, M Gratacós, R Solà, R Martín-Santos. European Psychiatric Association, Niça 2013.
- ✓ Polimorfismos del gen transportador de serotonina y del gen productor de IL-6 como factores de riesgo de síntomas neuropsiquiátricos inducidos. M. Udina, J. Moreno-España, R. Navinés, D. Giménez, K. Langohr, M. Valdés, R. Martín-Santos. Congreso Nacional de Psiquiatría, Bilbao 2012 (Premi al millor accèssit)
- ✓ Incidence and risk factors of Interferon-induced depression. J Moreno-España, M. Udina, S. Cañizares, R. Solà, R. Martín-Santos. International Society of Affective disorders, Londres 2012.
- ✓ Genetic markers related with inflammation as risk factors for interferon-induced depression. R. Navinés, J. Moreno-España, M. Udina, D. Gimenez, K. Langohr, M. Gratacós, R. Solà, R. Martín-Santos. International Society of Affective disorders, Londres 2012.
- ✓ Interferon-induced depression in chronic hepatitis C: A systematic review. M. Udina, R. Navinés, J. Moreno-España, P. Castellví, E. Vieta, M. Valdés, R. Martín-Santos. International Society of Affective disorders, Londres 2012.
- ✓ Genetic risk factors for IFN-induced depression. R. Martín-Santos, R. Navinés, M. Udina, J. Moreno-España, D. Gimenez, K. Langohr, M. Gratacós, R. Solà. European Psychiatric Association, Praga 2012. *European Psychiatry*, *Volume 27, issue (2012), p. 1; DOI: 10.1016/S0924-9338(12)74875-7*.

- ✓ Incidencia y factores de riesgo de depresión inducida por Interferon en pacientes con hepatitis C crónica. M. Udina, J. Moreno-España, R. Navinés, D. Giménez, K. Langohr, M. Valdés, R. Martín-Santos. Congreso Nacional de Psiquiatría, Oviedo 2011 (Primer premi).
- ✓ Interferon-induced disorders and quality of life of substance use patients with hepatitis C. J. Moreno-España, R. Navinés, P. Castellví, M. Udina, D. Gimenez, C. Marquez, M. Torrens, R. Solà, R. Martín-Santos. II International Congress of Dual Disorders, Barcelona 2011.

A destacar que el doctorand ha rebut dos premis científics relacionats amb la investigació de la tesi:

- ✓ Premi accèssit *Amadeo Sanchez Blanqué* de la "Sociedad Española de Psiquiatría", 2012.
- ✓ Premi al millor Póster de Neuropsicofarmacologia de la "Sociedad Española de Psiquiatría Biológica" en col·laboració amb el "European College of Neuropsychopharmacology", 2011.

Aquesta tesi doctoral s'ha desenvolupat conjuntament pel Servei de Psiquiatria i la Unitat d'Hepatitis de l'Hospital Clínic i la Secció d'Hepatologia de l'Hospital del Mar de Barcelona. Ha tingut el el suport dels projectes d'investigació "Estudio farmacogenético y de predicción de la depresión inducida por el tratamiento de la Hepatits C crónica con Interferón alfa-pegilado y ribavirina" (PSIGEN-VHC; Fondos de Investigación Sanitaria, ECO8/00201, 2009-10), "Bases neurobiológicas de la depresión inducida por interferón en la hepatitis C crónica" (PSYCOCIT; Fondos de Investigación Sanitaria, P110/02206, 2011-13), dels Fons Europeu de Desenvolupament Regional (FEDER) de la Unió Europea "One way to make Europe" i de la Generalitat de Catalunya (SGR2009/1435). El doctorand té un contracte d'investigador predoctoral adscrita al projecte de la beca FIS, PI10/02206 (IP: Dra. R. Martín-Santos).

Índex

Resum del projecte

Introducció

En malalties com la hepatitis C crònica (HCC) l'administració exògena de citocines (interferó alfa; IFN alfa) s'ha associat amb l'aparició de símptomes neuropsiquiàtrics com pot ser un episodi depressiu major. El coneixement de la incidència i dels factors de risc (sociodemogràfics, clínics i genètics) de depressió en aquests pacients, així com dels potencials tractaments profilàctics, pot facilitar el maneig clínic i aportar una millor comprensió dels mecanismes fisiopatològics implicats en els trastorns afectius.

Objectius

Estudiar en els pacients amb HCC i en tractament amb IFN alfa i ribavirina:

- ✓ La incidència de depressió durant el tractament antiviral i la seva associació amb variables clíniques, biològiques i sociodemogràfiques basals.
- ✓ L'associació de la simptomatologia depressiva amb els polimorfismes genètics del transportador de la serotonina (*SERT)* i de la interleucina-6 (*IL-6*).
- ✓ El benefici clínic de l'administració profilàctica d'antidepressius.

Mètodes

✓ Revisió sistematitzada i metanàlisi de la literatura amb protocol "a priori" seguint les guies MOOSE (per estudis observacionals) o PRISMA (per assajos clínics randomitzats). En funció de les variables d'estudi es van calcular les odds ratios (OR) o les diferències mitjes (DM) i els seus corresponents intervals de confiança al 95% (IC95%). Càlcul del número necessari de pacients a tractar per a prevenir un episodi (NNT). Evaluació de qualitat, estudi de biaixos (Cochrane), estudi de sensitivitat i biaix de publicació (Begg i Egger). Es va utilizar el programa RevMan v. 5.0 (*estudis 1 i 3*).

✓ Estudi de cohorts: 385 pacients caucàsics, eutímics, amb HCC i tractats amb IFN alfa i ribavirina. Van ser evaluats basalment, a les 4, 12, 24 i/o 48 setmanes de tractament i a les 24 setmanes post-tractament: variables sociodemogràfiques, clíniques, entrevista psiquiàtrica (PHQ i SCID-DSM-IV), símptomes depressius (HADS-D), ansiosos (HADS-A) i de fatiga (VAS), i RNA viral (resposta virològica sostinguda; RVS). Anàlisi genètica: Extracció i quantificació ADN; genotipació dels polimorfismes del transportador de serotonina (*SERT*, 5-HTTLPR), i interleucina 6 (*IL-6*, rs1800795). Anàlisi estadística: descriptiva, univariant i multivariant (model de regressió logística). Es va utilitzar el paquet estadístic *R* v. 2.13.1 i *SPSS* v.19 (*estudi 2*).

Resultats

La incidència acumulada d'espisodi depressiu major va ser del 0.25 (IC 95% 0.16-0.35) i del 0.28 (IC95% 0.17- 0.42) a les 24 i a les 48 setmanes de tractament antiviral. El número de pacients que presenten "de novo" un episodi depressiu augmenta sobretot entre les setmanes 8 i 12 de tractament. Pel que fa als factors de risc: nivells elevats de IL-6 (DM 1.81, IC95% 1.09 a 2.52), el gènere femení (OR 1.40, IC95% 1.02-1.91), els antecedents de depressió (OR 3.96, IC95% 2.52-6.21), els antecedents psiquiàtrics (OR 3.18, IC95% 1.60-6.32), la simptomatologia depressiva subsindròmica (DM 0.96, IC95% 0.31 a 1.61), i un baix nivell educatiu (DM -0.99, IC95% -1.59 a -0.39) són variables predictives de depressió associada al tractament antiviral, segons el metanàlisis (*estudi 1*).

En la cohort estudiada es va observar que els símptomes depressius segueixen un patró diferent al de símptomes neurovegetatius com la fatiga, d'aparició més precoç durant el tractament. Els pacients amb variants funcionals del polimorfisme de la *IL-6* (genotip "CC", associat amb baixes concentracions de IL-6 plasmàtiques) presentaven un increment menor de simptomatologia depressiva (p= 0.005) i ansiosa (p= 0.004) al llarg del tractament antiviral. Respecte al polimorfisme del SERT es va observar que els pacients portadors del genotip "LL" presentaven menys símptomes depressius (p= 0.21) i ansiosos (p= 0.15) durant el tractament, però aquestes diferències no eren estadísticament significatives. A nivell basal els diferents genotips entre sí no presentaven diferències considerables (diferència mitja estandaritzada < 0.2) respecte a la majoria de variables, incloent aquells factors potencialment de risc de depressió induïda com els antecedents de depressió o la puntuació de la HADS (*estudi 2*).

Els inhibidors selectius de la recaptació de la serotonina (ISRS) reduiren la incidència de depressió major durant el tractament antiviral (OR 0.53, IC95% 0.33-0.84). El NNT va ser de 12 (IC95% 7.0-37.9). A les 24 setmanes de tractament el grup tractat amb ISRS presentava menys símptomes depressius que els pacients tractats amb placebo (DM -2.18, IC95% -4.25 a -0.10). Els antidepressius van mostrar un bon perfil de tolerabilitat i no van alterar la RVS ni el número de pacients que van abandonar el seguiment (*estudi 3*).

Conclusions

La investigació realitzada mostra que la depressió associada al tractament amb IFN alfa i ribavirina en la HCC té una alta incidència i que existeixen variables clíniques, sociodemogràfiques i genètiques, com certes variants funcionals del gen de la *IL-6*, que són factors de risc. El tractament profilàctic amb ISRS podria ser beneficiós en aquests pacients.

Resumen del proyecto

Introducción

En enfermedades como la hepatitis C crónica (HCC) la administración exógena de citocinas (interferon alfa; IFN alfa) se ha asociado a efectos indeseados neuropsiquiátricos, como la aparición de un episodio depresivo mayor. El conocimiento de la incidencia y de los factores de riesgo (sociodemográficos, clínicos y genéticos) de depresión en estos pacientes, y de potenciales tratamientos profilácticos, puede facilitar el manejo clínico y aportar una mejor comprensión de los mecanismos fisiopatológicos implicados en los trastornos afectivos.

Objetivos

Estudiar en los pacientes con HCC y en tratamiento con IFN alfa y ribavirina:

- ✓ La incidencia de depresión durante el tratamiento antiviral y su asociación con variables clínicas, biológicas y sociodemográficas basales.
- ✓ La asociación de la sintomatología depresiva con los polimorfismos genéticos del transportador de la serotonina (*SERT*) y de la interleucina-6 (*IL-6*).
- ✓ El beneficio clínico de la administración profiláctica de antidepresivos.

Métodos

✓ Revisión sistematizada y metaanálisis de la literatura con protocolo a "priori" siguiendo las guías MOOSE (estudios observacionales) o PRISMA (ensayos clínicos). En función de las variables se calcularon las odds ratios (OR) o las diferencias medias (DM) y sus intervalos de confianza al 95% (IC95%). Cálculo del número necesario de pacientes a tratar (NNT). Evaluación de calidad, estudio de sesgos (Cochrane), y sesgo de publicación (Begg-Egger). Se usó programa RevMan v. 5.0 (*estudios 1 y 3*).

✓ Cohorte clínica: 385 pacientes caucásicos con HCC, eutímicos, y tratados con IFN alfa y ribavirina. Evaluados a nivel basal, a las 4, 12, 24 y/o 48 semanas, y 24 semanas post-tratamiento: variables clínicas, sociodemográficas, entrevista psiquiátrica (PHQ y SCID-DSM-IV), síntomas depresivos (HADS-D), ansiosos (HADS-A) y de fatiga (VAS), RNA viral (respuesta virológica sostenida; RVS). Análisis genética: Extracción y cuantificación ADN; genotipación de los polimorfismos del transportador de serotonina (*SERT,* 5-HTTLPR) e interleucina 6 (*IL-6*, rs1800795). Análisis estadístico: descriptivo, univariante y multivariante (regresión logística) con paquete estadístico *R* v. 2.13.1 y *SPSS* v.19 (*estudio 2*).

Resultados

La incidencia acumulada de episodio depresivo mayor fue del 0.25 (IC95% 0.16-0.35) y del 0.28 (IC95% 0.17-0.42) a las 24 y a las 48 semanas de tratamiento. Respecto a los factores de riesgo: niveles elevados de IL-6 (DM 1.81, IC95% 1.09 a 2.52), el género femenino (OR 1.40, IC95% 1.02-1.91), los antecedentes de episodio depresivo mayor (OR 3.96, IC95% 2.52-6.21), los antecedentes psiquiátricos (OR 3.18, IC95% 1.60-6.32), la presencia de sintomatología depresiva subsindrómica (DM 0.96, IC95% 0.31 a 1.61) y un bajo nivel educativo (DM -0.99, IC95% -1.59 a -0.39) son variables predictivas de depresión asociada al tratamiento antiviral (*estudio 1*).

En el estudio de cohortes se observó que los síntomas depresivos siguieron un patrón distinto al de síntomas neurovegetativos como la fatiga, de aparición más precoz durante el tratamiento. Los pacientes con el genotipo CC (*IL-6)*, asociado a bajas concentraciones de IL-6 plasmáticas, presentaban un incremento menor de sintomatología depresiva (p= 0.005) y ansiosa (p= 0.004) a lo largo del tratamiento. En relación con el polimorfismo del *SERT* se observó que los pacientes portadores del genotipo LL presentaban menos síntomas depresivos (p= 0.21) y ansiosos (p= 0.15) durante el tratamiento, pero estas diferencias no eran estadísticamente significativas. A nivel basal, los genotipos entre sí no presentaban diferencias considerables (diferencia media estandarizada < 0.2) en relación con la mayoría de variables clínicas y sociodemográficas estudiadas, incluyendo potenciales factores de riesgo de depresión inducida como los antecedentes de depresión o la puntuación de la escala HADS (*estudio 2*)

Los inhibidores selectivos de la recaptación de serotonina (ISRS) redujeron la incidencia de depresión mayor durante el tratamiento antiviral (OR 0.53, IC95% 0.33-0.84). El NNT fue de 12 (IC95% 7.0-37.9). A las 24 semanas de tratamiento el grupo tratado con ISRS presentaba menos síntomas depresivos el grupo placebo (DM -2.18, IC95% -4.25 a -0.10). Los antidepresivos mostraron un buen perfil de tolerabilidad y no alteraron la RVS ni el número de pacientes que abandonaron el seguimiento (*estudio 3*)

Conclusiones

La investigación muestra que la depresión asociada al tratamiento con IFN alfa y ribavirina en la HCC tiene una alta incidencia y que existen variables clínicas, sociodemográficas y genéticas, como ciertas variantes funcionales del gen de la *IL*-6, que son factores de riesgo. El tratamiento profiláctico con ISRS podría ser beneficioso en estos pacientes.

Summary

Background

Administration of exogenous cytokines such as interferon-alpha (IFN-alfa) in chronic hepatitis C patients (CHC) has a high profile of neuropsychiatric side effects, including a full major depressive episode. The knowledge of the incidence and risk factors (sociodemographic, clinical and genetics) for depression in these patients, as well as potential prophylactical treatments, may help to optimize clinical management and to better understand pathways involved in the pathophysiology of the affective disorders.

Aims

To evaluate in patients with CHC under treatment with IFN-alfa and ribavirin:

- ✓ The incidence of a major depressive episode during antiviral treatment and the identification of the risk factors related to depression.
- ✓ The association between depressive symptoms appeared during antiviral treatment and functional genetic variants at the interleukin-6 gene (*IL-6*) and at the serotonin transporter gene (*SERT*).
- ✓ The utility of the prophylactic administration of antidepressants.

Methods

✓ A systematic review and meta-analysis of data using an advanced document protocol in accordance with the PRISMA (observational studies) or the MOOSE (clinical trials) guidelines. The odds ratios (OR) and mean differences (MD) with 95% confidence interval (95%CI) were used. The number needed to treat statistic (NNT) was calculated. Quality assessment, biases (Cochrane risk of bias), sensitivity analyses and publication bias (Begg-Egger). We used the RevMan v. 5.0 (*studies 1* and *3*).

✓ Clinical cohort: Three hundred and eighty-five euthymic, Caucasian outpatients with CHC who were candidates to receive combined treatment with IFN-alpha and ribavirin. Evaluation at baseline, 4, 12, 24 and/or 48 weeks, and at 24 weeks after treatment: Extraction of clinical and sociodemographic variables, psychiatric interview (PHQ and SCID-DSM-IV), depressive (HADS-D) and anxiety (HADS-A) symptoms, fatigue (VAS). Evaluation at: HADS, VAS. Evaluation: HCV RNA levels. Genetic analysis: DNA extraction and quantification; genotyping of the serotonin transporter (*SERT,* 5-HTTLPR) and interleukin-6 (*IL-6*, rs1800795) polymorphisms. Statistical

analysis: descriptive, univariant and multivariant performed with software *R* v. 2.13.1 and *SPSS* v.19 (*Study 2*).

Results

Overall cumulative incidence of depression was 0.25 (IC95% 0.16-0.35) and 0.28 (95%CI 0.17-0.42) at 24 and 48 weeks of treatment, respectively. Most of the new cases of depression were observed between 8 and 12 weeks of treatment. As regard with risk factors: high baseline levels of interleukin 6 (MD 1.81, 95%CI 1.09 to 2.52), female gender (OR 1.40 95%CI 1.02-1.91), history of depression (OR 3.96, 95%CI 2.52-6.21), history of any psychiatric disorder (OR 3.18, 95%CI 1.60-6.32), subthreshold depressive symptoms (MD 0.96, 95%CI 0.31-1.61), and low educational level (MD −0.99, 95%CI –1.59 to −0.39) were predictive variables of major depressive episode appeared during antiviral treatment according the meta-analysis (*Study 1*).

In the cohort study, we observed that changes in depressive symptoms followed a different pattern from neurovegetative symptoms such as fatigue, which appeared mainly during the first four weeks of treatment. During antiviral treatment we reported that subjects with CC genotype in the *IL-6* gene (associated with low IL-6 plasmatic concentrations) presented significantly lower changes from baseline in IFN-induced depression (p=0.005) and IFN-induced anxiety (p=0.004). We did not find statistically significant differences on depression (p=0.21) or anxiety (p=0.15) between SS/SL and LL genotypes of *SERT*. At baseline, there were not differences between the genotypes (standardized mean difference < 0.2) in respect to most clinical and sociodemographic variables evaluated such as depressive history or HADS scores (*Study 2*).

Selective serotonin reuptake inhibitors (SSRIs) reduce the incidence of a major depressive episode during antiviral treatment (OR 0.53, 95%CI 0.33 to 0.84). The estimated number needed to treat (NNT) was 12 (95%CI 7.0 to 37.9). SSRIs reduce depressive symptoms at 24 weeks of treatment (MD -2.18, 95%CI -4.25 to -0.10). Antidepressants showed a good tolerability and there were neither differences in sustained virological response nor in treatment discontinuation (*Study 3*).

Conclusions

The study confirms a high incidence of depression during treatment with IFN-alfa and ribavirin for CHC. Moreover, sociodemographic, clinical and genetic variables such as functional variants of the *IL-6* gene are risk factors for IFN-induced depression. Prophylactic administration of SSRI may be useful in these patients.

CAPÍTOL 1
Introducció

1. Introducció

1.1 El trastorn depressiu major a la societat

El trastorn depressiu major és una malaltia comú que podria afectar fins al 20% de la població general al llarg de la seva vida [1, 2]. És un trastorn que causa un gran impacte en les persones que el pateixen i al seu entorn, alterant la productivitat, minvant les relacions interpersonals i afectant negativament la qualitat de vida dels pacients [3, 4]. Es considera que la depressió és la primera causa de discapacitat al llarg de la vida i una de les malalties més costoses per a la societat, tant en termes de costos directes com indirectes [5, 6]. Un dels objectius de l'Organització Mundial de la Salut (OMS) és atenuar l'impacte que causa la depressió en la societat millorant les eines de prevenció i diagnòstic precoç, establint potencials grups de risc i reduint el gran número de persones que pateixen la malaltia a nivell mundial però que no reben cap dels actuals tractaments disponibles [5].

1.2 Immunitat i depressió

Durant els últims anys ha augmentat l'evidència científica que suggereix una associació entre alteracions en paràmetres immunitaris i depressió major [7-11] .

El sistema immunitari engloba un conjunt de mecanismes humorals i cel·lulars que tenen com a funció principal la detecció i eliminació d'agents potencialment nocius per a l'organisme, com patògens o cèl·lules tumorals [12]. És un sistema complex on intervenen múltiples molècules que modulen la seva funció i que faciliten la comunicació entre els diferents elements que el conformen. Un gran grup d'agents immunomoduladors reben el nom de citocines, dintre de les quals trobem molècules com les interleucines (IL), els interferons (IFN), les quimiocines o els factors de necrosi tumoral (TNF) [12]. Les citocines realitzen la seva funció fisiològica a través de l'activació de receptors cel·lulars i segons missatgers a gairebé tot l'organisme, incloent el sistema nerviós central (SNC). La condició que implica una activació de diversos processos immunològics al SNC s'ha anomenat neuroinflamació [13]. La neuroinflamació sol ser un fenòmen beneficiós per a l'individu per a combatre processos patològics aguts com lesions

traumàtiques o infeccions del SNC. Per altra banda, però, s'ha descrit que un "estat" de neuroinflamació crònica pot alterar la homeòstasis cerebral, relacionant-se amb malalties neurològiques neurodegeneratives, deteriorament cognitiu i amb trastorns psiquiàtrics [14, 15].

Diverses metanàlisis focalitzades en depressió major han descrit que elevacions en sang perifèrica de les concentracions de interleucina-6 (IL-6), TNF-alfa i de la proteïna C reactiva són troballes freqüents en els pacients amb trastorn depressiu [16]. A més a més, alguns estudis han observat una correlació entre les concentracions de citocines i la severitat de la depressió [17], i una associació entre la presència de marcadors inflamatoris elevats i la resistència als tractaments antidepressius actuals [18]. S'ha descrit que els estressors psicosocials, uns dels factors de risc de depressió major més replicats, podrien alterar la resposta immunològica i elevar alguns marcadors proinflamatoris [19]. Alguns autors suggereixen que els individus que pateixen factors vitals estressants crònics o precoços podrien presentar elevació de citocines com la IL-6 i estar en un risc incrementat de patir depressió [20]. Cal esmentar que la prevalença de depressió és més elevada en els pacients que pateixen malalties mèdiques relacionades amb processos inflamatoris com poden ser les malalties cardiovasculars, l'artritis reumatoide, trastorns autoimmunes o la obesitat [21-23]. A més a més, hi ha àmplia evidència que els tractaments farmacològics que inclouen citocines podrien induir símptomes depressius en animals i en humans [24, 25]. En models animals s'ha observat que l'administració exògena de citocines provoca una activació del sistema immunològic i una sèrie de canvis conductuals amb trets en comú amb els símptomes depressius observats en humans (*depressive-like behaviour*) [26-28]. En concret, l'administració de IL-1β o de TNF-alfa en ratolins indueix un espectre de canvis conductuals que inclouen: aïllament social, enlentiment psicomotor, reducció de la ingesta alimentària i alteracions en el ritme de la son [29]. En humans s'ha observat que la utilització com a fàrmacs de l'interferó alfa (IFN alfa) i beta, citocines de perfil proinflamatori, s'associa a l'aparició de símptomes depressius i d'episodis depressius "de novo". [30] Aquest fet s'ha descrit en malalties de diferent espectre com el melanoma maligne, l'esclerosis múltiple o l'hepatitis C crònica (HCC) entre altres [24, 30-32].

1.3 Hepatitis C crònica i tractament antiviral

La infecció del virus de l'hepatitis C (VHC) és un destacat problema de salut pública que afecta entre 130 i 170 millons de persones a tot el món [33], causant sovint una HCC que pot evolucionar a cirrosis hepàtica i a hepatocarcinoma. El VHC és la primera causa de cirrosis i representa la principal indicació de trasplantament hepàtic a nivell mundial [34]. La teràpia mes utilitzada els últims anys en la HCC és la combinació d'interferó alfa (IFN-alfa) i ribavirina durant 24 o 48 setmanes [35]. Amb aquest tractament els pacients assoleixen una adequada resposta terapèutica, anomenada resposta virològica sostinguda (RVS), en un percentatge que oscil·la entre el 50 i el 70% depenent principalment del genotip del virus [36-40]. Recentment, estudis que han afegit al tractament estàndard un inhibidor de la proteasa com el telaprevir o el boceprevir han mostrat augments significatius de la RVS en els pacients amb genotip-1 del VHC [41, 42]. Un dels inconvenients de la teràpia antiviral, però, és la freqüent presència d'efectes indesitjats, incloent alteracions cognitives, irritabilitat, ansietat, fatiga, insomni i símptomes depressius que poden en ocasions acomplir criteris d'episodi depressiu major, anomenant-se depressió induïda per interferó [25, 43, 44]. És important monitoritzar i detectar les alteracions neuropsiquiàtriques relacionades amb el tractament ja que s'ha observat que els pacients que presenten símptomes psicopatològics tenen menys qualitat de vida, ideació suïcida, pitjor adherència terapèutica i alteracions en la RVS [30, 45-47].

