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A Functional Serotonin Transporter Gene Polymorphism and Depressive Effects Associated with Interferon-Alfa Treatment

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Abstract

Interferon-alpha (IFN-α) treatment frequently induces depression, potentially leading to early dose reductions or a shorter duration of treatment, which can adversely affect outcomes, including the quality of life. Defining relevant risk factors for IFN-α induced depression is essential in order to identify prophylactic treatment strategies. We examined whether a functional polymorphism (5-HTTLPR) in the gene encoding the serotonin transporter moderates IFN-α-induced depressive symptoms in 1,015 patients with chronic hepatitis C (CHC) receiving pegylated IFN-α and ribavirin. Depressive symptoms were assessed at 0, 12, and 20 weeks of treatment. Depressive symptoms increased during antiviral treatment. 5-HTTLPR genotype moderated IFN-α-induced depressive symptoms in both Non-Hispanic Caucasians (NHCs; $p = 0.009$) and Hispanics ($p = 0.036$), though the opposite risk allele was associated with depression in the two populations. 5-HTTLPR may moderate risk for the development of depressive symptoms during IFN-α-therapy for CHC in a population-specific manner.

Keywords

depression; hepatitis C; interferon-α; serotonin transporter promoter polymorphism; 5-HTTLPR

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INTRODUCTION

Infection with the hepatitis C virus (HCV), which affects over 170 million people worldwide, (1–3), is a leading cause of chronic liver disease and the main indication for liver transplantation in the United States (3, 4). Currently, the most effective and available treatment for chronic HCV infection is the combination of pegylated interferon-alpha (IFN-α) and ribavirin. This combination therapy leads to a sustained virological response in over 40% of treated patients who complete 48 weeks of therapy (5–8). However, psychiatric side effects of IFN-α, including fatigue, sleep disturbances, irritability, appetite suppression and depressed mood, are common (9, 10). In particular, depressive symptoms that arise in 20–50% of patients receiving IFN-α may lead to early dose reductions or a shorter duration of treatment. Furthermore, depressed mood can occasionally lead to potentially serious complications such as suicide attempts or need for hospitalization (9, 10). These symptoms vary directly with the dosage of interferon administered and are typically manifested over the first 12–24 weeks of therapy (11–16). One factor that may increase the risk of developing depressive symptoms during cytokine therapy is a lifetime history of depression (17). The identification of other factors that increase vulnerability to the depressive effects of IFN-α-therapy may help to identify patients who are most in need of preventive strategies, including prophylactic antidepressant therapy.

Although the pathogenesis of IFN-α-induced depressive and other neuropsychiatric symptoms is poorly understood, hypotheses proposed to explain this effect include impairment of serotonergic function. Two studies (18, 19) have shown that cytokines known to be up-regulated by IFN-α serve to down-regulate serotonin synthesis by lowering the availability of the serotonin precursor tryptophan through activation of the tryptophan-metabolizing enzyme indoleamine-2,3-dioxygenase (IDO). IDO metabolizes tryptophan and when IDO is overactive it can lead to a reduction to plasma tryptophan (Russo et al. 2003), thereby reducing the brain serotonin concentration (Heyes et al. 1992).

The serotonin transporter protein (5-HTT) appears to play a key role in the biology of depression (for reviews see refs. 25 and 26) and is the major site of action of selective serotonin reuptake inhibitors (SSRIs), the most widely used class of antidepressant medications. Indeed, several SSRIs have been shown to be efficacious in treating the depression induced by IFN-α (11, 21–24). Consequently, we hypothesized that variation in *SLC6A4*, which maps to chromosome 17q11.2 and encodes the 5-HTT, could moderate IFN-α-induced depressive symptoms.

The promoter region of *SLC6A4* is characterized by an insertion-deletion polymorphism (5-HTTLPR), which produces a short ("S") allele, with lower transcriptional efficiency than the long ("L") allele (27). A common A→G single nucleotide polymorphism (SNP) has been identified within the insertion-deletion polymorphism, making it, in effect, tri-allelic due to the existence of two forms of the L allele: L_A and L_G (28, 29). The L_G and S alleles have comparable levels of 5-HTT expression and both are lower than that of L_A (29). The frequency distribution of these alleles in the general US population varies by ethnic/racial group and was estimated in African-Americans (AAs) to be 24%, 25% and 51% and in Non-Hispanic Caucasians (NHCs) to be 14%, 36%, and 50%, respectively for the L_G, S, and L_A alleles (29–31). Published data are not available concerning the genotype frequency distribution in Hispanics. To simplify the nomenclature for this polymorphism, the L_G and S alleles are referred to here as S' and the L_A allele as L' (29).

The present study examined: 1) the association between the 5-HTTLPR polymorphism and a lifetime history of depression obtained using a computerized questionnaire and standardized diagnostic criteria, 2) the relationship between the 5-HTTLPR polymorphism and baseline

depressive symptoms based on a self-administered symptom score, and 3) the role of 5-HTTLPR polymorphisms and the development of IFN-induced depression as defined by a self-administered symptom score during the first 20 weeks of IFN-α and ribavirin treatment in 1,015 subjects enrolled in the HALT-C trial.

