Antidepressant prophylaxis reduces depression risk but does not improve sustained virological response in hepatitis C patients receiving interferon without depression at baseline: A systematic review and meta-analysis

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BACKGROUND: Depression complicates interferon-based hepatitis C virus (HCV) antiviral therapy in 10% to 40% of cases, and diminishes patient well-being and ability to complete a full course of therapy. As a consequence, the likelihood of achieving a sustained virological response (SVR [ie, permanent viral eradication]) is reduced.

OBJECTIVE: To systematically review the evidence of whether preemptive antidepressant prophylaxis started before HCV antiviral initiation is beneficial.

METHODS: Inclusion was restricted to randomized controlled trials in which prophylactic antidepressant therapy was started at least two weeks before the initiation of HCV antiviral treatment. Studies pertaining to patients with active or recent depressive symptoms before commencing HCV antiviral therapy were excluded. English language articles from 1946 to July 2012 were included. The MEDLINE, Embase and Cochrane Central databases were searched. Where possible, meta-analyses were conducted evaluating the effect of antidepressant prophylaxis on SVR and major depression as well as on Montgomery-Asberg Depression Rating Scale and Beck Depression Index scores at four, 12 and 24 weeks. The Cochrane Collaboration tool was used to assess bias risk.

RESULTS: Six randomized clinical trials involving 522 patients met the inclusion criteria. Although the frequency of on-treatment clinical depression was decreased with antidepressant prophylaxis (risk ratio 0.60 [95% CI 0.38 to 0.93]; P=0.02; I^2=24%), no benefit to SVR was identified (risk ratio 1.08 [95% CI 0.74 to 1.57]; P=0.69; I^2=58%).

CONCLUSION: This practice is not justified to improve SVR in populations free of active depressive symptoms leading up to HCV antiviral therapy.

Key Words: *Antidepressant; Antiviral treatment; Depression; Hepatitis C; Prophylaxis*

Les antidépresseurs en prophylaxie réduisent le risque de dépression mais n'améliorent pas la réponse virologique soutenue chez les patients atteints d'hépatite C qui reçoivent de l'interféron sans être déprimés au départ : une analyse systématique et une méta-analyse

HISTORIQUE : La dépression complique l'antivirothérapie à l'interféron conte le virus de l'hépatite C (VHC) chez 10 % à 40 % des patients et réduit leur bien-être et leur capacité de terminer le traitement. Par conséquent, la probabilité d'obtenir une réponse virologique soutenue (RVS [c.-à-d. une éradication virale permanente]) est réduite.

OBJECTIF : Procéder à l'analyse systématique des données probantes pour déterminer si une prophylaxie préventive aux antidépresseurs amorcée avant le début du traitement antiviral du VHC est bénéfique.

MÉTHODOLOGIE : L'inclusion était limitée aux essais aléatoires et contrôlés où on avait commencé à donner les antidépresseurs en prophylaxie au moins deux semaine avant le début du traitement antiviral contre le VHC. Les études sur les patients qui présentaient des symptômes de dépression actifs ou récents avant le début de l'antivirothérapie contre le VHC étaient exclues. Les articles en anglais publiés entre 1946 et juillet 2012 étaient inclus dans l'étude. Les auteurs ont fouillé les bases de données MEDLINE, Embase et Cochrane Central. Dans la mesure du possible, ils ont effectué des méta-analyses sur l'effet de la prophylaxie aux antidépresseurs sur la RVS et la dépression majeure ainsi que sur l'échelle d'évaluation de la dépression de Montgomery-Asberg et sur les indices de dépression de Beck au bout de quatre, 12 et 24 semaines. Ils ont utilisé l'outil de la Collaboration Cochrane pour évaluer le risque de biais.

RÉSULTATS : Six essais aléatoires cliniques auprès de 522 patients respectaient les critères d'inclusion. Même si la fréquence de dépression clinique pendant le traitement était réduite grâce à la prophylaxie aux antidépresseurs, (risque relatif de 0,60 [95 % IC 0,38 à 0,93]; P=0,02; I^2=24 %), la RVS ne s'associait à aucun avantage perçu (risque de de 1,08 [95 % IC 0,74 à 1,57]; P=0,69; I^2=58 %).

CONCLUSION : Cette pratique n'est pas justifiée pour améliorer la RVS au sein de la population sans symptômes de dépression active avant une antivirothérapie contre le VHC.

Chronic hepatitis C virus (HCV) infection is a major cause of liver cirrhosis and hepatocellular carcinoma, and the most common indication for liver transplantation in Europe and the United States (1). Combination therapy with pegylated interferon (peginterferon)-alpha and ribavirin represents standard treatment for chronic HCV infection (2,3). A sustained virological response (SVR) is achieved in 46% to 80% of patients (4-6). Despite this success rate, the challenging side-effect profile of HCV antiviral therapy limits treatment uptake. A key neuropsychiatric side effect of interferon-alpha (IFN-α) is major depression (7,8). The risk has been reported to range between 10% and 40% (4,5,9-12). In many cases, antidepressants are required, mental health services provided, IFN doses reduced and/or antiviral therapy interrupted.

