Effects of Escitalopram Prophylaxis During Antiviral Treatment for Chronic Hepatitis C in Patients With a History of Intravenous Drug Use and Depression

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ABSTRACT

Objective: We aimed to identify those patients with hepatitis C virus who benefit most from prophylactic treatment with selective serotonin reuptake inhibitors (SSRIs) during antiviral therapy.

Method: We performed post hoc analyses on a prospective randomized controlled trial (n = 79) of escitalopram versus placebo during antiviral therapy with pegylated interferon and ribavirin, conducted between August 2005 and June 2008. Our primary outcome measure was the association of baseline characteristics with the development of depression and/or depressive symptoms. Further, we studied effects of prophylactic escitalopram on depressive symptoms. Presence of a major depression was diagnosed using Mini-International Neuropsychiatric Interview (MINI), a short, structured interview used to diagnose *DSM-IV-TR* and *ICD-10* disorders. Depressive symptoms were monitored during treatment by using the depression scale of Symptom Checklist-90 (SCL-90), Montgomery-Asberg Depression Rating Scale (MADRS), and Beck Depression Inventory (BDI) at baseline and weeks 4, 12, and 24 of antiviral therapy.

Results: Depression occurred in 14 patients receiving placebo and in 5 patients receiving escitalopram (Pearson χ^2, $P = .01$). Combination of history of depression and intravenous drug use was associated with depression (odds ratio = 12.60; 95% CI, 2.47–64.34; $P < .01$). Moreover, treatment with selective serotonin reuptake inhibitor compared to placebo was associated with a significant reduction in estimated mean depressive symptoms measured by SCL-90 ($P = .03$) and BDI ($P = .048$), but not with MADRS ($P = .64$).

Conclusions: Patients infected by hepatitis C virus with a history of depression and intravenous drug use carry the highest risk to develop interferon-induced depression. In this subset of patients, prophylaxis with escitalopram results in the most substantial decrease of interferon-induced depressive symptoms on the SCL-90 depression scale and the BDI.

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Chronic hepatitis C virus (HCV) infection is a major health problem, with 130–150 million people being infected worldwide.[1] Antiviral therapy with pegylated interferon and ribavirin leads to sustained virologic response in 41%–83% of patients after 24 to 48 weeks of therapy.[2] However, this antiviral therapy is associated with many side effects, and these side effects are an important reason for dose reductions and treatment discontinuation in clinical practice.[3] In fact, psychiatric side effects of antiviral therapy have been shown to be the most important cause of early treatment discontinuation. Irritability and depression are the most frequently reported psychiatric side effects, with an incidence of 24% and 37% respectively.[4–6] Notably, sustained virologic response rates may be similar in patients with psychiatric disorders to the response rates in other HCV patients, provided that interdisciplinary care and antidepressant treatment are available.[7] In fact, 1 study[8] even suggested that interferon-induced depression might be positively correlated with sustained virologic response, but a prospective study[9] addressing this question directly found no effect of depression on sustained virologic response.

In our previously described retrospective cohort of HCV-infected patients treated with pegylated interferon/ribavirin,[10] we found a similarly high incidence of depression (30%) and association of the presence of a history of intravenous drug use with new-onset depression during antiviral therapy. Despite this high incidence of depression, depressive symptoms may be overlooked by routine clinical interviews, which are usually focused on physical rather than psychiatric complaints.[6] Although new direct-acting antiviral regimens are being developed, these agents still require pegylated interferon as a backbone of therapy, and it can therefore be anticipated that interferon-induced depression will remain a major challenge in the treatment of HCV.

Several baseline characteristics have been identified as predictors of depression, of which higher depression scores at baseline and depression with previous interferon-based therapy are the most consistent ones in literature.[11] A recent study[12] suggested that antidepressant prophylaxis for each patient might prevent depressive symptoms and a major depressive episode, although other research groups could not demonstrate a significant advantage for selective serotonin reuptake inhibitor (SSRI) prophylaxis in reducing the likelihood of developing major depression.[13–15] A disadvantage of prophylactic SSRI treatment is that a significant number of patients who would never have developed depressive symptoms would receive antidepressant treatment. Since interferon-induced depression affects only a subgroup of patients and has been shown to be highly responsive to SSRI treatment, we hypothesized that the efficacy of SSRI prophylaxis in the prevention of interferon-induced depression would vary among HCV-infected patients. Therefore,

we aimed to identify those patients with HCV who would benefit the most from prophylactic SSRI treatment during pegylated interferon/ribavirin and to quantify the effect of prophylactic treatment in these patients.

METHOD

We performed post hoc analyses of a recent randomized, double-blind, placebo-controlled trial[12] that investigated the effect of prophylactic treatment with escitalopram versus placebo. The study was conducted between August 2005 and June 2008. We defined *benefit of SSRI prophylaxis* as absence of a major depressive episode according to current *DSM-IV* classification[16] and/or significant reduction in estimated mean depression score during antiviral therapy when subjects were given doses of escitalopram instead of placebo. Hence, our primary outcome measure was the association of baseline parameters with the development of depression during antiviral therapy; our second outcome measure was the score on the depression scales of the Symptom Checklist-90 (SCL-90), Montgomery-Asberg Depression Rating Scale (MADRS), and Beck Depression Inventory (BDI) during antiviral therapy. Further, relation between success of antiviral therapy, sustained virologic response, and risk factors for depression were investigated.