MATERIALS AND METHODS

Overview of the HALT-C Trial

The HALT-C trial is a randomized, multi-center controlled study designed to determine whether continuing interferon treatment over several years suppresses HCV, prevents progression to cirrhosis and liver cancer, and reduces the need for liver transplantation (32, 33). Inclusion criteria for the trial included detectable serum HCV RNA, a liver biopsy within 12 months of enrollment demonstrating bridging fibrosis or cirrhosis, and lack of complete response to prior IFN (± ribavirin) treatment for at least 12 weeks (32, 33). Patients with any other co-existent liver disorder, a Child-Turcotte-Pugh score >6, or a history of variceal hemorrhage, ascites, or hepatic encephalopathy were excluded. Additional exclusion criteria included intolerance to IFN, reactivity to anti-HIV, active use of illicit injection drugs, ongoing excessive alcohol consumption, a suicide attempt or hospitalization for depression within the preceding 5 years, and a history of a severe or uncontrolled psychiatric condition within the preceding 6 months, as determined by the principal investigators of the clinical sites of the trial. The clinical judgment of these investigators was based on experience treating large numbers of patients with HCV infection. The trial was longitudinal, with blood samples and mood measures collected at baseline and at 12 and 20 weeks of therapy.

During the lead-in phase of the trial, all patients were treated with pegylated IFNα2a 180 mcg/week (Pegasys®, Roche Laboratories, Nutley, NJ) and ribavirin 1.0–1.2 g/day (Copegus®, Roche Laboratories, Nutley, NJ). The duration of therapy in the lead-in phase was either 24 or 48 weeks. If patients did not show a complete response to the treatment at 20 weeks (HCV RNA still detectable in serum), the lead-in treatment was stopped at 24 weeks, and they were invited to enter the randomized phase of the trial. If patients showed a full response at 20 weeks, the lead-in treatment was continued.

Study Sample

The HALT-C study and associated consent forms were approved by the National Institute of Diabetes and Digestive and Kidney Disease, and institutional review boards, General Clinical Research Centers, and other regulatory bodies within the participating centers. The study was conducted according to the principles of the Declaration of Helsinki regarding the proper procedures for human research. All subjects participating in this study signed individual informed consents for the HALT-C trial. The HALT-C trial is registered with NIH (NCT00006164).

Pretreatment data on psychiatric disorders, longitudinal data on depressive symptoms, and a blood sample for genetic analysis were obtained from 1,042 individuals treated during the lead-in phase of the HALT-C Trial. Of this number, 27 patients were not classified into one of the three major population groups: Non-Hispanic Caucasian (NHC), African American (AA), and Hispanic. Consequently, the sample examined in the present study consisted of 1,015 individuals; nearly three-quarters were NHCs (n=776), with smaller groups of AAs (n=154) and Hispanics (n=85).

Baseline Assessment

Demographic and clinical characteristics including age, gender, years of education, occupation, and baseline psychotropic medication usage were recorded at baseline. Race/ethnicity was based on self-report. Lifetime psychiatric history was obtained using the self-administered, computerized version of the Composite International Diagnostic Interview (CIDI; (34) to categorize subjects as having experienced an anxiety disorder, depressive disorder, alcohol abuse or dependence, or drug abuse or dependence. A semi-quantitative estimate of lifetime alcohol consumption was obtained using an adaptation of the Lifetime Drinking History (35).

To measure depressive symptoms, the Beck Depression Inventory-II (BDI-II) (36), a 21–item, self-administered questionnaire, was administered at baseline and at 12 and 20 weeks of treatment. Each item is scaled from 0–3 and a total score is calculated by summing the responses to the individual items (range: 0–63). For analytical purposes, BDI-II scores were coded as no depression ≤ 10; minimal depression 11–14; mild depression 15–19; moderate depression 20–28; and severe depression ≥ 29 (36).

5-HTTLPR Genotyping

We genotyped the 5-HTTLPR tri-allelic insertion$_A$/insertion$_G$/deletion polymorphism using a two-stage TaqMan™ 5'nuclease allelic discrimination assay modified from that originally described by Hu et al. (29, 37). This method identifies the presence of the 14- vs. the 16-repeat variable number of tandem repeats [short (S) vs. long (L)], as well as two subtypes of the 16-repeat variant, L_A, and L_G, which are the products of the A→G SNP present at the sixth nucleotide of the first of two of the 23-bp repeat elements present in the 16-repeat L allele (28). Both the S and L_G alleles have a 2-fold lower level of gene expression than the A allele variant (L_A) (29).