Antidepressants are a mainstay for treating depression associated with IFN-α-based HCV therapy (6,13). Multiple studies have reported success in retaining patients on HCV antiviral therapy with the use of antidepressants in the management of IFN-induced depression (14,15). However, it remains unclear as to whether this practice benefits SVR rates (10,16,17).

An alternative approach to the management of IFN-induced depression is the use of antidepressant prophylaxis started before or at the time of HCV antiviral initiation. Several studies have attempted

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to address the effectiveness of this strategy without clearly resolving the issue (1,18-22). To address this unresolved question, we conducted a meta-analysis on the use of prophylactic antidepressants in patients initiating IFN-based HCV antiviral treatment. The impact on virological response, SVR rates and measures of mental health status were specifically addressed.

METHODS

Search strategy

A review protocol and search strategy was developed to capture articles describing HCV antiviral treatment in which prophylactic antidepressant therapy was used. English language articles from 1946 to July 2012 were included. The MEDLINE, Embase and Cochrane Central databases were searched. Reference lists of selected articles were also screened for eligible reports. The search strategies used are presented in Appendix 1.

Eligibility criteria

Inclusion was restricted to randomized controlled trials (RCTs) in which prophylactic antidepressant therapy was started at least two weeks before the initiation of HCV antiviral treatment.

Study selection and data extraction

All titles and abstracts of the citations identified by the literature search were independently screened by two investigators (AA-O and CC). Relevant articles were reviewed in their entirety. Each investigator made a recommendation for inclusion or exclusion of single articles and, if discordant, a third investigator (JC) resolved the discrepancy. When two or more articles had overlap of their populations and reported on the same outcomes, only the most inclusive article was considered with supplementary information taken from the overlapping articles.

Using a standardized form, two investigators (AA-O and JC) systematically collected data on the outcomes of interest, population characteristics and several aspects of study setting and methodological design. Virological response to treatment (ie, SVR) and major depression were specifially addressed. The Montgomery-Asberg Depression Rating Scale (MADRS) and Beck Depression Index (BDI) were also evaluated. The MADRS is a 10-item, clinician-administered measure of current depressive symptoms. It provides a measure of depressive symptomatology in patients with chronic medical conditions that is less influenced by physical symptoms and more sensitive to changes in depressive symptoms. The BDI, Second Edition, is a 21-item, self-reported tool used to evaluate depression symptom severity that is well validated and reliable in HCV patients and in IFN recipients (23-25).

Individual studies were assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials by two investigators (AA-O and JC) (26). Reporting of the following individual components were assessed: description and method of generation of the randomization sequence; method of allocation concealment; method of blinding; report of incomplete outcome data; selective reporting bias; and other biases such as baseline imbalance or early termination due to some data-dependent process.

Synthesis and meta-analysis

Where possible, measures of effect were pooled using standard meta-analysis methods. Pooled risk ratios (RR) and mean differences (MD) with associated 95% CIs were for calculated for dichotomous and continuous outcomes, respectively. Studies were pooled using random-effects models by the generic inverse variance method (27). However, where homogeneity allowed, both fixed- and random-effects results were calculated. Where studies reported medians, effect distribution was assessed and variance estimates were calculated using standard methods (28). Clinical and methodological heterogeneity was investigated and sensitivity analyses performed where necessary. Statistical heterogeneity was measured using the I^2 statistic (29); all meta-analyses were conducted irrespective of statistical heterogeneity. No subgroup analyses were performed. Study outcomes not eligible for inclusion in meta-analyses were reported descriptively across studies.

RESULTS

A total of 400 potentially eligible trials were retrieved through electronic searches; 310 nonduplicate publications were identified (Appendix 1). Twenty-one full-text articles were reviewed, of which 15 were excluded as companion studies or nonrandomized trials. In total, six RCTs met the inclusion criteria and were included in the meta-analysis (Table 1, Figure 1). Antidepressants evaluated included paroxetine (n=2 [20,21]) escitalopram (n=3 [1,18,22]) and citalopram (n=1 [19]). The period of time required to be free of ongoing depression or psychiatric symptoms ranged from two to six months. All but one study (1) excluded patients with past or current mood disorders, bipolar and psychotic psychiatric conditions. All studies excluded individuals with active substance abuse. The time to randomization before HCV antiviral treatment initiation ranged from zero to four weeks. Some studies used dose escalation and intensification strategies while others used a single, fixed dose. Four of six studies administered antidepressants for the entire duration of HCV antiviral therapy. The exceptions included the Diez-Quevedo et al (18) evaluation, in which patients were randomly assigned to escitalopram or placebo for the initial 12 weeks of treatment, and the de Knegt et al (1) assessment, in which citalopram was dosed for 26 weeks. All study participants received one of several IFN formulations administered subcutaneously and daily oral ribavirin. The targeted duration of HCV antiviral therapy was consistent across studies: 48 weeks for genotypes 1 and 4, and 24 weeks for genotypes 2 and 3.