The original trial intended to obtain a study sample representative of the HCV-infected patient population in Western countries and therefore permitted use of psychotropic medication such as methadone and benzodiazepines. The existence of a major depressive episode at screening was an exclusion criterion. Both treating hepatologist and psychiatrist were blinded with regard to type of study drug, which was initiated simultaneously with antiviral therapy.[12] Psychiatric evaluation was performed at baseline; weeks 4, 12, and 24 of antiviral therapy; and at 24 weeks of follow-up after cessation of antiviral therapy. The evaluation included conduct of the relevant module of the Mini-International Neuropsychiatric Interview (MINI) and the SCL-90. One of the investigators (G.B.) performed the psychiatric ratings after extensive training. The MINI is a short, structured diagnostic interview for *DSM-IV-TR* and *ICD-10* psychiatric disorders and was used to diagnose the event "depressive episode," or, briefly, "major depressive disorder." The SCL-90 is a well-validated, multidimensional self-report symptom inventory, designed to assess various dimensions of psychopathology, including depressive symptoms. The SCL-90 was used to study the degree and course of depressive symptoms over time. The score of the depression scale is constructed with the results of 16 questions and interpreted according to its classification in 1 of the 7 groups (very low, low, below average, average, above average, high, very high). In the general Dutch population, the observed range is 16–76, with 16–19 corresponding to the classifications very low to below average, 20–23 to average, 24 to above average, 25–35 to high, and ≥ 36 to very high.[17] Depressive symptoms were assessed using the MADRS, a clinician-rated depression scale and 1 of the most commonly used symptom severity scales in depression,[18] consisting of 10 items, each of which is scored from 0 to 6. The BDI is a well-validated and reliable 21-item self-report questionnaire designed to measure depressive symptoms.[19] Five somatic items (eg, measuring fatigue and loss of appetite) of the BDI were also recorded.

- During pegylated interferon/ribavirin therapy for chronic hepatitis C virus (HCV), patients who have a history of both intravenous drug use and depression compared to those who do not are more vulnerable to the development of depression.
- This subgroup of patients has more depressive symptoms during pegylated interferon/ribavirin therapy than chronic HCV-infected patients without a history of both intravenous drug use and depression.
- Within this subset of HCV-infected patients, antidepressant prophylaxis with the selective serotonin reuptake inhibitor escitalopram should be considered at the initiation of pegylated interferon/ribavirin therapy because it results in fewer depressive symptoms during antiviral therapy.

Clinical Points

First, we studied baseline covariates in relation to the development of depression. The following baseline covariates were collected: patient characteristics (gender, age, genotype 1 or other, race, living situation), data on psychiatric history (history of depression, history of psychosis, or previous suicide attempt; admission to a psychiatric hospital or admission to a center for addiction treatment; intravenous drug use as route of transmission; former or current use of alcohol or tobacco; drug use and type of drug used; or use of psychotropic medication), routine laboratory examinations (sodium, albumin, bilirubin, prothrombin time, γ-glutaminyl transferase, alanine transaminase, thyroid function, creatinine), and 2 specific laboratory values hypothesized to underlie psychiatric side effects of interferon-based antiviral therapy (serotonin, tryptophan) prior to initiation of antiviral therapy. After identification of baseline risk factors for the development of interferon-induced depression, we compared depression scores during antiviral therapy to identify which patients would benefit from antidepressant prophylaxis.

Statistics

Univariate logistic regression analysis was used to identify baseline factors associated with the development of depression in the placebo group. In a multivariate logistic model, we investigated the same factors with the addition of the prophylactic therapy to determine which factors were associated with depression in the total group, with correction for study treatment (escitalopram/placebo). Determinants with statistical significance at the .20 level in the univariate analysis were included in the multivariate analysis with backward selection based on the likelihood ratio. Data were analyzed using SPSS 17.0 statistical software (SPSS Inc). The covariates "admission to psychiatric hospital/ward," "suicide attempt in history," and "having ever been treated with psychoactive drugs" were mostly covered by the variable

Table 1. Baseline Characteristics of Participants in the Study on Prevention of Depression

