

PAROXETINE FOR THE PREVENTION OF DEPRESSION INDUCED BY HIGH-DOSE INTERFERON ALFA

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ABSTRACT

Background Depression commonly complicates treatment with the cytokine interferon alfa-2b. Laboratory animals pretreated with antidepressants have less severe depression-like symptoms after the administration of a cytokine. We sought to determine whether a similar strategy would be effective in humans.

Methods In a double-blind study of 40 patients with malignant melanoma who were eligible for high-dose interferon alfa therapy, we randomly assigned 20 patients to receive the antidepressant paroxetine and 20 to receive placebo. The treatment was begun 2 weeks before the initiation of interferon alfa and continued for the first 12 weeks of interferon alfa therapy.

Results During the first 12 weeks of interferon alfa therapy, symptoms consistent with a diagnosis of major depression developed in 2 of 18 patients in the paroxetine group (11 percent) and 9 of 20 patients in the placebo group (45 percent) (relative risk, 0.24; 95 percent confidence interval, 0.08 to 0.93). Severe depression necessitated the discontinuation of interferon alfa before 12 weeks in 1 of the 20 patients in the paroxetine group (5 percent), as compared with 7 patients in the placebo group (35 percent) (relative risk, 0.14; 95 percent confidence interval, 0.05 to 0.85). The incidence of adverse events was similar in the two groups.

Conclusions In patients with malignant melanoma, pretreatment with paroxetine appears to be an effective strategy for minimizing depression induced by interferon alfa. (N Engl J Med 2001;344:961-6.)

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INTERFERON- α is an important cytokine in the early immune response to viral infection and has both antiproliferative and antiviral properties.¹ Interferon alfa has been used at high doses (1 million to 50 million U) for the treatment of malignant disorders and infectious diseases, including malignant melanoma and chronic hepatitis C. Interferon alfa, in combination with ribavirin, is the only therapy approved by the Food and Drug Administration for hepatitis C, which affects 4 million to 5 million persons in the United States and is the most common cause of cirrhosis leading to liver transplantation.² Although it is an effective therapy, interferon alfa has been associated with high rates of central nervous system side effects, including symptoms that overlap with those found in major depression — for example, anhedonia, fatigue, anorexia, impaired concentration,

and sleep disturbance.^{3,4} Suicidal ideation has also been reported, as have several cases of suicide.⁵ Studies of open-label treatment and case reports have suggested that opioid-receptor antagonists, stimulants, and antidepressants may provide some relief from these troublesome psychiatric side effects.³

Pretreatment of laboratory animals with the tricyclic antidepressant imipramine has been reported to reduce the intensity of behavioral side effects, also referred to as “sickness behavior” (anhedonia, anorexia, and decreased social exploration), after cytokine administration.^{6,7} To determine whether antidepressants similarly attenuate cytokine-induced depression in humans, we conducted a prospective, double-blind, placebo-controlled trial of the antidepressant paroxetine in patients undergoing high-dose interferon alfa therapy for malignant melanoma. Paroxetine is a selective serotonin-reuptake inhibitor that was chosen because of its ease of administration (once-daily dosing), absence of active metabolites, and favorable side-effect profile, including lower levels of cardiotoxicity than those of tricyclic antidepressants.⁸

METHODS

Patients

Forty patients with malignant melanoma that had been resected but was estimated to have a greater than 50 percent chance of recurrence were recruited from the Winship Cancer Institute of Emory University School of Medicine between March 1997 and April 2000. Criteria for exclusion included unresectable metastases, a score of less than 24 on the Mini-Mental State Examination,⁹ a diagnosis of schizophrenia or bipolar disorder as determined by the structured clinical interview for the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV),¹⁰ and evidence of unstable cardiovascular, endocrine, hematologic, hepatic, renal, or neurologic disease. The Human Investigations Committee of Emory University School of Medicine approved the study, and all patients gave written informed consent. Of 56 patients screened, 40 patients met the criteria for eligibility and were randomized.

