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Psychopathological changes and quality of life in hepatitis C virus-infected, opioid-dependent patients during maintenance therapy

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ABSTRACT

Aims To examine among maintenance patients (methadone or buprenorphine) with and without hepatitis C virus (HCV) infection (i) the frequency of psychopathological symptoms at baseline and 1-year follow-up; (ii) the association between antiviral interferon (IFN) treatment and psychopathological symptoms; and (iii) to explore whether IFN therapy has an effect on 1-year outcome of maintenance treatment. **Design** Naturalistic prospective longitudinal cohort design. **Setting** A total of 223 substitution centres in Germany. **Participants** A nationally representative sample of 2414 maintenance patients, namely 800 without and 1614 with HCV infection, of whom 122 received IFN therapy. **Measures** HCV infection (HCV^+/HCV^-), IFN (IFN^+/IFN^-) treatment status and clinical measures. Diagnostic status and severity (rated by clinician), psychopathology (BSI—Brief Symptom Inventory) and quality of life (EQ-5D—EuroQol Group questionnaire). **Findings** HCV^+ patients revealed indications for a moderately increased psychopathological burden and poorer quality of life at baseline and follow-up compared to HCV^- patients. HCV^+ patients showed a marked deterioration over time only in the BSI subscale somatization ($P = 0.002$), and the frequency of sleep disorders almost doubled over time (12.8% at baseline; 24.1% at follow-up; $P < 0.01$). IFN treatment, received by 10% of HCV^+ patients, did not impair efficacy or tolerability of maintenance therapy and was associated overall with neither increased psychopathological burden nor reduced quality of life. **Conclusions** Findings suggest no increased risk among HCV^+ patients on maintenance therapy for depressive or other psychopathological syndromes. In our patient sample, IFN treatment was not associated with increased psychopathological burden, reduced quality of life or poorer tolerability and efficacy of maintenance treatment.

Keywords Antiviral treatment, buprenorphine, depression, hepatitis C, interferon-α, methadone, psychopathology, quality of life, substitution.

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INTRODUCTION

Depression and other psychopathological syndromes are observed frequently in opioid-dependent patients during methadone or buprenorphine maintenance therapy [1]. Psychopathological symptoms are also very common in patients with chronic hepatitis C virus (HCV) infection [2], a condition that is particularly frequent in opioid-dependent populations. In addition, there is some evidence that interferon (IFN)-based antiviral therapy may aggravate depressive symptomatology further [3].

Chronic HCV infection constitutes a global medical challenge. Around the world, some 130–170 million people are estimated to be infected [4–7]. Epidemiological research suggests that more than 50% of new HCV infections result from drug-related risk behaviour. It has been estimated that more than 90% of all intravenous drug users test positive for acute or chronic HCV infection;

however, the precise proportion is unclear because of the variability of findings [8–12]. The effective state-of-the-art treatment against chronic hepatitis C infection is combination therapy with pegylated IFN-α (pegIFN-α) and ribavirin [13,14], aiming at virus elimination. In the majority of cases a sustained virological response (SVR) can be achieved, as confirmed by absence of virus 6 months after the end of IFN treatment [13,14]. Although IFN has a well-documented efficacy in HCV patients, there is also a range of associated side effects such as depressive syndromes, suicidal ideation, fatigue and other neuropsychiatric complications [3,5] demanding caution in the application of this treatment, especially in vulnerable patient populations, such as psychiatric and substance-dependent patients.

There is considerable consensus, however, that under defined conditions (e.g. interdisciplinary setting, psychometric monitoring, psychiatric support), HCV patients with a history of intravenous drug use (IVDU) undergoing maintenance therapy [15,16] may also benefit from antiviral combination treatment [17,18]. Most studies published so far have focused mainly upon efficacy and compliance with regard to either maintenance therapy (e.g. retention rates) or antiviral treatment (compliance with therapy, adherence, SVR). Little is known, however, about the range and severity of specific complications that may arise in such high-risk populations; for example, in terms of the frequency and type of psychopathological syndromes, their course and the degree to which such syndromes are affected by IFN-based treatment [19,20]. Although the assumption has been that IFN therapy is not affected adversely by drug substitution treatment [21,22], little systematic clinical and epidemiological research has been conducted regarding, for example, the effect of untreated HCV infection on maintenance patients' mental health and quality of life or the effects of IFN therapy on the course and outcome of maintenance treatment with either methadone or buprenorphine [1,8]. In fact, few epidemiological data are available informing us about the precise prevalence of treated and untreated HCV infections among maintenance patients and their distribution by region, country, time and other factors [1,23].

In response to these research deficits, we examined the following questions:

1 Is HCV^+ associated with an increased burden of psychopathological symptoms and syndromes and reduced quality of life (QOL) in opioid-dependent patients in maintenance treatment at baseline and at 12-month follow-up?
2 Is antiviral treatment during maintenance treatment among HCV^+ patients associated with an increased burden of psychopathological symptoms and syndromes and reduced QOL at 12-month follow-up?
3 Is antiviral treatment during maintenance therapy associated with changes in patients' course and outcome patterns as well as with regard to tolerability of maintenance treatment with agonists?