Risk of bias in included studies

An assessment of each study against the individual methodological quality criteria described in the method section is provided in the table of risk of bias summary (Appendix 2). All studies were reported as 'randomized', although one article (20) did not describe the method of randomization. There is only one study that had low risk of bias across all domains. The study by Morasco et al (19) did not address incomplete outcome data and the study code was broken to several patients in the de Knegt et al (1) article. The study by Schaefer et al (22) had a baseline imbalance at the time of randomization in which baseline MADRS was higher in the placebo group even though this score normalized at the time of study. Overall, the included trials were assessed to be of reasonable quality.

SVR rate was not improved by prophylactic antidepressant use

Four studies including 382 patients reported SVR rates (18-20,22) (Table 2).The pooled estimate of effect resulted in no statistical difference in SVR rate between recipients of prophylactic antidepressants and the placebo group (RR 1.08 [95% CI 0.74 to 1.57]; P=0.69; I^2=58%) (Figure 2).

Prophylactic antidepressant therapy protected against clinical depression

All studies reported information describing the proportion of patients who developed clinical depression during the study period and/or at the end of the trial (Table 2). DSM-IV criteria were used to identify patients with clinical depression in four studies (18-21). The Mini-International Neuropsychiatry Interview (MINI) was used to diagnose depression in one study (1). A score of ≥13 on the MADRS was considered to be clinical depression in one study (22). The percentage of clinical depression was 10.51% (27 of 257) in the treatment group and 18.49% (49 of 265) in the placebo group (RR 0.60 [95% CI 0.38 to 0.93]; P=0.02; I^2=24%) (Figure 3A). The same analysis was conducted excluding a directional outlier with similar results (Figure 3B).

Psychiatric assessment scores used to grade depression severity did not differ between treatment and the control groups

Most studies reported MADRS results at four, 12 and 24 weeks

TABLE 1
Baseline characteristics

Author (reference), year	Group	Cases, n	Age, years*	Sex, M:F, %	HCV genotype: %	Duration of HCV antiviral treatment	History of psychiatric illness, %	Psychiatric scoring (at baseline)	Antidepressant prophylaxis
Raison et al (21), 2007	Treatment	28	51.1±6.5	53.6:46.4	NA	24 weeks	MD, 25 SA, 64	MADRS = 3.5±3.6† MADRS = 3.5‡	Paroxetine up to 40 mg/day 2 weeks before antiviral treatment
	Placebo	33	46.6±8.2	60.6:39.4	NA		MD, 24 SA, 64	MADRS = 5.2±5.2† MADRS = 3.0**	
Morasco et al (20), 2007	Treatment	14	50.6±5.4	100:0	1: 76.9 2+3: 23.1	G1, 48 weeks G2/3, 24 weeks	MD, 14.3 ETOH, 85.7	HAM-D = 2.9±5.6† HAM-A = 4.0±6.9†	Paroxetine up to 40 mg/day 4 weeks before antiviral treatment
	Placebo	19	46.4±4.9	100:0	1: 73.7 2+3: 26.3		MD, 15.8 ETOH, 68.4	HAM-D = 1.8±3.3† HAM-A = 1.5±2.5†	
Morasco et al (19), 2010	Treatment	19	51.8	94:6	1: 63.2 2+3: 36.8	Physician discretion	MD, 10.5	MADRS = 3.8±4.2† BDI-II = 3.3±3.9†	Citalopram 20 mg/day 2 weeks before antiviral treatment
	Placebo	20	54.2	90:10	1: 45 2+3: 55		MD, 15	MADRS = 3.0±3.0† BDI-II = 5.3±4.6†	
de Knegt et al (1), 2011	Treatment	40	48.5±9.7	67.5:32.5	1+4: 45 2+3: 55	G1/4, 48 weeks G2/3, 24 weeks	DE, 10 SA, 12.5	MADRS = 4.58±3.9† BAS = 0.83±1.0†	Escitalopram 5 mg/day for 2 weeks then 10 mg/day until week 24 then 5 mg/day for 2 weeks
	Placebo	39	44.6±7.5	89.7:10.3	1+4: 46.2 2+3: 53.8		DE, 25 SA, 15	MADRS = 4.69±4.7† BAS = 0.95±1.0†	
Diez-Quevedo et al (18), 2011	Treatment	66	46.7±10.6	59.1:40.9	1: 66.7 2: 7.6 3: 18.2 4: 7.6	Physician discretion	MD, 13.6 ETOH, 7.6	MADRS = 2.6±3.5† HADS = 2.5±2.8†	Escitalopram 15 mg/day 2 weeks before antiviral treatment
	Placebo	63	48±10.8	63.5:36.5	1: 82.5 2: 1.6 3: 12.7 4: 3.2		MD, 12.7 ETOH, 9.5	MADRS = 2.3±2.8† HADS = 2.4±2.5†	
Schaefer et al (22), 2012	Treatment	90	46.2	54:46	1: 60 2: 10 3: 21 4: 9	G1/4, 48 weeks G2/3, 24 weeks	No previous psychiatric illnesses	MADRS = 2.1±2.6† MADRS = 1.3‡	Escitalopram 10 mg/day 2 weeks before antiviral therapy. Stopped at the end of antiviral therapy
	Placebo	91	48.5	53:47	1: 65 2: 5 3: 23 4: 7			MADRS = 2.7±3.9† MADRS = 1.6‡	

