Psychiatric Symptoms in Patients With Chronic Hepatitis C Receiving Interferon Alfa-2b Therapy

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Background: Psychiatric side effects of interferon alfa are frequently observed in the therapy of patients with chronic hepatitis C infection. The goal of the present study was to assess prospectively the incidence, spectrum, and extent of psychiatric symptoms of patients receiving interferon alfa therapy as compared with an untreated reference group.

Method: 104 patients with chronic hepatitis C were consecutively enrolled in a prospective longitudinal study. The treatment group (N = 84) received interferon alfa-2b for up to 12 months, and the reference group (N = 20) received no treatment. Patients who began treatment between November 1996 and August 1998 (N = 44) received interferon alfa-2b, 5 million units 3 times per week. Patients who began treatment in September 1998 or later (N = 40) received a combination of interferon alfa-2b, 3 to 5 million units 3 times per week, and ribavirin, 1000–1200 mg/day. Diagnostic scores for depression and anxiety were obtained by means of the psychometric instrument Hospital Anxiety and Depression Scale, and scores for anger/hostility were obtained with the Symptom Checklist-90 Revised.

Results: In contrast to the untreated reference group, we found significantly increased scores for depression ($p < .001$) and anger/hostility ($p < .001$) during interferon alfa therapy in the treatment group. Even before therapy, scores of those in the treatment group were above the respective cutoff values for clinically relevant symptoms of depression in 15.5% of the patients, anxiety in 13.1% of the patients, and anger/hostility in 11.3% of the patients. These proportions rose to 35.0% (depression), 25.6% (anxiety), and 24.5% (anger/hostility). The cumulative frequency of clinically relevant emotional distress (depression, anxiety, or anger/hostility) during interferon alfa therapy was 57.7%, as compared with 22.5% before therapy. However, interferon alfa therapy had to be stopped prematurely because of untreatable psychiatric symptoms in only 8.3% of patients.

Conclusion: In view of the high frequency and extent of psychiatric symptoms with interferon alfa therapy, we recommend a close follow-up of patients receiving this therapy with respect to potential limiting mood changes.

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Chronic hepatitis C is one of the most frequent chronic infectious diseases worldwide. The number of people infected with hepatitis C virus (HCV) has been estimated to exceed 100 million.[1] The mode of acquisition is often unclear, but typical ways of infection are blood transfusions and intravenous drug use.[2,3] When the disease is detected, approximately 20% of patients with chronic hepatitis C already have liver cirrhosis.[4] As a consequence, chronic hepatitis C is now the leading indication for orthotopic liver transplantation in the United States and other western countries.[5,6]

Medical treatment for hepatitis C is still unsatisfactory, although at present about 50% of patients can reach a sustained loss of HCV through the use of new therapeutic strategies (pegylated interferon alfa plus ribavirin).[7] However, interferon alfa therapy is expensive and often poorly tolerated. An additional problem is the high prevalence of clinically relevant depression and anxiety[8] found even in untreated patients with chronic hepatitis C. These symptoms may be aggravated to a serious degree by interferon alfa therapy. Although physicians treating patients with chronic hepatitis C are well aware of these problems, very few prospective evaluations have been conducted so far.[9,10]

Previously published studies on this subject as listed in review articles[11,12] bear several shortcomings related to study method (e.g., case reports, retrospective studies, assessment of psychiatric symptoms without using validated psychiatric instruments). Therefore, we investigated psychiatric symptoms in HCV-infected patients before, during, and after therapy with interferon alfa.

The main objectives of the present study were to prospectively assess incidence, spectrum, and extent of psychiatric symptoms associated with interferon alfa therapy in patients with hepatitis C.

METHOD

Patients

The participants were 104 consecutive patients in whom chronic hepatitis C was diagnosed at our institution or who were referred for interferon alfa therapy of known chronic hepatitis C. At the Clinic for Internal Medicine of Würzburg University, a multispecialty group of physicians (specialists of gastroenterology/hepatology and psychosomatic medicine) cares for patients from a wide geographic radius on outpatient and inpatient bases. The first patients were recruited in November 1996, and the latest data included in the present analysis are from December 2001.

