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Methodological approaches in the assessment of interferon-alfa-induced depression in patients with chronic hepatitis C – a critical review

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Abstract

In recent years, research on interferon (IFN)-induced depressive symptoms in antivirally treated patients suffering from chronic hepatitis C (CHC) has considerably intensified. Profound scientific knowledge of this complication is of great relevance with regard to adherence, compliance, and premature therapy discontinuation.

Presently, there is considerable variability of both, the frequency and extent of IFN-induced depression reported in different cohorts of patients.

The aim of the presented study was to systematically review recent literature of research within this field; and particularly (1) to identify to what extent methodological bias contributed to inconsistent results in different studies, (2) to critically appraise methods and results of studies published so far, and (3) to suggest directions for future work, especially with respect to alternative and improved methodological approaches.

The results of this critical review suggest that the variability of findings seem to be largely due to different study populations, treatment regimens, methodological approaches, and sometimes arbitrary or at least poorly defined choice of screening instruments for depression, particularly criteria for clinically relevant depression (cut-off criteria).

Study designs and methodological approaches to investigate IFN-alfa-induced depression in patients with CHC have been incoherent. Future research in this field needs agreement on the use of standardized assessment of IFN-induced depression in CHC. Furthermore, objective criteria and guidelines for the treatment of IFN-induced depression in these patients are needed in clinical practice. Copyright © 2008 John Wiley & Sons, Ltd.

Key words: interferon, depression, hepatitis C, methodological approaches, psychometric instruments

Introduction

Chronic hepatitis C (CHC) is a common blood-borne viral infection with an estimated world-wide prevalence rate of 2.2% to 3%, i.e. approximately 130 to 170 million infected individuals (Heathcote and Main, 2005; Price and Goyette, 2003). Geographically, hepatitis C virus (HCV) prevalence rates vary widely with comparably low rates in Western Europe (e.g. 0.6% in Germany) and North America (1.8% in the US) and markedly higher rates, e.g. in developing countries (e.g. 4% in Pakistan and 5.3% in Africa) (Shepard et al., 2005). Highest HCV seroprevalence, up to 20% in some areas, has been reported for Egypt (Frank et al., 2000).

Compared with the general population, HCV infection rates are significantly increased in certain risk groups such as persons with mental illness (6–30%) or injection drug users (up to 98%) (Dinwiddie et al., 2003; Diamantis et al., 1997).

The current standard treatment for CHC consists of pegylated interferon (IFN) alfa (given subcutaneously once weekly) in combination with oral ribavirin (given daily). Sustained virological response (SVR) is achieved in 40–80% of patients (Fried et al., 2002; Manns et al., 2001). Despite this considerable success and continuous increase in SVR rates over the last decade due to the introduction of ribavirin and pegylated formulations of IFN alfa, the profile of side effects of IFN alfa-based therapies represents a major problem (Fried et al., 2002; Kraus et al., 2005b; Loftis and Hauser, 2004).

Interferons are a class of cytokines produced by human blood cells which have antiviral, immunomodulatory, and antiproliferative properties. They are associated with a number of adverse effects such as irritability, insomnia, fatigue, and loss of appetite. Furthermore, an influenza-like syndrome associated with IFN alfa therapy is well known (e.g. fever, malaise, chills, anorexia, and myalgias) (Angelino and Treisman, 2005; Loftis and Hauser, 2004; Valentine and Meyers, 2005). Moreover, psychopathological symptoms, especially depression (including suicidal ideation and suicide attempts in some cases), are among the most commonly reported adverse effects of the therapeutic use of IFN alfa that may lead to therapy discontinuation, and, respectively, the additional use of antidepressant or other psychopharmacological drugs (Angelino and Treisman, 2005; Kraus et al., 2003; Loftis and Hauser, 2004; Malek-Ahmadi, 2001; Scalori et al., 2005; Valentine and Meyers, 2005; Zdilar et al., 2000).

Of note, psychopathological symptoms (depression, reduced quality of life) are to some extent associated with HCV infection even in the absence of current IFN-based antiviral therapy, which might be due to e.g. direct HCV neurotoxicity (Foster et al., 1998; Kraus et al., 2000; Golden et al., 2005; Angelino and Treisman, 2005).