Characteristic	Escitalopram (n = 40)	Placebo (n = 39)	Total N = 79
Male gender, n (%)	27 (68)[a]	34 (87)[a]	61 (77)
Age, mean (range), y	48 (22–68)	45 (30–61)	47 (22–68)
Born in the Netherlands, n (%)	22 (55)	25 (64)	47 (60)
Living situation, n (%)			
With partner	31 (78)	23 (59)	54 (68)
Other	9 (23)	16 (41)	25 (32)
Paid job, n (%)	20 (50)	15 (39)	35 (44)
Route of transmission, n (%)			
Intravenous drug use	19 (48)	21 (54)	40 (51)
Other	21 (53)	18 (47)	39 (49)
Race, n (%)			
Caucasian	34 (85)	34 (87)	68 (86)
Other	6 (15)	5 (13)	11 (13)
Genotype, n (%)			
1	16 (40)	15 (38)	31 (40)
2	7 (18)	5 (13)	12 (15)
3	14 (35)	16 (41)	30 (38)
4	2 (5)	3 (8)	5 (6)
Unknown	1 (3)	0 (0)	1 (1)
Psychiatric medical history, n (%)			
1 or more episodes of depression	8 (20)	16 (41)	24 (30)
Suicide attempts/drug overdose	5 (13)	6 (15)	11 (14)
Psychosis	15 (38)	20 (51)	35 (44)
Previous use of heroin and/or cocaine	19 (48)[a]	28 (72)[a]	47 (60)
Intravenous use of heroin and/or cocaine in past 3 mo	1 (3)	0 (0)	1 (1)
Nonintravenous use of heroin and/or cocaine in past 3 mo	2 (5)	3 (8)	5 (6)
Admission to addiction facility	11 (28)	17 (44)	28 (35)
Current contact with Mental Health or Addiction Service	9 (23)	13 (33)	22 (28)
Current use of psychotropic medication	9 (23)	3 (8)	12 (15)
Baseline scores, mean (SE)			
SCL-90	24.79 (1.48)	25.74 (1.40)	25.26 (1.02)
MADRS	4.57 (0.62)	4.69 (0.75)	4.63 (0.48)
BDI	9.05 (1.24)	8.21 (1.24)	8.64 (0.88)

[a]Statistically significant following Pearson χ^2.
Abbreviations: BDI = Beck Depression Inventory, MADRS = Montgomery-Asberg Depression Rating Scale, SCL-90 = Symptom Checklist-90, SE = standard error.

"depression in history." Therefore, we used "depression in history" in our multivariate analysis.

In general, strong collinearity between 2 factors hampers the interpretation of the results of a multivariate logistic model. The baseline characteristic "presence of a history of intravenous drug use" almost fully covered patients who reported a past depressive episode. However, previous depression and psychiatric comorbidity have been described in relation to interferon-induced depression. Therefore, we investigated these 2 covariates in the same multivariate model and separately.

To study the development and severity of depressive symptoms over time, we investigated the scores on the SCL-90 subscale depression, the BDI, and the MADRS sum score as continuous variables. We corrected for baseline values and estimated the mean scores of the SCL-90, the BDI, and the MADRS by using SAS mixed procedures with an autoregressive covariance structure taking the repeated measurement structure of the data into account. Covariates that had been identified as risk factors for depression with the above-described logistic regression analysis were selected; these covariates (depression in history, presence of a history of intravenous drug use) and the interaction with study treatment were studied in the mixed procedure as fixed effects.

RESULTS

Forty patients were randomized to escitalopram, and 39 patients were randomized to placebo. Table 1 summarizes the baseline characteristics of these patients. In the escitalopram group, more female patients participated ($P = .04$, Pearson χ^2), and fewer patients had ever used hard drugs ($P = .03$, Pearson χ^2); otherwise, baseline characteristics were comparable. Overall, 24 patients (30%) had a history positive for depression, 34 patients (44%) had been hospitalized in mental health centers or addiction centers, and 22 patients (28%) were in contact with outpatient mental health service or addiction service at the time of intake. Forty-seven patients (60%) reported ever having used heroin or cocaine, of which the majority (46 of 47 patients, 98%) reported intravenous drug use; henceforth, these 47 patients will be referred to as patients with presence of a history of intravenous drug use. At screening, 6 of these 46 patients reported use of heroin/cocaine within the past 3 months. Baseline scores of SCL-90 were comparable between the escitalopram and placebo groups. Sustained virologic response was achieved in 23 patients (58%) of the escitalopram arm and 19 patients (48%) of the placebo arm ($P = .59$).

Depression occurred in 14 of 39 patients (36%) randomized to placebo and in 5 of 40 patients (13%) randomized to escitalopram (Pearson χ^2, $P = .01$). In the univariate logistic analysis in placebo-dosed patients, history of depression, past intravenous drug use, and intravenous drug use as route of transmission were associated with the occurrence of depression during antiviral therapy. More importantly, the combination of history of depression and intravenous drug use was strongly associated with the occurrence of depression. No association was found between the occurrence of depression and baseline scores of the psychiatric questionnaires or baseline laboratory results In univariate analysis, there was an association between baseline BDI and occurrence of depression (OR = 1.193 [95% CI, 1.005–1.417], $P = .044$) and of baseline serotonin and occurrence of depression (OR = 0.865 [95% CI, 0.771–0.971], $P = .014$) (Table 2).

Multivariate logistic regression analysis was hampered by collinearity of history of depression and presence of a history of intravenous drug use; 18 of the 24 patients (75%) with a history of depression had injected drugs. Thirty-eight percent of patients who had ever injected drugs reported a history of depression. This collinearity was even stronger with the presence of the event depression; within this group, 85% of patients with a history of depression reported ever having injected drugs, and 73% of patients who ever