Patients with documented antibody to HCV and serologic confirmation of chronic hepatitis C (HCV-RNA: sensitive assay based on reverse-transcription polymerase chain reaction [Cobas-Amplicor HCV Monitor, Roche Diagnostics, Basel, Switzerland]) were included.

Patients were excluded from the study (treatment and reference group) if they were aged under 18 years or over 65 years or had coinfections such as hepatitis B virus or human immunodeficiency virus, severe internal diseases (e.g., cancer, ischemic heart disease, autoimmune disease), major depressive disorder (according to DSM-IV criteria), psychosis, active intravenous drug use or alcohol abuse, obvious intellectual impairment, or insufficient knowledge of the German language.

Study Design

This prospective, nonrandomized, longitudinal study included 1 treatment group and 1 untreated reference group (2-factorial design: time × subject group). Subjects eligible for the treatment group were patients in whom therapy with interferon alfa was indicated and who gave written consent to receive this therapy and participate in the study before enrollment. The reference group consisted of patients who were not treated for their chronic hepatitis C because of nonpsychiatric comorbidities, because they refused interferon alfa therapy, or because previous interferon alfa therapy had been unsuccessful (N = 20). The study was approved by the Ethics Committee for Medical Research of Würzburg University in accordance with the Declaration of Helsinki.

In the treatment group, 13 patients could not be included in the final evaluation and statistical analysis (dropouts). Six patients stopped interferon alfa therapy prematurely within the first 6 weeks of treatment (insufficient compliance due to subjective intolerability; however, no clinical signs of depression), and 7 patients withdrew their consent to study participation; these patients were not considered part of the study sample of 104 patients. Therefore, 84 of 97 patients in the treatment group could be included in the final evaluation.

Patients were treated from November 1996 to August 1998 with interferon alfa-2b monotherapy (44/84 patients; 52.4%) according to the changing recommendations in Germany during the study period. If effective (on the basis of virological response), 5 million units of interferon alfa-2b were given 3 times per week for up to 12 months. Patients who began therapy in or after September 1998 (40/84 patients; 47.6%) received combination therapy for up to 12 months (interferon alfa-2b, 3 to 5 million units 3 times per week, and ribavirin, 1000–1200 mg/day).

Before study entry, all eligible patients participated in a manualized structured interview (German version of the Anxiety Disorders Interview Schedule-Revised[13]) conducted face-to-face by a psychologist to exclude severe psychiatric illness according to DSM-IV[14] classification (psychotic disorders, major depressive disorder, anxiety disorders) and to explain the nature and aims of the study. Sociodemographic factors recorded included gender and age. Data on the course of the disease and mode of infection were obtained as well.

In treatment-group subjects, psychometric scores were obtained before therapy (t1) and after 4 weeks (t2), 3 to 4 months (t3), and 6 to 8 months of interferon alfa medication (t4), as well as 4 weeks (t5) and 6 months (t6) after termination of therapy.

Reference group patients were assessed after corresponding time intervals ($t1_0$–$t5_0$). $T5_0$ was set to 12 months after $t1_0$. There was no evaluation in the reference group at t6.

Psychometric Instruments

Hospital Anxiety and Depression Scale. Anxiety and depression were assessed with the well-validated Hospital Anxiety and Depression Scale (HADS, German version, as published by Herrmann et al.[15]). HADS is a 14-item questionnaire with the dimensions anxiety and depression. All items exclusively refer to the emotional state and do not reflect somatic symptoms. Recently, the cutoff value for clinically relevant depressive symptoms was set to ≥ 9, and the cutoff value for anxiety was set to ≥ 11 on the respective subscale.[15]

