An Open-Label Trial of Citalopram for Major Depression in Patients With Hepatitis C

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Background: Hepatitis C affects nearly 4 million Americans. Depression is a common comorbid condition in this population and may be induced by interferon alfa, an approved treatment for hepatitis C. Depression is a major indicator for discontinuation of interferon therapy. This open-label study examines the effect of citalopram on measures of depression and quality of life and tests of liver function in subjects with hepatitis C and major depressive disorder.

Method: Subjects were recruited by advertisement; those with DSM-IV major depressive disorder were included in the study. Subjects received citalopram for 8 weeks starting at 20 mg/day. Dosage adjustments were made as the physicians deemed clinically necessary. No dosages were increased prior to week 4 of the study. Hamilton Rating Scale for Depression (HAM-D) scores, Clinical Global Impressions-Severity of Illness scale (CGI-S) scores, Medical Outcomes Study Short Form Health Survey (SF-36) ratings, Symptom Checklist-90-Revised (SCL-90-R) scores, and liver function tests were obtained at baseline, 4 weeks, and 8 weeks.

Results: A total of 15 patients (10 men, 5 women) participated in this study. The mean daily dose of citalopram at endpoint was 26.67 mg. Mean HAM-D scores decreased significantly with treatment ($F = 36.3$, $df = 2,42$; $p = .0001$). Thirteen of the 15 subjects demonstrated a clinical response, defined as a 50% or greater reduction in HAM-D scores. CGI-Severity of Illness scores also improved significantly ($p = .0001$). Subjects demonstrated statistically significant improvement ($p < .05$) on all of the SF-36 subscales. Statistically significant improvements ($p < .05$) were also demonstrated on all subscales of the SCL-90-R. Tests of liver function showed no significant worsening of aspartate aminotransferase, alanine aminotransferase, or γ-glutamyltransferase levels.

Conclusion: These results suggest that depression in patients with hepatitis C may be effectively and safely treated with citalopram.

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Hepatitis C affects an estimated 4 million Americans and an estimated 100 million people worldwide.[1] It is currently the major indication for liver transplantation in adults in the United States.[2] Medical therapy of hepatitis C remains suboptimal, with only 40% to 50% of patients clearing the virus 6 months posttherapy,[3,4] and is often poorly tolerated. Interferon alfa, an approved treatment for the virus, is known to induce psychiatric side effects, including confusion, mental status impairment, depression, mania, and suicidal ideation.[5–10] Depression is the most common reason for discontinuation of interferon therapy.

The rates of depression in patients with hepatitis C prior to interferon therapy have not been well established; however, a recent prospective study conducted by Kraus and colleagues[11] examined 113 adult patients aged 18 to 65 years with chronic hepatitis C who were without evidence of decompensated liver disease. The authors of the study found that 22.4% of patients demonstrated positive depression scores using the Hospital Anxiety and Depression Scale (German version). In another recent study, Dwight and colleagues[12] found a 28% rate of depressive disorders in 50 patients with chronic hepatitis C. Findings in both of these studies were consistent with an earlier retrospective study by Lee and colleagues,[13] who reviewed the medical records of 500 consecutive cases of chronic hepatitis C and found that depression was reported in 24% of the 359 patients who were not being treated with interferon. These rates are higher than the 12.5% lifetime prevalence reported in the general population.[14]

The treatment of depression in this population requires consideration of several factors. If antidepressant medication is utilized, the degree of hepatic impairment needs to be considered. Impaired hepatic function as well as portal

hypertension can lead to decreased metabolism of drugs and increased drug toxicity. On the other hand, associated impairment in gastric motility may result in decreased absorption of the compound, and ascites due to cirrhosis may result in decreased serum blood levels due to an increased volume of distribution.[15]

Psychiatrists and primary care physicians can expect to see increasing numbers of patients presenting with both depression and hepatitis C. There are case reports of successful use of the selective serotonin reuptake inhibitors sertraline and fluoxetine in the treatment of depression induced by interferon.[16,17] However, there are no published systematic studies examining the effect of antidepressant therapy on the course of major depression in hepatitis C in general. This study assessed the safety and efficacy of citalopram for the treatment of depression in 15 patients with hepatitis C in an 8-week, open-label trial. Citalopram was chosen because of its favorable side effect profile and its limited interaction with cytochrome P450 enzymes. The objectives of the study were to estimate the response rate of major depression in an 8-week trial of citalopram, to examine the effect of citalopram on quality-of-life measures, and to evaluate the effect of citalopram therapy on markers of hepatic function.