1.4 La depressió associada al tractament amb interferó-alfa i ribavirina

L'aparició de simptomes neuropsiquiàtrics en els pacients amb HCC tractats amb IFN alfa es va descriure precoçment a l'inici de la introducció d'aquesta teràpia [48]. Tot i això, la incidència aproximada d'episodi depressiu major durant el tractament antiviral és avui en dia encara controvertida [49-51]. Una probable explicació d'aquest fet és la manca o la divergència en l'ús d'instruments validats per al diagnòstic de depressió major. Inicialment, molts estudis clínics van descriure l'aparició de símptomes depressius sense utilitzar escales adequades o sense seguir criteris clínics acceptats, com el Diagnostic and Statistical Manual of Mental Disorders (DSM) o la Classificació Internacional de Malalties (CIM) de la OMS [52, 53]. A més a més, cal tenir en compte que els pacients amb malalties mèdiques com la HCC ja presenten una incidència més elevada d'alteracions psiquiàtriques que la població general [54]. És per aquest fet que

per a descriure la incidència de depressió major o per a observar l'aparició de simptomatologia depressiva són necessaris estudis longitudinals que avaluin de forma adequada els pacients abans d'iniciar i durant el tractament. També s'ha de tenir en compte que aquests pacients poden presentar altres símptomes somàtics i neuropsiquiàtrics que es poden confondre i solapar amb els característics d'un episodi depressiu. De fet, diversos autors han descrit que durant el tractament antiviral caldria diferenciar un sèrie de símptomes neurovegatitus que solen aparèixer a l'inici del tractament com per exemple la fatiga o l'anorèxia, de símptomes "més pròpiament" afectius com l'apatia, l'anhedònia, l'hipotímia o les idees de desesperança que solen aparèixer a partir de les 8-12 setmanes de l'inici del tractament antiviral [55]. Aquests dos síndromes podrien tenir una base fisiològica i una resposta als tractaments farmacològics diferent [56]. Aquest fet, ratifica la importància d'utilitzar eines diagnòstiques adequades per al diagnòstic de depressió major, com per exemple aquelles basades en criteris diagnòstics DSM, o escales validades en pacients amb malalties mèdiques per a la quantificació de la simptomatologia depressiva, com podria ser la Hospital Anxiety and Depression Scale (HADS) [57]. En aquesta línia, caldria esmentar que el nostre grup ha validat recentment l'escala Patient Health Questionnaire (PHQ), basada en els criteris diagnòstics DSM-IV, per a l'screening de trastorns afecius i ansiosos en els pacients amb HCC. A més a més, en aquest mateix estudi es va demostrar una validesa convergent entre el diagnòstic realitzat amb el PHQ de qualsevol trastorn depressiu o trastorn depressiu major i la puntuació de la subescala de depressió del HADS (HADS-D) [58].

Un altre factor que explicaria la divergència en la incidència de depressió induïda descrita entre els diferents estudis és la característica de la mostra estudiada. S'ha observat que alguns subjectes tenen més risc de patir símptomes depressius després de l'administració d'interferó alfa i altres no presenten cap mena de simptomatologia, suggerint que existirien factors de vulnerabilitat i protectors per a patir depressió associada al tractament amb citocines [59]. És important destacar que el coneixement dels factors protectors o de vulnerabilitat pot ser útil per a detectar precoçment pacients de risc i establir potencials mesures profilàctiques, així com per a comprendre els mecanismes biològics subjacents implicats en la fisiopatologia dels símptomes i dels trastorns depressius [60, 61]. És per aquest motiu que, durant els últims anys, la investigació científica s'ha centrat en identificar diferents factors socials, clínics i biològics que podrien incrementar el risc de patir depressió en els pacients sota tractament antiviral [50,

62, 63]. Estudis clínics longitudinals ja suggereixen que la presència de símptomes depressius subsindròmics abans de començar el tractament, els antecedents de depressió o certs trets de personalitat, podrien ser factors de risc de presentar un episodi depressiu durant el tractament [30, 50, 59, 64]. Factors genètics i bioquímics també podrien determinar la vulnerabilitat d'alguns subjectes de patir depressió induïda. En aquest sentit, s'ha observat que nivells elevats de citocines proinflamatòries [65, 66] i certes variacions en gens (polimorfismes) involucrats en la funció de la resposta inflamatòria, en la neurotransmissió o en altres funcions cerebrals podrien ser factors de risc [63, 67]. En tot cas, la relativa petita mostra de pacients inclosos en alguns estudis i la manca de revisions sistematitzades relacionades amb el tema fa que els resultats s'hagin d'interpretar amb cautela.

1.5 Fisiopatologia de la depressió induïda per interferó-alfa

Durant el tractament antiviral s'ha observat que existeix un increment significatiu dels nivells de citocines sèriques [65]. Aquesta activació del sistema immunològic és probablement necessària per a una bona resposta antiviral però sembla que també podria associar-se amb canvis conductuals i amb depressió. A nivell experimental s'ha observat que, quan s'administren exògenament citocines com l'IFN alfa, hi ha una activació de diversos marcadors proinfamatoris, tal i com pot passar en cas d'infeccions o en models d'estrés, que podrien produir alteracions en eixos endocrins, en la plasticitat cerebral i en la neurotransmissió, causant canvis conductuals [9, 68, 69]. El mecanisme mitjançant el qual les citocines causen alteracions a nivell del sistema nerviós central és actualment controvertit. Tot i que les citocines són polipèptids d'un tamany gran, que dificulta el pas a través de la membrana hemato encefàlica, es creu que algunes, com la IL-6, sí que podrien accedir al sistema nerviós central atravessant les zones més permeables de la membrana [70]. Les citocines, per altra banda, també podrien activar cèl·lules endotelials i altres tipus cel·lulars del revestiment vascular cerebral que secretarien mediadors inflamatoris al SNC, o bé podrien activar nervis aferents que facilitarien l'alliberament d'altres citocines o mediadors en certes àrees cerebrals com l'hipotàlam [29, 71]. En línia amb aquestes hipòtesis, s'ha observat que els pacients tractats amb IFN-alfa mostren concentracions elevades de IL-6 al líquid cefaloraquidi [72]. A més a més, estudis clínics també han descrit que concentracions elevades de IL-6 o de IL-10 abans de començar el tractament antiviral podrien ser factors de risc de depressió, i que les concentracions de

IL-6 prediuen i es correlacionen amb la simptomatologia depressiva induïda per IFN [65, 66]. Per altra banda, estudis bàsics amb animals han demostrat que altes concentracions de citocines en certes àrees cerebrals podrien relacionar-se amb l'aparició de simptomatologia "depressive-like" en ratolins. Concretament, un estudi de Kim et al. (2012), descriu que l'administració de IL-6 a l'hipocamp de ratolins s'associa a l'aparició de símptomes depressius que es podrien deure a alteracions de la neurotransmissió serotoninèrgica causades per l'estimulació de l'enzim indoleamina 2,3 dioxigenasa (IDO) [73]. L'enzim IDO determina la disponibilitat de serotonina a nivell del SNC, regulant la síntesi de serotonina a partir de triptòfan, i també participa en la síntesi de kinurenina, un compost neuractiu que també s'associat a l'aparició de simptomatologia depressiva [74]. En línia amb aquest fet, hi ha força evidència en poblacions clíniques que suggereix que l'administració exògena de citocines pot alterar les vies de neurotransmissió serotoninèrgiques. Alguns estudis s'han focalitzat en avaluar la importància de les variacions funcionals (polimorfismes) de gens que regulen la fisiologia de la neurotransmissió monoaminèrgica. S'ha observat que variants genètiques funcionals de l'enzim IDO s'associen a la depressió induïda per interferó [63]. Per altra banda, també s'ha evaluat el paper d'altres factors relacionats amb la fisiologia de la neurotransmissió serotoninèrgica, com el transportador de serotonina (SERT) o els receptors serotoninèrgics (5HT1A i 5HT2A). Kraus et al. (2007) van observar que els pacients amb HCC tractats amb IFN alfa i ribavirina tenen més risc de desenvolupar depressió durant el tractament en cas d'ésser homozigots (GG) d'un polimorfisme genètic de la regió de control transcripcional del receptor 5HT1A [75]. En aquest mateix estudi, però, no es va observar una relació amb un polimorfismes del transportador de serotonina (al·lels S i L del *SERT*). Per contra, un estudi més recent sí que va descriure que el polimorfisme del *SERT* s'associa a la depressió induïda a interferó [76]. La divergència dels resultats es podria explicar per les diferents característiques de mostres estudiades i de les eines utilitzades per a l'avaluació de la simptomatologia depressiva. Tal i com s'ha comentat anteriorment, hi ha autors que han destacat la importància d'avaluar els símptomes neuropsiquiàtrics que apareixen durant el tractament amb interferó amb escales d'avaluació que permetin diferenciar adequadament la simptomatologia neurovegetativa de la simptomatologia pròpiament afectiva [55, 56].

1.6 Tractament i prevenció de la depressió induïda

Estudis oberts suggereixen que la depressió induïda per interferó té una bona resposta clínica al tractament antidepressiu, especialment als inhibidors selectius de la recaptació de serotonina (ISRS) [77]. Els ISRS bloquen selectivament la recaptació de serotonina a la terminal neuronal presinàptica i inicien el seu efecte terapèutic a través de l'increment de la disponibilitat de serotonina a la sinapsis [78]. S'ha suggerit que podria ser útil l'administració profilàctica d'un ISRS en els pacients que inicien tractament amb IFN alfa o, almenys, en alguns grups de risc, donada la freqüent presència de depressió en aquests pacients i els canvis en la neurotransmissió serotoninèrgica que podria causar l'administració exògena de citocines [61, 79] Durant els darrers anys s'han publicat diversos assajos clínics de tractament profilàctic amb ISRS comparats amb placebo, amb mostres relativament petites i amb resultats contradictoris [80, 81].

CAPÍTOL 2
Hipòtesi

2. Hipòtesi

2.1 Hipòtesis principals del projecte

- ✓ Tenint en compte que l'administració exògena de citocines modula el sistema de resposta immunològica i podria afavorir un estat de neuroinflamació que alteri funcions cerebrals com la neurotransmissió serotoninèrgica, considerem que els pacients amb HCC i en tractament amb IFN alfa i ribavirina presentaran una elevada incidència de depressió.
- ✓ Variables clíniques, sociodemogràfiques, biològiques i genètiques com la presència de símptomes subdepressius basals, els antecedents de depressió, certs trets de personalitat o alteracions en paràmetres relacionats amb la resposta immunológica seran factors de risc de depressió induïda per IFN alfa i ribavirina.
- ✓ La depressió induïda estarà modulada per variacions funcionals de gens relacionats amb el sistema serotoninèrgic i amb el sistema de regulació de la resposta immunològica.
- ✓ L'administració profilàctica de fàrmacs antidepressius abans d'iniciar el tractament antivirial disminuirà l'incidència de depressió induïda, almenys en aquells grups de més risc.
- ✓ Els antidepressius seran ben tolerats i no disminuiran l'efectivitat del tractament antiviral de la HCC.

CAPÍTOL 3

Estudi 1

3. Estudi 1

Interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. Marc Udina, Pere Castellví, José Moreno-España, Ricard Navinés, Manuel Valdés, Xavier Forns, Klaus Langohr, Ricard Solà, Eduard Vieta i Rocío Martín-Santos. Journal of Clinical Psychiatry, 2012; 73 (8): 1128-38 (DOI: 10.4088/JCP.12r07694). Factor d'impacte (JCR 2011): 5.799 (1er decil de Psiquiatria).

3.1 Resum de l'estudi

Objectiu

Revisar sistemàticament la literatura publicada que avalua l'aparició d'un episodi depressiu major al llarg del tractament amb IFN alfa i ribavirina per a la HCC en la pràctica clínica habitual. Aquesta revisió permetria conèixer:

- ✓ La incidència de depressió major al llarg del tractament.
- ✓ Aquelles variables sociodemogràfiques, clíniques, biològiques o genètiques que puguin ser factors de risc per a la posterior aparició de depressió major durant el tractament.

Metodologia

Es va realitzar una revisió sistemàtica i metanàlisi d'estudis prospectius i observacionals en pacients amb HCC i en tractament antiviral. Es va el·laborar un protocol previ seguint pas a pas les pautes indicades al MOOSE (Meta-analysis of Observational Studies in Epidemiology) [82]. Es van seleccionar només els estudis amb una bona descripció metodològica, de mostra major de 10 subjectes i que realitzaven un diagnòstic d'episodi depressiu mitjançant un instrument validat heteroadministrat o una entrevista semiestructurada realitzada per un clínic (criteris DSM). Tots els pacients dels estudis havien d'estar eutímics abans d'iniciar el tractament antiviral. Es van excloure els estudis no prospectius i aquells que eren intervencionistes (assajos clínics d'antidepressius profilàctics, per exemple). La cerca d'articles es va realitzar de forma

sistematitzada a través de MEDLINE, PsycINFO i de la Cochrane Library mitjançant les paraules clau: Hepatitis and C and (Interferon-alpha or Peginterferon or (Pegylated and Interferon) and (Depression or Mood). La cerca i l'extracció de dades es va realitzar per dos autors de l'estudi de forma independent (Marc Udina i Pere Castellví).

La qualitat dels articles seleccionats es va avaluar mitjançant una escala que vam desenvolupar basant-nos en la Newcastle Ottawa Scale [83] i la guia STROBE per a estudis observacionals [84]. Un cop seleccionats els articles es van extreure les dades i es va realitzar una revisió sistemàtica amb metanàlisi. Es va calcular la incidència acumulada de depressió durant el tractament en funció del temps i, pel que fa a les potencials variables de risc, es van calcular les Odds ratios (OR) per les variables qualitatives i les diferències mitjes (DM) per les variables quantitatives amb el corresponent interval de confiança del 95% (IC95%), estimant-se així la seva associació amb la depressió induïda. Es va avaluar l'heterogenitat i el risc de biaix de publicació, que es va expressar en forma de *Funnel Plot* (Begg i Egger) [85 86]. Es va utilizar el programa Review Manager versió 5.0.

Resultats

Dels 627 articles inicials trobats a través de la cerca sistematitzada, només es van poder incloure 26 articles. Vint i dos es van utilitzar per a l'anàlisi d'incidència i 17 per a l'estudi dels factors de risc.

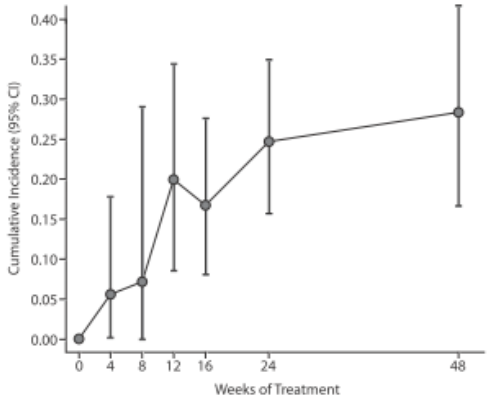

Figura. Incidència acumulada d'episodi depressiu major al llarg del tractament.

La incidència acumulada de depressió va ser del 0.25 (IC95% 0.16 a 0.35) i del 0.28 (IC95% 0.17 a 0.42) a les 24 i a les 48 setmanes de tractament. Cal esmentar que, per tal d'aconseguir que l'estimació d' incidència de depressió s'aproximés al màxim a la pràctica clínica habitual, vam realitzar el càlcul tenint només en compte aquells estudis que no tenien com a criteri d'exclusió els pacients amb antecedents psiquiàtrics i que utilitzaven el tractament antiviral estàndard (IFN alfa i ribavirina).

Pel que fa als factors de risc: nivells elevats de IL-6 abans de començar el tractament (DM 1.81, IC95% 1.09 a 2.52), el gènere femení (OR 1.40, IC95% 1.02-1.91), els antecedents d'episodi depressiu major (OR 3.96, IC95% 2.52-6.21), els antecedents psiquiàtrics (OR 3.18, IC95% 1.60-6.32), la presència de simptomatologia depressiva subsindròmica (DM 0.96 IC95% 0.31-1.61), i un baix nivell educatiu (DM -0.99, IC95% -1.59 a -0.39) eren variables predictives de depressió associada al tractament antiviral, segons la metanàlisi.

Per altra banda, algunes variables no es van poder incloure a la metanàlisi ja que havien estat descrites en només un estudi o havia heterogeneitat en la seva evaluació. D'aquests factors cal esmentar que certs trets de personalitat (elevat neuroticisme o baixa autodirecció), nivells elevats d'IL-10 abans de començar el tractament, antecedents de símptomes maniformes subsindròmics, aleracions del patró de la son i polimorfismes de la via inflamatòria (cicloxigenasa-2 i fosfolipasa-2) i serotoninèrgica (SERT) suggerien també que podrien ser factors de risc per a la depressió associada al tractament antiviral.

3.2 Article original

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

Marc Udina, MD; Pere Castellví, PhD; José Moreno-España, MD; Ricard Navinés, MD, PhD; Manuel Valdés, MD, PhD; Xavier Forns, MD, PhD; Klaus Langohr, PhD; Ricard Solà, MD, PhD; Eduard Vieta, MD, PhD; and Rocío Martín-Santos, MD, PhD

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

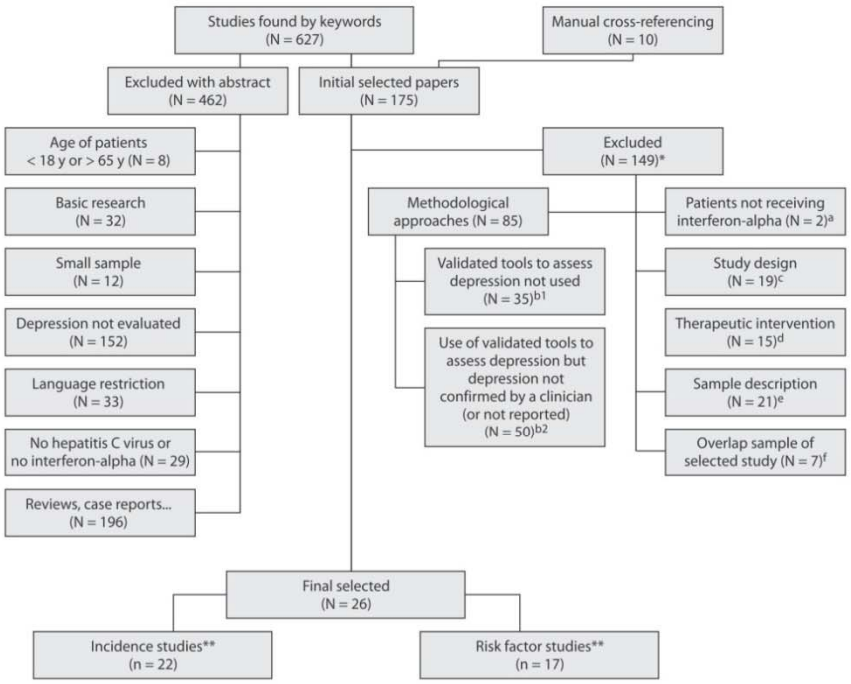
All studies established depression diagnoses using *DSM* criteria and excluded patients who presented a depressive episode before starting treatment.

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).

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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
Castèra 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
Castèra 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 Controls n = 21	19 M 7 F 12 M 9 F	42.8 ± 10.8 44.1 ± 12.0	NR	No	Yes	MINI	30 0	PegIFN-α2b (80–150 μg), PegIFN-α2a (90–180 μg)	Yes (0.8–1.2 g)	12	16
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 Controls n = 13	12 M 8 F 6 M 7 F	47.6 ± 6.3 46.8 ± 6.6	NR	No	No	SCID	20 0	PegIFN-α2a, PegIFN-α2b (NR)	Yes (NR)	12	17
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

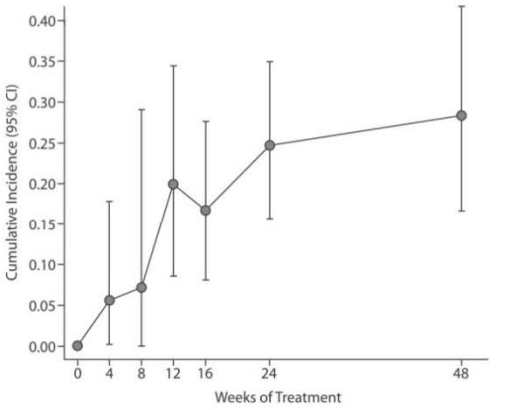
Study	N	Cumulative Incidence [95% CI] 4 Weeks	8 Weeks	12 Weeks	16 Weeks	24 Weeks	48 Weeks
Studies that do not specify patients with past psychiatric history and use monotherapy with interferon-alpha							
Miyaoka et al,[40] 1999	60					0.48 [0.35–0.62]	
Studies that exclude patients with past psychiatric 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.

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



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

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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

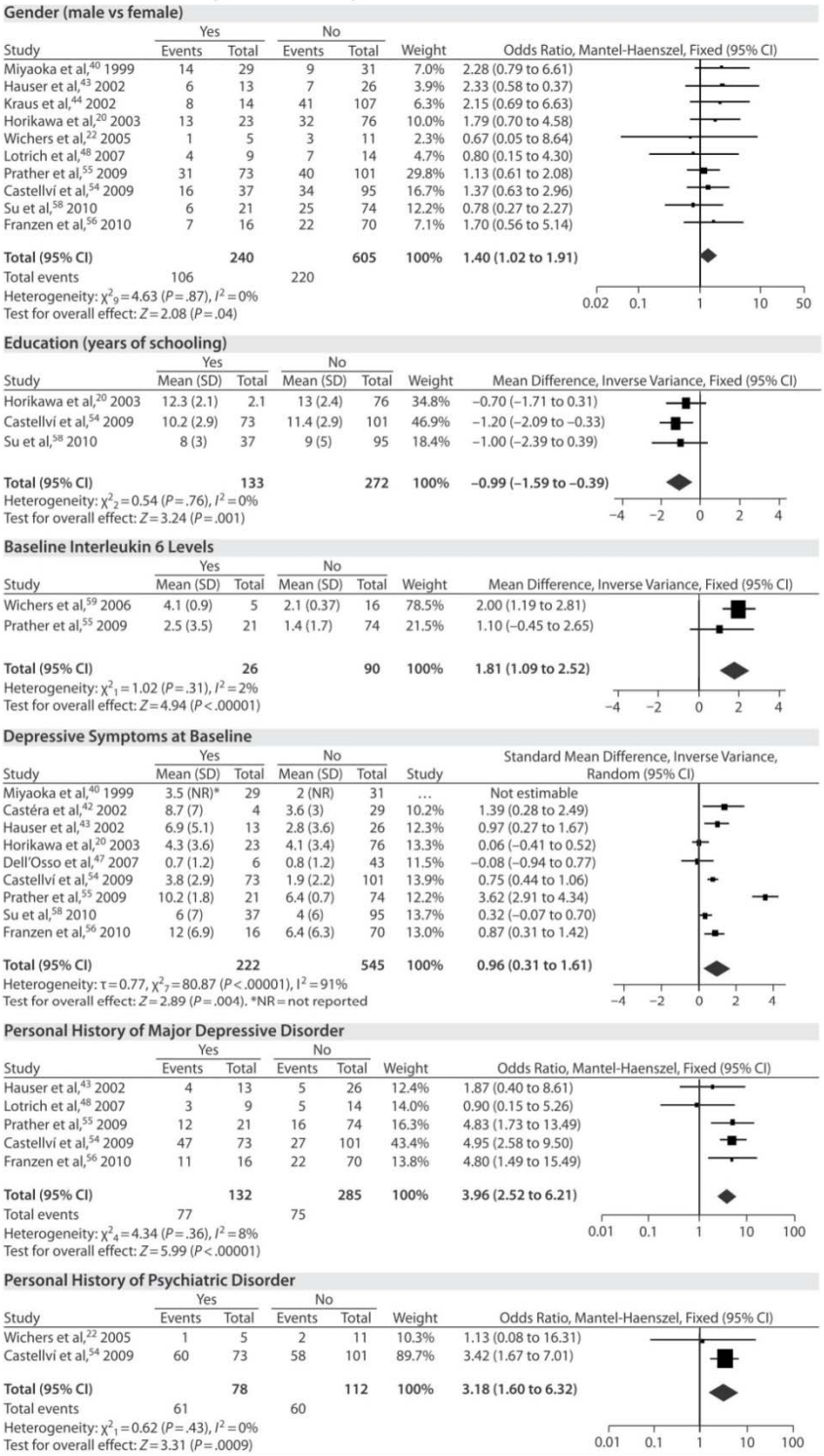
Heterogeneity in the reported incidence of depression was observed between studies. Significant heterogeneity was identified only in comparisons of baseline depressive score ($\chi^2 = 16.02$, $P < .001$) and race variables ($\chi^2 = 16.02$, $P < .001$), justifying the use of random effects models. 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



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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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See eAppendix 1 for this article at PSYCHIATRIST.COM.

3.3 Material complementari

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Supplementary Material

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

Author(s): Marc Udina, MD; Pere Castellví, PhD; José Moreno-España, MD; Ricard Navinés, MD, PhD; Manuel Valdés, MD, PhD; Xavier Forns, MD, PhD; Klaus Langohr, PhD; Ricard Solà, MD, PhD; Eduard Vieta, MD, PhD; and Rocío Martín-Santos, MD, PhD

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

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B2. Validated tools to assess depression but depression not confirmed by a clinician (or not reported)

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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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CAPÍTOL 4
Estudi 2

4. Estudi 2

Serotonin and interleukin-6: The role of genetic polymorphisms in IFN-induced neuropsychiatric symptoms. Marc Udina, José Moreno-España, Ricard Navines, Dolors Giménez, Klaus Langohr, Mònica Gratacòs, Lucile Capuron, Rafael de la Torre, Ricard Solà i Rocío Martín-Santos. Psychoneuroendocrinology, 2013 (en premsa, http://dx.doi.org/10.1016/j.psyneuen.2013.03.007). Factor d'impacte (JCR 2011): 5.809 (1er decil psiquiatria).