Twenty-five μL PCR reactions contained 200 nM each of forward and reverse primers (5' GCAACCTCCCAGCAACTCCCTGTA-3' and 5' GAGGTGCAGGGGGATGCTGGAA-3'), 1M Betaine, 1× ABI TaqMan Universal master mix (Applied Biosystems Inc., Foster City, CA), 25 ng genomic DNA, 120nM of an L allele specific Fam-labeled probe (6FAM-TGCAGCCCCCCCAGCATCTCCC-MGB) and 60 nM of a Vic-labeled internal control probe (VIC-TCCCCCCCTTCACCCCTCGCGGCATCC-MGB) whose target is present in the 5-HTTLPR region adjacent to the L-specific insertion, which served to distinguish the L vs. S insertion/deletion status. Samples were heated to 95°C for 10 minutes, followed by 40 thermal cycles of 98°C for 15 sec, followed by 62.5°C for 90 sec. The number of L alleles (0, 1, or 2) for each patient was identified by examination of scatter plots of endpoint Fam vs. Vic fluorescence levels captured using an ABI 7500 Sequence Detection System. A second TaqMan™ 5'nuclease allelic discrimination assay served to distinguish L_A vs. L_G alleles by using the same primers and amplification conditions as for the L vs. S allele assay but using L_A vs. L_G allele-specific probes, (6FAM-CCCCCCTGCACCCCCAGCATCCC-MGB and VIC-CCCCTGCACCCCCGGCATCCCC-MGB, respectively). We validated the closed-tube fluorescent assay of 5-HTTLPR L vs. S allele by comparing results obtained for 492 samples using this 5'nuclease TaqMan assay with those from a traditional 5-HTTLPR agarose gel-based PCR fragment length assay, with 100% agreement between methods. Additionally, we sequenced 8 samples for each of the genotypes (L_A/L_A, L_A/L_G and L_G/L_G) with 100% agreement between direct sequencing and the TaqMan L_A vs. L_G assay. We did not observe the G allele in samples from S allele homozygotes, consistent with the findings of Hu et al. (29).

Statistical Analysis

Prior to analysis, the distribution of data was examined to determine whether transformation was required to support the assumption of normality, so that parametric analytic methods could be used. Consistent with Hu et al. (29), genotypes were reclassified according to their level of expression as follows: L_G/L_G, L_G/S, and S/S were designated as S'S' (low expression levels), L_A/S and L_A/L_G were designated as L'S' (intermediate expression levels), and L_A/L_A was designated as L'L' (high expression levels).

We examined the frequency and correlates of lifetime and current major depression and their association with 5-HTTLPR alleles. We also used the *proc mixed* procedure in SAS (38) to examine the relations between genotype (with the number of S' alleles being a three-level variable: 0, 1, or 2) and scores on the BDI, with a lifetime depression diagnosis that was made using the CIDI (a two-level variable: present or absent) as a factor in the analysis. Using *proc genmod* with the binomial distribution and logit link function, we also modeled current antidepressant usage (as a dichotomous variable) as the dependent variable, since this would be expected to vary during the treatment trial. It should be noted that *proc mixed* and *genmod,* in contrast to repeated measures ANOVA, are robust to missing observations and to variation in the interval between repeated measures. The time points for these analyses were 0, 12, and 20 weeks, corresponding to the baseline and two follow-up time points during treatment with IFN-α and ribavirin. Because the trajectory of BDI scores was not linear, time was treated as a three-level class variable. In contrast, given the linear trajectory of antidepressant usage, time was treated as a continuous variable in the analysis of that outcome measure. Any significant interactions in these models were followed up with specified contrasts to decompose the interaction. The impact of sex was also examined in all analyses, but was not a significant factor and, therefore, was not retained in the final models.

RESULTS

Demographic and Clinical Characteristics of the Study Sample (Table 1)

The sample was predominantly male (73%), moderately educated (over 90% with a high school degree and over 25% with a college degree), and mostly married (70%) and employed (76%). The mean age of the sample was 49.9 yr (SD=7.0), with a mean duration of chronic HCV infection of 28.2 years (SD=8.0). The most common co-occurring diseases were hepatic cirrhosis (39%), diabetes mellitus (23%), and systemic arterial hypertension (33%). Based on the CIDI, 13.6% of the sample met lifetime criteria for a major depressive disorder, with no difference in frequency by race or ethnicity ($\chi^2_{(2)}$=0.99, p=.61). However, as shown in Table 1, NHCs, AAs, and Hispanics differed significantly on several demographic and clinical variables. In view of the pretreatment differences and genetic heterogeneity (see below), we conducted analyses involving genotype separately by population.

Genotypes of the Serotonin Transporter Promoter Polymorphism

The genotype distribution in all groups was consistent with Hardy-Weinberg equilibrium expectations (NHCs: $\chi^2_{(2)}$=0.034, p=0.85; AAs: $\chi^2_{(2)}$=3.09, p=0.079; Hispanics: $\chi^2_{(2)}$=2.43, p=0.12). The frequency of the 5-HTTLPR S' allele among NHCs, AAs, and Hispanics was 50.8%, 46.7%, and 54.7%, respectively. These differences did not reach statistical significance when examined as a three-level variable ($\chi^2_{(4)}$ = 8.35, p=0.072). However, given the imbalance in the size of the sub-samples, we conducted pair-wise comparisons, which showed a significantly greater frequency of the S' allele among Hispanics than AAs ($\chi^2_{(2)}$ = 8.33, p=0.016). The frequency of the S' allele did not differ significantly between NHCs and either AAs ($\chi^2_{(2)}$ = 3.84, p=0.14) or Hispanics ($\chi^2_{(2)}$ =

3.41, p=0.18). The genotype distribution among NHCs and AAs also did not differ significantly from the published frequencies for these racial/ethnic groups [$\chi^2_{(2)}$ =3.97, p=0.14 and $\chi^2_{(2)}$ = 5.11, p=0.078, respectively] (Hu et al. 2007, Roy et al. 2007). We did not find published allele frequencies for Hispanics.