PATIENTS AND METHODS

Design

This is an observational, 12-month prospective longitudinal investigation in a nation-wide representative sample of opiate substitution doctors/centres in Germany and a random sample of their maintenance patients. A full description of design, sampling and methods has been published elsewhere [1,23]. Core design elements are (a) a pre-study to characterize the participating centres (not dealt with in this paper); (b) a comprehensive baseline assessment of patients enrolled; and (c) a 12-month course and outcome follow-up assessment of patients. Assessments consisted of a self-report questionnaire, urine tests and a comprehensive clinical interview and documentation of treatment by the treating physician [1,23].

Study sample at baseline

Based on a 2003 nation-wide register of more than 2500 substitution doctors in Germany, a random sample of registered substitution doctors ($n = 379$) was drawn, of whom 223 participated (response rate: 58.8%). A prevalence total sample of 2694 patients, chosen randomly from total patients' recruitment lists in each setting from all eligible patients, were enrolled from these 223 participating doctors at baseline. A total of 2013 patients were treated with methadone and 662 with buprenorphine. The total baseline response rate of all eligible patients was 71.7% [1,23].

Inclusion criteria

All patients on the recruitment list who were at least 16 years of age and currently in agonist maintenance therapy for opioid dependence with either buprenorphine or methadone were eligible for the study, irrespective of prior duration of treatment. This means that this is a prevalence treatment sample, not an incidence (new treatment onset) sample.

Exclusion criteria

Acute medical emergencies, cognitive impairments making the meaningful completion of the self-report forms unlikely, unwillingness to comply with study procedures, including the mandatory urine tests.

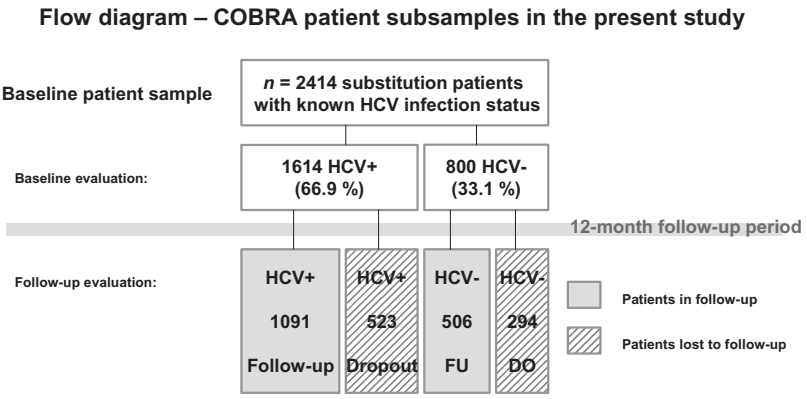

Figure 1 Overview of the baseline and follow-up sample in the present study; description of patients lost during the 12-month follow-up period

The study was approved by the Ethics Committee of the Medical Faculty, Technische Universität Dresden, Germany. Each patient enrolled gave written informed consent.

Baseline and follow-up sample, comparison groups

Sampling, patient flow and reasons for non-participation for the total sample have been presented in detail elsewhere [23]. Briefly, from the total baseline sample of originally 2649 maintenance patients in 223 settings, 233 patients were lost during the 12-month observation period, due to the premature withdrawal of 29 doctors and their settings. For these patients, no course and outcome information is available. Core course and outcome information, at least, was documented for the remaining 2416 patients. Two patients were excluded for whom baseline HCV status could not be established reliably, leaving a total of 2414 patients treated with methadone or buprenorphine [23,24] in the present overall analysis.

According to the doctors' diagnosis and virological information at baseline, 1614 (66.9%) of the 2414 patients were diagnosed as HCV^+ and 800 (33.1%) were diagnosed as not having HCV (HCV^-) (Fig. 1). For 523 of the HCV^+ group and 294 of the HCV^-baseline group, the follow-up assessment could not be completed comprehensively, predominantly because patients were no longer treated by their original study physician ($n = 712$; for details see [23]). Socio-demographic characteristics and relevant medical information concerning total baseline samples with and without known hepatitis C infection status are presented in Table 1. Of the 1614 HCV^+ patients, 1091 (67.6%) were still on maintenance treatment with either methadone or buprenorphine at the time of follow-up evaluation in the original doctor's office and therefore available for longitudinal analyses. Antiviral treatment rate in HCV^+ patients was 11.2% (122 of 1091 HCV^+ follow-up patients).

Attrition

The substantial proportion of patients (HCV^+: 523, HCV^-: 294; total: $n = 817$) not completing the full follow-up assessment could raise the question of selective attrition. Therefore, we examined carefully the potential reasons for attrition in both groups. Twenty-seven patients had died (21 HCV^+ patients; six HCV^- patients); 272 terminated their maintenance treatment within the observation period (either because they became 'clean' or were referred to an abstinence treatment setting); 250 patients discontinued the maintenance treatment (i.e. change of residence, imprisonment or change of doctor); in 119 patients the doctor terminated the treatment for disciplinary reasons; and 149 patients were lost for unknown reasons. Despite indications of higher mortality rates in the HCV^+ group (4% versus 2%) the reasons for premature substitution dropout did not differ between HCV^+ and HCV^- patients, suggesting no selective attrition ($F_{4.9,952.3} = 1$, $P = 0.407$).