4.1 Resum de l'estudi

Objectius

Avaluar en una cohort de pacients amb HCC i en tractament antiviral la rellevància de polimorfismes genètics de la via inflamatòria (IL-6) i serotoninèrgica (SERT) en l'aparició de simptomatologia depressiva. Tenint en compte que, segons alguns autors, els símptomes neuropsiquiàtrics associats a l'administració exògena de citocines poden tenir bases fisiològiques difererencials ens proposaríem avaluar diferenciadament la simptomatologia pròpiament afectiva, de l'ansiosa i d'un dels principals símptomes neurovegetatius (fatiga).

Metodologia

Estudi d'una cohort prospectiva reclutada i avaluada sota el protocol de l'estudi PSIGEN-VHC, aprovada pel CEIC de l'IMAS i de l'Hospital Clínic; i recolzada per l'estudi PSYCOCIT. Es van incloure 397 pacients dels dos sexes, majors de 18 anys, amb HCC i amb criteris per a iniciar tractament amb IFN alfa i ribavirina que, van ser avaluats a nivell basal, a les 4, 12, 24, 48 setmanes de tractament i a les 24 setmanes després de finalitzar el tractament.

Els subjectes firmaren un consentiment informat previ a la inclusió a l'estudi. Tots els pacients van ser explorats abans de començar el tractament amb l'escala de screening de depressió Patient Health Questionnaire (PHQ) i l'entrevista estructurada per a diagnòstic psiquiàtric (DSM-IV-SCID), es van avaluar variables clíniques i sociodemogràfiques

d'interès, i es va obtenir una mostra de sang perifèrica de 10 ml. Els símptomes ansiosos i depressius es van quantificar mitjançant l'escala HADS, que conté la subescala de depressió (HADS-D) i la subescala d'ansietat (HADS-A). La fatiga es va avaluar mitjançant una escala analògica (VAS). Tots els pacients es van avaluar durant el tractament amb la HADS-D, HADS-A i la VAS. En cas de simptomatologia neuropsiquiàtrica considerable els pacients van ser avaluats per un clínic que va iniciar tractament farmacològic si es considerava necessari. Vint i quatre setmanes després de finalitzar el tractament, els pacients es van avaluar per a quantificació del RNA del VHC i així determinar si assoliren una resposta virològica sostinguda (principal objectiu del tractament antiviral). Es van establir com a criteris d'exclusió la presència de trastorn depressiu major segons criteris DSM-IV a nivell basal, malaltia mèdica greu o hepatopatia avançada (cirrosis o hepatocarcinoma).

L'extracció i quantificació de l'ADN i la genotipació de les variants genètiques es va realitzar al Centre de Regulació Genòmica de Barcelona. El fenotip funcional localitzat a la regió promotora del gen *IL-6* (rs1800795) va ser genotipat utilitzant el VeraCode GoldenGate Genotyping Assay (Illumina San Diego, CA, USA) segons el protocol del fabricant. Respecte a la genotipació del gen *SERT*: es va definir un polimorfisme localizat a 1 kb de l'inici de la transcripció (5-HTTLPR), que defineix els al·lels "s" i "l", analitzant-se mitjançant amplificació per PCR i resolució de fragments en seqüenciador AB3730XL (Applied Biosystems).

Per a l'anàlisi de dades es van agrupar els genotips dels polimorfismes. En el cas de *IL-6* els genotips GG i GC, associats a concentracions elevades de IL-6 en sang [87], es van agrupar i comparar amb els subjectes amb genotip CC. En el cas del *SERT* els genotips SS i SL, associats a baixa activitat sertoninèrgica [88], es van agrupar i comparar amb els subjectes amb genotip LL. S'avaluà si havia diferències entre cadascun dels grups pel que fa a les puntuacions de les escales HADS-D, HADS-A, VAS i d'altres variables clíniques i sociodemogràfiques basals, quantificant-se a través de les mitjes de *Cohen D* (diferència mitja estandaritzada; DME) [89]. Es van avaluar les diferències en la simptomatologia ansiosa, depressiva i de fatiga durant el tractament entre diferents genotips tenint en compte el valor basal i el temps (4, 12, 24 i/o 48 setmanes). L'anàlisi estadística es va realitzar amb el programa R (versió 2.13.1) i SPSS v. 19.

Resultats

Dels 397 pacients inclosos, 12 que no eren de raça caucàsica es van excloure de l'anàlisi genètic. Dels 388 pacients restants, cap presentava criteris d'episodi depressiu major ni trastorn d'ansietat actiu abans de començar el tractament. La distribució dels genotips dels dos polimorfismes estava en l'equilibri de Hardy-Weinberg (SERT, p= 0.41; IL-6, p= 0.72).

A nivell basal els diferents genotips entre sí no presentaven diferències considerables (DME < 0.2) respecte a la majoria de variables clíniques i sociodemogràfiques evaluades, incloent aquells factors potencialment de risc o protectors de depressió induïda com: presència d'antecedents depressius, puntuació de HADS-D o HADS-A basal, gènere femení i ús d'antidepressius o ansiolítics a nivell basal. L'única diferència trobada a nivell basal va ser que els pacients amb genotip CC del polimorfisme de la *IL-6* presentaven valors superiors de fatiga que els pacients amb genotip GG/GC (DME = 0.34).

Es va observar que els pacients amb el genotip CC del polimorfisme de la IL-6 presentaven un increment menor de simptomatologia depressiva (p= 0.005) i ansiosa (p= 0.004) al llarg del tractament antiviral que els pacients amb el genotip GG/GC. Respecte al polimorfisme del SERT es va observar que els pacients portadors del genotip LL presentaven menys símptomes depressius (p=0.21) i ansiosos (p= 0.15) durant el tractament, però aquestes diferències no eren estadísticament significatives.

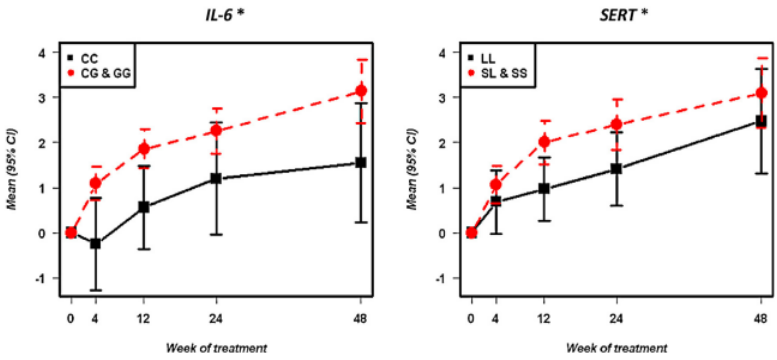

Figura. Evolució de la simptomatologia depressiva durant el tractament en funció dels genotips estudiats

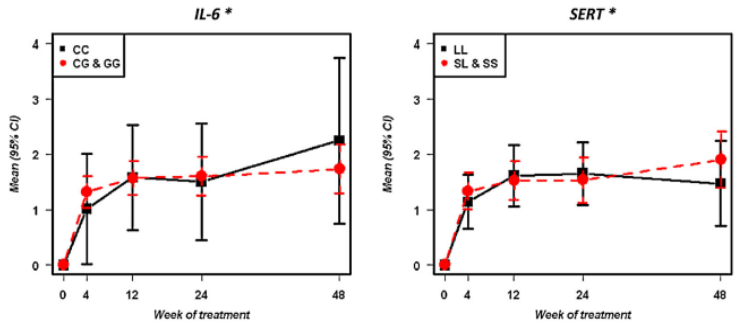

Figura. Evolució de la fatiga durant el tractament en funció dels genotips estudiats.

L'aparició de fatiga seguia un patró diferent al dels símptomes depressius i no havia cap assocació entre la fatiga induïda pel tractament antiviral i els genotips del polimorfisme de la *IL-6* (p= 0.055) o del *SERT* (p= 0.029).

No vam trobar cap interacció entre els polimorfismes de la IL-6 i del SERT en relació a la simptomatologia depressiva (p= 0.98), ansiosa (p= 0.99) o a la fatiga (p= 0.35).

4.2 Article original

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Serotonin and interleukin-6: The role of genetic polymorphisms in IFN-induced neuropsychiatric symptoms

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Genetic

Summary
Background: Cytokines and serotonin neurotransmission may play an important role on the development of psychopathological symptoms during interferon (IFN) treatment. The aim of the present study was to investigate the association between IFN-induced depression, anxiety and fatigue and functional genetic variants at the interleukin-6 gene (*IL-6*) and serotonin transporter gene (*SERT*).
Methods: 385 consecutive Caucasian outpatients with chronic hepatitis C initiating treatment with IFN-alpha and ribavirin were included. All patients were interviewed at baseline using the Structured Clinical Interview for DSM-IV (SCID-I) and those with a current major depressive disorder or anxiety disorder before starting treatment were excluded. Depression and anxiety were assessed at baseline during the treatment (at 4, 12, 24 and 48 weeks) using the Hospital Anxiety and Depression Scale and fatigue was evaluated using a visual analogue scale. The 5-HTTLPR region of *SERT* gene and the functional polymorphism located at the promoter region of *IL-6* gene (rs1800795) were genotyped.

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Results: Genotypic distribution was in the Hardy–Weinberg equilibrium for *SERT* ($p = 0.41$) and for *IL-6* ($p = 0.72$) polymorphisms. At baseline we found only a significant effect of *IL-6* polymorphism on fatigue symptoms. During antiviral treatment we reported that subjects with CC genotype (*IL-6*) presented significantly lower changes from baseline in IFN-induced depression ($p = 0.005$) and IFN-induced anxiety ($p = 0.004$). We did not find statistically significant differences on depression ($p = 0.21$) or anxiety ($p = 0.15$) between SS/SL and LL genotypes of *SERT*.

Conclusions: Genetic variations in the *IL-6* gene increase the risk of IFN-induced depression and anxiety. The *IL-6* polymorphism was associated with fatigue rates in patients with chronic hepatitis C before treatment. Our study confirms the role of inflammatory mechanisms in IFN-induced psychopathological symptoms.

1. Background

Hepatitis C virus (HCV) infection represents a serious public health problem that affects 130–170 million people worldwide (Wasley and Alter, 2000) and often causes chronic hepatitis C (CHC), liver cirrhosis and hepatocellular carcinoma (Schiff, 2011). The approved treatment for CHC is the combination of interferon-alpha (IFN-alpha) and antiviral ribavirin (RBV), which achieves a sustained virological response (SVR) of around 66%, although the rate varies considerably depending on the virus genotype (Maekawa and Enomoto, 2009). Interestingly, recent studies that added a protease inhibitor drug such as telaprevir or boceprevir to the standard treatment in patients with viral genotype-1 showed significantly higher SVR rates (Kwo et al., 2010; Jacobson et al., 2011). In 2011, the US Food and Drug Administration (FDA) and the European Medicines Agency approved both protease inhibitors (Pearlman, 2012). However, antiviral treatment has a high profile of side effects, including many depressive symptoms and even major depressive disorder (MDD) (Udina et al., 2012). Detecting and properly treating depression according to current guidelines and monitoring clinical issues are essential because patients developing psychopathological symptoms present poorer quality of life, lack of the treatment adherence, or alterations in virological response (Raison et al., 2005b; Martín-Santos et al., 2008).

Considering that some patients are more likely to present an IFN-induced depression during treatment, scientific research has focused on the identification of different social, clinical and biological factors that may lead to neuropsychiatric side effects (Smith et al., 2011). During antiviral treatment, a significant increase in serum cytokine levels has been observed (Bonaccorso et al., 2001). The activation of the immune system and the subsequent increase in cytokines are probably essential for good viral clearance, but they are also associated with behavioural changes and depression: patients with higher baseline levels of interleukin-6 (IL-6), interleukin-10 (IL-10) and the soluble form of the interleukin-2 receptor (sIL-2R), or those with a greater increase of IL-6 levels during treatment presented more depressive symptoms (Bonaccorso et al., 2001; Wichers et al., 2006). Moreover, when an exogenous cytokine like IFN-alpha is administered, mimicking certain infections or stress, proinflammatory cytokines are activated and induce alterations in brain neuroplasticity, neurotransmission and endocrine pathways (Dantzer, 2001; Capuron et al., 2001; Goebel et al., 2002; Anisman, 2009).

Genes related to the serotonin pathway may contribute in the genetic liability to both immune activation and depressive symptoms (Bufalino et al., 2012). Depression is widely related to alterations in serotonin neurotransmission, and specifically the serotonin transporter (SERT) may play an important role in their pathogenesis (Caspi et al., 2003). SERT protein is responsible for the reuptake of serotonin into the presynaptic terminal after it has been released in the synapses, thus decreasing serotonergic neurotransmission. Antidepressants like SSRIs selectively block this mechanism and initiate their therapeutic effect through the increase in serotonin at the synaptic cleft (Stahl, 1998). A polymorphism in the promoter region of the *SERT* gene (5-HTTLPR) has been reported to alter promoter function (Heils et al., 1996). Specifically, the presence of a long allele (L) is related to a higher transcription of SERT than the short allele (S) (Hariri et al., 2002). Subjects with a "higher transcription genotype" (LL homozygote) may present higher serotonin reuptake and therefore be less vulnerable to suffering depression (Caspi et al., 2003), and may also have better response to antidepressants like SSRIs (Serretti et al., 2007). The role of this and other polymorphisms involved in SERT function in IFN-induced depression has been previously studied, although in some cases with contradictory results (Kraus et al., 2007; Bull et al., 2009; Lotrich et al., 2009; Pierucci-Lagha et al., 2010). Small sample size and differences in subjects' characteristics, notably regarding ethnicity, may be the causes of the inconsistent results between studies.

As noted above, another factor that may play a fundamental role in IFN-induced depressive symptoms is the activity of pro-inflammatory cytokines, which directly regulate inflammatory response. Specifically, the activity of IL-6, a cytokine with an increased presence in cerebrospinal fluid during antiviral treatment, may be related to a central nervous system inflammatory response (Raison et al., 2009). Previous studies reported that a polymorphism in the promoter region of the *IL-6* gene (rs1800795) regulates its expression and thus IL-6 plasma concentrations (Fishman et al., 1998). Individuals who carry a G allele have higher concentrations of IL-6 (Belluco et al., 2003; Zakharyan et al., 2012), which is associated with a higher incidence of medical conditions such cardiovascular diseases (Riikola et al., 2009), and have a reduced chance of achieving SVR during IFN treatment in CHC (Yee et al., 2009). One recent study, which

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evaluated the association between the polymorphism at the promoter region of the *IL-6* gene and IFN-induced depression, showed that patients that carried the C allele ("low synthesizing IL-6") presented fewer depressive symptoms than those carrying the G allele (Bull et al., 2009). However, this study was based on a relatively small sample of patients evaluated with different depression scales.

Anxiety disorders are less common than depression during antiviral treatment but they may also be associated with a lower treatment adherence (Martín-Santos et al., 2008). Anxiety symptoms usually overlap with depressive symptoms, and both may share a common biological basis (Demirkan et al., 2011). Although anxiety has been poorly evaluated in previous biological and genetic studies of CHC, some studies have reported an association between anxiety and alterations of the inflammatory pathway such as elevations of plasma IL-6 or tumour necrosis factor alpha (TNF-alpha) concentrations (O'Donovan et al., 2010).

Fatigue is another common side effect of antiviral treatment, and the aetiology of fatigue symptoms in patients under antiviral treatment is controversial. There is evidence that fatigue may also be a "cytokine-mediated" illness since circulating concentrations of IL-6 are correlated with manifestations of acute sickness behaviour including fatigue (Vollmer-Conna et al., 2004). However, the polymorphism at the promoter region *IL-6* was not related with chronic fatigue syndrome (CFS) (Carlo-Stella et al., 2006) or fatigue in IFN-treated patients (Bull et al., 2009). Moreover, the serotonin system may also have a role in fatigue pathogenesis, since some studies have found a significant association between genetic variants at the 5HT transporter or serotonin 2A receptor (HTR2A) with CFS (Smith et al., 2008).

Based on the above evidence, the study of biological factors that may lead to IFN-induced neuropsychiatric symptoms is of potential interest, as they may help to improve management of patients under antiviral treatment and to understand the pathogenesis of depression and anxiety. The aim of the present study was to investigate the association between IFN-induced depression, anxiety and fatigue and functional genetic variants at the *IL-6* and *SERT* genes.

2. Methods

2.1. Selection of patients

The institutional review board approved the study protocol and all the participants provided written informed consent, including consent to genetic analysis. Three hundred and ninety-seven ($N = 397$) consecutive outpatients with chronic HCV infection who were candidates to receive combined treatment with IFN-alpha and ribavirin were recruited between 2005 and 2009 at the Liver Unit of a general teaching hospital in Barcelona (Hospital del Mar). The exclusion criteria for the study were as follows: insufficient knowledge of language, presence of concomitant liver diseases, decompensated cirrhosis or hepatocarcinoma, current drug or alcohol abuse, major depressive disorder or a current anxiety disorder within 24 weeks before starting treatment.

2.2. Study design

The study used a prospective cohort design. All patients were interviewed at baseline using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 1995) in order to assess current and past history of psychiatric disorders, and completed the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). The HADS is a self-administered questionnaire including 14 items scored on a 4-point Likert scale split into two sub-scales of depression and anxiety. It was specially designed to administer to patients with comorbid medical conditions, as it excludes somatic or vegetative symptoms from the depression subscale. To evaluate all patients the Spanish validated version of HADS was used (Herrero et al., 2003). The intensity of fatigue was assessed through a visual analogue scale (VAS), ranging from 0 to 100 mm (0 = no fatigue, and 100 = severe fatigue imaginable). Then, patients started treatment with pegylated interferon alpha-2a (PegIFN alpha-2a, 180 μg SC weekly) and RBV (800–1200 mg PO daily) for 24 or 48 weeks depending on the HCV genotype. After 4, 12, 24 and 48 weeks of treatment, patients again completed the HADS questionnaire and VAS. If at any point during the study patients showed clinically relevant anxiety or depressive symptoms as detected by the hepatologist, or had a HADS anxiety or depression score of 11 or greater, they were referred to a senior psychiatrist on the same day. The psychiatrists after a full clinical assessment, confirmed or ruled out the presence of a depressive or anxiety disorder diagnosis based on DSM-IV criteria using the anxiety or depression SCID module, and decided whether to initiate drug treatment. Psychopharmacological treatment was not controlled by study protocol, but the use of antidepressants and anxiolytics was recorded at baseline and during the follow-up. HCV RNA levels were measured with COBAS AMPLICOR-HCV (Roche) at weeks 4, 12, and 24 and at week 48 in patients with genotype 1, as well as at week 24 after completion of antiviral treatment to evaluate SVR.

2.3. Genotyping

A blood sample was obtained at baseline and genomic DNA was extracted from the peripheral blood leukocytes of the participants using Flexi Gene DNA kit (Qiagen Iberia, S.L., Spain) at the Banco Nacional de ADN (http://bancoadn.org) according to the manufacturer's instructions.

The 5-HTTLPR region of the *SERT* gene was genotyped through the amplification using polymerase chain reaction (PCR). The reaction mixture contained: 1× PCR amplification buffer and 1× PCR enhancer solution, 1.5 mM $MgSO_4$, 300 mM dNTPs, 0.5 pmol of each primer, 0.5 U of Taq DNA polymerase (Invitrogen) and 50 ng of genomic DNA as template. PCRs were performed with the following pairs of primers: FAM-50-GGCGTTGCCGCTCTGAA TGC-30 and 50-GAGGACTGAGCTGGACAACAACC AC-30, and FAM-50-GTCAGTATCACAGG-CTGCGAG-30 and 50-TGTTCCTAGTCTTACGCCAGT-30 for 35 cycles at 58 °C as annealing temperatures. A 10-ml total reaction volume was used and PCR products of allelic-specific amplifications (allele L, 528 bp; allele S, 484 bp) were detected on an automatic ABI 3730XL capillary sequencer and analyzed by GeneMapper Software v3.5 (Applied Biosystems).

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The functional polymorphism located at the promoter region of *IL-6* gene (rs1800795) was genotyped using a custom Illumina VeraCode GoldenGate Genotyping Assay (Illumina San Diego, CA, USA) according to the manufacturer's protocols. Raw data was processed using BeadStudio software (illumina San Diego, CA, USA) to infer SNP genotypes via a genotyping cluster. The genotyping assays were performed at the CeGen genotyping facilities, in the Barcelona Node (Centro Nacional de Genotipado, Genoma España).

2.4. Statistical analysis

To study the possible role of both the *IL-6* gene and the *SERT* gene in depression, anxiety, and fatigue, the study participants were grouped as follows: for *IL-6*, subjects with genotypes GG and GC, associated with higher IL-6 plasma levels, were grouped together (Fishman et al., 1998); for *SERT*, genotypes SS and SL, associated with lower basal activity, were grouped together (Hariri et al., 2002). Between-group differences with respect to baseline measures of the HADS and VAS scales, socio-demographics, and clinical variables of interest, were quantified by means of Cohen's *d*, the standardized mean difference (SMD) (Martocchio, 2009). To analyze the time course of the HADS and VAS scores, they were transformed to differences from baseline. Linear mixed models with repeated measures were used separately for each scale and polymorphism to study between-group differences – SS & SL vs. LL and GG & GC vs. CC, respectively – over time including only the corresponding baseline measure as well as time (4, 12, 24, and 48 weeks) as further covariates in the models. Other variables were not considered because of the similarity of their distribution between the study groups and the correlation structure used in all models was a general correlation structure not assuming any particular pattern for the correlations among repeated measures. These models were used for: (a) to estimate the between-groups mean differences over time and computing the corresponding 95% confidence intervals; and (b) to study whether HADS and VAS scales scores changed over time with respect to the baseline values within each group. For b, we used Dunnett's Many-to-one test. Time–polymorphism interactions were initially considered, but were subsequently removed from the models since the corresponding *p*-values were larger than 0.25 in all cases. In addition, a possible 5-HTTLPR*IL-6 interaction was tested in the framework of a linear mixed model with repeated measures – one for each scale of interest – including baseline value, time, both polymorphisms and the interaction between the two. All statistical analyses were performed with the statistical software package R (The R Foundation for Statistical Computing), version 2.13.1.

3. Results

Initially, 397 subjects with CHC were included. All of them were Caucasian except 12 subjects that were excluded for the sake of homogeneity of the sample. Hence, the final sample was composed by 385 Caucasian patients. Two hundred fifty-four patients (66%) were males and mean age was 44.2 years (standard deviation = 10.2). One hundred sixty subjects reported a history of substance abuse (41.6%); one hundred and eight presented a history of anxiety (28.1%) and one hundred fifty a history of depression (39%). All patients were euthymic and did not present a current anxiety disorder before starting treatment according DSM-IV criteria. At baseline, mean HADS-D score was 2.90 (SD = 3.08), HADS-A score 4.95 (SD = 3.72) and VAS score of fatigue 4.26 (SD = 2.66).

Details on the frequency of the *SERT* and *IL-6* variants are shown in Table 1. Genotypic distribution was in the Hardy–Weinberg equilibrium for *SERT* ($p = 0.41$) and for *IL-6* ($p = 0.72$) polymorphisms. At baseline, SS & SL and LL subjects (*SERT*, 5-HTTLPR) as well as GG & GC and C subjects (*IL-6*; rs1800795) were similar with respect to socio-demographic and clinical variables reported in Table 2, since for most of variables the SMD was less than 0.2, a value considered as a small effect size (Martocchio, 2009).

During follow-up, 45 patients dropped out (11.7%). Proportions of drop outs were fairly similar among genotypes (*SERT*: LL = 12.8%, LS/SS = 11.3%; *IL-6*: CC = 14.3%, CG/GG = 11.4%). Two hundred and twenty-eight patients achieved sustained virological response (*SERT*: LL = 61.5%, LS/SS = 58.8%; *IL-6*: CC = 54.8%, 59.8%). Table 3 reports the number of patients evaluated and patients taking antidepressants or anxiolytics at each time point.

3.1. Association between SERT polymorphism and neuropsychiatric symptoms

Baseline values of the HADS-D and HADS-A scales did not reveal significant differences between SS & SL and LL subjects (mean

Table 1 Details of the genetic variants studied.

Gene	Polymorphism	Change (alleles)	Location in gene	HWE *P* value	Genotyping rate (%)	MAF	Genotypes frequency *N* (%)	Function
SERT	5-HTTLPR	Indel 44bp	Promoter	0.41	100	47.7	L/L 109 (28.4) L/S 183 (47.8) S/S 91 (23.8)	L allele = three times the basal activity of the S variant[a]
IL6	rs1800795	G>C	Promoter	0.72	95	32.5	G/G 177 (46.0) C/G 166 (43.1) C/C 42 (10.9)	C allele = lower plasma concentration of IL-6 during immune activation[b]

[a] Lesch et al. (1996).
[b] Fishman et al. (1998).