Tables 2–4 show the pretreatment psychiatric and substance abuse histories for each genotype group by population. Among NHCs, although there was no difference between genotype groups in the percentage of subjects using any antidepressant ($\chi^2_{(2)}$=2.24, p=.32), there was a significant difference by genotype group in the use of the SSRI subtype of antidepressants ($\chi^2_{(2)}$=6.41, p=.041). Specifically, L' homozygotes were least likely, and heterozygotes most likely to have been treated with an SSRI (Table 2). There were no associations between antidepressant use at baseline and genotype in either the AA or Hispanic groups (Tables 3 and 4, respectively).

Effects of IFN-α Treatment on Depressive Symptoms

Using a score of ≥11 on the BDI as indicative of current depression, about one-quarter of the sample (25.3%) was depressed at baseline, which did not differ by ethnic or racial group ($\chi^2_{(2)}$=1.75, p=0.42). More than 60% of the sample reported increased BDI scores during treatment, with the frequency of IFN-α-induced depression differing by population. After 12 weeks of antiviral therapy, NHCs showed a significantly higher rate (39%) of current depression than AAs (29%; $\chi^2_{(1)}$=5.26, p=0.022) or Hispanics (28%; $\chi^2_{(1)}$=4.24, p=0.040). At 20 weeks, however, the prevalence of current depression decreased slightly from 12 weeks in both NHCs (37%) and AAs (28%), but increased slightly in Hispanic patients (31%), such that the differences between populations were no longer statistically significant (NHCs vs. AAs: $\chi^2_{(1)}$=3.76, p=0.052; NHCs vs. Hispanics: $\chi^2_{(1)}$=0.92, p=0.34). Differences over time that were seen in the prevalence of current depression do not appear to be explicable on the basis of differential attrition, since patients with elevated BDI scores were not significantly more likely to leave treatment prematurely than those with lower BDI scores among NHCs ($\chi^2_{(1)}$=3.23, p=0.072), AAs (Fisher's exact test: p=0.29), or Hispanics (Fisher's exact test: p=0.10). It should also be noted that there was no significant difference at week 12 (p=0.49) or week 20 (p=0.91) in the discontinuation rate among the three genotype groups.

Effects of 5-HTTLPR Genotype and Lifetime Depression Diagnosis on Depressive Symptoms as a Function of Antiviral Treatment

Non-Hispanic Caucasians—Among NHCs, during the 20 weeks of the study, individuals with a lifetime diagnosis of major depression had higher mean depressive symptom scores [mean baseline BDI score=13.1 (SD=8.9)] than those without such a diagnosis [mean baseline BDI score=8.0 (SD=7.0)] [$F_{(1,591)}$=16.99, p<0.001]. In addition, depression scores increased significantly [$F_{(2,1097)}$=14.57, p<0.001] following the initiation and maintenance of IFN-α treatment [mean BDI scores: 7.4 (SD=7.4), 10.1 (SD=7.9), and 9.9 (SD=8.0) at baseline, week 12, and week 20, respectively]. There was a trend for an interaction of lifetime depression diagnosis by time [$F_{(2,1097)}$=2.53, p=0.081], reflecting a marginally greater increase in depressive symptoms during IFN-α treatment in patients with a lifetime depression diagnosis. A significant three-way interaction of lifetime depression diagnosis × 5-HTTLPR genotype × time was also evident [$F_{(2,1097)}$=3.00, p=0.050]. Further analysis of the interaction revealed that the effects were limited to the subgroup with a lifetime diagnosis of major depression. In this subgroup, although BDI scores increased equally across genotype groups from baseline to week 12, S' homozygotes showed a decrease, heterozygotes showed no change, and L' homozygotes showed a modest increase in depressive symptoms from weeks 12 to 20 [$F_{(1,1097)}$=5.89, p=0.015].

African Americans—Among AAs, individuals with a lifetime diagnosis of major depression had significantly higher mean baseline BDI scores than those without such a diagnosis [11.6 (SD=6.6) and 8.0 (SD=7.0), respectively] [$F_{(1,108)}$=5.33, p=0.023]. In this group, there were no significant interactions of lifetime depression, genotype, or time, although the interaction of lifetime depression diagnosis × 5-HTTLPR genotype × time showed a trend towards statistical significance [$F_{(2,200)}$=2.17, p=0.12].

Hispanics—Among Hispanics, there was a trend for a main effect of lifetime major depression on BDI scores [$F_{(1,68)}$=3.45, p=0.068]. There was also a trend for an interaction of lifetime major depression diagnosis × time [$F_{(2,126)}$=2.80, p=0.065], such that patients with the diagnosis showed a greater increase in BDI at weeks 12 and 20 (i.e., during IFN-α treatment) than those who were never depressed. In this population, there was also a significant three-way interaction of depression × 5-HTTLPR genotype × time [$F_{(2,126)}$=4.33, p=0.015]. Further analysis revealed that the effects were present only in the subgroup with a lifetime history of major depression. In this subgroup, there were no significant changes in BDI score from baseline to 12 weeks as a function of genotype. However, from weeks 12 to 20, S' homozygotes showed a large increase, heterozygotes showed a slight decrease and L' homozygotes showed a large decrease in depression scores (Figure 2).

Antidepressant Usage as a Function of Time and Lifetime Depression Diagnosis

Table 5 shows the percentage of subjects in each of the three population groups who were receiving antidepressant therapy at each time point, by history of lifetime depression. The frequency of use of antidepressants was high at baseline, especially in those with a history of depression, and it rose significantly over time (i.e., with antiviral treatment; Z = 3.81, p = 0.0001) and as a function of a lifetime diagnosis of depression (Z=3.49, p=0.0005). However, these factors did not interact significantly (Z=1.1, p=0.26), nor did the effects differ by population group [$\chi^2_{(2)}$=0.35, p=0.84].