Table 2. Univariate Logistic Regression Analysis

	Event Depression Placebo Only			All Patients, After Correction for Study Drug			
Variable	OR	95% CI	*P* Value	OR	95% CI	*P* Value	*P* Value[a]
General characteristics							
Sex	0.857	0.125–5.874	.875	0.768	0.197–3.002	.705	
Age	1.011	0.922–1.109	.811	0.963	0.900–1.031	.282	.017
Non-Caucasian race	1.833	0.229–14.709	.568	1.679	0.355–7.947	.513	
IDU as transmission route	3.50	0.854–14.412	.083	2.78	0.890–8.702	.078	
No paid job	1.286	0.330–5.017	.718	0.152	0.018–1.304	.086	.024
Living alone	0.400	0.098–1.636	.202	0.314	0.084–1.166	.083	
rs12979860			.417			.828	
TT with TC as default	5.000	0.419–59.659	.203	1.833	0.150–22.366	.635	.472
CC with TC as default	2.500	0.361–17.315	.353	0.786	0.127–4.873	.796	.198
rs12980275			.145			.772	.292
AA with GA as default	5.500	0.545–55.494	.148	0.489	0.069–3.440	.472	.117
GG with GA as default	22.000	0.938–515.872	.055	0.000	0.000–NA	.999	.999
rs4803217			.610			.801	.789
CC with CA as default	2.500	0.389–16.049	.334	1.000	0.123–8.128	1.000	.521
AA with CA as default	2.500	0.146–42.800	.527	2.333	0.156–34.894	.539	.972
rs8099917			.646			.970	.653
TT with TG as default	0.500	0.067–3.745	.500	0.947	0.138–6.525	.956	.653
GG with TG as default	1.500	0.055–40.633	.810	1.500	0.055–40.633	.810	
rs8103142			.610			.530	
TT with TC as default	1.400	0.199–9.869	.736	1.115	0.268–4.631	.881	
CC with TC as default	3.500	0.284–43.161	.328	2.686	0.432–16.691	.289	
Genotype 1	1.250	0.326–4.788	.745	0.444	0.042–4.708	.501	.455
Sodium	1.060	0.770–1.458	.721	0.985	0.379–2.559	.975	1.037
Creatinine	0.985	0.928–1.044	.604	0.961	0.913–1.011	.128	.012
Thyroid stimulating hormone	1.106	0.705–1.735	.662	0.898	0.348–2.319	.824	.698
Bilirubin	0.896	0.724–1.109	.314	0.760	0.610–0.948	.015	
Alanine transaminase	1.002	0.993–1.011	.632	1.001	0.988–1.014	.897	.872
γ-Glutamyl transferase	1.002	0.996–1.008	.483	0.985	0.968–1.003	.112	.052
Albumin	0.897	0.703–1.146	.387	1.019	0.813–1.276	.873	.456
Platelets	0.994	0.982–1.007	.377	1.022	1.002–1.042	.028	.020
Prothrombin time	1.000	1.000–1.000	.812	1.000	1.000–1.001	.183	
Psychiatric comorbidity and substance use							
Depression in history	9.50	2.075–43.502	.04	9.317	2.763–31.420	< .001*	
Admission to psychiatric hospital/ward	6.111	0.996–37.490	.050	4.558	1.126–18.448	.033	
Suicide attempt in history	12.778	1.305–125.067	.029	9.468	2.094–42.814	.04	
Ever having been treated with psychoactive drugs	3.103	0.687–14.018	.141	4.980	1.258–19.721	.022	
Psychosis in history	2.127	0.548–8.259	.275	0.375	0.038–3.715	.402	.202
Admission to addiction treatment center	2.222	0.580–8.511	.244	0.625	0.062–6.301	.690	.352
Currently contact with Mental Health Service	0.667	0.161–2.769	.577	0.844	0.082–8.663	.886	.866
Previous use of cocaine/heroin	3.600	0.651–19.902	.142	2.677	0.761–9.414	.125	
Previous nonintravenous use of cocaine/heroin	2.955	0.721–12.107	.132	2.485	0.798–7.736	.116	
History of depression and use of cocaine/heroin	12.600	2.467–64.341	.002	10.259	2.862–36.777	< .001*	
Current alcohol abuse	0.778	0.199–3.035	.718	2.875	0.421–19.620	.281	.276
Previous use of cannabis/marijuana	3.00	0.537–16.767	.211	3.00	0.758–11.877	.118	
History of nonintravenous drug use	2.200	0.481–10.066	.310	2.029	0.619–6.651	.243	
Current use of cocaine/heroin, noninjecting	0.846	0.070–10.272	.896	0.635	0.062–6.507	.702	
Currently treated with psychoactive drug	0.000	0.000–infinite	.999	7.250	0.988–53.222	.051	.999
Current use of nicotine	0.333	0.060–1.863	.211	0.348	0.088–1.380	.133	
Current use of cannabis/marijuana	1.200	0.272–5.285	.810	1.915	0.557–6.590	.303	
Previous use of nicotine	0.000	0.000–NA	.999	1.938	0.171–21.923	.593	
Psychiatric questionnaires, baseline scores							
Event hostility	1.363	0.702–2.644	.360	1.398	0.826–2.368	.212	
Event concentration	1.458	0.882–2.409	.142	1.513	0.993–2.305	.054	
Event mentioned sadness	1.209	0.561–2.604	.629	1.366	0.754–2.743	.303	
BDI, sum	0.994	0.90–1.097	.909	1.193	1.005–1.417	.044	
SCL-90							
Depression scale	1.004	0.924–1.091	.923	1.026	0.960–1.097	.448	
Hostility	0.947	0.698–1.285	.727	1.102	0.894–1.359	.361	
Phobic anxiety	1.035	0.795–1.348	.797	1.035	0.824–1.302	.765	
Anxiety	1.027	0.902–1.170	.687	1.049	0.940–1.171	.391	
Insufficiency in thinking and acting	1.055	0.914–1.218	.462	1.109	0.981–1.254	.097	
Sleeping	1.048	0.852–1.289	.658	1.126	0.929–1.364	.228	
SCL-90, total score	1.001	0.984–1.019	.887	1.006	0.990–1.021	.477	
MADRS, sum	1.054	1.07–1.226	.495	1.080	0.942–1.237	.270	