Treatment and Follow-up

Two weeks before the initiation of interferon alfa therapy, patients were randomly assigned in double-blind fashion to begin taking either paroxetine (Paxil, SmithKline Beecham) or placebo, starting at one tablet per day for one week, followed by two tablets per day for one week. Two weeks after the initiation of interferon alfa (four

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weeks after the initiation of paroxetine therapy or placebo), the dosage of the study medication could be increased at the discretion of the study psychiatrist to up to four tablets per day. Each paroxetine tablet contained 10 mg. The average number of tablets taken daily, at the maximal dose, for each group was 3.1 (31 mg of paroxetine per day), although the average for the patients treated with placebo was calculated on the basis of data that included tablet counts from several patients who discontinued their study participation early (due to severe depression) before the study medication could be increased.

Patients received interferon alfa-2b (Intron A, Schering-Plough) at a dose of 20 million U per square meter of body-surface area intravenously five days per week for the first four weeks, followed by 10 million U per square meter subcutaneously three days per week for the remaining eight weeks of the study. After 12 weeks, the patients' physicians were informed of the treatment assignment for each patient. Allowable concomitant medications included acetaminophen and nonsteroidal antiinflammatory agents for pain and fever; diphenhydramine, temazepam, or zolpidem for insomnia; lorazepam, prochlorperazine, granisetron, and ondansetron for nausea; and narcotics for pain.

Patients were evaluated at base line (before the administration of the study drug) and at regularly scheduled intervals after the initiation of interferon alfa therapy, for the first 12 weeks of a planned 48-week treatment period. Assessments included the 21-item, observer-rated Hamilton Depression Rating Scale¹¹; the self-reported Carroll Depression Scale¹²; the observer-rated Hamilton Anxiety Scale¹³; and the self-reported Neurotoxicity Rating Scale developed by Meyers and Valentine.¹⁴ On all of these scales, higher scores indicate a greater severity of symptoms.

The Hamilton Depression and Carroll Depression rating scales quantify the severity of depressive symptoms, including depressed mood, loss of interest in usually pleasurable activities, insomnia, anorexia, fatigue, weight loss, and psychomotor retardation or agitation. A score of 0 to 6 on the Hamilton Depression Rating Scale indicates a normal state; a score of 7 to 17 indicates mild depression; a score of 18 to 24 indicates moderate depression; and a score of 25 or higher indicates severe depression.¹⁵ The Hamilton Anxiety Scale measures the severity of symptoms of anxiety, including anxious mood, tension, fear, and physical symptoms of anxiety. Scores range from 0 to 56, with a score of 14 indicating clinically significant anxiety.¹⁵ Moderate levels of depression and anxiety typically qualify patients for entry into clinical trials of pharmaceutical products for these conditions. The Neurotoxicity Rating Scale is used in the evaluation of psychiatric and physical symptoms related to cytokine therapy, including depressed mood, difficulties with memory or concentration, fatigue, nausea or vomiting, body aches, fever, visual disturbances, bowel or bladder problems, and joint pain. Scores range from 0 to 148 but have yet to be classified; the mean (\pm SD) score in patients in this study who discontinued interferon alfa therapy owing to severe depression or neurotoxicity was 42.6 ± 26.2 .

At each study visit, a psychiatrist determined whether the patient met the DSM-IV criteria for major depression, which requires the presence and persistence for at least two weeks of a specified set of depressive symptoms.¹⁶ According to DSM-IV nomenclature, a depressive syndrome that develops during interferon alfa therapy is a substance-induced mood disorder.¹⁶

Statistical Analysis

On the basis of the standard deviation of Hamilton Depression scores in patients with newly diagnosed cancer,¹⁷ the study was designed to have 86 percent power to detect a 10-point difference in scores on the Hamilton Depression Rating Scale at 12 weeks in 40 patients randomly assigned to paroxetine or placebo (20 patients per group) with a two-sided significance level of 0.05.