METHOD

Subjects

Adults aged 18 to 65 years with hepatitis C and major depression were recruited by advertisement. Interested subjects were instructed to call for a phone screening for preliminary eligibility. Subjects with documented hepatitis C and DSM-IV major depressive disorder were eligible for study participation after being informed of the potential risks and benefits involved, including possible medication side effects, and giving informed consent. Exclusion criteria included ongoing antidepressant or anxiolytic therapy, use of herbal supplements marketed for behavioral effects, evidence of cirrhosis (Child-Pugh grades B or C), evidence of liver failure, liver enzyme elevations greater than 2.5 times the upper limit of normal, and evidence of cognitive impairment demonstrated by Mini-Mental State Examination (MMSE)[18] scores of less than 23 or pathologic time on the Trailmaking A and B tests.[19] Subjects were not excluded based on current or past treatment with interferon, but subjects currently receiving interferon with Hamilton Rating Scale for Depression (HAM-D) scores of greater than 25 were excluded, as were actively suicidal subjects.

Subjects participated in the study for 8 weeks, which included 1 baseline visit, 1 telephone visit at week 2, and 2 office visits, 1 at week 4 and 1 at week 8. Data were collected in a research chart and then transferred to a computer database for analysis. Patient identifiers were left out of the computer database for protection of patient confidentiality.

Study Medication

Subjects were started on citalopram, 20 mg/day. Dosage adjustments were made as the physician deemed clinically necessary. At week 2 (visit 2), a telephone interview was conducted to assess patient response and drug tolerability. One subject had reduced the dose to 10 mg/day prior to visit 2 due to problems with sedation and was continued on this dose throughout the study. Dosage reductions were not necessary for any other subjects. At week 4 (visit 3), the dosage of citalopram was increased from 20 mg to 40 mg in 5 subjects and to 30 mg in 1 subject.

Clinical Measures

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV)[20] was administered at baseline to confirm the presence of major depressive disorder and to determine the presence of psychiatric comorbidity. Other baseline measures included the HAM-D,[21] the Hopkins Symptom Checklist-90-Revised (SCL-90-R),[22] the Medical Outcomes Study Short Form Health Survey (SF-36),[23] and the Clinical Global Impressions-Severity of Illness scale (CGI-S).[24] All scales with the exception of the SCID-IV were readministered at 4 and 8 weeks. Subjects were administered the MMSE and Trailmaking A and B tests at baseline to screen for hepatic encephalopathy or other evidence of cognitive impairment. Tests of liver function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], γ-glutamyltransferase [GGT]) were measured at baseline and at 4 and 8 weeks. Serum albumin and protime values were obtained at baseline for Child-Pugh staging.

Statistical Analysis

Changes in HAM-D and SCL-90-R scores and the mental and physical component summary from the SF-36 were analyzed using a repeated-measures analysis of variance based on measurements at baseline, 4 weeks, and 8 weeks. The continuous-measure analysis was performed on a last-observation-carried-forward basis. All determinations of statistical significance were made using a p value of .05.

A secondary analysis compared the effects of citalopram on hepatitis activity using the AST, ALT, and GGT values as dependent variables. Time and dose of citalopram were independent variables.

Subjects were grouped into a responder category on the basis of demonstrating at least a 50% reduction in HAM-D score from baseline to week 8. An estimate of the response rate was made by dividing the total number of responders by the total number of completers. A 95% confidence interval for the response rate was calculated using the method outlined by Fleiss.[25]

Figure 1. Hamilton Rating Scale for Depression (HAM-D) Scores for Subjects Based on Interferon Therapy Status

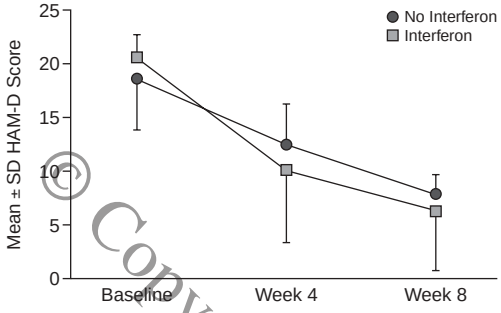

Table. 1 Effect of Citalopram on Quality of Life (SF-36 scores)[a]