Symptom Checklist-90 Revised. Anger/hostility was assessed with the well-validated Symptom Checklist-90 Revised (SCL-90-R, German version, as published by Franke[16]). The SCL-90-R is a brief, multidimensional self-report inventory designed to screen for a broad range of psychological problems and symptoms of psychopathology. We focused exclusively on the evaluation of 1 questionnaire subscale (subscale 6, "anger/hostility"). In accordance with the manual, the cutoff value for highly affected patients was set to ≥ 8.[16]

Clinical, Laboratory, and Histological Data

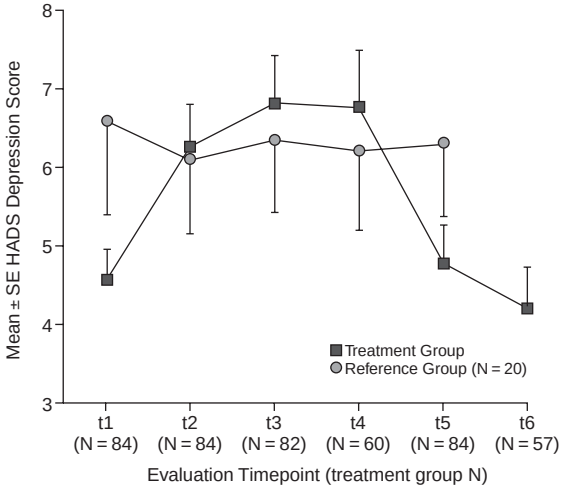
Blood samples were obtained during the patients' medical visits at timepoints t1 to t6 to evaluate the following parameters: blood count, transaminases, anti-HCV antibodies, and HCV-RNA. Genotype identification and

Table 1. Sociodemographic and Biomedical Characteristics of 104 Hepatitis C Patients Receiving Interferon Alfa-2b or No Treatment

Characteristic	Total Sample (N = 104)	Treatment Group (N = 84)	Reference Group (N = 20)	p Value
Age, y				
Mean ± SD	40.8 ± 9.2	39.2 ± 8.5	47.3 ± 9.6	< .001
Range	18–63	18–63	29–63	
Sex, N (%)				
Female	44 (42.3)	31 (36.9)	13 (65.0)	.026
Male	60 (57.7)	53 (63.1)	7 (35.0)	
Acquisition mode, N (%)				
Unknown	26 (25.0)	21 (25.0)	5 (25.0)	.105
Intravenous drug use	50 (48.1)	44 (52.4)	6 (30.0)	
Post-transfusion	28 (26.9)	19 (22.6)	9 (45.0)	
Virus genotype, N (%)[a]				
1	63 (61.8)	48 (57.1)	15 (83.3)	.104
2	9 (8.8)	9 (10.7)	0 (0.0)	
3	30 (29.4)	27 (32.1)	3 (16.7)	
Liver damage according to biopsy, N (%)[b]				
Hepatitis only	54 (56.3)	48 (58.5)	6 (42.9)	.302
Fibrosis	23 (24.0)	20 (24.4)	3 (21.4)	
Cirrhosis	19 (19.7)	14 (17.1)	5 (35.7)	

[a]Virus genotype data are missing for 2 patients.
[b]Biopsy was not performed in 8 patients.

Figure 1. Depression Scores on the Hospital Anxiety and Depression Scale (HADS) During Interferon Therapy



liver biopsy (staging and grading: inflammation, fibrosis, cirrhosis) were performed once before interferon alfa therapy. However, a liver biopsy conducted immediately before study entry was not an inclusion criterion. Finally, the mode of infection was documented.

Statistical Analysis

Data were registered and analyzed using the Statistical Package for Social Sciences (SPSS for Windows, German version 10.0.7).[17] All tests of significance were 2-tailed. p Values of < .05 were considered statistically significant. Because of the explorative character of the study, we did not consider alpha adjustment in multiple comparisons.

Data describing quantitative measures are expressed as median or mean ± SD. Qualitative variables are presented as counts and percentages.