DISCUSSION

In this study, we examined changes in IFN-α-induced depressive symptom levels in patients treated with pegylated IFN-α for HCV infection as a function of both a lifetime diagnosis of depression and a functional polymorphism (5-HTTLPR) in the gene encoding the serotonin transporter. Consistent with other studies (10, 11, 15, 39, 40), we found that over 60% of the sample experienced a worsening of their depressive symptoms following the initiation of antiviral therapy. Also, consistent with the increase in depressive symptoms, the percentage of patients receiving antidepressant medication increased over time. In addition, we found that the likelihood of developing IFN-α-induced depression differed by population, at least during the initial 12 weeks of treatment. During this time, NHCs showed higher rates of treatment-associated depressive symptoms than either AAs or Hispanics. To our knowledge, this is the first study comparing the prevalence of IFN-α-induced depression across racial/ethnic groups. It should be noted that the population differences with respect to the increase in depressive symptoms could not be attributed to a population difference in BDI score at baseline, attrition rates, or the rates of antidepressant use.

The observation that a lifetime diagnosis of depression was associated with a greater likelihood of antidepressant treatment during antiviral therapy is consistent with the findings of Capuron and Miller (17). These investigators found that patients exhibiting sub-syndromal levels of depression prior to cytokine therapy were more likely to develop pronounced depressive illness in response to treatment with the cytokine.

Interestingly, the populations differed with respect to the moderating effect of 5-HTTLPR genotype on risk of depressive symptoms during antiviral treatment. There was no effect of

this polymorphism in AA patients, which was the smallest sub-sample. Although in both NHCs and Hispanics, the 5-HTTLPR polymorphism increased the risk of developing IFN-induced depressive symptoms, the effects were opposite in direction in the two groups. In the NHC sample, L' allele homozygotes showed greater depressive symptoms during IFN-α therapy than did S' allele carriers. In contrast, among Hispanics, although L' allele homozygotes initially showed a worsening of mood symptoms compared to S' allele carriers, subsequently, S' allele homozygotes reported much higher depression symptom scores. One possible explanation for the difference between NHCs and Hispanics is the small number of Hispanics (only about 20% as many as NHCs) on which the findings are based, with disproportionate effects contributed by a few individuals. Alternatively, there may be real population differences in the moderating role of this polymorphism. Further research is warranted to address this question. Given what appears to be a complex interaction of 5-HTTLPR genotype with IFN-α-induced depression, statistical power is a key consideration for subsequent studies to take into consideration.

Statistical power considerations may help to explain findings reported recently by Kraus et al. (41). These investigators studied the 5-HTTLPR polymorphism in 139 German patients with HCV during treatment with IFN-α and ribavirin. They found no effect of that polymorphism on treatment-induced depressive symptoms, though a polymorphism in *HTR1A*, which encodes the 5-HT_{1A} receptor was a significant predictor. Recently, Bull et al. (2008) reported a small protective effect of variation in *SLC6A4* in 98 Caucasian patients treated with IFN-α, with the LL genotype being associated with a less marked increase in depressive symptoms. In this study, a polymorphism in the gene encoding IL-6 showed a more robust effect. In addition to the fact that the sample studied by these investigators was comparatively small, they did not genotype the SNP that has been identified within the insertion-deletion polymorphism studied here (i.e., the tri-allelic polymorphism), which limits the comparability of the two studies. Further study of the tri-allelic polymorphism in the promoter region of the gene encoding 5-HTT appears warranted.

The mechanism underlying IFN-α-induced mood disorders remains poorly understood. There are a number of pathways by which IFN-α may cause neuropsychiatric complications, one of which is the depletion of tryptophan (14, 24, 42), which results in reduced serotonin function. Capuron et al. (42) tested this hypothesis in 26 patients with malignant melanoma who were randomly assigned to receive the SSRI antidepressant paroxetine or placebo, beginning 2 weeks before and continuing for 12 weeks after initiation of IFN-α therapy. Paroxetine reduced depressive symptoms despite significant IFN-α-induced increases in plasma kynurenine and neopterin concentrations, as well as in the kynurenine/tryptophan ratio (42), consistent with findings previously described in patients with chronic HCV infection who were treated with IFN-α (15). These findings suggest that reduced tryptophan availability plays a role in IFN-α-induced depressive symptoms, and that paroxetine, although not altering the increased concentrations of kynurenine or neopterin, attenuates the behavioral consequences of IFN-α-mediated tryptophan depletion (42).

Additionally, interferon treatment may modulate 5-HTT activity levels. In human, placental choriocarcinoma cells, a 3-hour treatment with IFN-α or IFN-γ increased levels of 5-HTT mRNA, an effect that was blocked by actinomycin D, an inhibitor of transcription (43). Treatment with IFN-α or IFN-γ for 3–6 h, but not for 30 min, also increased 5-HTT uptake activity. These data are consistent with the hypothesis that IFN-induced psychiatric effects may be modulated by regulation of 5-HTT transcription. Treatment with IFN-α in humans increased 5-HTT expression, protein level and serotonin uptake, suggesting that increases in 5-HTT in circulating blood lymphocytes after IFN-α therapy may decrease levels of circulating serotonin, thereby causing depressive symptoms (44).