The incidence rates of major depression during interferon alfa therapy in the two groups were compared by means of the log-rank test.¹⁸ Kaplan-Meier plots were used to display the survival curves of each group.¹⁸ A similar analysis was used to assess the rates of discontinuation of interferon alfa therapy before 12 weeks because

of severe depression or related neurotoxic symptoms. Continuous variables were analyzed by a two-way repeated-measures analysis of variance.¹⁹ The factors included in the analysis were treatment group (placebo or paroxetine), time (base line, 4 weeks, 8 weeks, and 12 weeks), and the interactions of the two. Post hoc comparisons were made at 4, 8, and 12 weeks. Data were analyzed with the use of both parametric and nonparametric tests of significance, and similar results were obtained with all methods. All outcome analyses were based on the intention-to-treat principle, with use of two-sided P values and 95 percent confidence intervals.

To resolve the issue of missing data for patients who discontinued their participation in the study before 12 weeks of interferon alfa therapy (the majority because of severe depression), data were analyzed both with and without the last observation for these patients carried forward. This method assumes that depression scores would have remained at least as high for later visits had interferon alfa therapy been continued. Reported results are those obtained with the last observation carried forward, although no differences in statistical significance were found between analyses that used this method and those that did not.

RESULTS

The base-line characteristics of the 20 patients in the placebo group and the 20 patients in the paroxetine group are shown in Table 1. The two groups were similar in terms of age, sex distribution, and the proportions with recent surgical procedures and a history of major depression. The equal number of men and women in both groups occurred by chance. Two patients who underwent a base-line evaluation and were randomly assigned to receive paroxetine discontinued their participation in the study before treatment with the study medication and interferon alfa began: one was discovered to have unresectable metastases (and therefore was not eligible for interferon alfa therapy), and one could not arrange consistent transportation. According to the intention-to-treat principle, data for these patients were included in the statistical analyses. No patients dropped out of the study during the first two weeks of double-blind treatment (before the initiation of interferon alfa).

Paroxetine treatment significantly reduced the incidence of major depression among patients receiving interferon alfa therapy ($P=0.04$ by the log-rank test) (Fig. 1). Over the course of the study, symptoms consistent with a diagnosis of major depression developed in 2 of 18 patients in the paroxetine group (11 percent), as compared with 9 of 20 patients in the placebo group (45 percent) (relative risk, 0.24; 95 percent confidence interval, 0.08 to 0.93). In one additional patient in the placebo group (who was not coded in the analysis as having major depression), symptoms developed that met the criteria for major depression, but the patient discontinued interferon alfa (because of severe depression) before the symptoms had persisted for at least two weeks, as required by the DSM-IV definition. Two patients randomly assigned to paroxetine received diagnoses of major depression at screening (before the initiation of the study drug or interferon alfa). Both patients completed the study and by 12 weeks no longer had symptoms that met the crite-

TABLE 1. BASE-LINE CHARACTERISTICS OF PATIENTS WITH MALIGNANT MELANOMA.*

CHARACTERISTIC	PLACEBO (N=20)	PAROXETINE (N=20)
Age — yr		
Mean	50.1±13.4	52.8±7.6
Range	25–74	42–67
Sex — M/F	10/10	10/10
Surgery within previous 3 mo — no. (%)	16 (80)	18 (90)
History of major depression — no. (%)	5 (25)	4 (20)

*Plus-minus values are means ±SD.

ria for major depression, despite having received interferon alfa therapy. These two patients were not included in the analysis of survival free of major depression.

In addition to reducing the incidence of major depression, paroxetine had a significant effect (apparent in analyses of the interaction between group assignment and time) on the severity of depressive symptoms over the course of the study ($P<0.001$) (Table 2). By the 12th week of interferon alfa therapy, the scores on the Hamilton Depression Rating Scale among patients in the paroxetine group were not significantly different from the base-line scores and were almost 50 percent lower than those among patients in the placebo group ($P=0.01$). The self-reported Carroll Depression Scale produced similar results (data not shown). Paroxetine also had a significant effect on the severity of symptoms of both anxiety ($P<0.001$) and neurotoxicity ($P<0.001$), which were approximately 50 percent lower in the paroxetine group than in the placebo group during the 8th and 12th weeks of interferon alfa therapy (Table 2).