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Table 2 Variables at baseline considering different genotypes.

Variable	*SERT* polymorphism			*IL-6* polymorphism		
	LL (*N* = 109) *N* (%)/*x* (SD)	LS and SS (*N* = 274) *N* (%)/*x* (SD)	SMD	CC (*N* = 42) *N* (%)/*x* (SD)	CG and GG (*N* = 343) *N* (%)/*x* (SD)	SMD[a]
Gender						
Male	75 (68.8)	177 (64.6)	0.06	29 (69)	225 (65.6)	0.05
Female	34 (31.2)	97 (35.4)		13 (31)	118 (34.4)	
Age	44.2 (9.8)	44.2 (10.5)	0	44.6 (9.8)	44.0 (10.4)	0.05
Civil status						
Married/engaged	75 (68.8)	188 (68.9)	0.1	27 (64.3)	237 (69.3)	0.03
Single	16 (14.7)	51 (18.7)		8 (19)	60 (17.5)	
Divorced/widowed	18 (16.5)	34 (12.5)		7 (16.7)	45 (13.2)	
History of mood disorder						
No	59 (56.7)	170 (62.3)	0.08	29 (72.5)	200 (59)	0.19
Yes	45 (43.3)	103 (37.7)		11 (27.5)	139 (41)	
History of anxiety						
No	67 (64.4)	202 (74)	0.15	28 (70)	243 (71.7)	0.03
Yes	37 (35.6)	71 (26)		12 (30)	96 (28.3)	
History of substance abuse						
No	54 (51.9)	163 (59.7)	0.11	24 (60)	194 (57.2)	0.04
Yes	50 (48.1)	110 (40.3)		16 (40)	145 (42.8)	
Anxiolytics at baseline						
No	92 (84.4)	226 (82.8)	0.03	37 (88.1)	283 (82.7)	0.1
Yes	17 (15.6)	47 (17.2)		5 (11.9)	59 (17.3)	
Antidepressants at baseline						
No	92 (84.4)	243 (88.6)	0.06	38 (90.4)	298 (86.8)	0.09
Yes	17 (15.6)	31 (11.4)		4 (8.6)	45 (13.1)	
Genotype						
1	65 (59.6)	149 (54.4)	0.05	24 (57.1)	190 (55.4)	0.01
2, 3 or 4	44 (40.4)	125 (45.6)		18 (42.9)	153 (44.6)	
HADS-D score	2.90 (3.1)	2.91 (3.1)	0	2.76 (3.5)	2.91 (3)	0.05
HADS-A score	5.01 (3.7)	4.91 (3.7)	0.03	4.52 (3.7)	5 (3.7)	0.13
VAS of fatigue score	3.91 (2.6)	4.41 (2.7)	0.19	3.46 (2.8)	4.26 (2.6)	**0.34**

[a] Standardized mean differences higher than 0.2 are in bold (Martocchio, 2009).

Table 3 Patients evaluated during the follow-up.

	Polymorphism	Genotype	Baseline	4 weeks	12 weeks	24 weeks[a]	48 weeks[a]	24 weeks after completion[b]
Number of patients evaluated	*SERT*	LL	109	106	103	100	53	100
		LS/SS	274	270	267	250	131	253
	IL-6	CC	42	40	40	36	20	38
		CG/GG	343	338	332	316	165	317
Patients taking anxiolytics (%)	*SERT*	LL	17 (15.6)	19 (17.9)	30 (29.1)	33 (33.0)	19 (35.8)	–
		LS/SS	47 (17.2)	61 (22.6)	80 (29.9)	70 (28.0)	46 (35.1)	–
	IL-6	CC	5 (11.9)	6 (15.0)	10 (25.0)	9 (25.0)	6 (30.0)	–
		CG/GG	59 (17.3)	74 (21.9)	100 (30.1)	94 (29.7)	60 (36.3)	–
Patients taking antidepressants (%)	*SERT*	LL	17 (15.6)	16 (13.2)	16 (15.5)	13 (13.0)	12 (22.6)	–
		LS/SS	31 (11.3)	32 (11.1)	44 (16.5)	45 (18.0)	30 (22.9)	–
	IL-6	CC	4 (9.5)	3 (7.5)	7 (17.5)	6 (16.6)	5 (25.0)	–
		CG/GG	45 (13.2)	41 (12.1)	53 (15.9)	52 (16.4)	38 (23.0)	–

[a] Patients received antiviral treatment during 24 or 48 weeks according to medical criteria.
[b] Assessment of sustained virological response.

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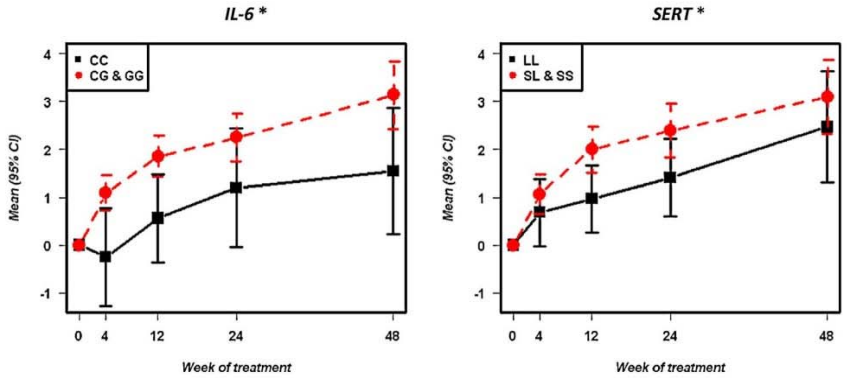

Figure 1 Evolution of depressive symptoms assessed by the Hospital Anxiety and Depression Scale (HADS scale rate) according to *IL-6* and *SERT* polymorphisms; linear mixed models with repeated measures were used to study between-group differences – SS & SL vs. LL and GG a GC vs. CC, respectively – over time. Baseline measure and time (4, 12, 24, and 48 weeks) were used as covariants in the models. *$p = 0.005$ and $p = 0.021$ for *IL6* and *SERT* respectively.

difference: −0.29; 95%-CI: [−1.08, 0.50]; $p = 0.47$ and −0.27; 95%-CI: [−1.12, 0.59]; $p = 0.54$).

During antiviral treatment subjects with LL genotype presented lower changes from baseline of depressive symptoms, although the differences were not statistically significant (0.47; [−0.26, 1.20]; $p = 0.21$). The mean scores were significantly different from baseline from week 4 onwards among SS & SL subjects ($p < 0.001$), and from week 12 onwards among LL subjects ($p = 0.002$). See Fig. 1.

With regard to anxiety, subjects with LL genotype presented lower changes from baseline, although the differences were not statistically significant either (0.46; [−0.17, 1.10]; $p = 0.15$). The mean scores differed significantly from baseline from week 24 onwards among SS & SL subjects ($p = 0.004$), but did not change significantly among LL subjects ($p > 0.6$ at all time points). See Fig. 2.

With regard to fatigue, baseline values of the VAS scale did not reveal significant differences between SS & SL and LL subjects (MD: 0.32; 95%-CI: [−0.27, 0.9]; $p = 0.29$). See Fig. 3. During antiviral treatment subjects with LL genotype presented lower changes from baseline in fatigue symptoms, although the differences were not statistically significant (0.28; [−0.15, 0.71]; $p = 0.2$). The mean scores were significantly different from baseline from week 4 onwards among both SS & SL subjects ($p < 0.001$) and LL subjects ($p < 0.001$). See Fig. 4.

3.2. Association between IL-6 polymorphism and neuropsychiatric symptoms

Baseline values of the HADS-D and HADS-A scales did not reveal significant differences either between GG & GC and C subjects (mean difference: 0.41; [−0.72, 1.54]; $p = 0.47$ and 0.69; [−0.53, 1.91]; $p = 0.26$).

We found a significant effect of the polymorphism on depressive symptoms: Subjects with CC genotype (*IL-6*) presented significantly lower changes from baseline of depression (1.51; [0.46, 2.56]; $p = 0.005$). The mean scores were

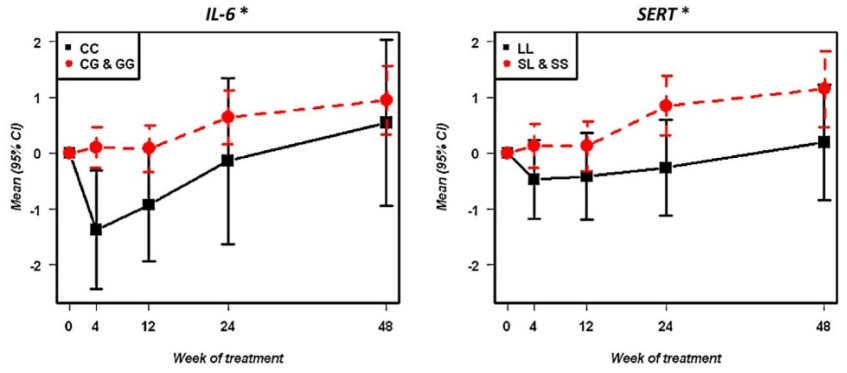

Figure 2 Evolution of anxiety symptoms assessed by the Hospital Anxiety and Depression Scale (HADS scale rate) according to *IL-6* and *SERT* polymorphisms; linear mixed models with repeated measures were used to study between-group differences – SS & SL vs. LL and GG & GC vs. CC, respectively – over time. Baseline measure and time (4, 12, 24, and 48 weeks) were used as covariants in the models. *$p = 0.004$ and $p = 0.15$ for *IL6* and *SERT* respectively.

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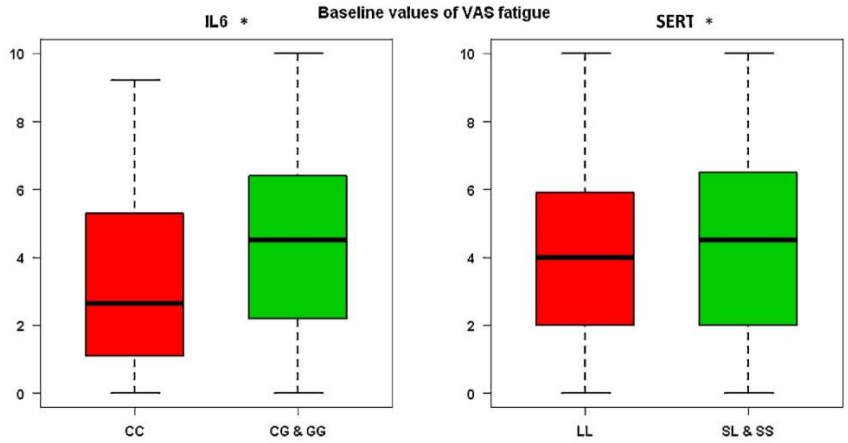

Figure 3 Baseline fatigue according to *IL-6* and *SERT* polymorphisms. *Standardized mean difference (Cohen's *d*) was 0.34 for *IL-6* and 0.19 for SERT.

significantly different from baseline from week 4 onwards among GC & GG subjects ($p < 0.001$), but did not change significantly among CC subjects ($p > 0.25$ at all time points) See Fig. 1.

As regards anxiety symptoms, subjects with CC genotype presented significantly lower changes in anxiety from baseline (1.34; [0.43, 2.25]; $p = 0.004$). The mean scores differed significantly from baseline from week 24 onwards among GC & GG subjects ($p = 0.007$), but did not change significantly over time among CC subjects ($p > 0.2$ at all time points) See Fig. 2.

With regard to fatigue, baseline values of the VAS scale revealed significant differences between GG & GC and CC subjects (0.94; [0.02, 1.87]; $p = 0.046$) See Fig. 3. During antiviral treatment, subjects with CC genotype presented non-significantly lower changes in fatigue from baseline (0.60; [−0.02, 1.26]; $p = 0.055$). The mean scores were significantly different from baseline from week 4 onwards among GC & GG subjects ($p < 0.001$) and from week 12 onwards among CC subjects ($p < 0.001$). See Fig. 4.

3.3. Interaction between genes

We did not find a gene−gene interaction effect on changes from baseline of the fatigue scores ($p = 0.35$), or on anxiety ($p = 0.99$), or on depression scores ($p = 0.98$).

4. Discussion

This study reports an association between a polymorphism in the *IL-6* gene and the presence of depression and anxiety

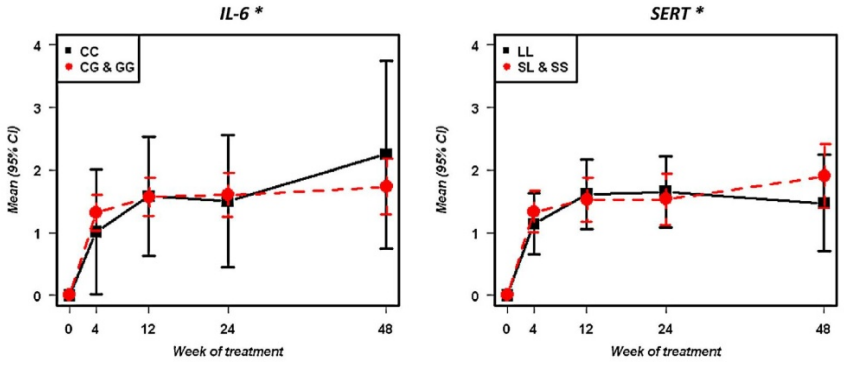

Figure 4 Evolution of fatigue symptoms assessed by the visual analogue scale of fatigue (VAS) according to *IL-6* and *SERT* polymorphisms; linear mixed models with repeated measures were used to study between-group differences − SS & SL vs. LL and GG & GC vs. CC, respectively − over time. Baseline measure and time (4, 12, 24, and 48 weeks) were used as covariants in the models. *$p = 0.06$ and $p = 0.2$ for *IL6* and *SERT* respectively.

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symptoms during antiviral treatment. Individuals carrying LL genotypes in the *SERT* polymorphism showed a trend towards lower rates of depression and anxiety, although the differences were not statistically significant. Fatigue was only related to the *IL-6* polymorphism at baseline.

This study replicates some of the results of a previous study (Bull et al., 2009) finding that homozygous CC carriers at rs1800795 (*IL-6* gene) were "less vulnerable" to IFN-induced depression. However, other authors did not find the same association between this genotype and moderate or severe IFN-induced depression (Smith et al., 2011). In fact, to our knowledge, this is the first report of an association between IFN-induced anxiety and the *IL-6* genotype observing that CC homozygous subjects were less likely to present anxiety symptoms than those carrying the G allele. Considering that CC genotype is associated with a low transcription of IL-6, these findings are consistent with previous studies on major depression or IFN-induced depression, where higher IL-6 levels have been associated with depressive symptoms (Bonaccorso et al., 2001; Howren et al., 2009). Moreover, higher levels of IL-6 have also been reported in anxious patients (O'Donovan et al., 2010). According to a recent meta-analysis of IFN-induced depression and previous studies, high baseline levels of IL-6 were found to be a risk factor for a major depressive episode during antiviral treatment (Udina et al., 2012).

We found a non-significantly lower rate of IFN-induced depressive symptoms in individuals carrying LL alleles in the *SERT* polymorphism. Lotrich et al. (2009) and Bull et al. (2009) reported a significantly lower rate of depression associated with antiviral treatment in L homozygote's individuals, but Kraus et al. (2007) did not find significant differences between polymorphisms. On the other hand, Pierucci-Lagha et al. (2010) reported that "Caucasian-non Hispanic" patients carrying LL alleles were more likely to present IFN-induced depression, and that the L allele was only protective in "Caucasian—Hispanic" patients. Regarding anxiety, we found lower scores in subjects carrying the LL genotype at *SERT* gene, but the differences were not significant. Previous studies have related this serotonin transporter genotype with depression (Caspi et al., 2003) and suicide (Gonda et al., 2011). Lesch et al. (1996) reported that the short form of the 5-HTTLPR polymorphism was associated with increased neuroticism, and a recent meta-analysis showed that 5-HTTLPR was related to selective attention, to negative information and was involved in the aetiology of anxiety, and identified it as a potential intermediate phenotype for anxiety disorders (Pergamin-Hight et al., 2012).

Our study suggests that inflammatory pathways may play an important role in the pathogenesis of both IFN-induced depression and anxiety. It is known that immune system activation induces numerous neuroendocrine, neurotransmitter and neuroplastic changes that may lead to a major depressive disorder through immune-signalling molecules such as IL-6, TNF-α, or IL-1β (Anisman, 2009; Eyre and Baune, 2012). These cytokines may modulate the serotonergic system by upregulating indoleamine 2,3-dioxygenase (IDO) (Fallarino et al., 2012) (Kim et al., 2012), an enzyme in the kynurenine/tryptophan pathway, decreasing levels of plasma tryptophan and therefore increasing levels of kynurenine and causing lower levels of serotonin in the brain, factors that may lead to depression (Raison et al., 2010b) (Smith et al., 2011). Anxiety and depressive symptoms have been associated with dysfunctions of serotonergic neurotransmission in areas such as the hippocampus, the amygdala and the prefrontal cortex (Anisman, 2009). However, according to the present data, the *SERT* polymorphism has a small or no effect on the pathogenesis of IFN-induced depression. As hypothesized by Bull et al. (2009), the effect of *SERT* polymorphism would be evident only in the presence of certain mechanisms of serotonin pathway such as normal tryptophan availability, a factor which may be altered (via IDO enzyme stimulation) in case of high levels of cyotkines. However, in our study we did not find an interaction between the two genes in the pathogenesis of depression or anxiety. The *SERT* polymorphism seems to have the same effect on depressive symptoms in patients carrying the "low IL-6 synthesizer" genotype ($N = 208$) as in those carrying the "high IL-6 synthesizer" genotype ($N = 177$). Interestingly, our results support the findings of a recent study where tryptophan availability in cerebrospinal fluid was not associated with depressive symptoms (Raison et al., 2010b). However, a high IDO activity (as in the case of IL-6 stimulation) may produce depressive symptoms through the activation of the kynunerine pathway (Raison et al., 2010b) (Dantzer et al., 2011). In any case, the increase of IL-6 concentrations and further upregulation of IDO enzyme expression in areas such the hippocampus (Kim et al., 2012) represent only a part of a complex physiopathological process (Eyre and Baune, 2012). Several factors may be related to physiological changes associated with neuropsychiatric symptoms such as alterations in the hypothalamic—pituitary—adrenal axis (Raison et al., 2010a), or a down-regulation of 5-HT_{1A} receptors (Cai et al., 2005). In regard to this fact, Kraus et al. (2007) reported that G/G-homozygosis for a 5-HT_{1A} polymorphism (HTR1A gene) increased the risk of developing depression during antiviral treatment. Moreover, polymorphisms of phospholipase A2 (PLA2) and cyclooxygenase 2 (COX2) (Su et al., 2010) have been associated with IFN-induced depression and the IL28B polymorphism has been associated with individual neuropsychiatric symptoms such as appetite, energy, and sleep complaints during antiviral treatment (Lotrich et al., 2010).

Interestingly, in agreement with previous studies (Bull et al., 2009; Raison et al., 2005a) we observed that changes in fatigue symptoms during antiviral treatment followed a different pattern from depressive symptoms. Fatigue appeared mainly during the first four weeks of treatment and then remained stable, while depression appeared later and increased in late stages of therapy. This result is consistent with previous data indicating different temporal dynamics for IFN-induced fatigue and mood symptoms (Capuron et al., 2002). We did not find an association between both polymorphisms and IFN-induced fatigue. However, CHC subjects carrying the CC genotype presented lower rates of fatigue before starting antiviral treatment. This finding supports the hypothesis that fatigue in chronic hepatitis C may be related with high levels of inflammation: for example, a high IL-6 concentration. However, it is likely that other biological factors play a leading role in IFN-induced fatigue since the increases in fatigue rates during treatment were similar in all the genotypes. According to previous studies, fatigue related with antiviral treatment may be produced through biological mechanisms other than depression; it may

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be caused by toxic effects of IFN-alpha on blood cell counts (Collantes and Younossi, 2005) as well as by cytokines targeting ganglia nuclei and altering the dopamine pathway, whereas depression may be mainly related to alterations in the serotoninergic neurotransmission (Capuron et al., 2007). Our study suggests that antiviral treatment may induce two overlapping syndromes through different biological mechanisms: a specific psychiatric syndrome including mood alterations, cognitive complaints or anxiety, and a more non-specific syndrome including neurovegetative symptoms such as fatigue (Raison et al., 2005a).

This study has some strengths and limitations. We controlled potential confounding variables such as baseline psychiatric medication, depression history and several socio-demographic variables. Results should be interpreted cautiously considering that the initiation of psychopharmacological treatment during follow-up was not controlled by the study protocol. However, we reported the use of antidepressants and anxiolytics at baseline and at each time-point of the follow-up. Proportions of patients under treatment were fairly similar among genotypes.

Although the total sample comprised 385 patients, only 42 were homozygous for the *IL-6* polymorphism (CC). This group presented lower fatigue scores at baseline, and lower levels of anxiety and depression, but since these subjects represented a small part of the Caucasian population (11%) and an even smaller part of the Asian population (Su et al., 2010), the clinical application of the results may be limited. This study was only based on a Caucasian population, limiting its interpretation and application to non-Caucasian patients. It must be noted, however, that previous studies with similar results were based on smaller samples than ours (Kraus et al., 2007; Lotrich et al., 2009), and that they studied patients assessed with different scales to evaluate depression (Bull et al., 2009). We decided to use the HADS scale, validated for patients with medical conditions, because it excludes neurovegetative symptoms and avoids overlapping with symptoms of depression. However, this scale does not evaluate insomnia, a common symptom of depression which previous studies have associated with cytokine concentrations (Prather et al., 2009; Franzen et al., 2010) and with SERT polymorphism (Lotrich et al., 2012). Lastly, three more limitations of the study were the use of a one-item single analogical scale of fatigue, the absence of novel allelic variants of *SERT* gene such as the A/G substitution in the L allele in the genotyping (Avula et al., 2011), and the lack of baseline IL-6 plasmatic concentration to correlate with clinical symptomatology and genetic results (Fishman et al., 1998; Bonaccorso et al., 2001; Zakharyan et al., 2012).

In conclusion, our study suggests that inflammation may play a leading role in the neuropsychiatric symptoms observed in CHC and during antiviral therapy. Subjects who carry genotypes associated with a low production of pro-inflammatory cytokines such IL-6 are less likely to present these symptoms. Although the *SERT* polymorphism did not present an association with neuropsychiatric symptoms, it is likely that other issues related to neurotransmission, neuroprotection or inflammation play a role in these conditions. Future research focused on genetic and other biological mechanisms underlying IFN-induced neuropsychiatric symptoms would be of particular interest.

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Conflict of interest

None of the authors have any conflicts of interest to declare with respect to this manuscript.

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CAPÍTOL 5
Estudi 3

5. Estudi 3

Prophylactic antidepressant treatment of interferon-induced depression in chronic hepatitis C: A systematic review and meta-analysis. Marc Udina, Diego Hidalgo, Ricard Navinés, Xavier Forns, Ricard Solà, Magí Farré, Lucile Capuron, Eduard Vieta i Rocío Martín-Santos. En el moment del dipòsit de la tesis, enviat per a la seva publicació i en procés de revisió externa a Annals of Internal Medicine.

5.1 Resum de l'estudi

Objectius

Revisar sistemàticament la literatura publicada que avalua l'efecte de l'administració profilàctica d'antidepressius en els pacients amb tractament antiviral. Aquesta revisió permetria conèixer:

- ✓ L'efectivitat dels antidepressius en la prevenció de la depressió major induïda pel tractament amb IFN-alfa i ribavirina per HCC.
- ✓ L'efectivitat dels antidepressius en la reducció de la simptomatologia depressiva durant el tractament antiviral
- ✓ El perfil de tolerabilitat (efectes indesitjats) dels antidepressius durant el tractament antiviral i el seu impacte en la resposta virològica sostinguda

Metodologia

Es va dur a terme una revisió sistemàtica i metanàlisi d'assajos clínics controlats i aleatoritzats, relitzant un protocol previ i seguint pas a pas les pautes indicades al PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [90, 91]. Es van seleccionar només els estudis amb una bona descripció metodològica, de mostra major de 10 subjectes, amb inici d'antidepressiu profilàctic a dosis terapèutiques, amb grup control tractat amb placebo, doble cec, i que realitzaven un diagnòstic d'episodi depressiu major mitjançant criteris diagnòstics DSM. Tots els pacients dels estudis havien d'estar eutímics abans d'iniciar el tractament antiviral. Es van excloure aquells estudis de

seguiment menor de 12 setmanes, els no aleatoritzats i els estudis naturalístics. La cerca d'articles es realitzà de forma sistematitzada a través de MEDLINE, PsycINFO, EMBASE, Cochrane Library i Clinicaltrials.gov mitjançant les paraules clau: "hepatitis C, interferon-alpha, peginterferon, pegylated, interferon, depression, mood, prevention, prophylactic, prophylaxis, antidepressant". La cerca i extracció de dades es va realitzar de forma independent per dos autors de l'estudi (Marc Udina i Diego Hidalgo).