SF-36 Subscale	Baseline	Week 4	Week 8	F Value	p Value
Physical functioning	71.3 (19.9)	74.7 (16.3)	81.0 (16.9)	3.69	.038
Role physical	30.0 (34.3)	48.3 (40.6)	65.0 (38.7)	7.94	.002
Bodily pain	59.5 (18.9)	65.2 (19.0)	80.0 (25.8)	5.73	.008
General health	47.3 (23.8)	49.3 (20.7)	55.7 (26.8)	4.55	.020
Vitality	22.0 (17.3)	31.7 (18.8)	46.0 (25.0)	5.27	.011
Social functioning	48.3 (20.0)	64.2 (27.1)	80.0 (25.8)	19.51	.001
Role emotional	26.7 (33.8)	46.7 (39.4)	84.4 (33.0)	16.75	.001
Mental health	42.8 (11.5)	54.1 (21.2)	74.4 (13.9)	21.54	.001

[a]Abbreviation: SF-36 = Medical Outcomes Study Short Form Health Survey. Subscale scores shown as mean (SD) for all subjects.

Table 2. Effect of Citalopram on SCL-90-R Scores[a]

SCL-90-R Subscale	Baseline	Week 4	Week 8	F Value	p Value
Somatization	15.6 (8.6)	9.1 (6.1)	7.8 (6.2)	15.92	.001
Obsessive-compulsive	17.5 (5.6)	10.5 (7.3)	7.3 (8.0)	33.07	.001
Interpersonal sensitivity	11.2 (6.0)	4.6 (5.8)	3.5 (6.0)	35.32	.001
Depression	24.5 (8.0)	14.4 (11.8)	8.3 (9.1)	26.94	.001
Anxiety	13.2 (6.6)	7.2 (6.6)	4.8 (5.6)	15.58	.001
Anger/hostility	9.4 (5.1)	4.5 (3.8)	2.3 (2.4)	16.50	.001
Phobic anxiety	3.3 (3.6)	1.2 (2.2)	0.9 (1.7)	7.66	.002
Psychoticism	8.5 (6.5)	4.9 (7.0)	2.9 (5.1)	7.31	.010
Paranoid ideation	5.3 (5.1)	2.7 (5.2)	2.0 (3.7)	5.40	.010
Insomnia	6.9 (3.6)	4.6 (2.7)	3.5 (2.0)	11.23	.001

[a]Abbreviation: SCL-90-R = Symptom Checklist-90-Revised. Subscale scores shown as mean (SD) for all subjects.

RESULTS

Study Group

Twenty-seven subjects were initially enrolled in the study. Nine of these subjects were excluded at the baseline visit: 4 subjects were excluded due to elevations in tests of liver function that were greater than 2.5 times the upper limit of normal, 3 were excluded due to use of medications or herbal preparations not allowed in the study (other antidepressants, monoamine oxidase inhibitors, antipsychotics, anticonvulsants, mood stabilizers, hypnotics, anxiolytics, herbal preparations marketed for behavioral effects, sumatriptan, melatonin, and tryptophan), 1 subject did not meet diagnostic criteria for major depressive disorder at the baseline visit, and another was on interferon therapy and had a HAM-D score greater than 25, the cutoff for patients with concomitant therapy with interferon. Three subjects were dropped prior to week 4 due to noncompliance, patient choice, or being lost to follow-up, leaving 15 subjects in the study group.

The study group consisted of 15 subjects, 10 men and 5 women. The mean ± SD age was 42.6 ± 6.4 years, and the mean education level was 13.4 years (high school graduate with some college or technical training). Eight subjects had been on interferon therapy at some time in their lives, 4 of whom received interferon alfa therapy during the course of this study. Seven of the subjects had never been treated with interferon. Diagnoses of comorbid alcohol and drug abuse were common. Eleven subjects (73.3%) met diagnostic criteria for lifetime alcohol abuse at some time, and 9 (60%) met criteria for abuse of another substance. No subject met active alcohol or substance abuse due to study exclusion criteria.

Subjects were all started on citalopram, 20 mg by mouth daily. Citalopram was increased to 40 mg/day in 5 subjects and to 30 mg/day in 1 subject at week 4. One subject self-reduced the dose of citalopram to 10 mg/day after 6 days due to excessive sedation and continued on the 10-mg/day dosage throughout the study. The mean daily dose of citalopram at endpoint was 26.7 mg.

HAM-D Scores

HAM-D scores decreased significantly over the 8-week period of treatment with citalopram ($F = 36.3$, $df = 2,42$; $p = .0001$) as shown in Figure 1. Mean HAM-D scores were 19.2 at the beginning of the study, 12 at week 4, and 7.7 at study completion. There was no difference in the response demonstrated by subjects who received interferon alfa compared with subjects who were not treated with interferon. Both groups demonstrated improvement. Thirteen (86.7%) of the 15 subjects demonstrated a clinical response, defined as a 50% or greater reduction in HAM-D score.