During antiviral treatment of CHC, IFN-associated depression may lead to reduced compliance or adherence and even end up in premature termination of IFN therapy, e.g. in the case of acute suicidal ideation (Malek-Ahmadi, 2001).

Reported rates of psychiatric symptoms and particularly depression vary widely across studies. For instance, the reported incidence rates of IFN-induced 'psychiatric side effects' range from 15% to 60% (Musselman et al., 2001; Pariante et al., 1999). There have even been studies reporting no significant association between IFN alfa administration and the occurrence of depressive symptoms (Mulder et al., 2000).

This broad range and enormous variability of results might be due to variation in methodological approaches including the use of assessment instruments for monitoring depression (Loftis and Hauser, 2004). Moreover, the evaluation of psychiatric and particularly depressive symptoms were frequently only a secondary endpoint of scientific studies or a 'by-product' of large licensing studies (Fried et al., 2002; Hadziyannis et al., 2004; Manns et al., 2001; McHutchison et al., 1998). The latter point has only been addressed sporadically in recent literature (Kraus et al., 2003; Loftis and Hauser, 2004).

The aim of this work was to review current information concerning frequency and quality of depressive symptoms in patients with chronic HCV infection and IFN-based antiviral treatment. Specifically, we focussed on evaluation of study methods, in particular assessment instruments and study designs.

Methods

A comprehensive PubMed database search was performed focussing on studies dealing with the assessment of IFN-associated depression or depressive symptoms in chronic HCV infection. The following search keywords were used: depression, interferon, and HCV/hepatitis C. Cytokines other than IFN alfa (e.g. IFN beta, IFN gamma) as well as other diseases (e.g. cancer) are not included in this review.

Studies published since 1990 and up to the year 2006 (up through 31 March 2006) in this field were included with only one exception – an important pilot study published in 1987 (Renault et al., 1987). The focus of the descriptive analysis was aimed at recent work published during the past 5 years, because we intended to update information from previous review studies that were not, however, focussing on methodological approaches (Fried, 2002; Loftis and Hauser, 2004a; Russo and Fried, 2003; Zdilar et al., 2000).

Table 1 provides an overview of the most important (inclusion and exclusion) criteria for the consideration of original articles. IFN-alfa-induced depression had to represent at least a secondary endpoint, and the methodological background needed to be described in detail. In particular, the applied psychometric instruments/depression criteria, choice of instruments, and the study design with respect to the assessment of depressive symptoms or depression had to be explained. Only

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articles published in English were considered. Moreover, studies needed to include a minimum sample size of n = 10 patients, longitudinal study design (repeated measures design: at least one evaluation time point before and one during IFN treatment), and a detailed description of psychometric instruments. Studies presented only in abstracts, letters to the editor, editorials, surveys, or reviews were excluded from this review. The selection process describing the different steps from the first PubMed data base search to the final list of discussed original publications is shown in Figure 1.

Table 1. Consideration criteria for original articles dealing with interferon alfa-induced depression in chronic hepatitis C (pre-selection by literature database search using the keywords: depression, interferon, HCV, and hepatitis C)

Content-related and methodological criteria for the inclusion of original articles (in the article's discussion)
- Interferon alfa-induced /interferon alfa-associated depression as primary or at least secondary study endpoint
- Publishing period between 1990 and 2006 (31 March)
- Articles published in English
- Detailed description of methods and methodological background (psychometric assessment instruments/ depression criteria and study design)
- Sample size of at least 10 patients
- Longitudinal/repeated-measures study design (at least one evaluation time point prior to and one during IFN treatment)

Exclusion criteria
- Patients treated with IFN alfa for diseases other than chronic hepatitis C (e.g. malignant melanoma)
- Patients treated with cytokines other than interferon alfa (e.g. interferon beta, interferon gamma)

The final list of hits was compared with search results from other, already published (review) articles focussing on similar subjects (Zdilar et al., 2000; Angelino and Treisman, 2005; Fried, 2002; Loftis and Hauser, 2004; Russo and Fried, 2003; Valentine and Meyers, 2005). So, publications referenced elsewhere but not identified by the PubMed database query were also included if they fulfilled the remaining inclusion criteria.

The final list of included studies (Table 2) was analysed using descriptive procedures focussing on methodological and design-related parameters such as rating instruments for IFN-related depression, cut-off-scores chosen for clinically relevant depression, and the study design. Although this review does not primarily consider risk factors for IFN-associated depression, some of these shall be discussed later in the context of high variability of reported incidence rates. Finally, the incidence and extent of IFN-associated depressive symptoms were evaluated.