(continued)

Table 2 (continued). Univariate Logistic Regression Analysis

	Event Depression Placebo Only			All Patients, After Correction for Study Drug			
Variable	OR	95% CI	*P* Value	OR	95% CI	*P* Value	*P* Value[a]
Psychiatric laboratory results, baseline							
Neopterin	1.010	0.938–1.086	.800	0.949	0.831–1.083	.438	
Tryptophan	1.029	0.941–1.125	.536	0.984	0.903–1.071	.704	.016
Hydroxytryptophan	1.005	0.979–1.032	.708	1.013	0.989–1.038	.301	
Serotonin	0.942	0.861–1.031	.193	0.865	0.771–0.971	.014	.011
Total biopterin	0.997	0.832–1.195	.973	0.798	0.602–1.058	.117	.043
Tetrahydrobiopterin	0.857	0.613–1.197	.365	0.867	0.657–1.144	.313	
Kynurenine	1.558	0.506–4.800	.440	0.487	0.147–1.610	.238	.011
Kynurenine/tryptophan ratio	1.025	0.965–1.089	.417	0.959	0.895–1.027	.231	.010

[a]*P* value if interaction study drug with variable stays in the model.
*Statistically significant following Pearson χ^2.
Abbreviations: BDI = Beck Depression Inventory, IDU = injecting drug use, MADRS = Montgomery-Asberg Depression Rating Scale, NA = not applicable, SCL-90 = Symptom Checklist-90.

Table 3. Results of Multivariate Logistic Regression Analyses on Incidence of Depression With Antiviral Therapy for Chronic Hepatitis C Virus

	Placebo Arm			All Patients[a]		
Multivariate Models	OR	95% CI	*P* Value	OR	95% CI	*P* Value
History of depression and IVDU × living without partner						
History of depression and IVDU	12.46	2.35–65.94	.003	10.52	2.80–39.57	< .001
Living without partner	2.43	0.46–12.77	.290	3.33	0.75–14.75	.113
History of depression and IVDU × baseline serotonin level						
History of depression and IVDU	13.16	1.56–109.18	.017	14.01	2.48–79.20	.003
Baseline serotonin level	0.93	0.84–1.04	.203	0.91	0.84–0.99	.105
History of depression and IVDU × gender						
History of depression and IVDU	13.53	2.55–71.75	.002	10.45	2.90–37.70	< .001
Gender	1.92	0.21–17.74	.567	1.52	0.34–6.91	.58
History of depression and IVDU × age						
History of depression and IVDU	12.48	2.37–65.66	.003	10.23	2.86–36.59	< .001
Age	1.00	0.90–1.12	.950	0.99	0.92–1.06	.72

[a]After correction for randomization escitalopram or placebo.
Abbreviations: BMI = body mass index, IVDU = intravenous drug use.

injected hard drugs had a history of depression. Multivariate analysis including the covariates history of depression, the presence of a history of intravenous drug use, and gender resulted in history of depression as the covariate associated with the event depression: odds ratio (OR) = 9.50; 95% CI, 2.08–43.50; *P* = .004, in the placebo arm; and OR = 10.61; 95% CI, 3.25–34.64; *P* < .001, in the overall study group, corrected for study medication. A subsequent multivariate analysis was performed to overcome the described collinearity, combining history of depression and intravenous drug use as a single covariate with other baseline covariates in a model. Because there were only 19 events (ie, the occurrence of depression), we performed these models with only 2 variables, with correction for study drug. We show these models in Table 3. We included the following clinically relevant covariates in our multivariate analysis: female gender, younger age, and living situation (alone or with partner) as a measure for lack of social support (Table 3).[20–23]

Because we identified the characteristic "history of both intravenous drug use and depression" as a risk factor for interferon-induced depression, we provided baseline characteristics according to this covariate in Table 4. Sustained virologic response rate was not significantly different in patients with (n = 8, 57%) and without (n = 34, 67%) a history of depression and intravenous drug use (*P* = .509).

Treatment Effect of Escitalopram

We studied the treatment effect of study drug regarding depressive symptoms. We took the presence of history of depression and intravenous drug use into account because these characteristics were associated with depression during antiviral therapy following logistic regression analysis. One patient did not complete the SCL-90 questionnaire at week 0; therefore, this patient was not included in this analysis of depression score over time. We selected patients with the presence of 1 of these 2 risk factors in both placebo arm and escitalopram arm. Subsequently, we compared the estimated mean scores of depressive symptoms over time using the SCL-90 depression subscale, MADRS, and BDI. Within the group of patients with a history of depression and intravenous drug use, escitalopram-dosed patients showed lower estimated mean scores on the SCL-90 during interferon treatment than placebo-dosed patients (*P* = .03) (Figure 1A). With a history of depression and intravenous drug use, escitalopram prevents the development of depressive symptoms and shows a reduction of 9.81 points (95% CI, 0.95–18.67) on the depression score (*P* = .03). Without a history of depression and/or intravenous drug use, escitalopram prevents the development of depressive symptoms and shows a reduction of 3.96 points (95% CI, 0.12–7.80) on the depression score (*P* = .04). With respect to