Es van calcular les OR de les variables qualitatives (depressió major, efectes indesitjats i resposta virològica sostinguda) i les DM de les quantitatives (símptomes depressius basals, a les 12 i a les 24 setmanes de tractament). Per a la variable principal (episodi depressiu major) es va calcular el número necessari de pacients a tractar per a prevenir un episodi (NNT). El risc de biaix es va avaluar mitjançant l'instrument recomanat per la Cochrane [92]. Es va realitzat estudi de sensitivitat. No es va fer metaregressió degut al baix nombre d'articles seleccionats [93]. Es va avaluar l'heterogenitat i el risc de biaix de publicació, que es va expressar en forma de *Funnel Plot* (Begg i Egger) [85 86]. Es va utilizar el programa Review Manager versió 5.0.

Resultats

Es van seleccionar set articles, que incloien 591 pacients amb HCC que iniciaven tractament amb IFN alfa i ribavirina. Prèviament al tractament els pacients es van aleatoritzar per a l'administració de escitalopram (n=197), paroxetina (n=42), citalopram (n=53) o placebo (n=299).

Els ISRS reduiren la incidència de depressió major durant el tractament antiviral (OR 0.53, IC95% 0.33 a 0.84). El NNT va ser de 12 (IC95% 7.0 a 37.9). L'anàlisi realitzat per a cada fàrmac per separat no va mostrar diferències significatives en relació a placebo. Pel que fa a la simptomatologia depressiva no havia diferències significatives entre els grups placebo i tractat amb ISRS a nivell basal i a les 12 setmanes de tractament. A les 24 setmanes de tractament el grup tractat amb ISRS presentava menys símptomes depressius que els pacients tractats amb placebo (DM -2.18, IC95% -4.25 a -0.10).

Pel que fa als efectes indesitjats, els antidepressius van augmentar l'aparició de símptomes de mareig durant el tractament (OR 2.65, IC95% 1.46 a 4.80) però van disminuir els símptomes de dolor muscular i articular (OR 0.63, IC95% 0.42 a 0.96). No

havia diferències entre grups pel que fa a la resposta virològica sostinguda (OR 1.22, IC95% 0.58 a 2.57). Tampoc va haver diferències en el número de pacients que no van completar el tractament per qualsevol causa (OR 0.77, IC95% 0.52 a 1.13) o a causa d'efectes indesitjats greus (OR 0.98, IC95% 0.51 a 1.90).

5.2 Article original (en revisió)

Udina et al, 2013 "Under review"

Words: 3137
Tables: 1
Figures: 3
Supplementary appendix: 1

Prophylactic antidepressant treatment of interferon-induced depression in chronic hepatitis C: A systematic review and meta-analysis

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Abstract (274 words)

Background: Prevention of depression related to antiviral treatment for chronic hepatitis C is essential, because depressive patients often show a poor quality of life, suicidal ideation, a lack of treatment adherence and alterations to their sustained virological response.

Purpose: To assess the utility of prophylactic administration of antidepressants in preventing a major depressive episode during antiviral treatment for chronic hepatitis C.

Data sources: The MEDLINE, PsycINFO, EMBASE, Clinicaltrials.gov and Cochrane databases.

Study selection: Double-blind, placebo, randomized-controlled trials using antidepressants prophylactically before starting antiviral therapy for chronic hepatitis C were included. At baseline, patients included did not present depression (DSM-IV-TR criteria).

Data extraction: Data were extracted independently by two investigators.

Data syntesis: Seven studies were included. In these, 591 patients were randomly assigned to antiviral treatment and another intervention: escitalopram (n=197), paroxetine (n=42), citalopram (n=53) or placebo (n=299). Selective serotonin reuptake inhibitors, as a group, reduce the incidence of a major depressive episode during antiviral treatment (odds ratio 0.53, 95% confidence interval 0.33 to 0.84). The estimated number needed to treat (NNT) was 12 (95% CI 7.0 to 37.9). Selective serotonin reuptake inhibitors reduce depressive symptoms at 24 weeks of treatment (mean difference -2.18, 95% CI -4.25 to -0.10). In regard to side effects, only dizziness was associated with administration of antidepressants (OR 2.65, 95% CI 1.46 to 4.80). There were no differences in sustained virological response (OR 1.22, 95% CI 0.58 to 2.57).

Limitations: There was a degree of heterogeneity between studies with respect to the sample characteristics.

Conclusions: Administration of selective serotonin reuptake inhibitors before starting antiviral treatment reduces the incidence of interferon-induced depression, with a relatively moderate prophylactic impact and good tolerability.

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Introduction

Major depressive disorder is the leading cause of life disability and one of the most expensive illnesses for society, both in terms of direct and indirect costs (1 - 2) The prevalence of depression is important in patients with medical conditions related to inflammatory processes, such as cardiovascular diseases, rheumatoid arthritis, autoimmune disorders, obesity or chronic hepatitis C (CHC) (3). Moreover, there is substantial evidence for the role of cytokine therapies in inducing depressive symptoms in clinical populations (4 - 5).

Hepatitis C virus infection is an important public health problem that affects 130-170 million people worldwide (6 - 7). The approved treatment for CHC is the combination of pegylated interferon-alpha (IFN-alpha) and antiviral ribavirin (RBV) for 24 or 48 weeks (8). Recently, the US Food and Drug Administration and the European Medicines Agency recommended the addition of a protease inhibitor in patients with viral genotype-1 (9 - 10). The problem with antiviral treatment is its high profile of side effects, including fatigue, insomnia, irritability and low mood, with a full major depressive episode (MDE) being observed in around 25% of patients treated (11) Prevention or proper management of IFN-induced depression is therefore essential, because depressive patients often show a poor quality of life, suicidal ideation, a lack of treatment adherence and alterations to their sustained virological response (SVR) (5).

Although the exact neurobiological basis of IFN-induced depression is not known, there is evidence that administration of an exogenous cytokine such as IFN-alpha leads to the activation of certain proinflammatory cytokines, causing alterations in brain apoptotic mechanisms and neurotransmission (4). Cytokine-induced alterations within the central nervous system (CNS) may rely on different mechanisms, including passage of cytokines through leaky regions of the blood-brain barrier and activation of nervous pathways. A high concentration of proinflammatory cytokines with a CNS action may modulate the serotonergic system, a factor related to depression (12). Antidepressants such as selective serotonin reuptake inhibitors (SSRIs) selectively block the reuptake of serotonin into the presynaptic terminal and initiate their therapeutic effect through the increase of serotonin at the synaptic cleft (13). SSRIs have been proposed as a useful treatment for IFN-induced depression (14). Given the high incidence of depressive illness during antiviral treatment and its potential impact

on quality of life and virological response, the prevention of IFN-induced depression would be a cost-effective intervention. However, prophylactic administration of antidepressants in all patients starting antiviral therapy for chronic hepatitis C is controversial (15 - 16).

The aim of this study was to carry out a systematic review and meta-analysis of data that could help to assess the benefits of using prophylactic antidepressants during antiviral treatment for chronic hepatitis C.

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Methods

Data for this systematic review were collected with an advanced document protocol in accordance with the PRISMA guidelines (17). (*Appendix, I-II*)

All steps in the literature search, study identification, study selection, quality assessment and data extraction were performed independently by two clinical researchers (MU and DH). Disagreements were resolved by discussion, and consensus was achieved in the selection of articles for analysis.

Study identification

A comprehensive, computerized literature search was conducted in MEDLINE, PsycINFO, EMBASE, the Cochrane Library and Clinicaltrials.gov. We searched for relevant studies published from the earliest available online year until October 2012, using the following phrase and Boolean logic algorithm: "hepatitis and c and (interferon-alpha OR peginterferon OR (pegylated and interferon)) and (depression OR mood) and (prevention OR prophylactic OR prophylaxis OR antidepressant)". We also searched for any additional studies in the reference list of the articles identified and conference proceedings. Only articles written in English, Spanish or French were included.

After examining the titles and abstracts, full-text articles of potentially relevant studies were obtained. Inclusion and exclusion criteria were then applied, and the selected articles were included in the systematic review.

Study selection

Articles were reviewed using the following inclusion criteria: 1) Randomized clinical trials using prophylactic antidepressants in patients receiving antiviral therapy for CHC; 2) Presence of control group treated with placebo; 3) Double-blind; 4) Articles with a detailed description of methods and methodological background that assess MDD using a validated instrument or a semi-structured interview performed by a trained clinician based on DSM-IV criteria; 5) Psychiatric assessment before starting the

treatment, and a good description of this; 6) Euthymia at baseline (not fulfilling criteria for a DSM-IV/ICD depressive episode); and 7) Initiation of antidepressants before starting antiviral therapy at therapeutic doses.

The following exclusion criteria were applied: 1) Naturalistic, non-randomized or non-placebo controlled studies; 2) Follow up < 12 weeks; 3) Articles concerning overlapping samples; and 4) Sample size < 10.

Quality of sequence generation, allocation concealment, blinding, missing outcome data, selective reporting and other biases were assessed with the Cochrane risk of bias method (18).

Summary measures (outcomes)

The primary outcome measure was the onset of a MDE according to DSM-IV criteria during the antiviral treatment.

The secondary outcomes were: 1) Rates of depressive symptomatology during antiviral treatment, based on a validated rating scale; 2) The presence of potential side effects attributed to combination treatment (antidepressant and antiviral therapy); and 3) Proportion of patients achieving SVR.

Data extraction

For each article we recorded the author, year of publication, design, characteristics of the sample, viral co-infection, adjunctive psychopharmacology, instruments for assessing depression, dose and type of IFN-alpha, adjunctive RBV follow-up time, and data about discontinuation and patients lost to follow-up. Outcomes of incidence of MDE, SVR, depressive symptoms and potential side-effects were abstracted for each group.

Statistical analysis

The odds ratio (OR) with 95% confidence interval was used to estimate the strength of association of dichotomous variables. For statistically significant results we calculated the number needed to treat statistic (NNT), and its 95% confidence interval as the inverse of the risk difference. The mean difference (MD) with 95% confidence interval was used to estimate the strength of association of quantitative variables.

Heterogeneity between trials was assessed using both the chi-square and I-square tests. Between-study heterogeneity was considered to be significant for a p-value < 0.10 on the chi-square test. If there was no heterogeneity, a fixed model was used. In the event of heterogeneity, a random effects model was used.

To establish the robustness of the primary outcome by sensitivity analyses, we applied a random effects model; and excluded studies with higher risk of bias and studies with short follow-up.

Publication bias was examined in a funnel plot of log OR against its standard error, using Begg's test, while the degree of asymmetry was tested statistically using Egger's unweighted regression asymmetry test (19, 20).

Statistical analyses were performed using Review Manager (RevMan) [Computer program] Version 5.0 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, Oxford, UK, 2008).

Results

Using keywords and cross-referenced bibliographies, 144 studies were identified and examined in depth. One hundred and thirty-seven articles were rejected because inclusion criteria were not met. (*Figure 1* and *Appendix, III*) Finally, seven different studies were selected for systematic review (15, 16, 21 – 25). Data were extracted from six full original articles (15, 16, 21, 23 - 25) and one poster presented at an international congress (26). The selected studies were published between 2007 and 2012 and all were reported in English. This review includes a total of 591 CHC patients who were randomly allocated to initiate antiviral treatment plus antidepressant (N=292) or placebo (N=299).

Characteristics of the studies

The characteristics of the selected studies are reported in *Table 1*. Three studies used escitalopram (10-15 mg/day) (15, 16, 21), two citalopram (20 mg/day) (22 – 23) and two paroxetine (20-40 mg/day) (24 – 25). All the studies excluded patients with a current major depressive episode and those treated with other antidepressants. Five studies included patients with a history of a depressive episode in both the case group and the control group (range of 10-40% for each group). Twenty-eight patients treated with a SSRI (9.6%) and 39 treated with placebo (13%) presented a past depressive episode.

In terms of potential bias, all studies were randomized but only 5 studies had an adequate description of randomisation and 4 of allocation concealment. All studies were described as double-blind. Some studies did not report lost to follow-up, SVR or potential side effects. Sources of other bias were: disbalance in risk factors for depression between groups and short follow-up (12 weeks). (*Appendix, IV-V*)

Incidence of depression

All the selected studies reported the incidence of depression during follow-up. A total of 292 patients treated with SSRI and 299 patients treated with placebo were included in the analysis of incidence. Thirty-three patients (11.3%) in the antidepressant

group and 59 (19.7%) in the placebo group presented a MDE during follow-up. According to our meta-analysis the use of any SSRI reduced the incidence of IFN-induced depression, as compared with placebo (odds ratio 0.53, 95% confidence interval 0.33 to 0.84). (*Figure 2*) The overall estimated number needed to treat (NNT) in order to prevent one depression was 12 (7.0 to 37.9).

The meta-analysis was also performed for each type of antidepressant separately. Three studies that included 197 patients treated with escitalopram and 192 patients treated with placebo reported no significant differences in depression rates (odds ratio 0.52, 95% confidence interval 0.17 to 1.59). Neither were there any differences in depression rates according to the analysis of 1) 42 patients treated with paroxetine versus 52 patients treated with placebo (0.84; 0.31 to 2.23), and 2) 53 patients treated with citalopram versus 55 patients treated with placebo (0.49, 0.18 to 1.35). (*Figure 2*)

Changes in depressive symptoms

Five of the seven studies reported mean rates and standard deviation of depressive symptoms at baseline and at least one follow-up point (15, 16, 21, 24 - 25). All of these studies reported depression rates using the Montgomery and Asberg Depression scale (MADRS), and these data were extracted for meta-analysis. Five studies examined MADRS rates at baseline and at 12 weeks of antiviral treatment, while four of these also did so at 24 weeks (16, 21, 24 - 25). At baseline, MADRS rates did not differ between cases and controls (mean difference 0.26, 95% confidence interval -0.36 to 0.88). However, the SSRI group presented significantly fewer depressive symptoms at 24 weeks of treatment (-2.18, -4.25 to -0.10), although this was not evident at 12 weeks (-1.45, -3.24 to 0.34). (*Figure 3*)

Side effects

Three studies reported a list of the incidence of different symptoms attributed to the combination of antiviral treatment and SSRI or placebo (15, 16, 25). Two studies used escitalopram and one paroxetine, and together they assessed a total of 184 patients treated with SSRI and 187 patients treated with placebo.

Compared with placebo, administration of a prophylactic antidepressant increased symptoms of dizziness (odds ratio 2.61, 95% confidence interval 1.44 to 4.72). Conversely, patients treated with SSRIs reported less muscle or joint ache (0.63, 0.42 to 0.96). According to our meta-analysis there were no differences between SSRI and placebo in relation to the following symptoms: sexual dysfunction (2.34, 0.97 to 5.61), fatigue (0.83, 0.56 to 1.25), sleep disturbance (0.76, 0.50 to 1.15), headache (0.81, 0.53 to 1.24), nausea (0.97, 0.63 to 1.48), gastrointestinal distress/diarrhoea (1.55, 0.93 to 2.58), skin problems (0.92, 0.61 to 1.40), loss of appetite (1.09, 0.65 to 1.82), hair loss (1.10, 0.64 to 1.90), respiratory symptoms (0.64, 0.40 to 1.03) or flu-like symptoms (0.81, 0.51 to 1.27). (*Appendix, VI*)

Sustained virological response

Four studies addressed SVR in patients treated with antidepressant (N=190) and in those given a placebo (N=192) (15, 16, 23, 24). According to our analysis there were no differences in SVR between these two groups (Odds ratio 1.22, 95% confidence interval, 0.58 to 2.57). (*Appendix, VII*)

Discontinuation and lost to follow-up

Six of the seven studies reported the number of patients who discontinued antiviral treatment or were lost to follow-up 15, 16, 21, 23, 25 – 26). These patients accounted for 80 subjects in the placebo group (28.6%) and 65 subjects in the SSRI group (23.4%) (odds ratio 0.77, 95% confidence interval 0.52 to 1.13). Only four studies specified the reasons for discontinuation (15, 16, 21, 25). Potential side-effects were the reason for discontinuation in 20 patients of the placebo group (8.8%) and in 19 patients of the SSRI group (8.4%) (0.98, 0.51 to 1.90). (*Appendix, VIII*)

Subgroup analysis, sensitivity analysis and meta –regression

We were unable to perform a sub-analysis examining the potential benefit of antidepressants among the subjects with a history of depression. Only one study

reported full data about incidence of MDE during antiviral treatment in this subgroup of patients: 37.5% of patients treated with escitalopram and 66.6% treated with placebo developed depression (N=23) (21).

Sensitivity analyses of the primary outcome showed that findings were similar when the random effects model was used (odds ratio 0.53, 95% confidence interval 0.32 to 0.90), including only studies with at least 24 weeks of follow-up (0.45, 0.27 to 0.74) and excluding articles with higher risk of bias (0.48, 0.28 to 0.82). (*Appendix, IX*)

Meta-regression was not performed due to number of selected articles was less than 10 (18).

Heterogeneity and publication bias

Significant heterogeneity was identified in the comparison of 1) escitalopram versus placebo (Chi^2=5.19/ p=0.07), 2) sustained virological response (Chi^2=7.35/ p=0.06) and 3) MADRS rates at 12 (Chi^2=36.44/ p<0.00001) and 24 weeks (Chi^2=16.97/ p=0.0007) of treatment, thereby justifying the use of random effects models. We found no significant heterogeneity between studies with respect to the other variables evaluated.

The funnel plots revealed no publication bias among the selected studies. (*Appendix, X*)

Discussion

In this systematic review we report that prophylactic administration of any SSRI before starting antiviral treatment for CHC reduces the subsequent incidence of a major depressive episode (DSM-IV). However, the impact of the intervention was moderate (NNT=12) and the reduction in depressive symptoms (MADRS scale) was not significant until week 24 of antiviral treatment. Adding a SSRI to the antiviral treatment was generally well tolerated, although our review found that it was associated with an increase in symptoms of dizziness. The use of a prophylactic antidepressant was not related with changes in sustained virological response to antiviral treatment.

Immunological and neurotransmitter factors may play an important role in the development of depression during antiviral treatment. Administration of exogenous cytokines activate other proinflammatory cytokines such as interleukin-6 (IL-6), which is related with a central nervous system (CNS) inflammatory response (4). A high concentration of proinflammatory cytokines with CNS action may modulate the serotonergic system through the up-regulation of enzymes such as indoleamine 2,3-dioxygenase (IDO), altering levels of serotonin and the expression of the serotonin transporter (SERT) or presynaptic receptors (5HT1A) (12). Cytokine-induced impaired serotonin synthesis may also be due to the effect of inflammatory factors on the synthesis and activity of tetrahydrobiopterin (BH4), a cofactor of amino acid monoxygenases including tryptophan-hydroxylas (27). SSRIs may modulate the changes induced by cytokines by increasing the reuptake of serotonin at the synaptic cleft (13). One in-vitro study showed that although administration of IFN-alpha produced a down-regulation of 5-HT1A receptors, this effect is attenuated if an antidepressant is administered previously (28). Clinical studies have also shown that certain genetic variants that determine the levels of expression of 5HT1A receptors are related to IFN-induced depression (29). These biological findings support the results of this review, which found that administration of a SSRI can prevent depression during antiviral treatment for CHC.

The meta-analysis performed for types of SSRI separately found no differences between escitalopram, citalopram or paroxetine and placebo. This finding is likely due to the small sample size in each group when analyzed separately, as well as to the relatively moderate impact of antidepressants in terms of preventing IFN-induced

depression in the general population. Some of the selected studies (16) excluded patients with a history of depression or those with a past severe psychiatric disorder. This probably means that the patients included in this review were at lower risk of developing IFN-induced depression than are the patients usually found in clinical practice. According to previous studies and a recent systematic review with meta-analysis (11), a personal history of depressive disorder is one of the most widely reported risk factors for developing depression during antiviral treatment. In fact, CHC patients with a history of depressive disorder have a four-fold higher risk of suffering a depressive episode during interferon treatment than do those without such a history. Prophylactic administration of antidepressants in this subgroup of patients may therefore be of particular benefit (30), although it should be mentioned that such patients represented a fairly small proportion of the subjects included in this review. Due to the small number of patients with a history of depression and the lack of data regarding clinical response in this subgroup, we were unable to perform a sub-analysis examining the potential benefit of antidepressants among these subjects. Of note, it has been shown that patients with a psychiatric diagnosis at the initiation of interferon treatment do not necessarily exhibit reduced viral clearance and more frequent treatment discontinuation than patients free of psychiatric disorder at baseline (31).

In conclusion, this review shows that the prophylactic administration of SSRIs does reduce depression during antiviral treatment for CHC. Considering that depression may be associated with major complications such as suicidal ideation or lack of treatment adherence, as well as the good tolerability of antidepressants, this review supports the benefit to initiate a SSRI prophilacticaly to prevent IFN-induced depression. However, should be taken into account that antidepressants showed a relatively moderate impact to prevent depression (NNT=12). In fact, recent guidelines do not generally recommend antidepressant pre-treatment for all CHC patients during antiviral therapy, suggesting instead that the decision should be based on a case-by-case approach and the patient's own view (14). Despite the lack of randomized controlled trials in patients at high risk of presenting IFN-induced depression, such as those with a past depressive episode, it seems reasonably to recommend prophylactic antidepressant treatment in these subjects given the reduction of depression rates and good tolerability of SSRI's. Future research should focus on these particular sub-groups of patients, who may well benefit from this intervention. This review and future studies should help not

only to optimize the management of patients with CHC, but also to draw up clinical guidelines based on stronger evidence.

Limitations

This study does have certain limitations. Firstly, there was a degree of heterogeneity between studies with respect to the sample characteristics. We sought to minimize this problem by reporting potential confounding variables such as age, gender, co-infection, exclusion of patients with psychiatric history, IFN dose and type, and co-treatment with RBV. Some of the selected studies excluded patients with a history of depression or a past severe psychiatric disorder, and this fact may limit the generalizability of our results to clinical practice. It is also acknowledged that randomized clinical trials are likely to present significant publication bias. We tried to minimize this bias by searching for reported trial designs before publication of results (Clinicaltrials.gov), and also by assessing potential publication bias using Begg-Egger funnel plots.

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Conflict of interest

Dr Forns has received grant support from Roche, Jansen and MSD. Dr. Vieta has received grants and served as consultant, advisor or CME speaker for the following entities: Almirall, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen-Cilag, Jazz, Johnson & Johnson, Lundbeck, Merck, Novartis, Organon, Otsuka, Pfizer, Pierre-Fabre, Qualigen, Sanofi-Aventis, Servier, Shering-Plough, Solvay, Takeda, the Spanish Ministry of Science and Innovation (CIBERSAM), the Seventh European Framework Programme (ENBREC), the Stanley Medical Research Institute, United Biosource Corporation, and Wyeth. None of the other authors have any conflicts of interest to declare with respect to this manuscript.

Contributors

Marc Udina and Rocío Martín-Santos designed the review and extracted data. Marc Udina, Diego Hidalgo and Ricard Navinés selected studies to be included. Marc Udina and Magí Farré did statistical analyses. Marc Udina, Xavier Forns, Ricard Solà, Lucile Capuron, Eduard Vieta, and Rocío Martín-Santos collaborated on data interpretation. All authors wrote the report.

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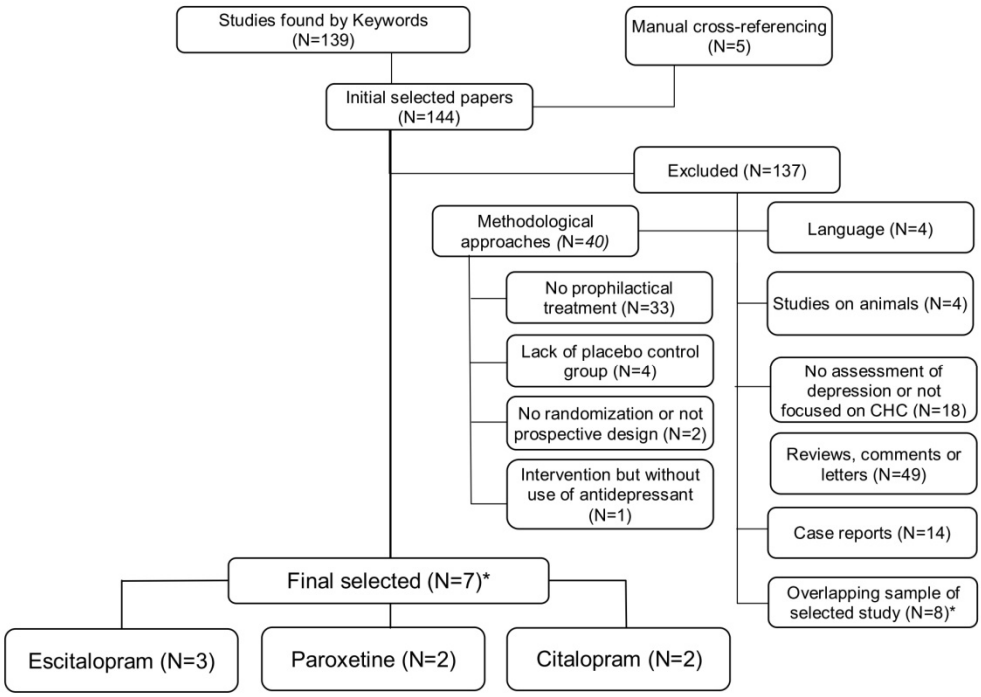
Table 1. Characteristics of the studies selected.