Quality of Life Measures

The SF-36 and the SCL-90-R assessed measures of quality of life and psychiatric symptoms, respectively. Statistically significant improvements were seen in scores on all subscales of these tests. The most significant improvements were demonstrated on SF-36 subscales measuring limitations due to mental health, emotional well-being, and social functioning and on SCL-90-R subscales measuring somatization, obsessiveness-compulsiveness, interpersonal sensitivity, depression, anxiety, insomnia, and anger/hostility ($p = .0001$) (Tables 1 and 2).

CGI Scores

The CGI is a 3-item physician-rated scale that assesses a patient's response to psychiatric treatment. The 3 items assessed are severity of illness, global improvement, and efficacy. The CGI-S is rated on a 7-point scale (1 = normal, 7 = among the most extremely ill patients). The mean ± SD CGI-S scores at baseline and at visit 4 were 4.4 ± 0.51 and 2.2 ± 1.01, respectively. This improvement was statistically significant (p = .001). The CGI-Global Improvement scale (CGI-I) is also rated on a 7-point scale (1 = very much improved, 7 = very much worse). Mean CGI-scores at baseline and at visit 4 were 2.7 ± 0.825 and 2.1 ± 0.864, respectively (p = .0506). The CGI-Efficacy scale (a 4-point scale) was not rated in this study.

Liver Function Tests

To assess the effect, if any, that citalopram would have on tests of liver function, AST, ALT, and GGT levels were obtained at baseline and at weeks 4 and 8. No statistically significant changes were seen during the 8-week trial (Table 3).

Table 3. Effect of Citalopram on Liver Enzyme Level[a]

Liver Enzyme	Baseline	Week 4	Week 8	F Value	p Value
AST	37.4 (19.2)	41.9 (28.2)	39.0 (25.8)	0.68	.517
ALT	53.7 (35.3)	49.4 (38.2)	47.3 (36.9)	2.33	.117
GGT	68.0 (51.8)	54.0 (32.7)	50.8 (30.5)	1.71	.200

[a]Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = γ-glutamyltranferase. Liver enzyme levels shown as mean (SD) U/L for all subjects.

DISCUSSION

In this open-label study, citalopram reduced levels of depression in patients with hepatitis C and major depressive disorder. Subjects also demonstrated improvement on measurements of quality of life. Citalopram did not worsen tests of liver function and was well tolerated.

Safe and effective treatment of depression is important given the large number of people infected with the hepatitis C virus worldwide and the apparent increased prevalence of depression in this population. Furthermore, patients with hepatitis C are at increased risk for the development of depression if their hepatitis C is treated with interferon alfa. This study is the first to systematically evaluate the effectiveness and safety of an antidepressant for the treatment of major depression in subjects with concomitant hepatitis C.

This study did not look specifically at the treatment of interferon-induced depression; however, 4 subjects were receiving interferon alfa during the course of the study. All 4 subjects responded to citalopram, with greater than 50% reductions in HAM-D scores.

Citalopram was associated with significant improvements in measures of quality of life. Lack of energy and excessive fatigue are very common complaints among patients with hepatitis C. In this study, citalopram improved subjects' perceived energy and reduced levels of fatigue. Improvements were also seen in the reduction of perceived limitations due to emotional and physical health. Improvements in these areas may lead to increased productivity and social functioning across a number of areas.

All currently available antidepressants undergo hepatic metabolism. Liver function tests were used as a means to assess the effect of citalopram on hepatic function. In this study, there was a slight increase in AST levels, and mild reductions in ALT and GGT levels, although none of the changes were statistically significant. Citalopram did not appear to adversely affect liver function in this study.

Limitations of this study include the use of an open-label study design, lack of a placebo-control group, and a relatively small sample size. The response rate observed in this study may be falsely elevated by placebo effects from various psychosocial interventions that are often associated with psychopharmacologic trials, e.g., attention to the patient and his or her problems may constitute a form of supportive psychotherapy. Larger, double-blind, placebo-controlled studies would be useful in clarifying this issue and confirming the results of this study.

Management of depression in the setting of hepatitis C is important not only in reducing suffering from depression; it may also improve the patient's candidacy for and possible successful completion of interferon therapy for hepatitis C, which otherwise may be contraindicated. The results of this study suggest that citalopram is a safe, effective, and well-tolerated agent for the treatment of depression in patients with hepatitis C and comorbid major depressive disorder.

Drug names: citalopram (Celexa), fluoxetine (Prozac and others), sertraline (Zoloft), sumatriptan (Imitrex).

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