Table 4. Baseline Characteristics Categorized by History of Depression and/or Substance Use

Characteristic	No History of Depression or IDU n = 26	History of Both Depression and IDU n = 18	History of IDU, No History of Depression n = 29	No History of IDU, History of Depression n = 6	*P* Value
Male gender, n (%)	18 (69)	15 (83)	26 (90)	2 (33)	.015*
Age, mean (range), y	48 (34–68)	45 (22–58)	45 (30–62)	51 (35–67)	.305
Born in the Netherlands, n (%)	13 (50)	13 (72)	19 (66)	2 (33)	.229
Living situation, n (%)					
With partner	21 (81)	13 (72)	15 (52)	5 (83)	.098
Other	13 (50)	8 (44)	11 (38)	3 (50)	.826
Paid job, n (%)	21 (81)	16 (89)	26 (90)	5 (83)	.783
Route of transmission, n (%)					
Intravenous drug use					.002*
Other	13 (50)	5 (28)	12 (41)	1 (17)	
Race, n (%)					
Caucasian	6 (23)	1 (6)	1 (3)	4 (67)	
Other	5 (19)	10 (56)	15 (52)	0 (0)	
Genotype, n (%)					
1	2 (8)	1 (6)	1 (3)	1 (17)	
2	0 (0)	1 (6)	0 (0)	0 (0)	
3	0 (0)	18 (100)	0 (0)	6 (100)	< .001*
4	0 (0)	7 (39)	3 (10)	1 (17)	.003*
Unknown	1 (4)	15 (83)	17 (58)	2 (33)	< .001*
Psychiatric medical history, n (%)					
1 or more episodes of depression	0 (0)	18 (100)	29 (100)	0 (0)	
Suicides attempts/overdose	0 (0)	0 (0)	1 (3)	0 (0)	.627
Psychosis	0 (0)	1 (6)	4 (14)	0 (0)	.179
Previous use of heroin and/or cocaine	0 (0)	13 (72)	15 (51)	0 (0)	< .001*
Intravenous use of heroin and/or cocaine in past 3 mo	1 (4)	7 (39)	14 (48)	0 (0)	.001*
Nonintravenous use of heroin and/or cocaine in past 3 mo	48 (34–68)	45 (22–58)	45 (30–62)	51 (35–67)	.305
Admission to addiction facility	13 (50)	13 (72)	19 (66)	2 (33)	.229
Current contact with mental health or addiction service	21 (81)	13 (72)	15 (52)	5 (83)	.098
Current methadone use	0 (0)	4 (22)	7 (24)	0 (0)	
Current use of psychotropic medication	2 (8)	5 (28)	0 (0)	5 (17)	.178
Baseline scores, mean (SE)					
SCL-90	22.68 (1.9)	36.86 (4.5)	27.00 (2.2)	29.69 (2.0)	.005
MADRS	3.13 (0.7)	5.9 (1.1)	4.83 (2.7)	4.30 (0.8)	.246
BDI	6.59 (1.5)	20.79 (2.88)	12.67 (3.0)	13.19 (1.7)	< .001

*Statistically significant following Pearson χ^2.
Abbreviations: BDI = Beck Depression Inventory, IDU = injecting drug use, MADRS = Montgomery-Asberg Depression Rating Scale, SCL-90 = Symptom Checklist-90, SE = standard error.

the BDI scale, with a history of depression and intravenous drug use, escitalopram prevents the development of depressive symptoms and shows a reduction of 7.58 points (95% CI, 0.07–15.10) on the depression score ($P = .048$) (Figure 1B). Without a history of depression and/or intravenous drug use, escitalopram prevents the development of depressive symptoms and shows a reduction of 4.22 points (95% CI, 1.03–7.42) on the depression score ($P = .01$).

Regarding the MADRS score, in subjects with a history of depression and intravenous drug use, escitalopram does not prevent the development of depressive symptoms ($P = .64$). In subjects without a history of depression and/or intravenous drug use, escitalopram prevents the development of depressive symptoms and shows a reduction of 3.22 points (95% CI, 0.55–5.89) on the depression score ($P = .02$) (Figure 1C).