However, there were a few noteworthy statistically significant differences in baseline characteristics between those who continued to the end of the study and those who did not. The latter were younger ($P < 0.001$) and had a slightly higher psychopathological burden as measured in the Brief Symptom Inventory (BSI: $P = 0.040$; due mainly to increased BSI scores for depression and anxiety) and they showed a markedly higher frequency of concomitant substance abuse ($P < 0.001$). This suggests that our study sample used for the subsequent analyses might be regarded as slightly less impaired than the patient group who discontinued the maintenance treatment.

Assessments

Patient questionnaire

After signing the informed consent form, patients were asked to complete a 12-page questionnaire which

Table 1 Baseline description of total sample ($n = 2442$): socio-demographic and medical data.

	$Total_{HCVstat.}$ ($n = 2414$)	HCV^+ ($n = 1614$)	HCV^- ($n = 800$)	HCV^+ *versus* HCV^-
	n/% mean (SD)	*n*/% mean (SD)	*n*/% mean (SD)	Test statistic
Mean age (years)	34.8 (8.1)	36.3 (7.9)	31.8 (7.7)	$F_{(1,208)} = 146.1^{***}$
Gender				
Female	761/31.5	538/33.3	223/27.9	$F_{(1,208)} = 8.0^{**}$
Male	1653/68.5	1076/66.7	577/72.1	
Professional status				
Employed	531/22.0	331/20.5	200/25.0	$F_{(2,415.3)} = 2.8$
Unemployed	1307/54.1	886/54.9	421/52.6	
Other	555/23.0	382/23.7	173/21.6	
Marital status				
Single	1340/55.5	836/51.8	504/63.0	$F_{(2,406.8)} = 14.6$
Married	303/12.6	217/13.4	86/10.8	
Other	763/31.6	558/34.6	205/25.6	
Substitution medication				
Methadone	1797/74.4	1261/78.1	536/67	$F_{(1,208)} = 29.3^{***}$
Dose: mean (SD)	76.2 (46.2)	79.5 (46.9)	68.4 (43.5)	$F_{(1,201)} = 23.3^{***}$
Duration: mean (SD)	5.9 (5.2)	6.6 (5.4)	4.2 (4.1)	$F_{(1,201)} = 93.9^{***}$
Buprenorphine	617/25.6	353/21.9	264/33	ref.
Dose: mean (SD)	6.9 (5.2)	6.9 (4.9)	6.8 (5.6)	$F_{(1,168)} = 0.1$
Duration: mean (SD)	4.6 (4.5)	5.4 (5.0)	3.6 (3.5)	$F_{(1,168)} = 22.6^{***}$
Provider setting				
Small (<10 *P*/d)	772/32.0	510/31.6	262/32.8	$F_{(1.9,398.8)} = 0.3$
Medium (10–40 *P*/d)	1142/47.3	775/48.0	367/45.9	
Subst. centre (>40 *P*/d)	500/20.7	329/20.4	171/21.4	

$^{**}P < 0.01$, $^{***}P < 0.001$. HCV: hepatitis C virus; SD: standard deviation; *P*/d: patients per day.

consisted largely of various components of established instruments, such as item groups of the European Addiction Severity Index (EuropASI) [25], BSI [26,27] and modules of the questions on substance use from the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI) [28,29]. The questionnaire covered the following domains: (a) basic biosocial and socio-demographic information; (b) social and legal life developmental history and status ratings; (c) past and current drug use and illness history; (d) mental health and substance use diagnostic status; (e) self-reported physical disorders [e.g. HCV, human immunodeficiency virus (HIV)]; (f) past and current impairments in social roles, as well as disabilities and problems specific to drug use; (g) past and current treatment history; (h) met and unmet subjective needs; (i) current and past experiences with treatments; (j) quality of life (EuroQol Group questionnaire: EQ5-D), [30–32]); and (k) risk behaviours.

Clinical interview and assessment

Each patient was evaluated by the doctor using a standardized interview and assessment that covered several factors, including: (a) current and past maintenance treatments (e.g. dosage, dosing status); (b) behaviours related to the use of legal and illegal substances; (c) past and current physical and mental disorders rated by severity using the Clinical Global Impression scale (CGI) [33]), and current and past treatments for mental disorders and somatic disorders such as HCV and HIV infection; (d) multi-dimensional evaluation of social and psychological functioning; (e) description and assessment of all past and current interventions related to maintenance therapy; and (f) compliance.

Further, standardized urine tests were taken as part of the baseline and follow-up assessment in addition to the mandatory random routine urine screens. Also throughout the follow-up period, doctors completed a brief course and outcome form to monitor problems, interruptions of therapy and treatment events.