**Data presented as mean ± SD or mean. †Mean ± SD; ‡Median. BAS Brief Anxiety Scale; BDI-II Beck's Depression Inventory (2nd Edition); DE Depressive episodes; ETOH Alcohol use disorder; F Female; G Genotype; HADS Hospital Anxiety and Depression Scale; HAM-A Hamilton Anxiety Scale; HAM-D Hamilton Depression Scale; HCV Hepatitis C virus; M Male; MADRS Montgomery-Asberg Depression Rating Scale; MD Major depression; NA Not applicable; SA Substance abuse*

(1,18,19,22) (Figure 4A). The scores ranged from 3.97 to 9.5 in the treatment group and 4.81 to 10.92 in the placebo group. The MD in MADRS scores between treatment and placebo was −1.42 (95% CI −3.15 to 0.31; P=0.11); −1.12 (95% CI −3.61 to 1.37; P=0.38) and −2.12 (95% CI −5.17 to 0.094; P=0.17) at four, eight and 12 weeks, respectively. The Schaefer et al (22) study reported MD at four, 12 and 24 weeks but not absolute mean MADRS for each study group. To address this, the mean MADRS and SDs at were calculated at weeks 4, 12 and 24 based on the reported baseline MADRS score. Sensitivity analysis was conducted excluding data extracted from Schaefer et al (22) to determine whether this methodology introduced bias in estimate of effect (data not shown). The MD of MADRS score at four, 12 and 24 weeks were not significantly different using this approach. The BDI score was reported in two studies (1,19). The BDI score at weeks 4, 8 and 24 did not differ between groups (Figure 4B).

DISCUSSION

Ultimately, the goal of antidepressant prophylaxis is to maintain patients on full doses of IFN and ribavirin and enable completion of the full duration of HCV antiviral therapy thereby maximizing the likelihood of achieving an SVR. Our meta-analysis, based on six RCTs with a low overall risk of bias (Appendix 2), suggests that this is not achieved, at least not in the populations evaluated. Individuals eligible for participation in these RCTs were characterized as being free from current

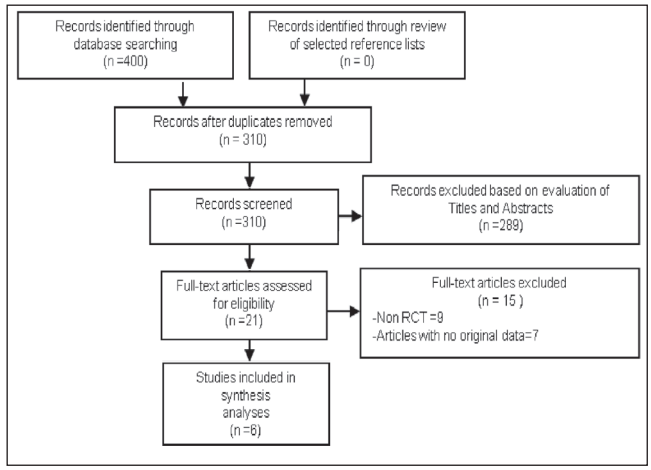

Figure 1) *Flow diagram of included studies. Flow diagram of records identified by search of electronic databases (MEDLINE, Embase, Cochrane Central) and reference lists of selected studies filtered according to hepatitis C antiviral treatment and prophylactic antidepressant therapy. The search was limited to studies indexed between 1946 and July 2012. The electronic search strategy is detailed in Appendix 1. RCT Randomized clinical trial*