Pre-treatment with an SSRI is a potentially useful strategy to prevent IFN-α-induced depressive symptoms (45). In addition to its moderating effects on IFN-α-induced depressive symptoms, several pharmacogenetic studies have shown that the 5-HTTLPR polymorphism moderates the response to SSRI antidepressants. Individuals with the LL genotype show an earlier and more robust response to SSRI treatment of major depression than is observed in individuals with the LS or SS genotype (46–51). Pollock et al. (49) found that elderly depressed L homozygotes had a greater response to paroxetine than individuals with the LS or SS genotype, an effect that was absent in patients treated with nortriptyline, suggesting that the differential response based on 5-HTTLPR genotype is unique to SSRI antidepressants.

Although depressive symptoms and other adverse effects limit treatment of HCV infection with IFN-α, Loftis et al. (52) showed that the rate of response to IFN-α treatment was significantly higher in patients who developed IFN-α-induced depression than in those who did not. This suggests that IFN-α-induced depression may be a predictor of a positive response to IFN-α therapy, or an indicator of optimal dosing or of greater susceptibility to biological responses to IFN-α. The dataset examined in our report included data only from the lead-in phase of the HALT-C trial, with information on treatment response limited to an examination of viral clearance by week 20. Unlike Loftis et al. (52) we did not observe an association between a change in treatment emergent depression and viral response during the 20-week study period. Subjects who achieved a viral response by week 20 did not have a greater increase in BDI during treatment (data not shown). Similiarly, subjects with a clinically significant increase in BDI (i.e., an increase ≥ 11 points) after the first 12 weeks of treatment were no more likely to have a negative HCV viral serum test result at week 20 than the other subjects for whom these data were obtained.

The data presented here support a moderating role of the serotonin transporter promoter polymorphism of 5-HTTLPR in IFN-α-induced depressive symptoms, although the pattern of findings is complex. The small size of the AA and Hispanic sub-samples limits confidence in the findings for those groups. The use of self-reported race/ethnicity, rather than ancestry informative markers (53) may have resulted in some incorrect assignments to population group. Further, the HALT-C trial was not designed to evaluate the genetic moderator hypothesis and patients with a history of suicide attempt or hospitalization for depression within the preceding five years were excluded. Thus, it is likely to have underestimated the level of IFN-α-induced depressive symptoms and could have underestimated the moderating role of the 5-HTTLPR polymorphism in those symptoms. Because antidepressant treatment and other factors directly relevant to the hypotheses were not controlled, these may also have confounded the results. The fact that homozygous subjects' showed a greater likelihood of having been treated with an antidepressant may represent a chance finding. A prospective study in a larger, less select sample is needed to determine the validity of these findings.

If confirmed, these results could have important clinical implications, in that it could be possible to identify patients who are at increased risk to develop depressive symptoms with this antiviral therapy. This may be important both for the therapeutic response to IFN-α therapy (52) and patients' capacity to tolerate the medication. Improved accuracy of risk assessment may enhance the potential therapeutic effects of IFN-α therapy without subjecting individuals who are not predisposed to depression to unnecessary antidepressant prophylaxis, which carries with it unwanted adverse effects and costs.

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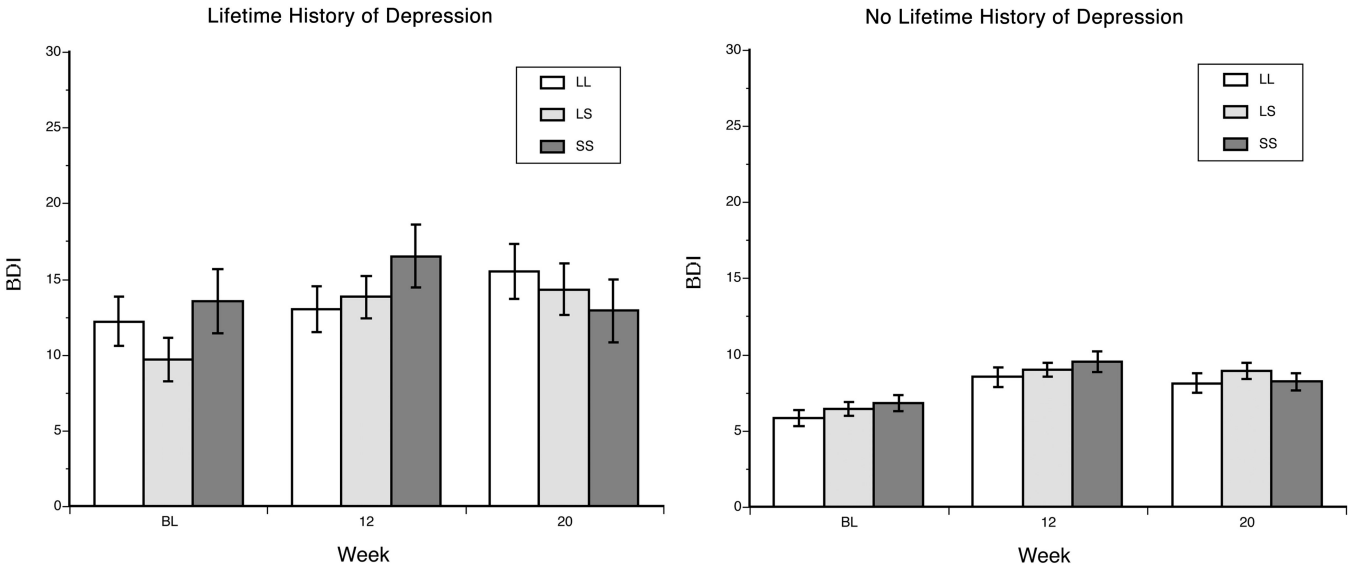

Figure 1.