It should be noted that no sophisticated meta-analytical statistical methods are used in this paper, because it would not have been possible to compare results across studies on the basis of techniques of inferential statistics.

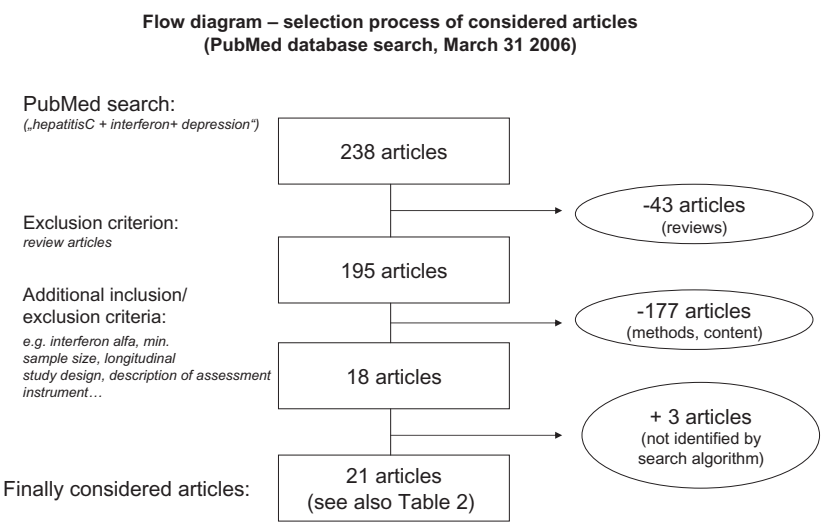

Figure 1. Selection process of finally considered original articles.

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Table 2. Psychometric assessment of depression in patients with CHC receiving antiviral IFN alfa treatment (listing criteria: prospective studies with at least 10 patients, longitudinal approach with at least two time-points, use of well-validated psychometric instruments)

Reference (Authors, publishing year)	*N* (sample size)	Assessment: psychometric instrument(s)	Findings, frequency of IFN-induced depression	Methodological approach	Comments
Renault et al. (1987)	58	SCL-90, interview	17% with neuropsychiatric symptoms, 5% depressive symptoms	Prospective, longitudinal study, psychiatric adverse events as main objective of the study	Heterogeneous study sample ('chronic viral hepatitis'), HCV virus not yet identified in 1987 Monotherapy with standard IFN alfa
Hunt et al. (1997)	26	HADS, BDI	20% of patients with mild IFN-induced depression (moderate to severe: 12%; according to BDI)	Prospective, longitudinal study, psychiatric adverse events as main objective of the study	HCV patients Monotherapy with standard IFN alfa
McHutchison et al. (1998)	912	Doctor assessment Patient reports	Monotherapy: 37% with IFN-induced depression Combination therapy: 36% with IFN-induced depression	Prospective study, licensing trial, assessment of IFN-induced depression not among the main study objectives	HCV patients Monotherapy and combination therapy (IFN + ribavirin)
Malaguarnera et al. (1998)	96	ZSRDS	Significant increase in depression scores; no significant change in untreated controls	Prospective study, psychiatric adverse events as main objective of the study	HCV patients Four groups with IFN monotherapy
Davis et al. (1998)	345	Doctor assessment	Depressed mood in 11% (monotherapy) and 16% (combination therapy), respectively	Prospective study, licensing trial, assessment of IFN-induced depression not among the main study objectives	HCV patients Two groups: IFN + ribavirin versus IFN + placebo
Miyaoka et al. (1999)	66	HAM-D DSM-III R	44% cumulative depression rate (period of 6 months) with respect to newly developed depression	Prospective, longitudinal study, assessment of psychiatric side effects as main study goal	HCV patients IFN alfa monotherapy
Pariante et al. (1999)	50	DSM-III R SCID	20% with mild to severe depression	Prospective study, descriptive assessment of psychiatric side effects not major study objective	HCV patients IFN alfa monotherapy