Study		N	Gender	Age (SD)	Includes past psychiatric Disorder	Proportion of patients with history of depression	Drug used (dose/day)	Instrument used for DSM diagnosis	Scale used to assess depressive symptoms	Incidence of MDE during follow-up	IFN type	RBV	Follow-up in weeks
Morasco et al, 2007 (24)	Active	14	14 ♂ 0 ♀	50.6 ±5.4	Yes	0.143	Paroxetine (40mg)	SCID	HAM-D	0.357	PegIFN-α-2b	Yes	24-48
	Placebo	19	19 ♂ 0 ♀	46.4 ±4.9		0.152				0.316			
Raison et al, 2007 (25)	Active	28	15 ♂ 13 ♀	51.1 ±6.5	Yes	0.25	Paroxetine (20mg)	SCID	MADRS	0.13	IFN-α-2b PegIFN-α-2a PegIFN-α-2b	Yes	24
	Placebo	33	20 ♂ 13 ♀	46.6 ±8.2		0.24				0.207			
Diez-Quevedo et al, 2009 (15)	Active	66	39 ♂ 27 ♀	46.7 ±10.6	Yes	0.136	Escitalopram (15mg)	SCID	MADRS HADS	0.076	PegIFN-α-2a	Yes	12
	Placebo	63	40 ♂ 23 ♀	44.8 ±10.8		0.137				0.032			
Morasco et al, 2010 (23)	Active	19	18 ♂ 1 ♀	51.8 ±5.1	Yes	0.105	Citalopram (20mg)	SCID	MADRS BDI	0.105	PegIFN-α	Yes	24
	Placebo	20	18 ♂ 2 ♀	54.2 ±8.9		0.150				0.20			
de Knegt et al, 2011 (21)	Active	40	27 ♂ 13 ♀	48.5 ±9.7	Yes	0.2	Escitalopram (10mg)	MINI	MADRS BDI	0.125	PegIFN-α2a	Yes	24
	Placebo	39	35 ♂ 4 ♀	44.6 ±7.5		0.41				0.359			
Schaefer et al, 2012 (16)	Active	90	48 ♂ 42 ♀	46.2 ±11	No	0	Escitalopram (10mg)	MINI	MADRS	0.32	PegIFN-α2a	Yes	24
	Placebo	91	48 ♂ 43 ♀	48.5 ±11		0				0.59			
Klein et al, 2012* (26)	Active	36	26 ♂ 10 ♀	45.3 ±NR	Yes	NR	Citalopram (20mg)	SCID	BDI	0.15	PegIFN-α2b	Yes	24
	Placebo	39	39 ♂ 0 ♀	46.7 ±NR		NR				0.26			

*Data extracted from a poster presentation. The entire sample in this study was coinfected with Human immunodeficiency virus.
Abbreviations: AD=Antidepressant, BDI=Beck Depression Inventory,DSM=Diagnostic and Statistical Manual of Mental Disorders, MDE= Major depressive episode, MINI=Mini-International Neuropsychiatric Interview, NR=not reported data, PegIFN=Pegylated-Interferon, RBV=Ribavirin, SCID=Structured Interview for DSM-IV-R, VD=variable dose,

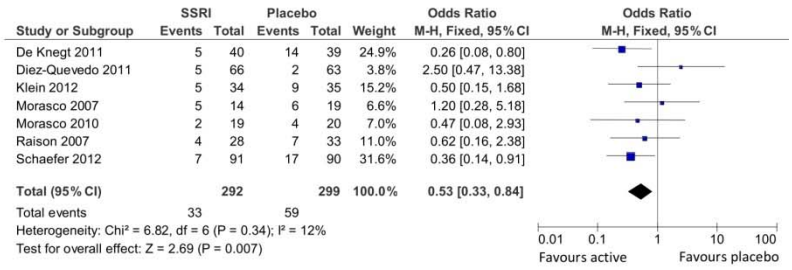
Figure 1. Flow chart of the studies considered and finally selected for review.



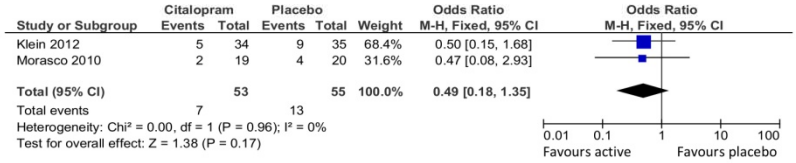
* One excluded article (Klein, 2009) was the full protocol of a selected study with preliminary data (Klein, 2012). Both articles were used to report characteristics of the study. Excluded articles are cited in the *Appendix, III*.
Abbreviations: CHC= chronic hepatitis C.

Figure 2. Incidence of depression.

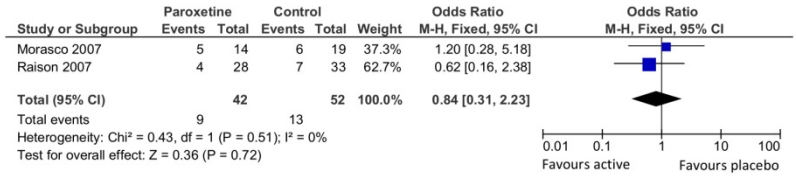
Any selective serotonin reuptake



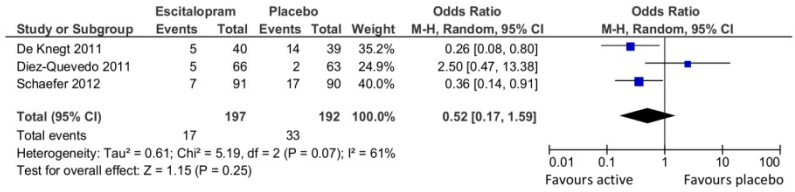
Citalopram



Paroxetine



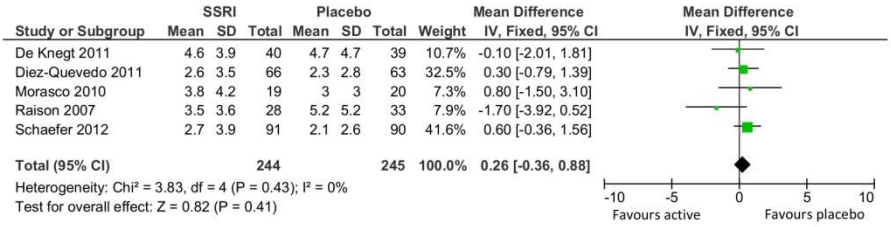
Escitalopram



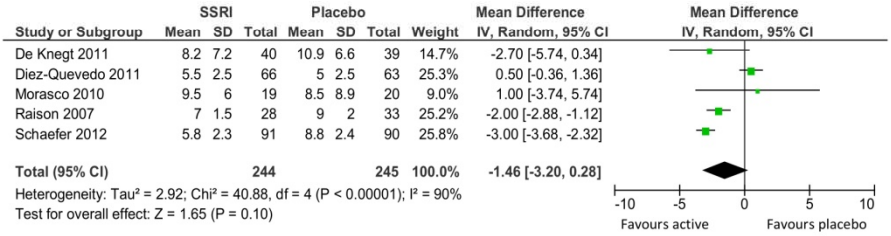
Abbreviations: IFN= Interferon IV= Inverse variance; df= degrees of freedom; M-H= Mantel-Haenszel test; $I^{2=}$ I-square test; 95%CI= 95% confidence interval; Chi^2= Chi square test; fixed= fixed effects model; random= random effects model; SSRI: selective serotonin reuptake inhibitors, Z= Z score

Figure 3. Depressive symptoms at baseline and during the follow-up

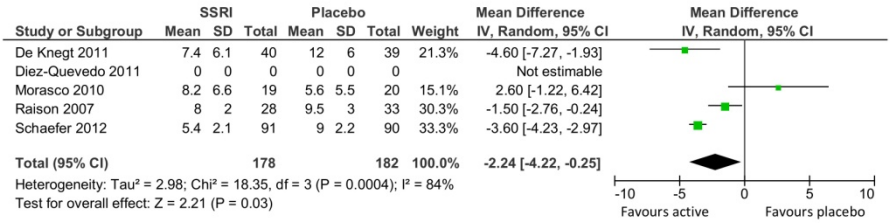
At baseline



At 12 weeks of treatment



At 24 weeks of treatment



Abbreviations: IV= Inverse variance; df= degrees of freedom; M-H= Mantel-Haenszel test; $I^{2=}$ I-square test; 95%CI= 95% confidence interval; Chi^{2}= Chi square test; fixed= fixed effects model; random= random effects model; SSRI: selective serotonin reuptake inhibitors, Z= Z score

5.3 Material complementari

Content of supplemental material

I. Protocol

Background

Description of the condition

Major depressive disorder (MDD) is the leading cause of life disability and one of the most expensive illnesses for society, both in terms of direct and indirect costs (1 - 2). The prevalence of depression is important in patients with medical conditions related to inflammatory processes, such as cardiovascular diseases, rheumatoid arthritis, autoimmune disorders, obesity or chronic hepatitis C (3). Moreover, there is substantial evidence for the role of cytokine therapies, such interferon-alpha (IFN-alpha) in inducing depressive symptoms in clinical populations (4 - 5).

Hepatitis C virus (HCV) infection is a public health problem that affects 130-170 million people worldwide (6 - 7). Currently, the approved treatment for chronic hepatitis C (CHC) is the combination of pegylated IFN-alpha and antiviral ribavirin (RBV) for 24 or 48 weeks (9 - 10). The problem with antiviral treatment is its high profile of side effects, including fatigue, insomnia, irritability and low mood, with a full major depressive episode (MDE) being observed in around 25% of patients treated (11). Prevention or proper management of IFN-induced depression is therefore essential, because depressive patients often show a poor quality of life, suicidal ideation, a lack of treatment adherence and alterations to their sustained virological response (SVR) (5).

Description of the intervention

Antidepressant drugs are the mainstay of treatment for mood disorders. Selective serotonin reuptake inhibitors (SSRIs) are currently the most used antidepressants given the relatively good side-effects profile. SSRIs have been proposed as a useful treatment for IFN-induced depression (11 - 12). However, prophylactic administration of antidepressants in all patients starting antiviral therapy for chronic hepatitis C is controversial (15 - 16).

How the intervention might work

Depression is related with serotonin alterations in the the limbic system. SSRIs may modulate the changes induced by cytokines by increasing the reuptake of serotonin at the synaptic cleft (14).

Why it is important to do this review

It is not clear if prophilactical use of antidepressants before starting antiviral therapy for chronic hepatitis C reduces incidence of depression.

Objectives

To carry out a systematic review and meta-analysis of data that could help to assess the benefits of using prophylactic antidepressants during antiviral treatment for chronic hepatitis C.

Methods

Types of studies

Randomized clinical trials: using prophylactic antidepressants in patients receiving antiviral therapy for CHC.

Types of participants

We included patients with CHC, inititating antiviral therapy with IFN-alpha and ribavirin and with euthymia (not fulfilling criteria for a DSM-IV/ICD depressive episode).

Types of interventions

1. Antidepressant drugs: Oral. Any dose.
2. Placebo

Primary outcomes

During the antiviral treatment (IFN-alpha and ribavirin): Onset of a major depressive episode (DSM-IV criteria).

Secondary outcomes

1) Rates of depressive symptomatology during antiviral treatment, based on a validated rating scale; 2) The presence of potential side effects attributed to combination treatment (antidepressant and antiviral therapy); and 3) Proportion of patients achieving SVR.

Searches

Databases: MEDLINE, PsycINFO, EMBASE, the Cochrane Library, Clinicaltrials.gov, hand searches and conference proceedings

Keywords: hepatitis and c and (interferon-alpha OR peginterferon OR (pegylated and interferon)) and (depression OR mood) and (prevention OR prophylactic OR prophylaxis OR antidepressant).

Date: From the earliest available online year until October 2012

Language: English, Spanish or French

Selection of studies

Study selection was performed independently by two clinical researchers (MU and DH). Disagreements were resolved by discussion, and consensus was achieved in the selection of articles for analysis.

Data extraction and management

Extraction: Data were independently abstracted by both reviewers (MU and DH), who recorded the author, year of publication, design, characteristics of the study population, viral co-infection, adjunctive psychopharmacology, instruments for assessing depression, dose and type of IFN-alpha, adjunctive RBV follow-up time, and data about discontinuation and patients lost to follow-up. Outcomes of incidence of MDE, SVR, depressive symptoms and potential side-effects were abstracted for each group.

Management: Data were extracted in simple forms

Data: Categorical data (major depression) was obtained using DSM criteria. We included data from rating scales only if the instrument has been validated and described in a peer-reviewed journal.

Assessment of risk of bias in included studies

Two authors assessed risk of bias using the tool described in the Cochrane Library

This tool recommends evaluation of: Sequence generation, allocation concealment, blinding, the completeness of outcome data, selective reporting and other biases.

The risk of bias in each domain and overall were assessed and categorized into:

A. Low risk of bias: plausible bias unlikely to seriously alter the results; B. High risk of bias: plausible bias that seriously weakens confidence in the results; C. Unclear risk of bias: plausible bias that raises some doubt about the results.

Measures of treatment effect

Categorical data: The primary outcome of this review was a dichotomic variable (depression; no depression). The odds ratio (OR) with 95% CI was used to estimate the strength of association of dichotomous variables.

For statistically significant results we calculated the number needed to treat statistic (NNT), and its 95% confidence interval (CI) as the inverse of the risk difference.

Continous data: The mean difference (MD) with 95% CI was used to estimate the strength of association of quantitative variables.

Dealing with missing data

Discontinuation is common during antiviral treatment for CHC due to lack of treatment response or side-effects. Discontinuation and loss to follow up may lose credibility of the study. We reported in both groups (antidepressant and placebo) the number of patients that dropped out for any reason and number of discontinuation due to potential side-effects. We used the odds ratio (OR) with 95% CI to estimate the strength of association of these variables.

Assessment of heterogeneity

We inspected all the studies to judge clinical and methodological heterogenity.

Heterogeneity between trials was assessed using both the chi-square and I-square tests I^2 statistic was used to estimate the percentage of inconsistency thought to be due to chance. Between-study heterogeneity was considered to be significant for a p-value < 0.10 on the chi-square test. If there was no heterogeneity, a fixed model was used. In the event of heterogeneity, a random effects model was used (17).

Assessment of reporting biases

Publication bias was examined in a funnel plot of log OR against its standard error, using Begg's test, while the degree of asymmetry was tested statistically using Egger's unweighted regression asymmetry test (18 - 19).

Data synthesis

The fixed or the random-effects model by DerSimonian and Laird (17) were used for all analyses. Random effects were used in case of high heterogenity (p-value < 0.10 on the chi-square test).

Subgroup analysis, sensitivity analysis and meta –regression

We tried to examine the subgroup of people who presented a personal history of depression due to high incidence of IFN-induced depression (11). Senistivity analysis was done. All subgroup and sensitivity analyses were made only for the primary outcome. Meta-regression was performed if at least ten studies per comparison were available (20).

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II. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	p 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	p 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	p 3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	p 5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	p 5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	p 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	p 5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	p 5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for	p 6

		obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	p 6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	p 6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	p 6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	p 7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	p 7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	p 7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	p 8 and Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	p 8 and Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	p 8 and Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	p 9-10 Figure 2 Figure 3 Appendix
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	p 9 and 10 Figure 2 Figure 3 Appendix
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	p 11

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	p 11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	p 12-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	p 14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	p 13-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	p 15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

III. Exluded studies

Reason to exclude

- Language (1 - 4)
- Studies on animals (5 - 8)
- No assessment of depression or not focused on CHC (9 - 26)
- Reviews, comments or letters (27 - 75)
- Case reports (76 - 89)
- Methodological approaches
    - No prophilactical treatment (90 - 122)
    - Lack of placebo control group (123 - 126)
    - No randomization or not prospective design (127 - 128)
    - Intervention but without use of antidepressant (129)
- Overlapping sample of selected study (130 - 137)

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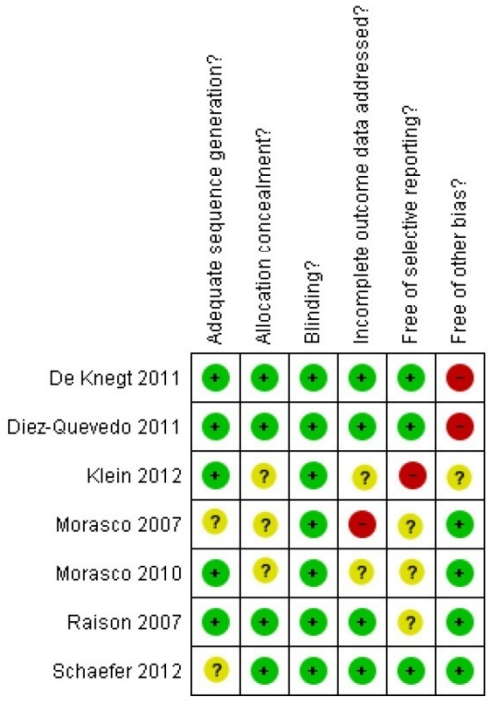
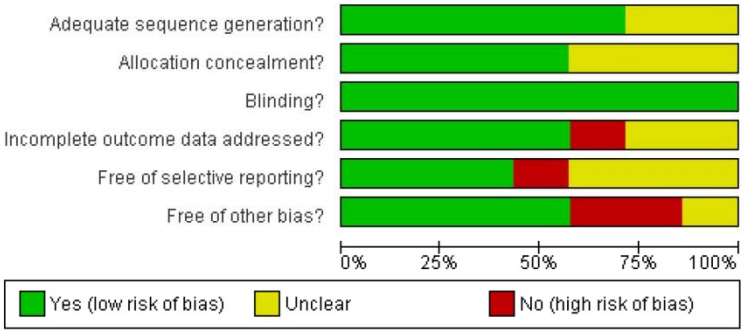
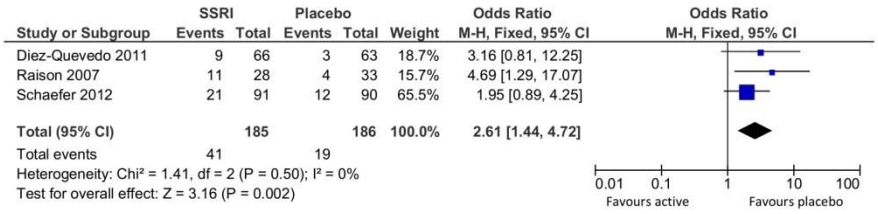
IV. Risk of bias graph: Distribution of judgments (Yes, Unclear and No) across studies for each risk of bias item.



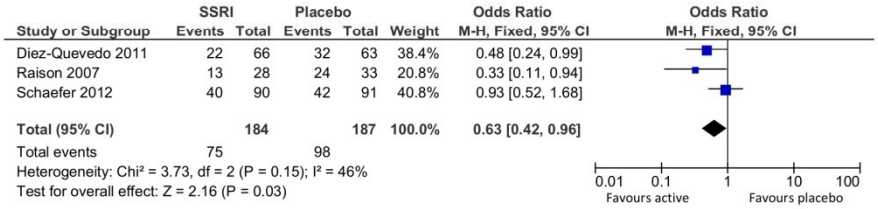
V. Risk of bias summary: Summary table of judgments for each risk of bias item for each study.



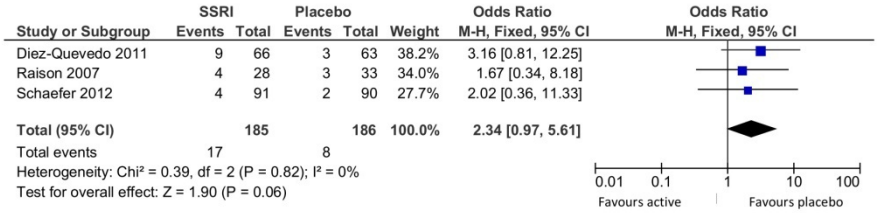
VI. Side effects figures



Side effect: Dizziness
MH = Mantel-Haenszel; fixed = fixed effects model

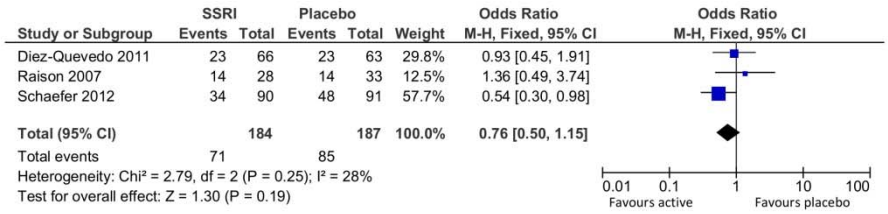


Side effect: Muscle or joint pain
MH = Mantel-Haenszel; fixed = fixed effects model

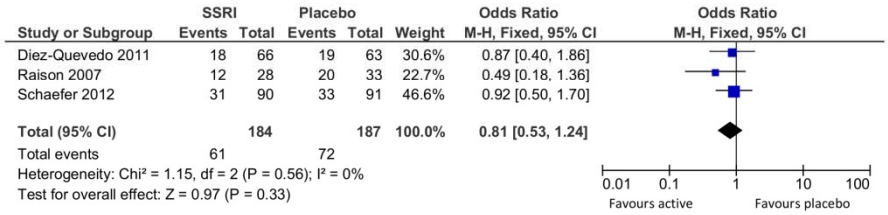


Side effect: Sexual dysfunction
MH = Mantel-Haenszel; fixed = fixed effects model

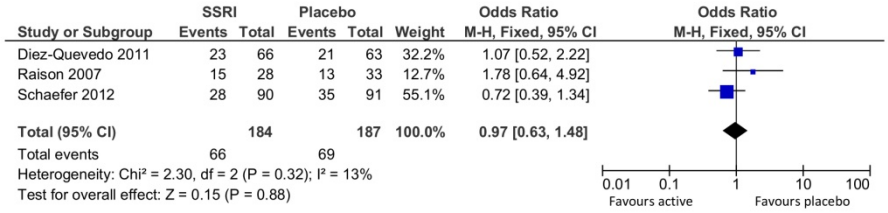
Side effect: Fatigue
MH = Mantel-Haenszel; fixed = fixed effects model



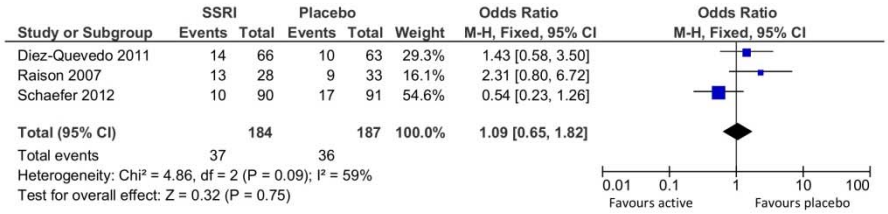
Side effect: Sleep disturbance
MH = Mantel-Haenszel; fixed = fixed effects model



Side effect: Headache
MH = Mantel-Haenszel; fixed = fixed effects model



Side effect: Nausea
MH = Mantel-Haenszel; fixed = fixed effects model



Side effect: Loss of appetite
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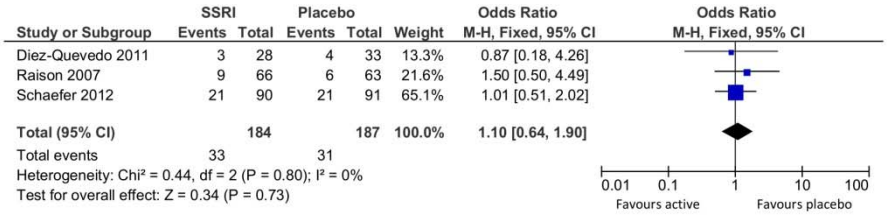
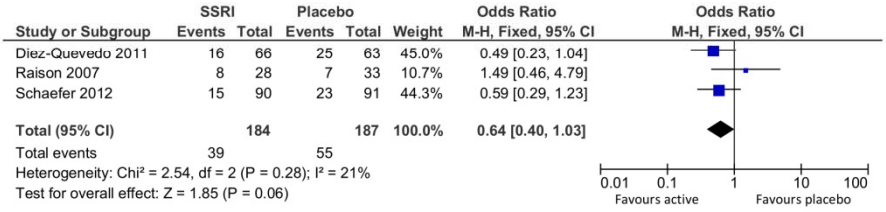
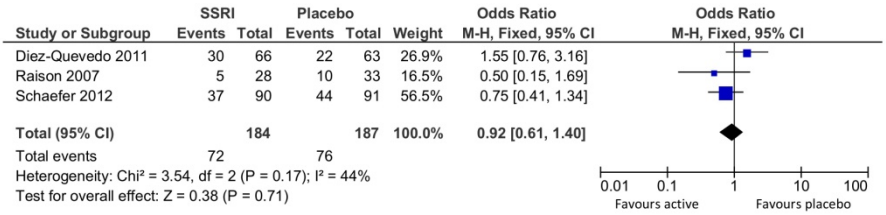