Comparison of variables representing categorical data was performed using the chi-square statistic (CHISQUARE subcommand in SPSS). Mean differences of continuous variables between patient subgroups were examined by either t tests for independent samples (comparison of 2 subgroups, e.g., treatment group vs. reference group) or analysis of variance (ANOVA) if more than 2 subgroups were included (1-factorial ANOVA with more than 2 factor categories; General Linear Model [GLM] procedure).

Group means of dependent samples (e.g., time course of continuous variables before/during interferon alfa therapy within the treatment group) were compared by means of ANOVA (repeated-measures design, GLM procedure in SPSS for Windows, 10.0.7).

Pearson correlation was used when appropriate (assessment of associations between quantitative variables).

RESULTS

Demographic and Biomedical Data

The sociodemographic and biomedical characteristics of the 84 patients receiving interferon alfa therapy are presented in Table 1. The distributions of the variables age, gender, virus genotype, and grade of liver damage are comparable to those observed in other hepatitis C therapy studies. However, the rate of patients with a history of intravenous drug use (52.4%) was higher than commonly reported.[3]

Depression

Figure 1 shows the significant increase of depression scores in the treatment group during interferon alfa therapy (t1–t4; $p < .001$). At 4 weeks (t5) and at 6 months (t6) after termination of interferon alfa treatment, depression scores had decreased to pretreatment levels. The decrease of sample size in the treatment group (as indicated in Figure 1) over the treatment period can be explained as follows: at t3, N = 82 (2 patients had major depressive disorder), and at t4, N = 60 (17 patients showed nonresponse to interferon alfa monotherapy, 5 patients had major depressive disorder).

The depression scores of the reference group (no interferon alfa treatment; N = 20) were considerably higher than the pretreatment scores of the interferon alfa group but remained stable during the whole observation period ($t1_0$ to $t5_0$).

The percentage of patients in the treatment group with a depression score above the cutoff value before inter-

Figure 2. Scores Above the Cutoff Value for the Scales of Depression, Anxiety, and Anger/Hostility During Interferon Therapy

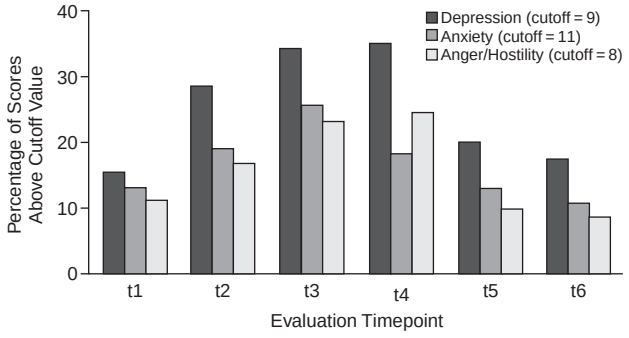
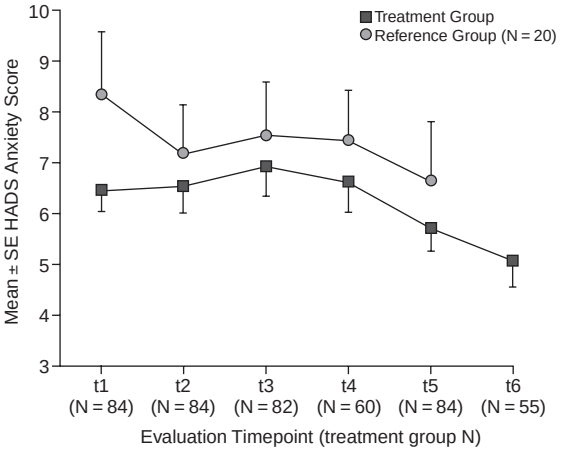


Figure 3. Anxiety Scores on the Hospital Anxiety and Depression Scale (HADS) During Interferon Therapy



feron alfa treatment was 15.5% (13/84). During interferon alfa therapy, there was a continuous increase to a maximum of 35.0% (21/60) at t4. After termination of therapy, this rate decreased to pretreatment value (t5: 20.2%, 17/84; t6: 17.5%, 10/57) (Figure 2). Among the 13 patients with clinically relevant pretherapeutic depression scores (above the cutoff), 5 had to discontinue treatment because of severe psychiatric side effects of interferon alfa. Only 2 patients with pretreatment depression scores below the cutoff developed major depressive disorder that required discontinuation of interferon alfa treatment.