Outcome measures for statistical analyses

Patients were classified as HCV carriers (HCV^+) if, at the time of enrolment in the study, they were anti-HCV positive and had circulating HCV RNA, or if patients were currently receiving IFN-based antiviral therapy. Patients were classified as receiving IFN-α treatment (IFN^+) if they

were treated antivirally for their chronic hepatitis C infection at any time during the study period until the follow-up at 12 months. According to the current treatment recommendations for Germany at the time of study recruitment, the vast majority of patients received combination therapy with oral ribavirin (Copegus™ or Rebetol™) and pegIFN-α-2a (Pegasys™) or pegIFN-α-2b (Pegintron™).

Mental health

Mental health was assessed using clinician-rated ICD-10 diagnoses [34,35] across a total of 12 groups of mental disorders. Doctors were encouraged to code all applicable diagnoses present definitively over the preceding 12 months. Additionally, data provided by the Brief Symptom Inventory (BSI), a self-assessment instrument [26,27], are reported.

QOL

Quality of life was assessed using the WHO EuroQOL EQ-5D instrument [30–32].

Tolerability and success

Tolerability and success of maintenance treatment in patients with and without IFN treatment as assessed by the physicians were analysed by adopting the following criteria: (a) interruptions of agonist maintenance therapy during the 12-month follow-up period for any reason; (b) physician's assessment of maintenance therapy course (e.g. efficacy, tolerability, compliance, motivation, patient satisfaction with the substitution drug); and (c) physician's assessment of the extent to which therapy goals were achieved (e.g. abstinence, reduction of comorbidity, reduction of risk behaviour).

Statistical analysis and statistical procedures

Cross-sectional and longitudinal comparisons relating baseline to follow-up results were calculated separately for each outcome measure using Wald *F*-tests [36,37]. The statistical tests included adjustments for clustering of observations within primary care settings, using the Huber–White variance estimate [38–40]. For associations between categorical variables, *F*-tests for independence in cross-tabs were used. For differences in dimensional outcomes, the Wald *F*-test was based on linear regression, and the analysis took into account clustering of observations within primary care settings. *P*-values below 0.05 were considered statistically significant. Alpha adjustment for multiple comparisons was not considered because of the epidemiological and exploratory nature of the present study. Exact *P*-values are usually provided here in order to ensure maximum transparency in the presentation of results.

All mathematical and statistical analyses were performed by statisticians in the Combination Therapy in Early Rheumatoid Arthritis (COBRA) study headquarters (TU Dresden University of Technology), using the statistical software package Stata, version 10.0 [41].

RESULTS

Socio-demographic and clinical characteristics of HCV$^+$ and HCV$^-$ patients: baseline

Table 1 (first column) presents selected baseline characteristics for the total study sample ($n = 2442$), as well as by HCV infection status (second and third columns). At baseline, HCV$^+$ patients did not differ from HCV$^-$ patients with regard to marital status, occupational status and the type of provider setting. They differed, however, with regard to a significantly higher mean age (HCV$^+$: 36.3 versus 31.8 years, $P < 0.001$), a higher proportion of females (33.3% versus 27.9%; $P < 0.001$) and a higher proportion of patients treated with methadone (78.1% versus 67.0%; $P < 0.001$), and consequently a lower proportion of patients treated with buprenorphine. It should be noted further that HCV$^+$ patients also received significantly higher dosages of methadone (mean dose: 79.5 versus 68.4, $P < 0.001$), but not of buprenorphine, and that they had a longer duration of methadone and buprenorphine treatments ($P < 0.001$). The generally higher rates for methadone reflect the currently predominant use of methadone in the clinical practice of German drug substitution centres.

The association of HCV$^+$ with psychopathological syndromes and QOL in opioid-dependent patients in maintenance treatment

Figure 2 indicates that our study sample of maintenance patients—irrespective of their HCV status—is characterized by a very high psychopathological burden and reduced QOL in terms of the patient-rated psychopathological symptoms, clinician-rated mental disorders and fairly low measures in quality of life. Figure 2a reveals that HCV$^+$ patients, as measured by the standardized BSI total score, have a significantly higher psychopathological burden at baseline (mean difference = 0.08, $P = 0.003$) and follow-up (mean difference = 0.12, $P < 0.001$) than HCV$^-$ patients.

At follow-up, both groups indicate some—although non-significant—reduction in psychopathology.

Because it appeared that the reduction in the HCV$^-$ patient group was more pronounced, we also examined the BSI subscore changes from baseline to follow-up separately in both groups. A significant reduction was