Paroxetine treatment also significantly decreased the likelihood that interferon alfa therapy would have to be discontinued (a decision made by the study oncologist) because of severe depression or related neurotoxic effects ($P=0.03$ by the log-rank test). In only one patient assigned to paroxetine (5 percent) was interferon alfa discontinued before 12 weeks, as compared with seven patients in the placebo group (35 percent) (relative risk, 0.14; 95 percent confidence interval, 0.05 to 0.85) (Fig. 1).

Depression scores in the placebo group at base line were significantly correlated with depression scores at four weeks ($r=0.61$, $P=0.005$). Similar correlations were found for symptoms of anxiety in the placebo group ($r=0.77$, $P<0.001$). No such correlations were found for depression or anxiety in the paroxetine group ($r=0.23$, $P=0.34$, and $r=0.26$, $P=0.26$, respectively).

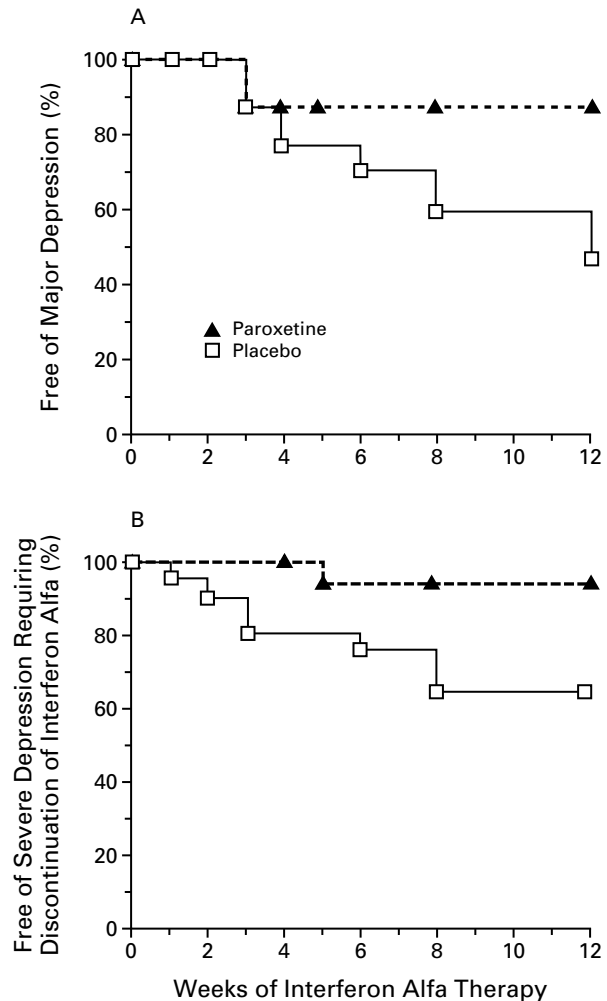


Figure 1. Kaplan-Meier Analysis of the Percentage of Patients in the Placebo and Paroxetine Groups Who Were Free of Major Depression (Panel A) and of Severe Depression Requiring the Discontinuation of Interferon Alfa (Panel B).

In Panel A, a comparison of the curves for the 20 patients in the placebo group and the 18 patients remaining in the paroxetine group shows a significant difference between the groups in the development of major depression (relative risk in the paroxetine group, 0.24; 95 percent confidence interval, 0.08 to 0.93; $P=0.04$ by the log-rank test). In Panel B, a comparison of the curves for the 20 patients in the placebo group and the original 20 patients in the paroxetine group shows a significant difference between groups in the development of severe depression requiring the discontinuation of interferon alfa before 12 weeks (relative risk in the paroxetine group, 0.14; 95 percent confidence interval, 0.05 to 0.85; $P=0.03$ by the log-rank test). Observations in patients who were withdrawn from the study for reasons other than severe depression were recorded as censored at the appropriate study visit.