During treatment, patients receiving combination therapy (interferon alfa/ribavirin) were significantly more depressed than patients receiving interferon alfa monotherapy ($p = .005$), but the percentage of patients above the cutoff value was not significantly different between the groups.

Our data showed no significant associations between incidence or extent of psychiatric symptoms during interferon alfa therapy and sociodemographic factors (age, gender), stage of disease (histology), or mode of acquisition. Therefore, our results do not confirm the repeatedly stated observation that patients with former drug abuse are more frequently affected by emotional problems during interferon alfa treatment.

Anxiety

The change in anxiety scores before, during, and after therapy with interferon alfa was statistically significant (main effect of time: $p = .03$), while the mere observed increase (t1 vs. t3) was not (Figure 3). After termination of interferon alfa treatment, anxiety scores decreased below pretreatment levels (statistical trend: $p = .07$). Changes in sample size (see Figure 3) were due to the reasons listed above in the Depression section. Two subjects left too many anxiety items unanswered on the HADS at t6 and are not included in the t6 results.

As with depression, the anxiety scores of the reference group were higher than those of the treatment group at the beginning of the observation period and did not change significantly during follow-up. Even before interferon alfa treatment, 11/84 patients (13.1%) in the treatment group had an anxiety score above the cutoff value. During interferon alfa therapy, this rate increased to a maximum of 25.6% (21/82) at t3, but decreased again to the pretreatment rate (t5: 13.1%, 11/84; t6: 10.9%, 6/55) (Figure 2).

Patients receiving combination therapy (interferon alfa/ribavirin) showed significantly higher anxiety scores than patients with interferon alfa monotherapy (main effect of therapy: $p = .032$). However, the proportion of patients above the cutoff value did not differ significantly between the groups.

Anger/Hostility

Anger/hostility (SCL-90-R subscale) was evaluated in a subset of 71 patients due to the fact that the psychometric instrument used was introduced after the study had already started.

In the treatment group, scores of anger/hostility increased significantly (t1–t4, $p < .001$) during interferon alfa therapy (Figure 4). At 4 weeks (t5) and 6 months (t6) after termination of therapy, anger/hostility scores had nearly returned to baseline levels. Reference group scores of anger/hostility did not change significantly during the observation period (see Figure 4).

Before starting interferon alfa therapy, 8/71 patients (11.3%) showed an anger/hostility score above the cutoff value. During therapy, the proportion increased to a maximum of 24.5% (13/53) at t4. After termination of therapy, this rate decreased below the pretreatment rate (t5: 9.9%, 7/71; t6: 8.7%, 4/46) (Figure 2).

Patients who received combination therapy with interferon alfa and ribavirin showed significantly higher anger/hostility scores than patients who received inter-

Figure 4. Anger/Hostility Scores on the Symptom Checklist-90 Revised (SCL-90-R) During Interferon Therapy