TABLE 2
Outcomes

Author (reference), year	Group	Primary outcome: SVR	Primary outcome: Adherence*, n (N)	Secondary outcome: Depression† n (%)	Psychiatric scoring system			Suicidal ideation	Medication toxicity
Raison et al (21), 2007	Treatment	NA	5 (28)	3 (13.0)	MADRS	<15: n=13 (57%) ≥15: n=138 (35%) ≥25: n=2 (9%) ≥31: n=0 (0%)		ND	Dizziness 39% versus 12% Muscle/joint pain 73% versus 46%
	Placebo	NA	15 (33)	6 (20.7)	MADRS	<15: n=5 (17%) ≥15: n=16 (55%) ≥25: n=6 (21%) ≥31: n=2 (7%)		ND	
Morasco et al (20), 2007	Treatment	n=7	3 (14)	5 (35.7)	HAM-D‡ HAM-A	13.2±12.8 12.3±12.7		ND	ND
	Placebo	n=2	3 (19)	6 (31.6)	HAM-D HAM-A	15.5±15.7 9.6±9.3		ND	ND
Morasco et al (19), 2010	Treatment	G1, n=5 G2/3, n= 2	3 (19)	2 (10.5)		MADRS§	BDI-II	ND	Neurotoxicity scale 21%
					4 weeks	7.5±6.2	7.3±5.8		
					12 weeks	9.5±6.0,	6.0±4.1		
					24 weeks	8.2±6.6	6.3±5.7		
	Placebo	G1, n=3 G2/3, n=7	5 (20)	4 (20.0)		MADRS	BDI-II	ND	Neurotoxicity scale 16%
					4 weeks	7.8±7.3	6.8±4.7		
					12 weeks	8.5±8.9	7.8±7.8		
					24 weeks	5.6±5.5	4.6±3.6		
de Knegt et al (1), 2011	Treatment	G1, 46% G2, 83% G3, 73%	12 (40)	5 (12.5)		MADRS	BDI	ND	ND
					4 weeks	6.7±5.4	8.9±7.7		
					12 weeks	8.3±7.2	10.8±9.6		
					24 weeks	7.4±6.1	8.1±6.7		
	Placebo	G1, 50% G2, 80% G3, 86%	5 (39)	14 (35.9)		MADRS	BDI	ND	ND
					4 weeks	10.3±7.3	13.5±10.1		
					12 weeks	10.9±6.6	14.7±9.2		
					4 weeks	12.0±6.0	14.6±8.8		
Diez-Quevedo et al (18), 2011	Treatment	n=36	ND	5 (7.6)		MADRS		n=0	Muscle/joint pain OR 2.065
					4 weeks	3.97±0.68			
					12 weeks	5.62±0.83			
	Placebo	n=38	ND	2 (3.2)		MADRS		n=0	
					4 weeks	4.81±0.66			
					12 weeks	5.07±086			
Schaefer et al (22), 2012	Treatment	n=50 G1/4, 42% G2/3, 73%	12 (90)	7 (8.0)		MADRS¶		n=0	Fatigue: n=44 (48%) Insomnia: n=34 (37%) Headache: n=31 (34%)
					12 weeks	2.8 (95% CI 0.9–4.7)			
					24 weeks	3.1 (95% CI 1.1–5.1)			
	Placebo	n=42 G1/4, 35% G2/3, 85%	11 (91)	17 (19.0)	48 weeks	5.2 (95% CI 2.1–8.4)		n=0	Musculoskeletal pain: n=40 (44%)

**Participants not completing treatment for hepatitis C virus (HCV) treatment; †Participants experiencing major depression during HCV treatment; ‡HAM-A Hamilton Anxiety Scale; HAM-D Hamilton Depression Scale (HAM-D) score as outcome was mean highest score during treatment; §Author-reported mean ± SD Montgomery-Asberg Depression Rating Scale (MADRS) score, significantly different at week 16 and 20 post-treatment; ¶Mean difference; BDI Beck Depression Inventory (2nd Edition); G Genotype; MINI Mini-International Neuropsychiatry Interview; ND No data*

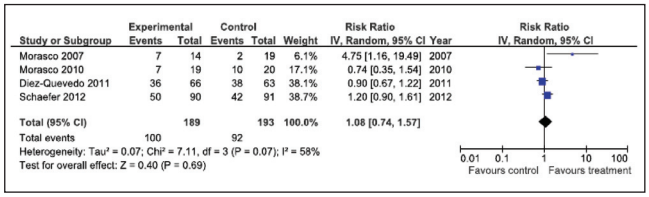

Figure 2) *Sustained virological response (SVR) rate. Forest plot of the SVR rate compared between recipients of prophylactic antidepressants and the placebo group*

or recent clinical depression, or other concurrent active psychiatric conditions. Furthermore, these participants were not taking any mental health medications at the time of enrollment. Our analysis established that antidepressant prophylaxis in advance of initiating HCV antiviral therapy is not beneficial in improving SVR in individuals with stable mental health. This does not resolve the question with regard to individuals with mild depression or other active psychiatric conditions planning to start HCV treatment. It is plausible that this benefit may have a more clinically significant effect in those with borderline depression or active, but stable, concurrent mental health concerns during the lead-up period to HCV therapy. Our analysis indicated that the risk for developing on-treatment depression was reduced in those randomly assigned to receive antidepressant prophylaxis, although the Diez-Quevedo et al (18) study, which has the highest internal validity or lowest risk of bias among the six trials, did not show decreased rate