Estimated mean (SEM) BDI score by 5-HTTLPR genotype, stratified by lifetime diagnosis of major depression in the non-Hispanic Caucasian sample. BDI = Beck Depression Inventory, L'L' = L' allele homozygotes, L'S'= heterozygotes, and S'S'= S' allele homozygotes. BL = at baseline, prior to IFN therapy

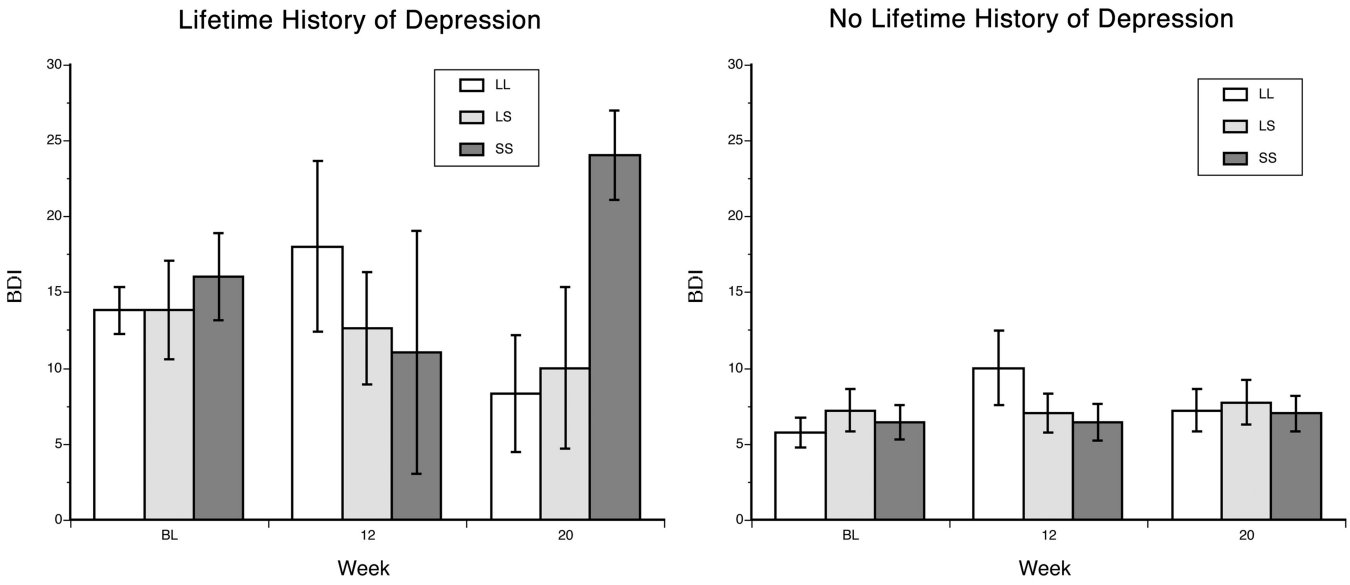

Figure 2.
Estimated mean (SEM) BDI score by 5-HTTLPR genotype, stratified by lifetime diagnosis of major depression in the Hispanic sample. BDI = Beck Depression Inventory, L'L' = L' allele homozygotes, L'S'= heterozygotes, and S'S'= S' allele homozygotes. BL = at baseline, prior to IFN therapy

Table 1

Demographic, Clinical Characteristics and Genotypes of the Study Sample by Race/Ethnicity (N=1,015)

	NHC (n=776)	AA (n=154)	Hispanic (n=85)	p-value
Sex (%)				
Male	75.4	58.4	71.8	<0.001
Female	24.6	41.6	28.2	
Age [yr; mean (SD)]	49.6 (7.1)	51.8 (6.6)	49.5 (7.9)	0.001
Education (%)				
Did not complete high school	7.7	11.2	27.7	<0.001
High school	30.1	34.9	27.7	
Some college	34.1	38.2	25.3	
College degree	19.7	10.5	14.5	
Graduate school	8.4	5.3	4.8	
Marital Status (% married)	72.6	55.2	70.2	<0.001
Working Status (% employed)	77.0	69.9	72.6	0.14
Duration of HCV Infection [yr; mean (SD)]	27.9 (7.7)	28.9 (9.0)	29.2 (9.1)	0.20
Baseline Laboratory Values [mean (SD)]				
Serum albumin (g/dL)	3.92 (0.40)	3.79 (0.38)	3.76 (0.40)	<0.001
Serum total bilirubin (mg/dL)	0.80 (0.44)	0.76 (0.37)	0.81 (0.29)	0.49
Platelet count (per L × 10^3)	168 (64.8)	183 (65.2)	152 (60.4)	0.001
Log HCV RNA	6.44 (0.53)	6.35 (0.54)	6.25 (0.50)	0.002
Co-morbid Conditions (%)				
Anxiety Disorder (Lifetime)	13.4	19.6	11.3	0.17
Major Depression (Lifetime)	13.7	16.1	16.9	0.66
Alcohol Use Disorder (Lifetime)	57.5	42.0	53.5	0.010
Drug Use Disorder (Lifetime)	43.1	42.9	40.8	0.94
Cirrhosis	37.2	34.4	57.6	0.001
Diabetes mellitus	13.1	33.8	20.0	<0.001
Systemic Arterial Hypertension	30.2	59.1	25.9	<0.001
Genotype (%)				
L'L'	24.1	24.7	24.7	0.072
L'S'	50.3	57.1	41.2	
S'S'	25.6	18.2	34.1	