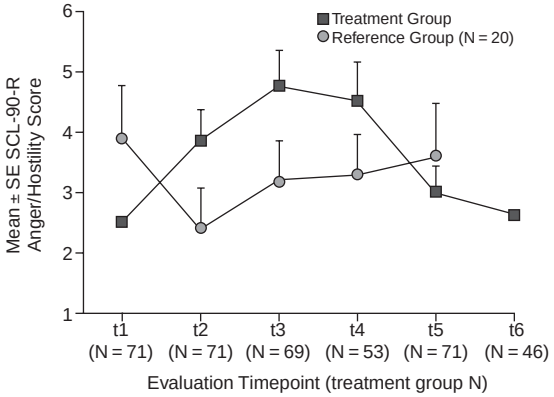
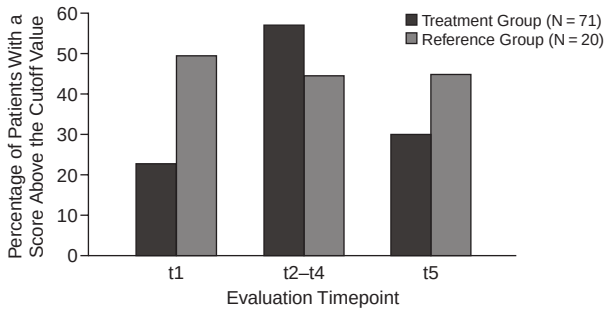


Figure 5. Emotional Distress During Interferon Therapy (cumulative frequencies of patients with a depression, anxiety, or anger/hostility score above the cutoff)



feron alfa monotherapy (main effect of therapy: p = .044). However, the rate of patients above the cutoff value did not differ significantly between the groups.

Emotional Distress During Interferon Alfa Therapy (cumulative frequencies)

Seventy-one patients in the treatment group could be included in the emotional distress assessment because in this subgroup the 3 relevant scales depression, anxiety, and anger/hostility were evaluable (Figure 5).

At t1 (before interferon alfa therapy), 16/71 patients (22.5%) in the treatment group had a clinically relevant score above the respective cutoff value on at least 1 of the 3 subscales. Emotional distress occurred in 57.7% of the patients while on therapy. Forty-one of the 71 patients reached values above the cutoff at least on 1 of the 3 mentioned subscales at 1 or more timepoints. Four weeks after treatment (t5), this proportion was still 29.6% (21/71), and only 6 months after therapy (t6), it had decreased to 19.3% (11/57).

In contrast to this marked therapy-related change in the treatment group, cumulative evaluation revealed no significant changes during the observation period in the reference group. Before, during, and at the end of the study, the proportion of patients with emotional distress was stable (Figure 5).

Seven (8.3%) of 84 patients received antidepressant therapy (paroxetine, 20 mg/day) because of interferon-induced major depressive disorder, 6 of whom were able to complete interferon therapy as scheduled. Despite antidepressant medication, in 1 patient, major depressive disorder worsened and interferon therapy had to be terminated prematurely. Another 6/84 patients (7.1%) became unable to continue interferon alfa therapy because of severe depressive symptoms or suicidal ideation, for a total of 13 cases of interferon-induced major depressive disorder.

DISCUSSION

The substantial variation in the incidence of depression on interferon alfa across published studies may be due to different dosing schedules, composition of study cohorts, and exclusion criteria.[11] Additional factors may be varying study designs (e.g., retrospective studies, case reports, small and variable sample sizes), as well as sensitivities or specificities of various instruments.[12,18] Therefore, we followed a prospective study design fulfilling the following criteria: psychiatric symptoms as the main focus, sufficient sample size, reference group without interferon alfa therapy, and use of well-validated and applicable psychometric instruments. To ensure homogeneity concerning data acquisition and patient care, the study was performed in a single center.

The intensive patient care and exhaustive interviews might partially account for the high rate of intravenous drug users detected—obviously, hardly any patients sought to persistently hide this acquisition mode in our study context.

In our total sample (N = 104 patients), 84 subjects were evaluable for the treatment group and 20 subjects comprised the reference group without interferon alfa therapy. The latter subsample cannot be called the "control group" in terms of method, because it was not recruited by means of randomization or matched in age or gender to the treatment group. However, this reference group can provide additional valuable information concerning the time course of psychiatric symptoms in untreated patients with chronic hepatitis C. In addition, inclusion of the group facilitates the interpretation of longitudinal data obtained in the treatment group.