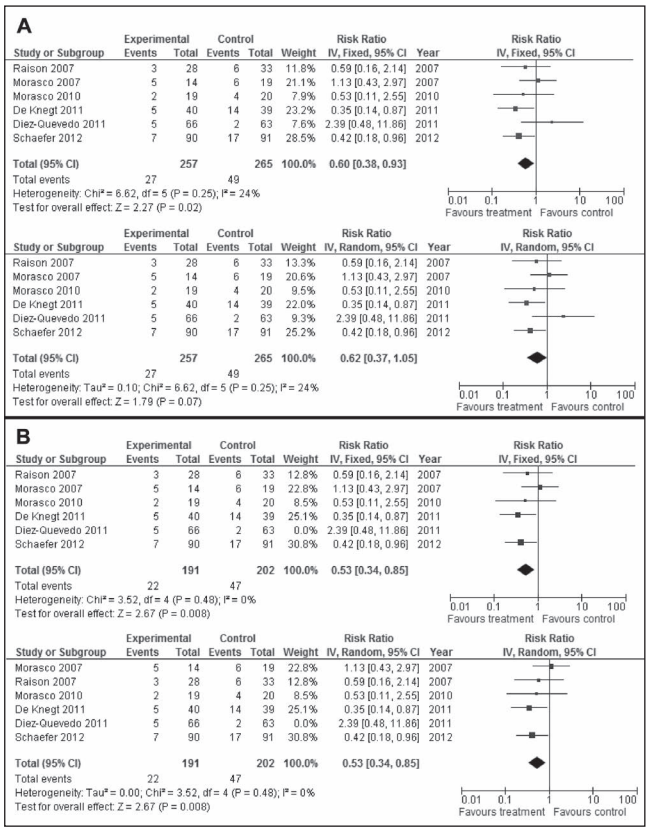

Figure 3) A *Depression rate, all studies included. Forest plot of the depression risk compared between recipients of prophylactic antidepressants and the placebo group. Fixed- and random-effects analyses are represented.* **B** *Depression rate excluding directional outlier (18). Forest plot of the depression risk compared between recipients of prophylactic antidepressants and the placebo group excluding one outlying study (18). Fixed- and random-effects analyses are represented*

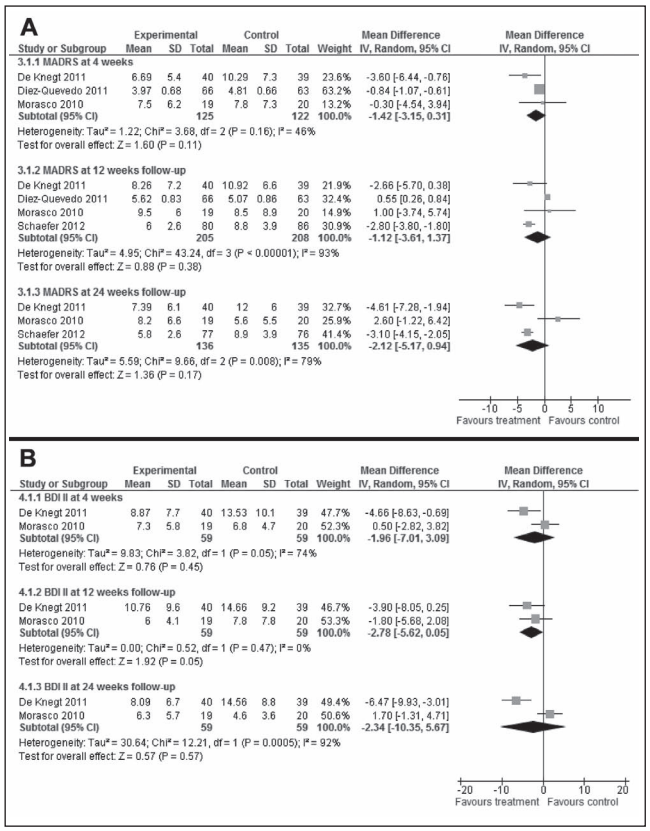

Figure 4) A *Montgomery-Asberg Depression Rating Scale (MADRS) results at four, 12 and 24 weeks. Forest plot of the mean difference in MADRS scores compared between recipients of prophylactic antidepressants and placebo group at four, eight and 12 weeks.* **B** *Beck Depression Inventory (BDI) score at four, 12 and 24 weeks. Forest plot of the mean difference in BDI scores compared between recipients of prophylactic antidepressants and placebo group at four, eight and 24 weeks*

of on-treatment clinical depression using DSM-IV criteria. Clearly, the severity of these cases and/or the reduced frequency of depression in those receiving prophylactic antidepressants was insufficient to impact SVR. However, this remains an important outcome because it suggests that the burden of psychiatric side effects experienced on treatment may be partially alleviated with prophylactic antidepressants.