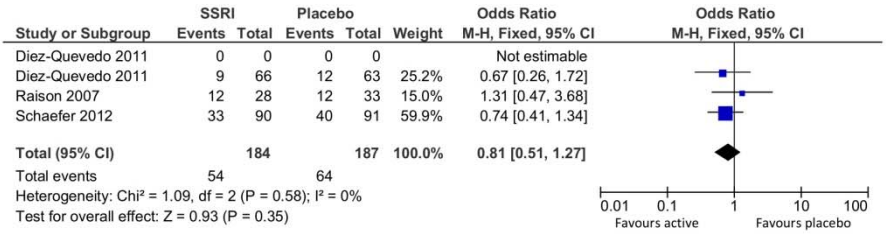
Side effect: Skin problems
MH = Mantel-Haenszel; fixed = fixed effects model



Side effect: Hair loss
MH = Mantel-Haenszel; fixed = fixed effects model

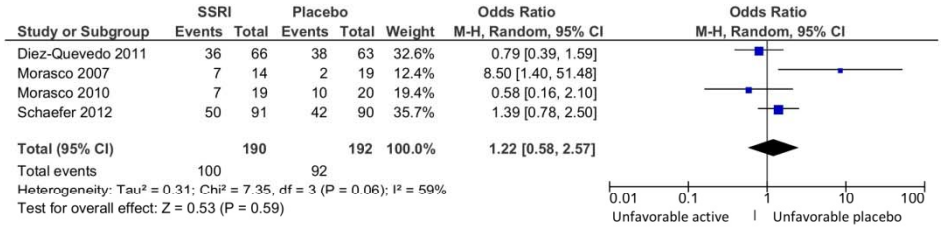


Side effect: Respiratory symptoms
MH = Mantel-Haenszel; fixed = fixed effects model



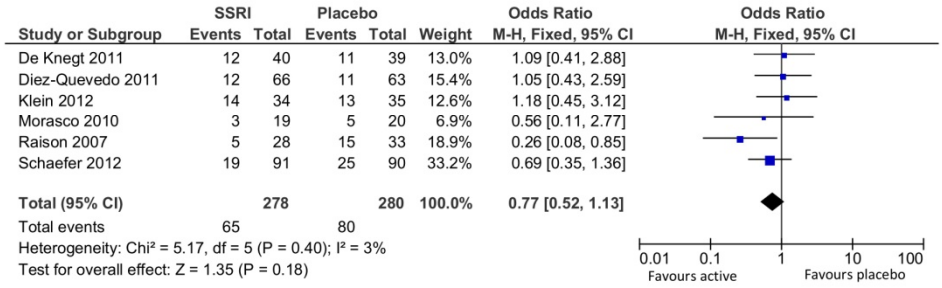
Side effect: Flu-like symptoms
MH = Mantel-Haenszel; fixed = fixed effects model

VII. Sustained virological response figure

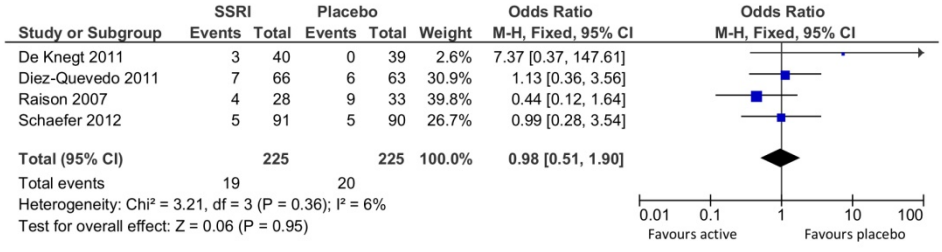


Sustained virological response
MH = Mantel-Haenszel; random = random effects model

VIII. Discontinuation and lost to follow up figures

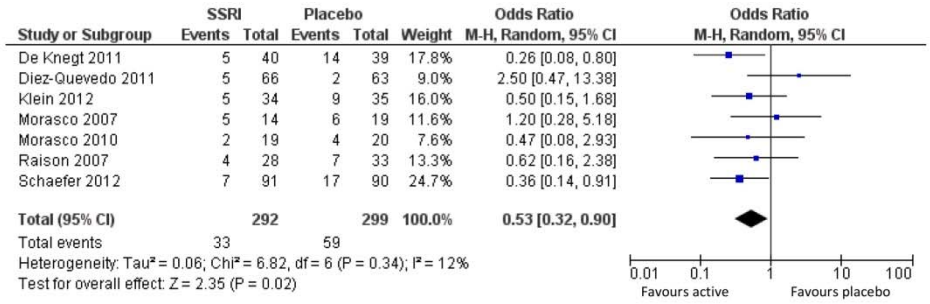


Discontinuation for any cause
MH = Mantel-Haenszel; fixed = fixed effects model

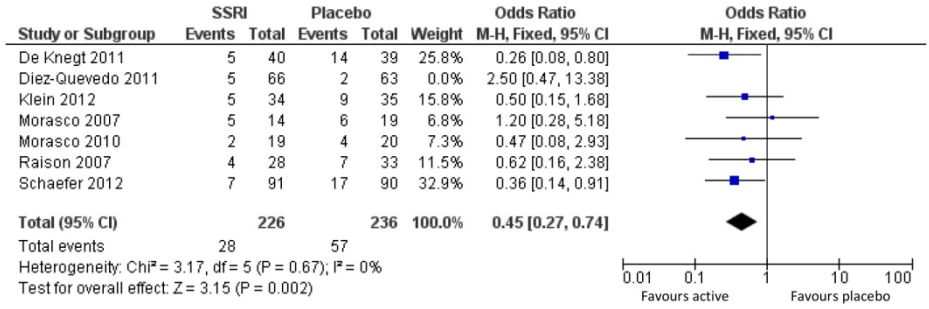


Discontinuation due to presence of side effects
MH = Mantel-Haenszel; fixed = fixed effects model

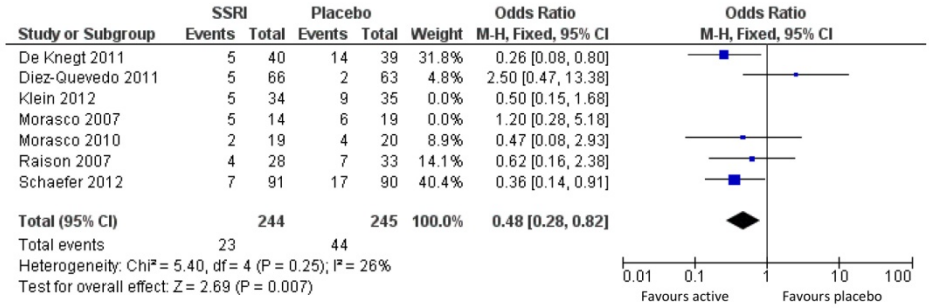
IX. Sensitivity analyses



Primary outcome (major depressive episode) using random effects model
MH = Mantel-Haenszel; random = random effects model

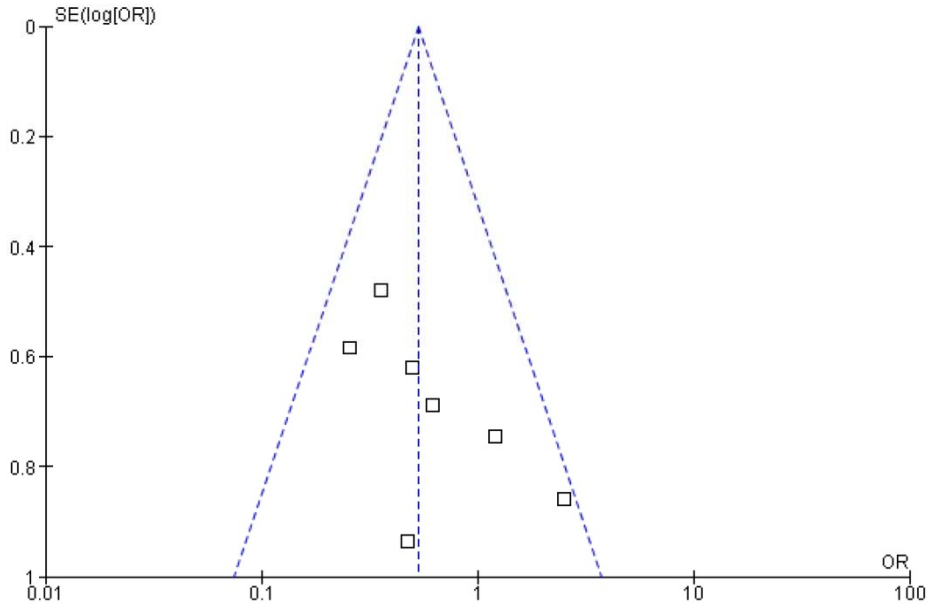


Primary outcome (major depressive episode) using studies with at least 24 weeks of follow-up
MH = Mantel-Haenszel; fixed = fixed effects model



Primary outcome (major depressive episode) excluding studies with higher risk of bias
MH = Mantel-Haenszel; fixed = fixed effects model

X. Funnel plot figure



Funnel plot of standard error (publication bias)
SE= standard error OR = Odds ratio

CAPÍTOL 6
Discussió

6. Discussió

6.1 Resultats més rellevants de la investigació realitzada

Aquest projecte ha realitzat per primer cop una revisió sistematitzada i amb metanàlisi de la depressió induïda pel tractament amb IFN alfa i ribavirina en la HCC. Podem afirmar que un de cada quatre pacients que inicien tractament antiviral presentarà un episodi depressiu major durant el tractament (criteris DSM), i que existeix un grup de pacients amb major risc de patir-ne. Aquells pacients amb antecedents d'episodi depressiu, amb presència de simptomatologia depressiva subsindròmica abans de començar el tractament, o amb certes variables sociodemogràfiques com el gènere femení o un baix nivell eductatiu, tenen un risc incrementat de patir depressió. Per altra banda, paràmetres implicats en la regulació de la resposta immunològica, com la IL-6, podrien tenir un paper destacat en la fisiopatologia dels símptomes depressius. Nivells elevats de IL-6 abans de començar el tractament antiviral s'associen a un risc incrementat de patir depressió induïda. En congrüència amb aquests resultats hem descrit, en una cohort prospectiva de pacients amb HCC i en tractament amb IFN alfa i ribavirina, que la simptomatologia depressiva i ansiosa que apareix durant el tractament antiviral s'associa a variants funcionals del gen de la IL-6, suggerint que el sistema de resposta immunològica té un paper rellevant en la fisiopatologia d'aquests símptomes. La neurotransmissió serontoninèrgica també podria estar implicada en l'etiopatogènia de la depressió induïda. Les variants funcionals del gen del *SERT* estudiades mostren una tendència a l'associació amb la simptomatologia depressiva induïda pel tractament antiviral i, per altra banda, aquesta tesi també inclou la primera revisió sistemàtica i metanàlisi d'assajos clínics controlats i randomitzats on es suggereix que l'administració d'un ISRS abans de començar el tractament amb IFN alfa i ribavirina disminueix la incidència de depressió. Els ISRS van mostrar una bona tolerabilitat i no van alterar la RVS.

6.2 Incidència i evolució de la depressió induïda per interferó alfa

Segons els resultats de l'*estudi 1* la incidència d'episodi depressiu major induït és del 25% a les 24 setmanes i del 28% a les 48 setmanes de tractament. Cal tenir en compte que en la pràctica clínica habitual els pacients amb HCC reben tractament antiviral amb IFN alfa i ribavirina durant 24 o 48 setmanes en funció de diversos criteris mèdics i del genotip del virus (els pacients amb genotip-1 del VHC solen realitzar 48 setmanes de tractament). És per aquest motiu que per al càlcul d'incidència es va estimar la incidència acumulada d'episodi depressiu major en funció del temps i tenint només en compte els estudis realitzats amb IFN alfa i ribavirina i que no van excloure els subjectes amb antecedents psiquàtrics. La incidència d'episodi depressiu major descrita a l'*estudi 3* és lleugerament menor, i el grup de pacients tractats amb placebo presenten una incidència del 19.7% (els estudis inclosos fan un seguiment d'entre 12 i 24 setmanes).

Segons l'observat a l'*estudi 1* la majoria de nous casos d'episodi depressiu major es dónen entre les 8 i les 12 setmanes de tractament. Una proporció menor de nous casos es dóna entre les 12 i les 24 setmanes i, posteriorment, la incidència de nous casos de depressió es redueix considerablement. Raison et al (2005) ja van descriure que la simptomatologia depressiva sol aparèixer a partir de les 8 setmanes, assolint un pic entre les 12 i les 24 setmanes de tractament antiviral [55]. Per altra banda, la fatiga o altres símptomes neurovegetatius apareixerien de forma precoç a l'inici del tractament [55]. És interessant destacar que aquest fet l'hem observat en la cohort de pacients descrita a l'*estudi 2*. En aquesta mostra hem observat que la fatiga s'incrementa considerablement en la majoria de pacients poc després de l'inici del tractament, assolint un pic cap a la quarta setmana per a posteriorment mantenir-se estable. Per altra banda, i en coincidència amb l'*estudi 1,* la simptomatologia depressiva mesurada de forma quantitativa (HADS-D) s'incrementa més tardanament, observant-se el major increment poc abans de les 12 setmanes de tractament antiviral.

6.3 Factors de risc clínics i sociodemogràfics de la depressió induïda

L'*estudi 1* ha descrit que diversos factors clínics i sociodemogràfics són factors de risc per a patir episodi depressiu major durant el tractament antiviral per a HCC. Cal destacar que un dels factors més reproduïts i que implica un major increment de risc és la

presència d'antecedents de depressió abans de començar el tractament; aquest subgrup de pacients tenen un risc fins a quatre vegades major. Els pacients amb simptomatologia depressiva subsindròmica basal, les pacients de gènere femení i aquells amb menor nivell educatiu també presentarien un risc incrementat de patir depressió induïda. Amb menys evidència, certs trets de personalitat com un alt neuroticisme o una baixa autodirecció, alteracions en el patró de la son abans d'iniciar el tractament i antecedents de simptomatologia subsindròmica maniforme també podrien ser factors de risc.

Aquests resultats aconsellarien de realitzar, abans d'iniciar el tractament antiviral, una avaluació clínica complerta, incloent antecedents psiquiàtrics i una quantificació de la simptomatologia subdepressiva, que permetria detectar fàcilment pacients de risc. Aquests grups de pacients es podrien beneficiar d'intervencions individualitzades, d'un seguiment més exhaustiu o de l'administració profilàctica d'un ISRS abans de començar el tractament. En l'*estudi 3* hem descrit que l'administració profilàctica d'un antidepressiu redueix la incidència i els símptomes depressius del pacients amb tractament antiviral amb un acceptable perfil de tolerabilitat. En aquest mateix estudi vam intentar avaluar si aquells grups "de risc", com per exemple els pacients amb antecedents depressius, mostraven un especial benefici amb la profilaxis antidepressiva. No es va poder fer una metanàlisi d'aquest subgrup a causa de la manca de dades, però estudis aïllats sí que mostren que els pacients de risc podrien beneficiar-se especialment de l'administració d'un antidepressiu abans del tractament antiviral [94, 95]. Aquest fet recolza les recomanacions terapèutiques de guies clíniques publicades recentment on es recomana, sempre individualitzant i en funció de les preferències del pacient, valorar iniciar un antidepressiu profilàctic en els pacients de risc [96].

6.4 Citocines i neurotransmissió en la fisiopatologia de la depressió induïda.

En l'*estudi 1* vam trobar que variables biològiques relacionades amb la resposta immunològica s'associaven a la depressió induïda per interferó. Concretament, i segons la nostra metanàlisi, concentracions elevades en sang de IL-6 abans de començar el tractament antiviral són un factor de risc de presentar depressió. La revisió sistemàtica també orientà que les concentracions d'IL-10 o de sIL-2R podrien associar-se a depressió durant el tractament antiviral.

En relació amb aquestes troballes, vam avaluar l'associació entre el polimorfisme funcional del gen de la *IL*-6 (rs1800795) en una cohort de pacients en tractament amb IFN alfa i ribavirina (*estudi 2*). Aquest estudi mostra que els pacients amb el genotip CC del polimorfisme de la *IL-6* presenten menys símptomes ansiosos (HADS-A) i depressius (HADS-D) que els pacients portadors de l'al·lel G. Cal destacar que hi ha força evidència en la literatura que descriu que els pacients portadors de l'al·lel G presenten nivells de IL-6 en sang més elevats [87, 97, 98], cosa que suggeriria que concentracions elevades de IL-6 podrien estar involucrats en la fisiopatologia dels símptomes ansiosos i depressius durant el tractament antiviral per HCC, en congrüència amb els resultats que hem descrit a l'*estudi 1* i amb altres estudis previs en depressió induïda i primària [65, 99]. La troballa reprodueïx els resultats previs d'un estudi amb una mostra considerablement menor de pacients, que també va descriure que els pacients amb genotip CC del polimorfisme del gen de la IL-6 presenten menys símptomes depressius durant el tractament antiviral [100]. Smith et al (2011), però, no van trobar una associació entre aquest polimorfisme i l'episodi depressiu associat a IFN alfa, detectat amb l'escala Center for Epidemiologic Studies Depression Scale (CES-D), que no exclou simptomatologia neurovegetativa [63]. A més a més, en l'*estudi 2* hem trobat una associació entre la simptomatologia ansiosa i el polimorfisme de la IL-6, fet que no havia estat descrit anteriorment i que és congrüent amb estudis previs en població general, on concentracions plasmàtiques de IL-6 s'han associat també amb la presència d'ansietat [101]. Per altra banda, l'*estudi 2* ha mostrat que els pacients portadors del genotip LL del *SERT* presentaven una tendència a patir menys símptomes ansiosos i depressius que els portadors de l'al·lel S.

És interessant destacar que l'estudi no va trobar cap associació entre les variants genotípiques dels polimorfismes de la *IL-6* o el del *SERT* i la fatiga induïda per interferó que, tal i com hem comentat anteriorment, té un curs evolutiu diferenciat del de la simptomatologia depressiva. Aquests fets suggereixen que la fatiga tindria una base fisiopatològica diferent que els símptomes ansiosos i depressius, que sí que podrien compartir una etiologia comuna. En aquesta línia, diversos autors han suggerit que durant el tractament amb interferó els símptomes neurovegetatius com la fatiga podrien estar lligats a alteracions en vies cereberals dopaminèrgiques i, els símptomes afectius estar relacionats predominantment amb alteracions en vies serotoninèrgiques [56, 102].

Concentracions elevades de citocines proinflamatòries com la IL-6 podrien modular el sistema serotoninèrgic i la producció de metabòlits neurotòxics a través de l'increment

de la funció de l'enzim IDO en certes àrees cerebrals com l'hipocamp [73]. S'ha descrit que una alta activitat de l'enzim IDO podria alterar el metabolisme del triptòfan i determinar una disminució en la disponibiliat de serotonina. En tot cas, no hem observat una interacció entre el polimorfisme de la SERT i el de la IL-6, fet que suggereix que la funcionalitat del transportador de serotonina no canvia en funció de la disponibilitat de serotonina determinada per l'increment d'activitat de l'enzim IDO. Aquest fet estaria en la línia de l'estudi realitzat per Raison et al (2011), on es va observar que l'administració d'inteferó alfa no alterava les concentracions de triptòfan al SNC però sí que incrementava els nivells de kinurenina, un metabòlit que afavoreix l'activació de fenòmens neurotòxics i que s'ha correlacionat amb la presència de símptomes depressius [74, 103]. Un estudi recent també suggereix que l'activitat de l'enzim IDO podria tenir una importància destacable en la fisiopatologia de la depressió induïda, ja que s'ha associat una variant funcional del gen IDO (rs9657182) amb l'aparició de depressió durant el tractament antiviral per a HCC [63]. Aquests fets suggereixen que la depressió induïda per interferó és un complex mecanisme on les alteracions serotoninèrgiques no són la única base fisiopatològica. L'administració exògena de citocines podrien alterar la neurotransmissió serotoninèrgica però també l'eix hipotàlam pituitari adrenal i mecanismes reguladors de la homeòstasi de factors neurotòxics i neuroprotectors. S'ha descrit que alteracions en la funcionalitat de neurotrofines com el BDNF podrien relacionar-se amb la depressió induïda [104, 105]. A més a més, l'administració crònica d'interferó podria produir una desensitivització de l'eix hipotàlam pituitari adrenal, alterant l'expressió de receptors de glucocorticoids i incrementant els nivells plasmàtics de cortisol, factors associats també a la simptomatologia depressiva, i que podrien ser modificables amb l'administració d'antidepressius [79, 106, 107].

En tot cas hi ha força evidència de la importància de la neurotranmissió serotoninèrgica en la fisiopatologia dels símptomes depressius durant el tractament antiviral per a HCC. Després d'aquest treball (*estudis 1* i *2),* el rol del transportador de serotonina en la depressió induïda és encara controvertit, però cal tenir en compte que altres factors implicats en la neurotransmissió serotoninèrgica també poden tenir un rol important en la seva patogènia. S'ha descrit que l'administració d'IFN alfa en línies cel·lulars altera l'expressió de receptors serotoninèrgics (5HT1A), fet que és atenuat o revertit amb l'administració profilàctica o posterior d'un ISRS [79]. A més a més, Kraus et al (2007) va descriure que el pacients portadors del genotip GG del polimorfisme del

gen 5HT1A (associat amb alteracions en l'expressió d'aquest receptor) presentaven més risc de patir depressió induïda per citocines [75]. En relació amb aquests fets, l'*estudi 3* mostra que l'administració profilàctica d'ISRS en poblacions clíniques amb HCC disminueix la depressió relacionada amb el tractament amb IFN alfa i ribavirina. Els antidepressius podrien atenuar alguns dels efectes produits per les citocines en la via serotoninèrgica, com l'alteració en l'expressió de receptors 5HT1A, i d'aquesta manera reduir la incidència de depressió induïda.

6.5 **Ús d'antidepressius profilàctics**

Tal i com s'ha comentat anteriorment, l'*estudi 3* ha descrit que l'administració profilàctica d'un ISRS abans d'iniciar el tractament amb IFN alfa i ribavirina per a HCC redueix la incidència d'episodi depressiu major (criteris DSM) i la simptomatologia depressiva a les 24 setmanes de tractament (escala MADRS). En aquest estudi també es va avaluar el perfil de tolerabilitat dels antidepressius. S'observà que l'únic efecte indesitjat que presentaven amb més freqüència els pacients tractats amb ISRS era la sensació de mareig. El grup tractat amb ISRS no va presentar més efectes indesitjats greus que el grup tractat amb placebo, i el número de pacients que van abandonar el seguiment per qualsevol causa o a causa d'efectes indesitjats greus va ser igual en els dos grups. Per altra banda, els pacients tractats amb antidepressius van presentar menys símptomes de dolor muscular o articular que aquells tractats amb placebo. Pel que fa a la resposta virològica sostinguda, no es van observar diferències entre els dos grups d'estudi.

Cal destacar, però, que l'*estudi 3* no va trobar diferències significatives en la prevenció de la simptomatologia depressiva a les 12 setmanes de tractament ni quan l'anàlisi es va fer per separat en funció del tipus d'antidepressiu. Aquest fet es podria deure a la limitada mostra de pacients analitzats al realitzar subgrups i al moderat efecte dels antidepressius per a prevenir un episodi de depressió durant el tractament antiviral (NNT= 12). És possible que els pacients amb alt risc de presentar depressió induïda, com per exemple aquells amb antecedents de trastorn depressiu, tinguin un benefici particular de l'administració d'un ISRS profilàctic, tot i que aquest fet no es va poder corroborar en la metanàlisi degut a la manca de dades publicades. Cal destacar, però, que un estudi inclòs en la revisió sistemàtica i un estudi obert orienten que els pacients amb antecedents

depressius podrien tenir un benefici major amb l'administració profilàctica d'un ISRS [94, 95].

6.6 Aplicabilitat dels resultats de l'estudi

Els resultats d'aquest estudi tenen una aplicabilitat tant en l'aspecte clínic com en l'àmbit de la investigació biomèdica.

Pel que fa a l'aspecte clínic, l'estudi descriu que l'administració d'IFN alfa i ribavirina s'associa freqüentment a l'aparició d'un episodi depressiu major, suggerint als clínics que és un factor que s'ha de conèixer i tenir en compte en els pacients amb HCC i que van a iniciar tractament antiviral. El coneixement dels factors associats a la depressió induïda, alguns clínics i sociodemogràfics fàcilment detectables, permet als professionals detectar grups de pacients de risc i realitzar un seguiment més exhaustiu o recomanar mesures terapèutiques preventives, com l'administració profilàctica d'un ISRS. Aquest estudi aporta evidència que l'admistració d'un antidepressiu profilàctic disminueix la incidència de depressió major i de simptomatologia depressiva en aquest pacients. Els clínics, per tant, poden optar per un tractament farmacològic de bona tolerabilitat després de fer un balanç del factors de risc i en funció de les preferències del pacient. Tot i que l'estudi s'ha focalitzat en la HCC, l'evidència que l'administració exògena de citocines s'associa a la presència de simptomatologia depressiva també en altres malalties, podria ser d'utilitat a molts clínics que poden recomanar aquest tractament per a diversos trastorns.

L'estudi també té una rellevància i una aplicabilitat en el camp de la investigació translacional. L'estudi de la depressió induïda per interferó es podria considerar com un model "in vivo" per a l'estudi de la fisiopatologia de la depressió. Les troballes d'aquest estudi, per tant, podren orientar a investigacions dirigides a l'estudi de la fisiopatologia de la depressió primària i facilitar la troballa de dianes per a nous tractaments antidepressius, com fàrmacs de perfil immunoregulador, antagonistes de la IL-6 o del TNF alfa com l'etanercept [108, 109] o antinflamatoris [110].