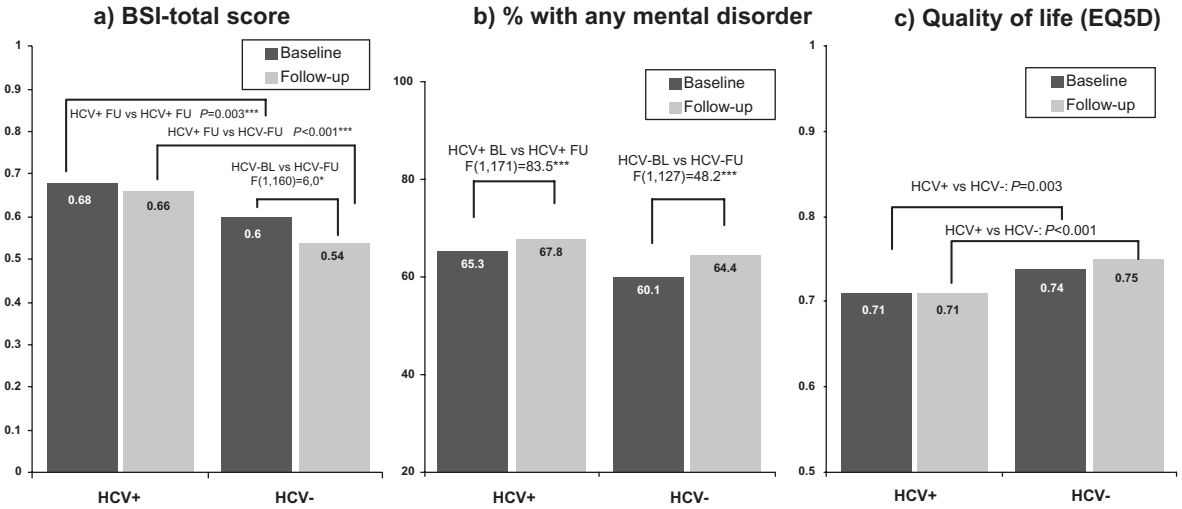

Figure 2 Mean Brief Symptom Inventory (BSI) score, percentage with any clinically significant mental disorder and quality of life by hepatitis C virus (HCV) status (HCV^+: $n = 1091$, HCV^-: $n = 506$) at baseline (BL) and 1-year follow-up (FU). Tests for significance were carried out for BSI scores and the EQ5D (EuroQol Group questionnaire) using the mean difference test; the significance level was set to $P < 0.001$. Rates of mental disorders were tested with the design-based *F*-test, accounting for clustering of observations within settings

found for four BSI scores among HCV^- patients during the follow-up period (obsessive–compulsive thoughts: $F_{1,159} = 6.7$, $P = 0.011$; interpersonal sensitivity: $F_{1,160} = 8.0$, $P = 0.005$; depression: $F_{1,160} = 5.9$, $P = 0.016$; anger/hostility: $F_{1,160} = 10.5$ $P = 0.001$); in contrast, the reduction of psychopathology in HCV^+ patients was significant in only two instances, namely somatization ($F_{1,189} = 9.5$, $P = 0.002$) and interpersonal sensitivity ($F_{1,187} = 5.1$, $P = 0.03$).

In contrast to reductions in the self-rated BSI symptoms (Fig. 2a), there was some increase in clinician-rated mental disorders (diagnoses according to ICD-10) at follow-up: at baseline, for example, there were 712 HCV^+ patients (65.3%) with 'any mental disorder'; this figure increased to 740 (67.8%) at the time of the 1-year follow-up evaluation (Fig. 2b; $F_{1,171} = 83.5$; $P < 0.001$). Except for sleep disorders, which doubled within the 12-month follow-up period (12.8% at baseline; 24.1% at follow-up; $F_{1,171} = 10.5$; $P < 0.01$) only in the HCV^+ subgroup, baseline to follow-up changes in clinician-rated mental disorders were not significantly different between HCV^+ and HCV^- patients.

The most frequent ICD-10 disorders as rated by the clinician at baseline (and follow-up) were: depressive disorders [HCV^+: 38.9% (56.2%) versus HCV^-: 31.4% (40.7%)], personality disorders [HCV^+: 19.6% (22.5%) versus 20.6% (21.9%)], anxiety disorders [HCV^+: 15.9% (19.9%) versus 16.4% (22.3%)] and sleep disorders [HCV^+: 12.8% (24.1%) versus 14.0% (20.2%)]; rates for psychotic disorders ranged between 3.0 and 3.4%.

The QOL measures (Fig. 2c) were practically the same at baseline and follow-up when comparing HCV^+ and HCV^- patients, with no indication of any group differences. However, univariate Wald *F*-tests for the EQ-5D domains revealed that at baseline, HCV^+ patients were found to carry a significantly higher burden in the EQ-5D subdomains of 'pain/discomfort' ($P < 0.001$) and 'mobility' ($P < 0.01$).

Is antiviral treatment during maintenance treatment among HCV^+ patients associated with increased burden?

Figure 3a–c displays the baseline and follow-up findings for the BSI total score, the proportion of subjects with mental disorders, and quality of life for the 122 HCV^+ patients with an IFN treatment in the observation period and the considerably larger group ($n = 969$) not receiving IFN treatment. With respect to the BSI total score, both subgroups revealed some slight—although statistically insignificant—reduction in the BSI total score.

To inform about the more or less subtle differences in the BSI symptom profile, Fig. 4 provides a comparison of the mean scores for each symptom group and a comparison to HCV^- subjects. It is noteworthy that somatization is increased mainly among those with IFN treatment (not statistically significant, data available on request).