MADRS and BDI scores are calculated, and continuous scoring systems are used to grade an individual's depressive state at any one time and to follow it over time. Although trending in favour of benefit with antidepressants, both MADRS and BDI scores were similar between randomization groups at weeks 4, 12 and 24 of HCV antiviral therapy. It is key to note that in individual studies, a relatively high baseline MADRS score was associated with a greater protection from on-treatment depression with the use of a prophylactic antidepressant (21). Moreover, de Knegt et al (1) noted a trend toward protection from on-treatment depression in recipients of escitalopram who had a history of depressive symptoms. It would have been of value to assess these scores during the initial month of therapy because the onset of depressive mood symptoms generally begins within the first four weeks of IFN-based HCV therapy. In clinical practice, therapy is often interrupted, doses of IFN are reduced and/or antidepressant therapy with or without additional mental health care is initiated before week 12 in an effort to manage on-treatment depressive symptoms. These measures would collectively serve to diminish any difference in the MADRS and BDI scores between groups at weeks 12 and 24. Unfortunately, the level of detail required to control for these on-treatment depression management factors was not reported in the individual publications.

Antidepressants are not without side-effect and adverse-event risk. However, there was no evidence from individual articles that the use of prophylactic antidepressants resulted in an increased symptomatic burden (19). Importantly, no suicides were reported. Raison et al (21) reported increased dizziness with paroxetine. At the very least, pill burden is increased with this practice, which is often a challenge for individuals receiving HCV antiviral therapy.

Several limitations of the present study are acknowledged. Relatively small, clinically and methodologically heterogeneous studies were evaluated. For continuous measures of effect, assumptions were made regarding normality. However, we do not believe that this altered the results. Only a small number of the many antidepressants currently in use were evaluated in the present study (ie, escitalopram, citalopram, paroxetine). It is plausible that other medications may be of greater value in preventing depression. Specifically, agents with anxiolytic and/or appetite-enhancing properties may be of overall benefit over the course of HCV treatment (30). It is noteworthy that the collective outcomes observed with any one of the three specific antidepressants assessed in the six RCTs included in our meta-analysis did not clearly differ from the overall findings (Figures 2, 3 and 4). Dose escalation was allowed in some but not all studies based on depressive symptomatology. It is possible that suboptimal doses may have been evaluated in some studies. Different IFN formulations were evaluated within and between studies. Theoretically, this could have influenced the risk of on-treatment depression and/or the response to antidepressant prophylaxis. However, several studies suggest that this is not the case (31-33). It is noteworthy that the mean maximum MADRS

scores did not differ between nonpegylated and pegylated IFN recipients in the evaluation by Raison et al (21).

On-treatment clinical depression may be reduced with the use of pre-HCV antiviral treatment antidepressant prophylaxis. However, this practice does not improve SVR rates in those without active pre-treatment depression. As such, this practice is not recommended to achieve this outcome in this population. We speculate that antidepressant prophylaxis may be of more value in those at greater risk for on-treatment depression (34). Additional study of more 'at-risk' populations would be of value.

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APPENDIX 1: SEARCH STRATEGIES

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <July 2012>

Search Strategy:

July 31, 2012

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1 exp Hepatitis C/ (1519)

2 (hep$ c or hcv).tw. (3424)

3 or/1-2 (3518)

4 exp Antidepressive Agents/ (8730)

5 (antidepress$ or anti depress$).tw. (5735)

6 (2-hydroxydesipramine or adinazolam or alaproclate or amineptin or aniracetam or bifemelane or clovoxamine or cyclobenzaprine or desmethyldoxepin or dibenzepin or duloxetine).mp. (500)

7 (femoxetine or flesinoxan or gepirone or hydroxymaprotilin or hypericin or indalpine or indeloxazine or L 701324 or melitracene or metapramine or milnacipran or minaprine or mirtazapine or MK 771 or nefazodone or norzimelidine or noxiptilin or O-desmethylvenlafaxine or pirlindole or progabide or reboxetine or sibutramine or sidnocarb or sulforidazine or talipexole or tianeptine or tofisopam or toloxatone or venlafaxine).mp. (2211)

8 (Benactyzine or Clorgyline or Deanol or Iproniazid or Isocarboxazid or Lithium or Moclobemide or Nialamide or Phenelzine or Pizotyline or Rolipram or Sertraline or Tranylcypromine).mp. (3557)

9 (5-hydroxytryptophan or amoxapine or bupropion or citalopram or fluoxetine or fluvoxamine or maprotiline or mianserin or paroxetine or quipazine or ritanserin or sulpiride or trazodone or tryptophan or viloxazine).mp. (8029)

10 (amitriptyline or clomipramine or desipramine or dothiepin or doxepin or imipramine or iprindole or lofepramine or nortriptyline or opipramol or protriptyline or trimipramine).mp. (5620)

11 "gamma-endorphin, des-Tyr(1)-".mp. (0)

12 or/4-11 (18383)

13 3 and 12 (33)

14 Chemoprevention/ (175)

15 (prophyl$ or prevent$).tw. (57814)

16 Secondary Prevention/ (64)

17 pc.fs. (58217)

18 or/14-17 (91430)

19 13 and 18 (16)

Database: Embase Classic+Embase <1947 to 2012 July 30>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 hepatitis C/ (85752)

2 (hep$ c or hcv).tw. (115886)

3 1 or 2 (134724)

4 exp antidepressant agent/ (289537)