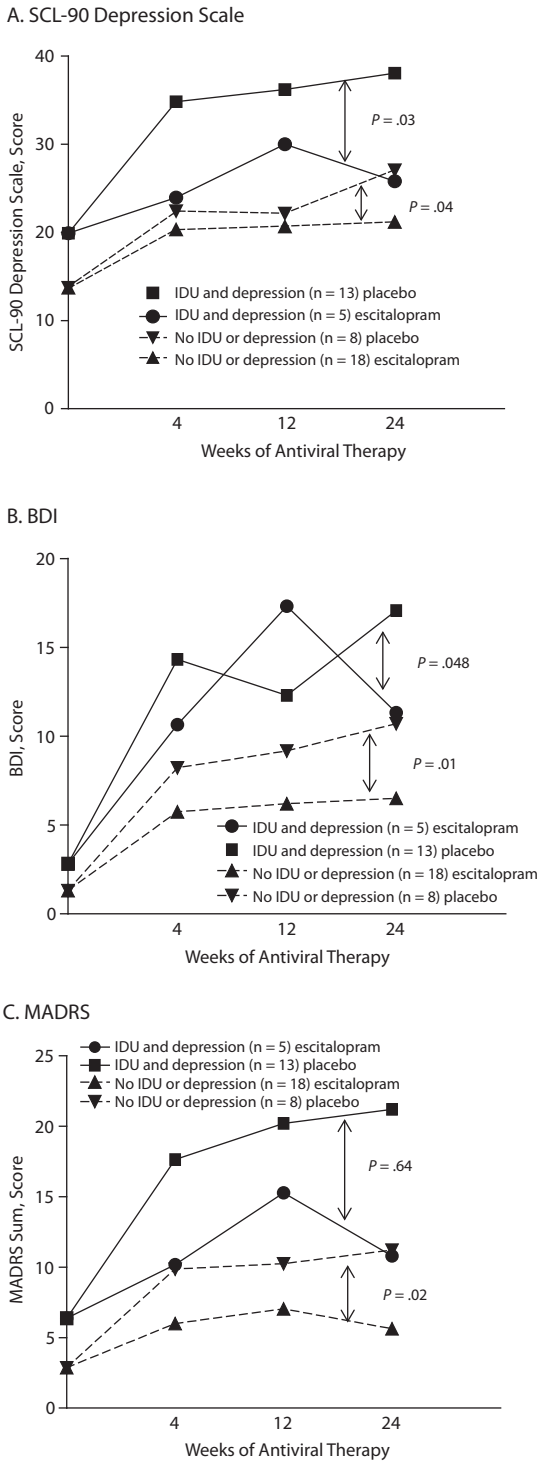
Thus, placebo-treated patients with a history of intravenous drug use and depression showed significantly higher scores on the estimated mean SCL-90 depression scale and significantly higher scores on the estimated mean BDI scores, but not on the estimated mean MADRS score during interferon treatment, compared with patients receiving escitalopram.

DISCUSSION

Our study shows that chronic hepatitis C patients with a history of depression and intravenous drug use are most vulnerable for the development of overt depression during treatment with pegylated interferon and ribavirin. Furthermore, it shows that the development of depressive symptoms in these patients might be prevented with prophylactic treatment with the SSRI escitalopram.

Our study is important for clinical practice because it identifies patients at baseline who are prone to interferon-induced depression irrespective of prior interferon treatment and who are most likely to benefit from primary prevention with SSRI prophylaxis. Previously, several baseline covariates have been identified as risk factors for interferon-induced depression, with elevation of depression scores just prior to initiation of antiviral therapy being the most consistent one.[24,25] In our study, we found no correlation between mood, anxiety, and depression scores at baseline and depression, probably because patients with depression at baseline were excluded from the study. Other previously described risk factors for interferon-induced depression are depression with a previous interferon-based regimen for chronic HCV,

Figure 1. Estimated Mean Scores in Patients on Antiviral Therapy With Treatment Effect of Study Drug According to the Presence of a History of Depression and/or Previous IDU During Antiviral Therapy[a]



[a]The mean scores of the SCL-90, the BDI, and the MADRS were estimated using SAS mixed procedures with an autoregressive covariance structure taking the repeated measurement structure of the data into account.

Abbreviations: BDI = Beck Depression Inventory, IDU = injecting drug use, MADRS = Montgomery-Asberg Depression Scale, SCL-90 = Symptom Checklist-90.

younger age, lower social support, the personal trait "low self-directedness," and reporting depressed feelings.[20,21,24,26,27] With respect to age, we could not demonstrate an association between age as continuous variable and the event depression in our study population.

The serotonin pathway is expected to be of great clinical importance in the development of depressive symptoms with antiviral therapy. Although the use of baseline and on-treatment serotonin concentrations could not be linked to interferon-induced depression in a study by Raison et al,[24] a more recent study by Loftis et al[28] did show a significant correlation between somatic symptoms of depression and lower serotonin levels at baseline.

Some reports suggest that a family history of depression may be a factor associated with interferon-induced depression.[29] This might point toward an underlying genetic vulnerability. Promising results have been reported in genetic studies where traits have been investigated and identified as related to interferon-induced depression. The recent results of Kraus et al[22] demonstrating the specific polymorphism in the serotonin receptor gene (C-1019G of the *HTR1A* gene: homozygosity for the G allele) to predispose to interferon-induced depression may be very important. Pierucci-Lagha et al[30] suggested a role of polymorphisms in the serotonin transporter as a risk factor for the development of interferon-induced depression as well. More specifically, Smith et al[31] demonstrated the importance of a polymorphism in the *IDO1-2,3* gene in Caucasian patients without a history of clinically relevant depression. If these genetic risk factors can be confirmed in other studies, they may provide additional tools to predict the development of depression in HCV patients treated with antiviral therapy.[22,31] In fact, previous depression and, for example, a family history of depression suggest a vulnerability to depression that might have a genetic basis.