In both groups, however, mental disorders increased (Fig. 3b). This increase was found to be due almost exclusively to significantly higher rates of sleep and depressive disorders in both groups (IFN^+ and IFN^- patients). In patients with IFN treatment, sleep disorder diagnoses increased markedly from 8.2% to 24.6% ($F_{1,55} = 4.8$, $P = 0.033$) and depressive disorders from 39.3% to 48.4% ($F_{1,55} = 2.4$, $P = 0.127$), for HCV^+ patients without IFN treatment, similar rates were found (sleep disorders:

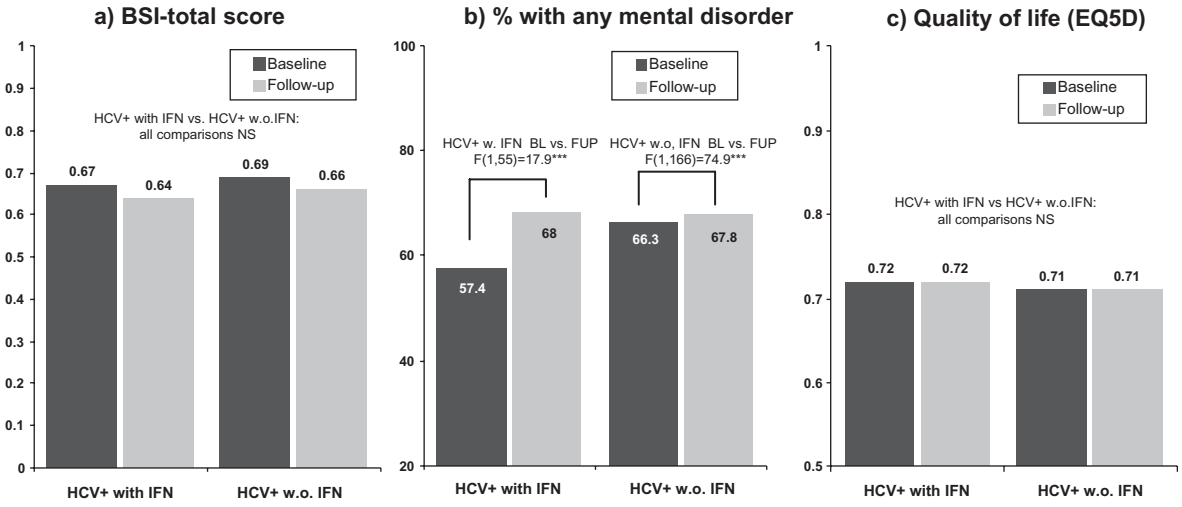

Figure 3 Mean Brief Symptom Inventory (BSI) score, percentage with any clinically significant mental disorder and quality of life among hepatitis C virus (HCV)$^+$ patients with ($n = 122$) and without ($n = 969$) antiviral treatment in the observation period at baseline (BL) and follow-up (FU). Tests for significance were carried out for BSI scores and the EQ5D using the mean difference test; the significance level was set to $P < 0.001$. Rates of mental disorders were tested with the design-based F-test, accounting for clustering of observations within settings. IFN: interferon; NS: not significant

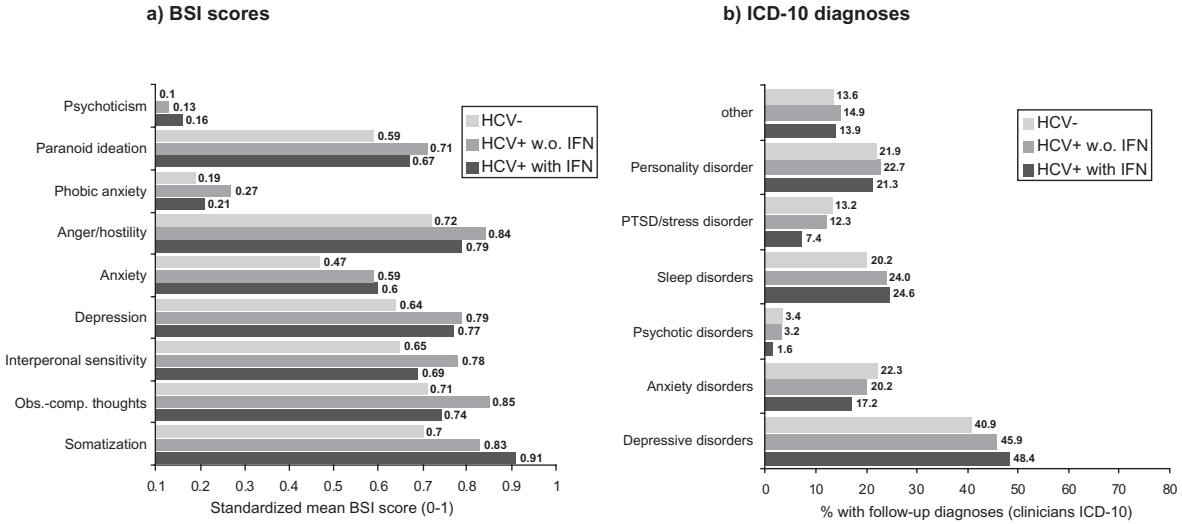

Figure 4 Brief Symptom Inventory (BSI) domain scores (a) and ICD-10 diagnoses (b) among hepatitis C virus (HCV)$^+$ patients with ($n = 122$) and without ($n = 969$) antiviral treatment in the observation period at follow-up compared to HCV$^-$ patients. PTSD: post-traumatic stress disorder; IFN: interferon

13.4% versus 24.0%, $F_{1,17} = 8,4$, $P = 0.010$; depression: 38.8% versus 45.9%, $F_{1,17} = 2.4$, $P = 0.140$).