Even when the pretreatment values are compared, the reference group had higher scores of depression, anxiety, and anger/hostility than the treatment group. These differences may be due to the fact that the subjects in the group without therapy were aware that, at present, a chance for cure of their chronic disease was not available. The base-

line difference in psychometric scale scores between the groups may additionally be due to the significantly higher age in the reference group.[8] However, the time-related stability of both the frequency and extent of psychiatric symptoms across the whole assessment period is more important with respect to the study objectives than the absolute scores of the reference group.

Our data show a significantly elevated incidence of psychiatric symptoms (depression, anxiety, and anger/hostility) among patients with chronic hepatitis C on interferon alfa therapy. In our treatment group, 35% of patients showed clinically relevant depressive symptoms with scores above the cutoff after 6 to 8 months of interferon alfa therapy (t4). In contrast to the lower incidence rates of depression found in the studies of Lee et al.[19] (15%) and Hunt et al.[20] (20%), our data are comparable to the results obtained by Otsubo et al.[21] (37.3%) and McHutchison et al.[22] (37%).

Concerning the time interval until occurrence of depressive symptoms, our findings agree with the results of Miyaoka et al.,[23] who found that the highest increase of depression scores was registered within the first 4 weeks of interferon alfa therapy. Thus, in our opinion, these data should be a challenge to physicians to monitor patients during the early treatment period for psychiatric symptoms, especially depression. This monitoring would offer a chance to start a necessary medical intervention (e.g., antidepressant medication) in a timely manner.[24,25]

In contrast to depression, anxiety and hostility experienced while on interferon alfa therapy have been scarcely systematically investigated so far. Our rate of patients with anxiety scores above the cutoff after therapy (25.6%) was higher than the percentage of patients with "anxiety" in the study by McHutchison et al.[22] (interferon alfa monotherapy, 13%; interferon alfa/ribavirin therapy, 18%). In the study by Hunt et al.,[20] the pretreatment proportion of patients with "definite anxiety" (25%) decreased to 4% after 4 weeks of treatment and to 19% after 6 months of treatment. These surprising results (obtained with the same psychometric instrument, the HADS) may be influenced by the low sample size (N = 29).

In clinical practice, patients on interferon alfa therapy often report interpersonal problems and increased impatience, irritability, and hostility. Our data confirm this general impression. Both the scores of anger/hostility and the rate of highly affected patients (t4: 24.5%) increased significantly during interferon alfa therapy. Similarly, McHutchison et al.[22] described the phenomenon of "irritability" in 32% of patients treated with interferon alfa and ribavirin.

In our study, regression analysis revealed that neither former drug experience nor pretherapeutically gained parameters (such as virus genotype, liver histology, or depression scores) were able to significantly predict patients with interferon-induced depression (data not shown).

To summarize, psychiatric symptoms are very common during interferon alfa therapy in patients with chronic hepatitis C. More than half of our patients in the treatment group experienced a clinically significant impairment of their emotional health status (depression, anxiety, or hostility). In contrast to this high proportion, the rate of inevitable premature discontinuation of therapy following psychiatric problems was comparably low (8.3%), which may be due to the fact that 6 patients received successful antidepressant therapy. Additionally, our repeated-measures study design creates the conditions of a more trusting physician-patient relationship. In usual clinical settings, we expect the percentage of therapy dropouts due to psychiatric symptoms to be higher. In a review, Fontana[25] similarly stated that only a "minority" of patients might develop severe depressive symptoms in the sense of a medical emergency while, however, delivering exact figures for only the extremely rare cases of suicide attempts during interferon alfa treatment.[26,27]

Regarding the high frequency and extent of psychiatric symptoms on interferon alfa therapy, as well as the possible consequences (e.g., premature discontinuation of therapy, problems with compliance), we recommend that physicians either use a psychometric monitoring instrument or ask regularly about occurring mood changes so that it is possible to recognize and assess psychiatric problems early enough to initiate adequate therapeutic procedures.[25,28]

Drug names: paroxetine (Paxil), ribavirin and interferon alfa-2b combination (Rebetron).

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