TABLE 2. DEPRESSION, ANXIETY, AND NEUROTOXICITY SCORES DURING HIGH-DOSE INTERFERON ALFA THERAPY, ACCORDING TO STUDY GROUP.*

VARIABLE	BASE LINE	4 Wk	8 Wk	12 Wk	P VALUE†
Hamilton Depression Rating Scale (21 items)					<0.001
Placebo	5.0±4.4	11.8±7.6	14.5±9.9	15.2±9.9	
Paroxetine	5.6±4.7	9.1±5.2	7.8±5.2‡	8.4±5.0§	
Hamilton Anxiety Scale					<0.001
Placebo	4.6±3.4	9.5±5.6	10.9±6.9	12.3±7.1	
Paroxetine	5.1±3.3	5.7±4.1‡	6.6±4.2‡	6.2±4.4§	
Neurotoxicity Rating Scale					<0.001
Placebo	11.3±9.7	19.5±17.8	26.4±22.8	28.3±23.0	
Paroxetine	8.8±6.0	11.4±8.1	11.0±7.6§	11.8±7.8§	

*On all scales, higher scores represent more severe symptoms. A score of 0 to 6 on the Hamilton Depression Rating Scale indicates a normal state; 7 to 17 indicates mild depression; 18 to 24 indicates moderate depression; and 25 or higher indicates severe depression. Scores on the Hamilton Anxiety Scale range from 0 to 56, with a score of 14 or more indicating clinically significant anxiety. Scores on the Neurotoxicity Rating Scale range from 0 to 148 but have yet to be classified. The average score in patients in this study who discontinued interferon alfa therapy because of severe depression or neurotoxicity was 42.6±26.2. Scores reported are the mean ±SD values derived with use of the last-observation-carried-forward method on the basis of the intention-to-treat principle; for patients who discontinued their participation in the study in the interval between base line and 4 weeks, 4 and 8 weeks, or 8 and 12 weeks, the scores obtained at the time of study discontinuation were carried forward to subsequent visits. At base line, there were 20 patients per group; at 4 weeks, 15 patients remained in the placebo group, and 18 in the paroxetine group; at 8 weeks, 14 remained in the placebo group, and 16 in the paroxetine group; at 12 weeks, 12 remained in the placebo group, and 14 in the paroxetine group.

†P values were calculated by analysis of variance and represent the interactions of group with time.

‡P<0.05 for the post hoc comparison with placebo at the corresponding time point.

§P≤0.01 for the post hoc comparison with placebo at the corresponding time point.

After discontinuation of interferon alfa therapy on completion of the 12-week study, all 20 patients in the placebo group were offered open-label paroxetine, and 15 accepted. Of these, nine had definite improvement in depressive symptoms, three discontinued paroxetine because of side effects, one (who did not have depression earlier) had no change, and two were lost to follow-up.

The types of adverse events did not differ between groups and included elevated liver-enzyme levels, leukopenia, neutropenia, thrombocytopenia, anemia, rash, and retinal hemorrhages and cotton-wool spots. After the 12-week study period, small, reversible retinal hemorrhages developed in two patients, and a third patient had more severe retinal hemorrhages, with associated irreversible loss of vision. All three patients were taking paroxetine at the time, but each also had other risk factors that could have contributed to bleeding.²⁰ Finally, there were no significant differences between the treatment groups in terms of the concurrent use of other medications (data not shown).

DISCUSSION

Previous studies have documented depressive symptoms in patients receiving treatment with interferon alfa for malignant melanoma. However, the development in 45 percent of the patients in our placebo

group of symptoms consistent with the DSM-IV criteria for major depression is remarkable and illustrates the substantial psychiatric morbidity associated with high-dose interferon alfa treatment.

Treatment with the antidepressant paroxetine significantly attenuated interferon alfa-associated symptoms of depression, anxiety, and neurotoxicity and decreased the incidence of major depression during high-dose interferon alfa therapy. There have been several case reports of the use of antidepressant drugs to treat depression induced by interferon alfa, including reports of the successful use of tricyclic antidepressants and selective serotonin-reuptake inhibitors.²¹⁻²³ Other pharmacologic strategies have included the use of methylphenidate for fatigue and naltrexone for neurotoxicity and cognitive dysfunction.^{3,14} Our double-blind, placebo-controlled study of the use of a pharmacologic treatment to prevent cytokine-induced psychiatric effects provides clinical evidence of the effectiveness of antidepressants as prophylaxis against depression in medically ill patients who are at high risk for neuro-psychiatric disorders.