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Table 2. *Continued*

Reference (Authors, publishing year)	*N* (sample size)	Assessment: psychometric instrument(s)	Findings, frequency of IFN-induced depression	Methodological approach	Comments
Scalori et al. (2000)	67	MMPI research interview	24.1% depressed after 3 months of IFN therapy	Prospective study, prediction of IFN-induced depression as major study aim	Patients with viral chronic active liver disease (heterogeneous study sample)
Mulder et al. (2000)	63	SCL-90 R SCID	No new diagnosis of MDD during IFN-treatment, no suicide (attempt)	Prospective, longitudinal study; assessment of psychiatric symptoms as primary study aim	Patients with CHC IFN alfa monotherapy
Bernstein et al. (2002)	448	BDI	33.7% of patients with mild to severe IFN-induced depression	Pooled secondary analysis of $n = 1441$ HCV patients Depression assessment no major study goal	HCV patients Combination therapy with peginterferon alfa and ribavirin
Hauser et al. (2002)	39	BDI SCID	33% with newly developed MDD during IFN therapy	Prospective, longitudinal study. Treatment of IFN-induced depression as major study objective	HCV patients Combination therapy with standard IFN alfa and ribavirin
Bonaccorso et al. (2002)	30	MADRS DSM-IV citeria	Statistically significant increase in depression scores; 40.7% with MDD on interferon therapy	Prospective, longitudinal study	HCV patients IFN alfa monotherapy
Castera et al. (2002)	33	MADRS DSM-III-R citeria	Significant increase in MADRS scores after 12 weeks, 24% developed depressive symptoms (MDD: 12%)	Prospective longitudinal study, letter, data not completely new at publication date	HCV patients IFN alfa monotherapy
Kraus et al. (2003)	104	HADS SCL-90 research interview	Significant increases in depression and anger/hostility; cumulative frequency (depression, anxiety, or anger/hostility) 57.7% as compared with 22.5% before therapy	Prospective longitudinal study design; assessment of depression as primary study objective	HCV patients Treatment with standard IFN alfa (+/−ribavirin) Reference group ($n = 20$) without interferon treatment
Horikawa et al. (2003)	99	HAM-D SCID DSM-IV criteria	Major depressive disorder occurred in 23.2% of patients (during IFN therapy)	Prospective, longitudinal study – designed to assess IFN-induced depression and predictive factors	HCV patients IFN alfa monotherapy

Schäfer et al. (2003)	81	DSM-IV criteria	Major depressive disorder newly occurred in 16% of patients; total MDD rate on IFN treatment: 25.9%	Prospective, longitudinal study – designed to assess adherence and IFN-induced mental side effects	HCV patients Combination with standard IFN alfa and ribavirin
Kraus et al. (2005b)	98	HADS SCL-90	No significant difference between subgroups with pegylated/standard interferon (33.3–40% with clinically relevant depression)	Prospective, longitudinal study design; comparison of standard and pegylated IFN formulations	HCV patients Combination therapy with (peg-) interferon and ribavirin
Wichers et al. (2005)	16	DSM-IV criteria MADRS	Significant increase in depression scores (maximum at week eight of treatment)	Prospective, longitudinal study design; assessment of risk factors for IFN-induced depression	HCV patients Combination therapy with (peg-) interferon and ribavirin
Reichenberg et al. (2005)	50	CES-D	'Possible MDD' in 82% of IFN-treated HCV patients	Prospective longitudinal study; assessment of both IFN-induced depression and cognitive impairment	HCV patients Combination therapy with peginterferon and ribavirin
Scalori et al. (2005)	185	MMPI/(depression scale)	17% of patients with IFN-induced 'psychiatric disorder'	Prospective longitudinal study design; test of suitability of MMPI, evaluation of efficacy of antidepressant treatment	HCV patients Combination treatment with standard IFN alfa and ribavirin
Dan et al. (2006)	271	CES-D SF-36 CLDQ	Statistically significant increase in CES-D scores (no rates given concerning clinically relevant depression)	Prospective longitudinal study, main target variables: HRQL (SF-36), disease-specific symptoms and depression	HCV patients Combination therapy with pegylated IFN alfa and ribavirin

Note: BDI, Beck Depression Inventory; CES-D, Centre for Epidemiologic Studies' Depression Scale; CHC, chronic hepatitis C; CLDQ, Chronic Liver Disease Questionnaire; DSM-III-R and DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, revised third edition and fourth edition, respectively; HADS, Hospital Anxiety and Depression Scale; HAM-D, Hamilton Rating Scale for Depression; HCV, Hepatitis C virus, IFN, interferon; MADRS, Montgomery–Asberg Depression Rating Scale; MDD, major depressive disorder (DSM-IV criteria); MMPI, Minnesota Multiphasic Personality Inventory; SCID, structured interview for DSM-III-R; SCL-90 R, Symptom Checklist 90 Items revised; SF-36, Short-form 36 Health Survey; ZSRDS, Zung Self-rating Depressive Scale.