La rellevància de l'estudi ha permès una àmplia difusió dels resultats a la comunitat científica: s'han presentat diverses comunicacions orals i pòsters en Congressos Nacionals i Internacionals de l'especialitat i ha donat lloc a publicacions en revistes

indexades d'alt impacte. Els *estudis 1* i *2* han estat publicats en revistes indexades del primer decil de l'especialitat de Psiquiatria. L'*estudi 3* resta, en el moment del dipòsit d'aquesta tesis, en procés de revisió externa.

6.7 Punts forts i limitacions de la investigació

Aquest estudi té una sèrie de limitacions que calen esmentar. L'estimació de la incidència i dels factors de risc (*estudi 1)* de depressió induïda es va basar en estudis observacionals, que solen tenir una qualitat metodològica més limitada que els assajos clíncis. En tot cas, la revisió sistemàtica es va realitzar seguint les pautes del MOOSE i incloent una evaluació de la qualitat de tots els estudis inclosos. També cal destacar que les mostres dels articles seleccionats en l'*estudi 1* mostraven certa heterogeneitat entre elles. Vam intentar minimitzar aquesta limitació describint les característiques mostrals de cada estudi (dades sociodemogràfiques, ús d'antidepressius abans de començar el tractament, exclusió de pacients amb antecedents psiquiàtrics, monoteràpia amb IFN alfa…). A més a més, l'estimació de la incidència de depressió major es va realitzar tenint en compte només els articles que no van excloure pacients amb antecedents psiquiàtrics i que utilitzaven tractament combinat (IFN alfa i ribavirina), per a una millor aproximació a la pràctica clínica habitual.

La segona revisió sistemàtica (*estudi 3*) es va basar amb assajos clínics, de bona qualitat metodològica i seguint les pautes del PRISMA. En tot cas, l'heterogenitat entre les mostres dels estudis seleccionats i les diferències en el temps de seguiment (12 o 24 setmanes) podria limitar la generalització de resultats. Per minimitzar aquest fet, vam descriure les característiques de cadascún dels articles seleccionats i vam realitzar una anàlisi de sensitivitat. Tot i això, no es va poder fer una subanàlisi en funció de factors de risc, com la presència d'antecedents de depressió, degut a la manca de dades disponibles. Per altra banda, en tota revisió sistemàtica s'ha de tenir en compte el risc de biaix de publicació. Aquest es va calcular en les dues revisions (*estudis 1* i *3*) utilitzant els *funnel plots* de Begg-Egger, que no suggerien un risc important de biaix. Cal tenir en compte que els assajos clínics tenen, potencialment, més risc de biaix de publicació. Per aquest motiu l'*estudi 3* va incloure una cerca sistematitzada de bases de dades de dissenys d'assajos clínics (Clinicaltrials.gov) per així localitzar potencials estudis no publicats.

Cal destacar que la cohort de pacients utilitzada en l'estudi és relativament gran i va ser evaluada sistemàticament i de forma prospectiva (*estudi 2*). En tot cas, el fet que alguns dels genotips estudiats són relativament poc freqüents fa que alguns dels grups d'estudi tinguin un reduit número de pacients, limitant la interpretació i l'aplicabilitat dels resultats. Per exemple, només 46 pacients eren homozigots de l'al·lel C del polimorfisme de la *IL-6*. També cal esmentar que l'estudi només va avaluar pacients de raça caucàsica limitant, per tant, l'aplicabilitat en altres grups poblacionals. L'estudi clínic va tenir en compte múltiples variables que podien alterar els resultats. En aquesta línia no es van detectar diferències significatives entre els genotips pel que fa al número de pacients amb antecedents psiquiàtrics, afectius i de consum de tòxics, puntuació de HADS, ús d'antidepressius i ansiolítics abans de començar el tractament, i altres paràmetres mèdics i sociodemogràfics. L'inici d'antidepressius o ansiolítics durant el tractament no va estar controlat per l'estudi i es podria considerar una limitació. En tot cas, es va descriure el percentatge d'ús d'aquests fàrmacs durant els diferents punts de seguiment. Per altra banda, l'ús de l'escala HADS és adequat ja que ha permès discriminar els símptomes més pròpiament afectius d'altres neurovegatitus com la fatiga. La HADS, però, no avalua símptomes com l'insomni, que s'han associat en estudis previs amb la concentració de citocines i amb l'aparició posterior de depressió durant el tractament antiviral [66, 111]. Finalment, cal esmentar que l'estudi no ha corroborat que els diferents genotips del polimorfisme de la *IL-6* s'associin a diferents concentracions de IL-6 ja que no s'han avaluat les seves concentracions plasmàtiques. En tot cas, és una limitació relativa ja que hi ha força evidència que l'al·lel G s'associa a més altes concentracions de IL-6 en plasma i, aquestes, amb l'aparició de simptomatologia depressiva [65, 87, 98].

6.8 Línies futures de recerca

Els resultats obtinguts en aquesta tesi suggereixen nous reptes d'investigació de cara al futur. Tenint en compte la complexitat de la fisiopatologia dels símptomes neuropsiquiàtrics induïts per l'administració de citocines, es podrien avaluar altres polimorfismes involucrats en la funcionalitat de la neurotransmissió serotoninèrgica o dopaminèrgica, en la regulació de l'eix hipotàlam pituitari adrenal o en la fisiologia dels factors neurotròfics i neurotòxics. Per altra banda, el desenvolupament d'estudis de neuroimatge, encara escassos en depressió induïda, ajudaria a comprendre millor els

factors neurobiològics implicats. En aquesta línia, estudis previs suggereixen que les citocines podrien modular la conectivitat cortico límbica, que s'associaria a la presència de simptomatologia depressiva [112], i alterar el metabolisme dels nuclis de la base [113]. Finalment, cal destacar que els resultats de les investigacions realitzades en la depressió induïda per citocines pot ajudar a comprendre millor la fisiopatologia dels trastorns afectius primaris i orientar a futures investigacions relacionades amb nous tractaments farmacològics o dirigides al trastorn depressiu major.

CAPÍTOL 7
Conclusions

7. Conclusions

7.1 Conclusions més rellevants

- ✓ Un de cada quatre pacients eutímics que inicien tractament antiviral per a la hepatitis C crònica presentarà un episodi depressiu major "de novo".
- ✓ L'increment de simptomatologia depressiva i de nous casos de depressió és especialment important entre les 4 i les 12 setmanes de tractament.
- ✓ La fatiga apareix abans de les 4 setmanes del tractament antiviral per a la hepatitis C crònica. Té un curs i una fisiopatologia diferent a la dels símptomes depressius o ansiosos.
- ✓ Existeixen factors de risc clínics i sociodemogràfics per a patir depressió induïda:
    - Alguns fàcilment detectables com la presència d'antecedents psiquiàtrics i depressius, simptomatologia depressiva subsindròmica basal, baix nivell educatiu, gènere femení o certs trets de personalitat.
- ✓ El sistema de la regulació de la resposta immunològica té un paper rellevant en la fisiopatologia dels símptomes depressius durant el tractament antiviral:
    - Concentracions plasmàtiques elevades de IL-6 abans del tractament i variants genètiques associades a la concentració de IL-6 (rs1800795) s'associen a la presència de simptomatologia depressiva i ansiosa.
- ✓ No s'ha trobat una associació entre el polimorfisme del transportador de serotonina (*SERT)* i els símptomes neuropsiquiàtrics induïts pel tractament antiviral (depressius, ansiosos o fatiga).
- ✓ Els inhibidors selectius de la serotonina disminueixen la incidència d'episodi depressiu major i de símptomes depressius durant el tractament per a la hepatitis C crònica.
- ✓ Els inhibidors selectius de la serotonina mostren una bona tolerabilitat i no alteren la resposta virològica sostinguda.

Capítol 8
Bibliografia

8. Bibliografia

8.1 Llistat de referències bibliogràfiques.

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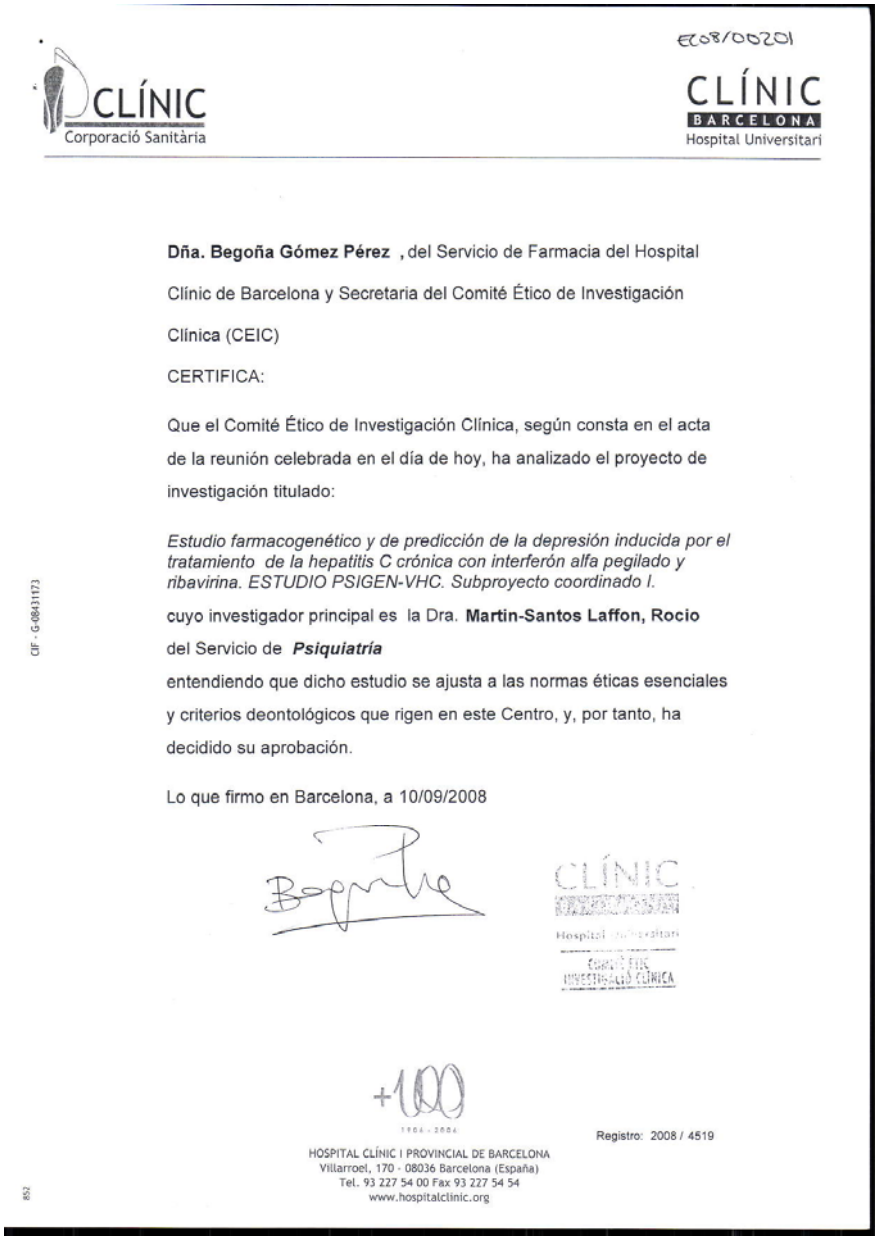
Annexes

Annexes

I. Aspectes ètics de l'estudi (certificat CEIC)

Durant l'estudi s'han seguit les directrius nacionals i internacionals (codi deontològic, Declaració de Hèlsinki) i la normativa legal sobre la confidencialitat de dades (Ley Orgánica 15/1999) del 13 de desembre de Protección de Datos de carácter personal (LOPD). Els participants de l'estudi han estat informats dels objectius i procediments abans de firmar el consentiment informat. L'estudi va ser aprovat pel CEIC del centre.



EC08/00201

CLÍNIC Corporació Sanitària

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Dña. Begoña Gómez Pérez , del Servicio de Farmacia del Hospital Clínic de Barcelona y Secretaria del Comité Ético de Investigación Clínica (CEIC)

CERTIFICA:

Que el Comité Ético de Investigación Clínica, según consta en el acta de la reunión celebrada en el día de hoy, ha analizado el proyecto de investigación titulado:

Estudio farmacogenético y de predicción de la depresión inducida por el tratamiento de la hepatitis C crónica con interferón alfa pegilado y ribavirina. ESTUDIO PSIGEN-VHC. Subproyecto coordinado I.

cuyo investigador principal es la Dra. **Martin-Santos Laffon, Rocio** del Servicio de ***Psiquiatría***

entendiendo que dicho estudio se ajusta a las normas éticas esenciales y criterios deontológicos que rigen en este Centro, y, por tanto, ha decidido su aprobación.

Lo que firmo en Barcelona, a 10/09/2008

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II. Consentiment informat per escrit

"Estudio farmacogenético y de predicción de la depresión inducida por el tratamiento con interferón alfa pegilado y ribavirina en pacientes con hepatitis C crónica."

ESTUDIO PSIGEN-VHC
Sección de Hepatología/HMAR-IMIM/Servicio de Psiquiatría/ICN/Hospital Clínic
Barcelona

INFORMACIÓN AL PACIENTE

A. OBJETIVO DEL ESTUDIO

Se está requiriendo su colaboración para participar en el estudio farmacogenético para estudiar variantes genéticas relacionadas con la posibilidad de presentar alteraciones del ánimo (tristeza, irritabilidad, ansiedad,..) en personas con hepatitis C crónica tratadas con interferón pegilado y ribavirina, medicamentos que usted va a recibir como tratamiento de la hepatitis C que padece. La farmacogenética es el estudio de la variabilidad de la respuesta de un medicamento en distintas poblaciones debido a factores hereditarios. Estas variantes genéticas de la normalidad son de genes relacionados con lo sistemas de neurotransmisión involucrados en la depresión, estrés e inmunidad.

Nuestro objetivo final es poder predecir que personas con hepatitis C crónica son mas vulnerables de presentar estos efectos secundarios con el tratamiento.

B. EN QUE CONSISTE SU PARTICIPACIÓN

Su participación en este estudio consiste en :
Una extracción de sangre de 10 ml de sangre que se realizará en el mismo centro donde le atienden de su enfermedad.

C. BENEFICIOS Y RIESGOS

El beneficio de este estudio es profundizar en el conocimiento de esta enfermedad que afecta a un número importante de personas de modo que podamos mejorar su diagnóstico, tratamiento y prevención. Estos resultados beneficiarán en el futuro a la población de hombres y mujeres que sufren de hepatitis C y son tratados con interferón. A corto plazo este estudio no supondrá un beneficio directamente para usted. Usted continuará siendo atendido por su equipo médico del Servicio de Digestivo del Hospital del Mar.

Realizaremos una extracción de 10 ml de sangre del brazo. Los riesgos de esta extracción son mínimos o inexistentes, y están limitados a que en algunas personas puede producir un hematoma que dure unos días. Este estudio ha sido aprobado por el Comité Ético de Investigación Clínica de los centros participantes en el estudio.

D. ASPECTOS ÉTICOS

Garantía de participación voluntaria

Su participación en este estudio es totalmente voluntaria y su decisión no afectará en ningún momento la asistencia que está recibiendo en el Servicio de Digestivo del Hospital del Mar ni la que pueda precisar en el futuro. Además en el caso de que acepte participar en este estudio es Ud libre de abandonarlo sin tener que dar explicaciones cuando lo desee, en cualquier momento del mismo.

En el caso de que no quiera participar en el estudio genético ello no impide que usted pueda participar en el estudio general.

Confidencialidad

Los investigadores de este centro se responsabilizan de que en todo momento se mantenga la confidencialidad respecto a la identificación del participante, tanto en los datos clínicos como en las muestras de sangre. El nombre y los datos de esta investigación quedarán archivadas con un código que será el mismo que aparecerá a lo largo de todo el estudio (datos clínicos y muestras de sangre). Estos procedimientos , que se llaman de anonimización, están sujetos a la Ley Orgánica 15/1999 del 13 de diciembre sobre protección de datos de carácter personal.

¿Qué hacen los investigadores con los datos que recogen?

Los datos se guardan en ficheros de papel o informáticos. Como ya hemos comentado previamente a cada participante se le adjudica un código, de manera que no aparezcan ni su nombre ni su apellido y se mantenga la confidencialidad. Con estos datos se realizarán análisis estadísticos para relacionar los resultados clínicos y de los cuestionarios con los resultados de los análisis genéticos. Finalmente los resultados se publicarán en revistas científicas.

Cada vez que los investigadores planteen un nuevo proyecto, este tendrá que ser evaluado por el Comité Ético de Investigación Clínica de los centros que participan en el estudio (IMAS-HClínic)

¿Qué hacen los investigadores con la muestra de sangre?

La muestra de sangre se procesan en un laboratorio para separar el plasma de las células. El plasma se guarda congelado para hacer posteriormente análisis bioquímicos relacionados con la depresión, el estrés y la inmunidad. De las células sanguíneas se extrae el material genético (ADN) con el que se harán los estudios genéticos. En el caso de que la muestra obtenida fuera insuficiente se le solicitaría una nueva muestra o se aplicarían técnicas de amplificación en el laboratorio. Parte del plasma y del ADN se deposita congelado a –80ºC para análisis futuros con el mismo objetivo, es decir estudiar aspectos genéticos relacionados con la depresión, estrés, y respuesta al tratamiento. El material se podrá tener almacenado hasta un máximo de 15 años, tras lo cual, el material será destruido según la normativa vigente. Este material podrá ser compartido con otros grupos de investigación de otros centros públicos o centros de investigación privados, españoles o extranjeros, procedimientos que siempre se realizarán bajo las normas de seguridad y confidencialidad necesarias.

En cualquier momento puede Ud solicitar que las muestras genéticas sean eliminadas.

Puede Ud realizar cualquier pregunta o duda en relación con el estudio. Los investigadores del estudio están a su disposición para contestarlas. Puede Ud encontrarlos: Dr. Ricard Sola, Servicio de Patología Digestiva. Hospital del Mar. Passeig Marítim 25-29. 08003 Barcelona. Dra. Rocío Martín-Santos, Servicio de Psiquiatría, Hospital Clínic. Villarroel 170. 08036 Barcelona.

Este protocolo has sido aprobado por el CEIC del IMAS/Hospital Clínic

"**Estudio farmacogenético y de predicción de la depresión inducida por el tratamiento con interferón alfa pegilado y ribavirina en pacientes con hepatitis C crónica.**"

ESTUDIO PSIGEN-VHC
Sección Hepatología/Hospital del Mar/IMIM/ Servicio Psiquiatría/ICN/Hospital Clínic/IDIBAPS
Barcelona
CONSENTIMIENTO INFORMADO POR ESCRITO

Yo (nombre y apellidos) _____

He leído la hoja de información que se me ha entregado

He podido hacer preguntas sobre el estudio.

He recibido suficiente información sobre el estudio.

He hablado con (nombre del investigador) _____

Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:

1. Cuando quiera
2. Sin tener que dar explicaciones
3. Sin que esto repercuta en mis cuidados médicos.

De conformidad con lo que establece la LO. 15/1999, de 13 Diciembre, de Protección de Datos de Carácter Personal, declaro haber sido informado:

1. De la existencia de un fichero o tratamiento de datos de carácter personal, de la finalidad de la recogida de éstos y de los destinatarios de la información.
2. Del carácter obligatorio o facultativo de mi respuesta a las preguntas que me son planteada.
3. De las consecuencias de la obtención de los datos o de la negativa a suministrarlo.
4. De la extracción de una muestra de sangre para la obtención de material genético.
5. De la identidad y dirección del responsable del tratamiento.
6. De la identidad y dirección del encargado del tratamiento.
7. De la posibilidad de solicitar la eliminación de las muestras en cualquier momento.

De la disponibilidad de ejercitar los derechos de acceso, rectificación, cancelación y oposición dirigiéndome por escrito a: Dr. Ricard Sola, Sección de Hepatología. Hospital del Mar. Passeig Marítim 25-29. 08003 Barcelona.

Y consiento que los datos clínicos referentes a mi enfermedad sean almacenados en un fichero automatizado, cuya información podrá ser manejada exclusivamente para fines científicos.

Presto libremente mi conformidad para participar en el estudio.

(firma del participante y fecha)

Barcelona, a ..... de .....200....

(firma del investigador y fecha)

Barcelona, a ..... de .....200...

Este procolo ha sido aprobado por el CEIC del IMAS/Hospital Clínic

III. Escales d'avaluació clínica de l'estudi

PHQ (mòdul screening depressió)

*Durante las **últimas 2 semanas**, ¿con qué frecuencia le han molestado cada uno de los siguientes problemas?*

1.	**Nunca**	**Unos cuantos días**	**Más de la mitad de los días**	**Todos o casi todos los días**
a) Tener poco interés o disfrutar poco haciendo cosas				
b) Sentirse desanimado, deprimido o sin esperanza				
c) Tener problemas para dormir (coger el sueño o mantenerlo), o tener más sueño de la cuenta				
d) Sentirse cansado o con poca energía				
e) Tener poco apetito o comer demasiado				
f) Sentirse mal consigo mismo – o sentirse fracasado o decepcionado de sí mismo, o pensar que ha decepcionado a los que le rodean				
g) Tener problemas para concentrarse, como por ejemplo para leer el periódico o ver la televisión				
h) Moverse o hablar tan lentamente que los demás lo han notado. O bien lo contrario, estar tan inquieto e intranquilo que ha estado moviéndose de arriba para abajo mucho más de lo habitual				
i) Tener pensamientos sobre que estaría mejor si se muriese o sobre hacerse daño a sí mismo de alguna manera				

HADS (amb subescales de depressió i ansietat)

A continuación encontrará una serie de preguntas con cuatro opciones cada una. Ha de escoger la opción que mejor coincide con su estado emocional **en la última semana** y marcar con una X el cuadrado que la precede.

A1. **Me siento tenso o nervioso**:

- ☐ Casi todo el día
- ☐ Gran parte del día
- ☐ De vez en cuando
- ☐ Nunca

D1. **Sigo disfrutando de las cosas como siempre**:

- ☐ Ciertamente, igual que antes
- ☐ No tanto como antes
- ☐ Solamente un poco
- ☐ Ya no disfruto con nada

A2. **Siento una especie de temor, como si algo malo fuera a suceder**:

- ☐ Sí, y muy intenso
- ☐ Sí, pero no muy intenso
- ☐ Sí, pero no me preocupa
- ☐ No siento nada de eso

D2. **Soy capaz de reírme y ver el lado gracioso de las cosas**:

- ☐ Igual que siempre
- ☐ Actualmente, algo menos
- ☐ Actualmente, mucho menos
- ☐ Actualmente, en absoluto

A3. **Tengo la cabeza llena de preocupaciones**:

- ☐ Casi todo el día
- ☐ Gran parte del día
- ☐ De vez en cuando
- ☐ Nunca

D3. **Me siento alegre**:

- ☐ Nunca
- ☐ Muy pocas veces
- ☐ En algunas ocasiones
- ☐ Gran parte del día

A4. **Soy capaz de permanecer sentado tranquilo y relajado**:

- ☐ Siempre
- ☐ A menudo
- ☐ Raras veces
- ☐ Nunca

D4. **Me siento lento y torpe**:

- ☐ Gran parte del día
- ☐ A menudo
- ☐ A veces
- ☐ Nunca

A5. **Experimento una desagradable sensación de "nervios y hormigueos" en el estómago**:

- ☐ Nunca
- ☐ Sólo en algunas ocasiones
- ☐ A menudo
- ☐ Muy a menudo

D5. **He perdido el interés por mi aspecto personal**:

- ☐ Completamente
- ☐ No me cuido como debería hacerlo
- ☐ Es posible que no me cuide como debiera
- ☐ Me cuido como siempre lo he hecho

A6. **Me siento inquieto como si no pudiera parar de moverme**:

- ☐ Realmente mucho
- ☐ Bastante
- ☐ No mucho
- ☐ En absoluto

D6. **Espero las cosas con ilusión**:

- ☐ Como siempre
- ☐ Algo menos que antes
- ☐ Mucho menos que antes
- ☐ En absoluto

A7. **Experimento de repente sensaciones de gran angustia o temor**:

- ☐ Muy a menudo
- ☐ Con cierta frecuencia
- ☐ Raramente
- ☐ Nunca

D7. **Soy capaz de disfrutar con un buen libro o con un buen programa de radio o televisión**:

- ☐ A menudo
- ☐ Algunas veces
- ☐ Pocas veces
- ☐ Casi nunca

Escala analògica de fatiga (VAS)

A continuación verá una línea. Representa el grado de cansancio o fatiga que usted ha tenido durante **las dos últimas semanas,** desde el 0, que representa el mayor estado de energía que pueda imaginarse, hasta el 100, que representa el mayor estado de cansancio y fatiga que pueda imaginarse. Nos gustaría que nos indicara en esta escala, en su opinión, el nivel de cansancio o fatiga que ha tenido en las dos últimas semanas.