5 (antidepress$ or anti depress$).tw. (100074)

6 (2-hydroxydesipramine or adinazolam or alaproclate or amineptin or aniracetam or bifemelane or clovoxamine or cyclobenzaprine or desmethyldoxepin or dibenzepin or duloxetine).mp. (10908)

7 (femoxetine or flesinoxan or gepirone or hydroxymaprotilin or hypericin or indalpine or indeloxazine or L 701324 or melitracene or metapramine or milnacipran or minaprine or mirtazapine or MK 771 or nefazodone or norzimelidine or noxiptilin or O-desmethylvenlafaxine or pirlindole or progabide or reboxetine or sibutramine or sidnocarb or sulforidazine or talipexole or tianeptine or tofisopam or toloxatone or venlafaxine).mp. (40745)

8 (Benactyzine or Clorgyline or Deanol or Iproniazid or Isocarboxazid or Lithium or Moclobemide or Nialamide or Phenelzine or Pizotyline or Rolipram or Sertraline or Tranylcypromine).mp. (147622)

9 (5-hydroxytryptophan or amoxapine or bupropion or citalopram or fluoxetine or fluvoxamine or maprotiline or mianserin or paroxetine or quipazine or ritanserin or sulpiride or trazodone or tryptophan or viloxazine).mp. (221473)

10 (amitriptyline or clomipramine or desipramine or dothiepin or doxepin or imipramine or iprindole or lofepramine or nortriptyline or opipramol or protriptyline or trimipramine).mp. (107989)

11 "gamma-endorphin, des-Tyr(1)-".mp. (119)

12 or/4-11 (581569)

13 3 and 12 (1665)

14 prophylaxis/ or prevention/ (226155)

15 (prophyl$ or prevent$).tw. (2026595)

16 pc.fs. (1775475)

17 14 or 15 or 16 (3334178)

18 13 and 17 (423)

19 remove duplicates from 18 (382)

20 19 use emczd (373)

21 exp Hepatitis C/ (98369)

22 (hep$ c or hcv).tw. (115886)

23 or/21-22 (136052)

24 exp Antidepressive Agents/ (400569)

25 (antidepress$ or anti depress$).tw. (100074)

26 (2-hydroxydesipramine or adinazolam or alaproclate or amineptin or aniracetam or bifemelane or clovoxamine or cyclobenzaprine or desmethyldoxepin or dibenzepin or duloxetine).mp. (10908)

27 (femoxetine or flesinoxan or gepirone or hydroxymaprotilin or hypericin or indalpine or indeloxazine or L 701324 or melitracene or metapramine or milnacipran or minaprine or mirtazapine or MK 771 or nefazodone or norzimelidine or noxiptilin or O-desmethylvenlafaxine or pirlindole or progabide or reboxetine or sibutramine or sidnocarb or sulforidazine or talipexole or tianeptine or tofisopam or toloxatone or venlafaxine).mp. (40745)

28 (Benactyzine or Clorgyline or Deanol or Iproniazid or Isocarboxazid or Lithium or Moclobemide or Nialamide or Phenelzine or Pizotyline or Rolipram or Sertraline or Tranylcypromine).mp. (147622)

29 (5-hydroxytryptophan or amoxapine or bupropion or citalopram or fluoxetine or fluvoxamine or maprotiline or mianserin or paroxetine or quipazine or ritanserin or sulpiride or trazodone or tryptophan or viloxazine).mp. (221473)

30 (amitriptyline or clomipramine or desipramine or dothiepin or doxepin or imipramine or iprindole or lofepramine or nortriptyline or opipramol or protriptyline or trimipramine).mp. (107989)

31 "gamma-endorphin, des-Tyr(1)-".mp. (119)

32 or/24-31 (591986)

33 23 and 32 (1698)

34 Chemoprevention/ (18441)

35 (prophyl$ or prevent$).tw. (2026595)

36 Secondary Prevention/ (13291)

37 pc.fs. (1775475)

38 or/34-37 (3233523)

39 33 and 38 (425)

40 39 use prmz (57)

41 remove duplicates from 40 (57)

42 20 or 41 (430)

43 remove duplicates from 42 (384)

APPENDIX 2
Risk of bias assessment

	Author (reference), year					
Criterion	Raison et al (21), 2007	Morasco et al (20), 2007	Morasco et al (19), 2010	Diez-Quevedo et al (18), 2011	De Knegt et al (1), 2011	Schaefer et al (22), 2012
Adequate sequence generation?	Low	High	Low	Low	Low	Low
Allocation concealment?	Unclear	Low	Low	Low	Low	Low
Blinding of participants and personnel?	Low	Low	Low	Low	Low	Low
Blinding of outcome assessment?	Low	Low	Low	Low	Low	Low
Incomplete outcome data addressed?	High	Low	Unclear	Low	Low	Low
Free of selective reporting?	Low	Low	Low	Low	Low	Low
Free of other bias?	Low	High	Low	Low	High	High

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