Thus, we found no evidence in our study that IFN treatment was linked significantly to increased psychopathological symptoms or reduced QOL.

Association between tolerability and success of maintenance treatment with agonists and IFN-based therapy in HCV patients

Table 2 compares patients with and without IFN-based antiviral therapy with regard to treatment problems, such as interruptions of maintenance therapy for any reason, indicators of the treatment process and the degree to which treatment goals were reached. Patients with antiviral therapy for their HCV infection did not show worse results with respect to agonist maintenance therapy. Rates of maintenance therapy interruptions were not significantly different between patients with (8.2%) and without (13.1%) IFN-based antiviral therapy ($F_{1,191} = 2.27$; $P = 0.134$). Doctors' assessments of the course of drug substitution treatment were significantly more favourable in patients with IFN-α therapy. This was due mainly to better tolerability ($F_{1,191} = 8.33$; $P = 0.004$), higher

Table 2 Impact of interferon (IFN) therapy on success and outcome of agonist maintenance therapy (physician ratings).

	Total HCV⁺ (n = 1091)	*IFN⁻ (n = 969)*	*IFN⁺ (n = 122)*	*IFN⁻ versus IFN⁺*
	n/% mean (SD)	*n/% mean (SD)*	*n/% mean (SD)*	*Test statistic*
Interruptions of maintenance therapy				
No therapy interruptions during follow-up period	926/84.9	815/84.1	111/91.0	
At least one interruption during follow-up period	137/12.6	127/13.1	10/8.2	$F_{(1,191)} = 2.27$
Assessment of therapy course				
Adherence	2.51 (0.7)	2.49 (0.7)	2.60 (0.7)	$F_{(1,191)} = 3.81$
Efficacy	2.40 (0.6)	2.38 (0.6)	2.48 (0.6)	$F_{(1,191)} = 3.09$
Tolerability	2.47 (0.5)	2.45 (0.5)	2.60 (0.6)	$F_{(1,191)} = 8.33^{**}$
Patient satisfaction	2.36 (0.6)	2.33 (0.6)	2.50 (0.6)	$F_{(1,191)} = 7.15^{**}$
Compliance/motivation	2.19 (0.7)	2.16 (0.7)	2.40 (0.7)	$F_{(1,191)} = 11.7^{***}$
Achievement of therapy goals				
Formation of motivation/confidence	6.46 (2.1)	6.35 (2.1)	7.22 (1.8)	$F_{(1,191)} = 16.91^{***}$
Drug-free status	3.77 (3.0)	3.74 (3.0)	3.98 (3.1)	$F_{(1,191)} = 0.41$
Planning to start therapy without substitution	4.02 (2.6)	3.99 (2.5)	4.28 (2.9)	$F_{(1,191)} = 0.47$
Social stabilization	6.11 (2.0)	6.00 (2.0)	6.96 (1.8)	$F_{(1,191)} = 21.21^{***}$
Reduction of somatic comorbidity	5.86 (2.2)	5.77 (2.2)	6.42 (2.0)	$F_{(1,191)} = 7.96^{**}$
Reduction of mental comorbidity	5.54 (2.1)	5.50 (2.0)	5.92 (2.2)	$F_{(1,191)} = 3.29$
Reduction of illicit drug use	6.28 (2.5)	6.16 (2.5)	7.07 (2.2)	$F_{(1,191)} = 13.08^{***}$
Abstinence from all illicit drugs	5.48 (3.0)	5.34 (3.0)	6.36 (2.8)	$F_{(1,191)} = 10.92^{**}$
Reduction of legal substance abuse	5.75 (2.6)	5.61 (2.6)	6.71 (2.4)	$F_{(1,191)} = 15.12^{***}$
Reduction of risk behaviour	7.40 (2.1)	7.31 (2.2)	8.03 (1.9)	$F_{(1,191)} = 11.33^{***}$
Reduction of criminal behaviour	7.68 (2.0)	7.63 (2.0)	7.99 (2.2)	$F_{(1,191)} = 6.79^{**}$

$^{**}P < 0.01$, $^{***}P < 0.001$. HCV: hepatitis C virus; SD: standard deviation.

patient satisfaction ($F_{1,191} = 7.15$; $P = 0.008$) and increased therapy motivation ($F_{1,191} = 11.70$; $P < 0.001$) in the subgroup of patients with IFN-based antiviral therapy. Similar results were found regarding therapy goals: in six of 11 subdomains, IFN⁺ patients showed significantly better results than the rest of the study sample (Table 2).

DISCUSSION

The major findings of this naturalistic, prospective longitudinal and nationally representative study in maintenance patients treated with methadone or buprenorphine are as follows.

- Two-thirds of all maintenance patients in the sample were found to be HCV⁺, but only slightly more than 10% received an antiviral treatment during the observation period of 1 year.
- HCV infections are associated significantly, although moderately, with increased psychopathological symptoms as well as reduced QOL both at baseline and at follow-up.
- HCV⁺ patients treated with IFN reveal few indications for increased psychopathological symptom burden or a significantly reduced quality of life different from HCV⁺ patients without IFN treatment. IFN treatment in our study was not associated with impaired tolerability or efficacy of maintenance therapy in the included patient sample.