More than one third of the patients in the placebo group in our study had to discontinue interferon alfa therapy because of severe depression or related neurotoxic effects. Similar rates of premature discontinuation have been reported for depressed patients re-

ceiving interferon beta for multiple sclerosis.²⁴ Given the high incidence of major depression in patients receiving interferon alfa for malignant melanoma and the association between depression and the discontinuation of treatment, there appears to be justification for treating these patients with paroxetine. However, given the limited information on the incidence of depression and neurotoxicity in patients receiving interferon alfa for other diseases, such as hepatitis C, more study is required before the widespread use of antidepressants can be recommended for patients with other illnesses. It should also be established whether the reduction in depressive symptoms associated with the use of antidepressants influences the effectiveness of therapy with interferon alfa. Given the number of patients who would have to be treated to make such a determination, this type of study would be easier to conduct in patients with chronic hepatitis C than in those with malignant melanoma.

Identification of which patients might be most vulnerable to depression during cytokine therapy would help physicians target their strategies for prevention. As was the case in the report of Capuron and Ravaut,²⁵ the scores indicating the severity of depression at base line among the patients in the placebo group were predictive of depressive symptoms after four weeks of therapy with interferon alfa. Base-line anxiety scores in the placebo group were also predictive of symptoms of anxiety in that group at four weeks. Thus, screening for symptoms of anxiety, as well as depression, before beginning interferon alfa therapy may help to identify patients at high risk for psychiatric complications of interferon therapy.

Paroxetine was well tolerated by study patients, with no evidence of an increase in the incidence of adverse events during the study period. Nevertheless, although retinal hemorrhage is a rare side effect of paroxetine (less than 1 in 1000), given the development of retinal hemorrhages after the completion of the 12-week study in a small number of patients taking paroxetine, and given the high rates of retinal complications in patients treated with interferon alfa,²⁰ regular funduscopic examinations should be performed and patients with visual symptoms should be referred promptly to an ophthalmologist, whether or not paroxetine is used.

The mechanisms by which interferon alfa causes depression and neurotoxic effects and the mechanisms by which paroxetine has a salutary effect on these symptoms remain obscure. Interferon alfa has been shown to induce the production of other, proinflammatory, cytokines such as tumor necrosis factor α , interleukin-1, and interleukin-6, all of which are potent inducers of sickness behavior and neurotoxic effects in humans and animals.^{4,26,27} Paroxetine may enhance endogenous feedback pathways that regulate the production of such cytokines. Previous studies have explored other mechanisms that may be involved in the effects of interferon alfa²⁸⁻³² and in those of paroxetine.^{33,34}

Regardless of the underlying mechanisms, however, the clinical effects are clear in this 12-week study. Whether the effects of paroxetine will be sustained and whether paroxetine will inhibit the therapeutic effects of interferon are unknown.

Supported by grants from Schering-Plough Pharmaceuticals, SmithKline Beecham, the National Institute of Mental Health (MH00680 and MH60723), and the National Institutes of Health (MO1-RR30039).

Dr. Musselman is a member of speakers' bureaus sponsored by multiple pharmaceutical companies, including Schering-Plough. Dr. Lawson is a member of speakers' bureaus sponsored by Schering-Plough and Chiron. Dr. Nemeroff is a consultant to and a member of speakers' bureaus sponsored by multiple pharmaceutical companies, including SmithKline Beecham.

We are indebted to Andrea Reemsnnyder, Cindy Von Hohenleiten, R.N., and Sasikanth Duggirala for their help with the evaluation of patients and the preparation of the manuscript; to the staff of the Ambulatory Infusion Center at the Winship Cancer Institute; to the Investigational Drug Service of the Pharmacy Department of the Emory University Hospital; to the Emory University General Clinical Research Center for statistical support; and to the study participants and their families and friends.

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