NHC = Non-Hispanic Caucasian

P values compare results among the three groups

Table 2

Psychiatric and Substance Abuse History Among Non-Hispanic Caucasians (N=776)

	5-HTTLPR Genotype			
	L'L' (n=187)	**L'S' (n=391)**	**S'S' (n=199)**	**p-value**
Lifetime Anxiety Disorder (%)	14.5	12.2	14.8	0.67
Lifetime Major Depression (%)	13.0	14.1	13.5	0.95
Baseline Depressive Symptoms				
BDI score [mean, (SD)]	7.01 (6.9)	7.12 (7.7)	8.18 (7.9)	0.21
Baseline Severity of Depression (%)	74.9	78.1	71.2	0.24
None (BDI<=10)	12.3	8.5	10.1	
Minimal (BDI=11–14)	4.8	6.4	11.1	
Mild (BDI=15–19)	6.4	4.4	5.1	
Moderate (BDI=20–29)	1.6	2.6	2.5	
Severe (BDI>=30)				
Lifetime Alcohol Use Disorder (%)	53.4	57.2	61.3	0.41
Lifetime Drug Use Disorder (%)	47.3	42.4	40.6	0.50
Medications at Baseline (% of patients)				
Anxiolytics	11.2	14.4	15.6	0.44
SSRI Antidepressants	15.0	23.3	17.6	0.041
Other Antidepressants	13.4	10.8	17.1	0.097

Table 3

sychiatric and Substance Abuse History Among African Americans (N=154)

	5-HTTLPR Genotype			
	L'L' (n=38)	**L'S' (n=87)**	**S'S' (n=28)**	**p-value**
Lifetime Anxiety Disorder (%)	21.4	20.6	14.3	0.79
Lifetime Major Depression (%)	17.9	19.0	4.8	0.29
Baseline Depressive Symptoms				
BDI score [mean, (SD)]	8.29 (7.1)	7.89 (6.9)	5.96 (4.7)	0.33
Baseline Severity of Depression (%)	73.7	72.7	82.1	0.38
None (BDI<=10)	13.2	8.0	10.7	
Minimal (BDI=11–14)	0.0	9.1	7.1	
Mild (BDI=15–19)	13.2	10.2	0.0	
Moderate (BDI=20–29)	0.0	0.0	0.0	
Severe (BDI>=30)				
Lifetime Alcohol Use Disorder (%)	42.9	41.3	42.9	0.99
Lifetime Drug Use Disorder (%)	50.0	36.5	52.4	0.30
Medications at Baseline (% of patients)				
Anxiolytics	10.5	3.4	3.6	0.23
SSRIs Antidepressants	15.8	15.9	7.1	0.49
Non-SSRIs Antidepressants	10.5	14.8	0.0	0.094

Table 4

Psychiatric and Substance Abuse History Among Hispanics (N=85)

	5-HTTLPR Genotype			
	L'L' (n=21)	**L'S' (n=35)**	**S'S' (n=29)**	**p-value**
Lifetime Anxiety Disorder (%)	12.5	12.9	8.3	0.85
Lifetime Major Depression (%)	25.0	16.1	12.5	0.58
Baseline Depressive Symptoms				
Mean (SD) BDI score	8.48 (7.7)	8.14 (7.1)	8.46 (7.5)	0.98
Baseline Severity of Depression (%)				0.46
None (BDI<=10)	66.7	71.4	67.9	
Minimal (BDI=11–14)	19.0	8.6	7.1	
Mild (BDI=15–19)	9.5	8.6	14.3	
Moderate (BDI=20–29)	0.0	11.4	10.7	
Severe (BDI>=30)	4.8	0.0	0.0	
Lifetime Alcohol Use Disorder (%)	62.5	48.4	54.2	0.65
Lifetime Drug Use Disorder (%)	50.0	38.7	37.5	0.70
Medications at Baseline (% of patients)				
Anxiolytics	14.3	5.7	0.0	0.11
SSRIs Antidepressants	9.5	17.1	20.7	0.57
Non-SSRIs Antidepressants	14.3	17.1	17.2	0.95

Table 5

Antidepressant Usage (% of Patients) By Ethnic/Racial Group, Diagnosis of Lifetime Depression, and Time on Interferon Therapy

	Lifetime Depression	No Lifetime Depression
Non-Hispanic Caucasian		
Baseline	65.9	29.0
Week 12	76.6	47.4
Week 20	82.2	52.0
African-American		
Baseline	55.6	17.0
Week 12	66.7	25.6
Week 20	70.6	28.7
Hispanic		
Baseline	83.3	18.3
Week 12	90.9	38.3
Week 20	100	43.1