Strengths and limitations

The strengths of the present study comprise the considerable sample size, the representativeness for routine care, the robustness of the methodological approach and design and the long evaluation period; the multi-method assessment, including structured clinicians' assessments and patient questionnaires, established validity and reliability.

However, there are also several important limitations: despite the fact that we were able to monitor course and outcome for almost all patients, there was also some considerable attrition. Although the differences between those who completed the follow-up assessments and those who did not were minor and are unlikely to influence the findings and conclusions substantially, they are indications that we might have lost more severely ill baseline patients. Secondly, we did not adjust for multiple comparisons in the statistical analyses. Further, we did not distinguish between different antiviral treatment regimens. This proceeding appears justified, however, in

view of previously published data showing that neuropsychiatric side effects are not significantly different between patients treated with standard IFN and pegIFN [42]. To some extent, a further aspect potentially limiting the external validity of our findings might be the fact that we did not examine the course of psychopathology and QOL during IFN treatment. Instead, we examined only at baseline and 1-year follow-up outcome measures among those who had had antiviral treatment at some point during the 12-month period and compared the results to patients without IFN therapy.

Frequency of HCV infections and IFN treatment

Our national study sample indicates overall an HCV infection rate that appears slightly lower than reported in other studies: the observed rate of less than 67% of maintenance patients scoring positive for chronic hepatitis C infection ranges at the lower end of findings from other studies with estimates of more than 90% of drug addicts [8–12]. This might be explained by the fact that we examined only patients with current drug substitution therapy [43], but might also reflect time trends suggesting decreasing rates of intravenous drug use in more recent years. Only 10% of HCV$^+$ patients in our study received IFN-based antiviral therapy. Previous work has shown these rates in more general HCV populations to reach or even exceed 30% [44]. In line with results reported elsewhere [17,45], this finding seems to indicate that there might be still considerable reluctance among maintenance doctors in Germany to offer IFN therapy to addicts, even when they are undergoing stable agonist maintenance treatment.

Effects of HCV infection and IFN treatment on psychopathology and QOL

In contrast to our initial expectation and previously published findings in more general hepatitis C patient populations [2,46], in this prevalence sample we found only quite moderate effects of HCV positivity among maintenance patients on psychopathological burden and QOL. One possible explanation for this finding might be that, in our study, HCV$^+$ effects on psychopathology and quality of life may be clouded by the generally high psychiatric burden of addicts on maintenance therapy [1].

Even more surprising is the finding that IFN therapy did not impair markedly psychopathological syndromes or QOL. This is in contrast with our own [3] and other previous clinical studies [5,13,14]. Similarly, physician-rated efficacy and tolerability of agonist maintenance treatment did not seem to be affected negatively by IFN therapy (Table 2).

However, in view of the comparably low antiviral treatment rate in our sample, it cannot be excluded that this was, to some extent, due to pre-selection bias: substitution doctors may have chosen preferably 'ideal' treatment candidates. Moreover, it has to be considered that our study dropouts had a higher psychopathological burden than the subsample used for follow-up evaluation, which may represent a further confounding factor. Based on the results presented, future research in this context should therefore control prospectively for putative selection bias in the longitudinal analyses (study dropouts, selection criteria for the initiation of antiviral treatment).

To conclude, in HCV$^+$ patients with maintenance and optimized interdisciplinary care, IFN-α-based medication does not seem to affect substitution medication negatively [47], nor is drug maintenance therapy or a history of intravenous drug abuse associated with significantly reduced compliance, adherence or outcome of antiviral therapy in chronic hepatitis C patients [19,20,22,48,49]. Rather, both kinds of therapies might profit from each other—drug substitution treatment as well as antiviral IFN-based therapy in opioid-dependent HCV patients.

Declarations of interest

Connection with tobacco, alcohol, pharmaceutical or the gaming industry: Hans-Ulrich Wittchen has, in the past three years, received research support, consulting fees and/or speakers' honoraria from: Eli Lilly and Co.; Novartis; Pfizer; Schering-Plough. GlaxoSmithKline Pharmaceuticals; Hoffmann-La Roche Pharmaceuticals and Wyeth. Markus Backmund, in the past three years, has received research support, consulting fees and/or speakers' honoraria from: Schering-Plough; Essex Pharma GmbH; Roche Pharma AG, Sanofi-Aventis Deutschland GmbH, Bristol-Myers Squibb. Michael Soyka has worked as a consultant for Sanofi Aventis, Essex Pharma, Alkermes, Lipha, Forrest Lab, and Bayer. Martin Schäfer has received research support, and/or speakers' honoraria from: Pfizer; Astra-Zeneca, UCB, Schering-Plough, Hoffmann La-Roche; Lundbeck; and UCB. Michael R Kraus has received, in the past three years, research support, consulting fees and/or speakers' honoraria from: Schering-Plough (Essex Pharma, Germany). The remaining authors have no conflicts of interest to declare.

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