Interestingly, interleukin-28B polymorphisms, which have been shown to predict treatment response to interferon in chronic hepatitis C patients, also predict interferon-induced neurovegetative symptoms such as appetite, energy, and sleep complaints.[32] Indeed, Raison et al[33] showed that chronic activation of the immune system and exposure to an innate immune cytokine affects sleep continuity and depth of sleep. However, no effect of interleukin-28b polymorphism was seen on development of major depressive disorder.[32]

Regarding prevention, previous research on prophylactic antidepressant treatment of the general HCV population has been inconsistent.[12,13,15,34–36] In high-dose interferon treatment for malignant melanoma, prophylactic treatment with paroxetine effectively prevented interferon-induced depression. In HCV patients, Morasco et al[13] demonstrated a reduction in depression of almost 50% with their double-blind placebo-controlled trial, but the study was underpowered to detect a clinically relevant significant difference. Hence, the authors concluded that prophylaxis was not beneficial. Diez-Quevedo et al[14] studied the effects of 14 weeks of escitalopram versus placebo on new-onset depression in 129 HCV patients. Rates of depression were

remarkably low (5.4%) and did not differ between placebo (3.2%) and escitalopram (7.6%). The results are difficult to translate to clinical practice, as patients with baseline mental disorders and/or recent or concomitant drug use were excluded. This selection of patients might explain the low depression rate in the total group of patients. Schaefer et al[34] demonstrated the beneficial effect of antidepressant prophylaxis in psychiatric HCV-infected patients on antiviral therapy, resulting in even lower rates of depression in HCV patients with psychiatric disorders than a control group of HCV patients without psychiatric risk factors. A recently conducted double-blind, randomized, placebo-controlled trial[12] with escitalopram proved the efficacy of prophylactic treatment with a significant decrease in the incidence of depression in patients randomized to escitalopram. These studies taken together, HCV-infected patients constitute a heterogeneous group of patients with varying degrees of psychiatric comorbidity, and results of such trials might be difficult to compare. Additionally, given the fact that about 70% of HCV-infected patients will not suffer depression with interferon-based antiviral therapy, a refinement of the indication for prophylactic SSRI treatment would seem necessary.[37] The results of the current study suggest that the effect of escitalopram is largest in the subgroup of patients with a history of depression and intravenous drug use. However, identifying a group of patients at high-risk to develop interferon-induced depression should not lower our attention on the rest of the population, who should be followed equally to monitor the development of psychiatric side effects.

An alternative strategy to prophylactic SSRI treatment is to detect and treat psychiatric symptoms as soon as they develop during antiviral therapy. Kraus et al[38] have demonstrated the high responsiveness of interferon-induced depression for serotonergic antidepressant medication when initiated after early detection with a psychometric instrument. Nevertheless, preemptive treatment of patients at high risk for depression may be favored since these symptoms may be underreported and are known to develop early in the course of antiviral therapy. We offer a practical strategy to prevent depressive symptoms in vulnerable patients with a minimal risk of excessive treatment. Although we could not demonstrate a difference in sustained virologic response with SSRI prophylaxis in patients who would experience less depressive symptoms during antiviral therapy, previous studies[6,39] have shown the presence of depression to be associated with a poorer rate of sustained virologic response. Therefore, prevention of interferon-induced side effects would mean an important step forward in the treatment of chronic hepatitis C. Further, our analysis is based on a randomized controlled trial. Both clinician and patient could be expected to be at least as or even more motivated to avoid early dropout. Therefore, it is unclear whether SSRI prophylaxis in patients prone to the development of depression and depressive symptoms would positively affect dropout rate in clinical practice and, as a consequence, increase the rate of sustained virologic response.

There are several limitations to our study. Since the size of our study population was limited, less than strong associations between baseline characteristics and depression may have remained undetected in our analysis. Nevertheless, the study population contained sufficient power to detect a strong association between history of depression and intravenous drug use with pegylated interferon/ribavirin therapy in the placebo-dosed patients and the total group of participants, when corrected for the use of SSRI.

More patients in the escitalopram group than in the placebo group withdrew before completing the trial. We do not believe that this led to underreporting of depressive symptoms, since these patients remained in follow-up after withdrawal. However, in theory, early withdrawal might have led to lower incidence of depressive symptoms due to shorter exposure to pegylated interferon.

In our study, no lead-in period with escitalopram was used. The treatment effect might have been more pronounced if a lead-in period had been used, so that the SRI would be fully active in the first weeks of antiviral therapy.

Finally, our study population includes a large percentage of patients with previous psychiatric and substance use disorders. It is entirely possible that studies in other populations with less psychiatric comorbidity may show different results. Nevertheless, we think that our study represents clinical practice, where psychiatric comorbidity is frequent among HCV patients, and these patients might actually be underrepresented in many randomized trials evaluating treatment for HCV.[10,40,41]

In conclusion, prophylactic treatment with escitalopram significantly reduces depressive symptoms in HCV-infected patients with a history of both depression and intravenous drug use during antiviral therapy and should therefore be considered in this subset of patients. Although HCV patients with a history of depression and intravenous drug use were more likely to develop interferon-induced depression, sustained virologic response rates were not affected.

Drug names: escitalopram (Lexapro and others), methadone (Methadose, Dolophine, and others), paroxetine (Paxil, Pexeva, and others).

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Additional information: The original randomized, double-blind placebo-controlled trial that investigated the effect of prophylactic treatment with escitalopram versus placebo can be found at ClinicalTrials.gov (identifier: NCT00133276).

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