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Results

Results from the literature database research

Figure 2 gives an overview of the current number of references provided by the PubMed/Medline database search depending on the respective choice of keywords. Beyond these absolute current numbers, Figure 3 additionally demonstrates that there has been an exponential increase in publications on the subject of IFN-associated depression in HCV (Figure 3a). The database search revealed that the number of papers published in this field of research has risen over the last decade to an enormous amount (1086 hits in total for 'interferon + depression', Figure 3b). Even when a narrower definition of the subject ('interferon + depression + hepatitis C') was used, there were still a total of 195 papers (including 43 reviews) selected by the search algorithm, representing the starting point for the subsequent article selection (Figures 1, 2 and 3a).

However, only a small fraction of the articles could be used for a more thorough descriptive analysis. As we intended to systematically compare scientific approaches across studies, we had to exclude all papers that did not provide the necessary background information or did not meet the previously defined methodological standards (see earlier). Thereby, we finally reduced the list to 21 original papers dealing with the assessment (and quantification) of IFN-induced depression in CHC in Table 2.

IFN alfa and depression in patients with CHC – prevalence, phenomenology, and clinical presentation

There is agreement that the administration of IFN alfa leads to 'IFN-induced depression' in a significant portion of antivirally treated HCV patients. The strength of this association is, however, not clear, and rates of IFN-induced depression range from 0% (Mulder et al., 2000) to more than 40% (Bonaccorso et al., 2002; Kraus et al., 2005b; Kraus et al., 2003; Loftis and Hauser, 2004; Valentine and Meyers, 2005), with some reported depression rates even markedly exceeding 50% of all treated patients (Reichenberg et al., 2005). Table 2 lists important studies dealing with the assessment of IFN-induced depression, demonstrating the earlier mentioned wide variability of reported incidence rates (column 'findings').

There is also agreement that IFN-induced symptoms are – according to the vast majority of studies – transient and reversible shortly after termination of IFN therapy (Kraus et al., 2005b; Kraus et al., 2003).

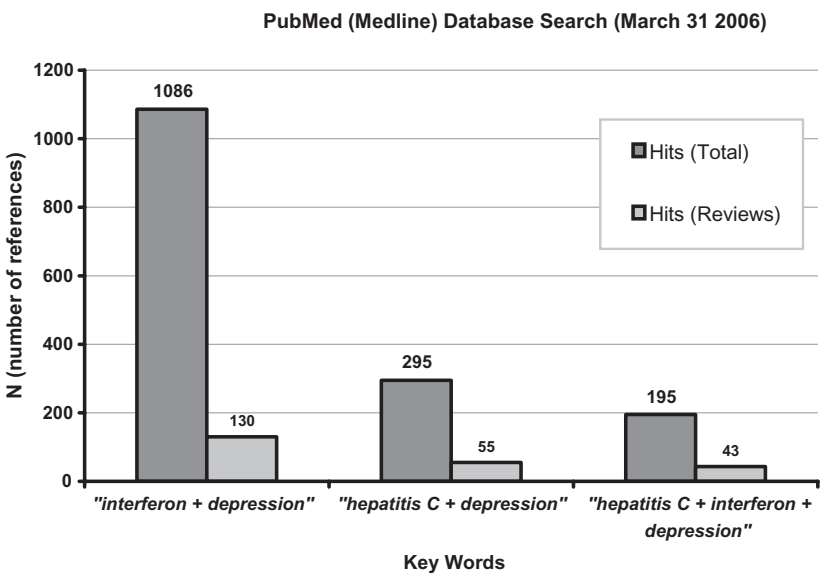

Figure 2. Results from the PubMed/Medline database searches – absolute number of provided hits depending on the included keywords [first study identified by 'hepatitis C + interferon + depression' (right column) was published in 1991; deadline: 31 March 2006].

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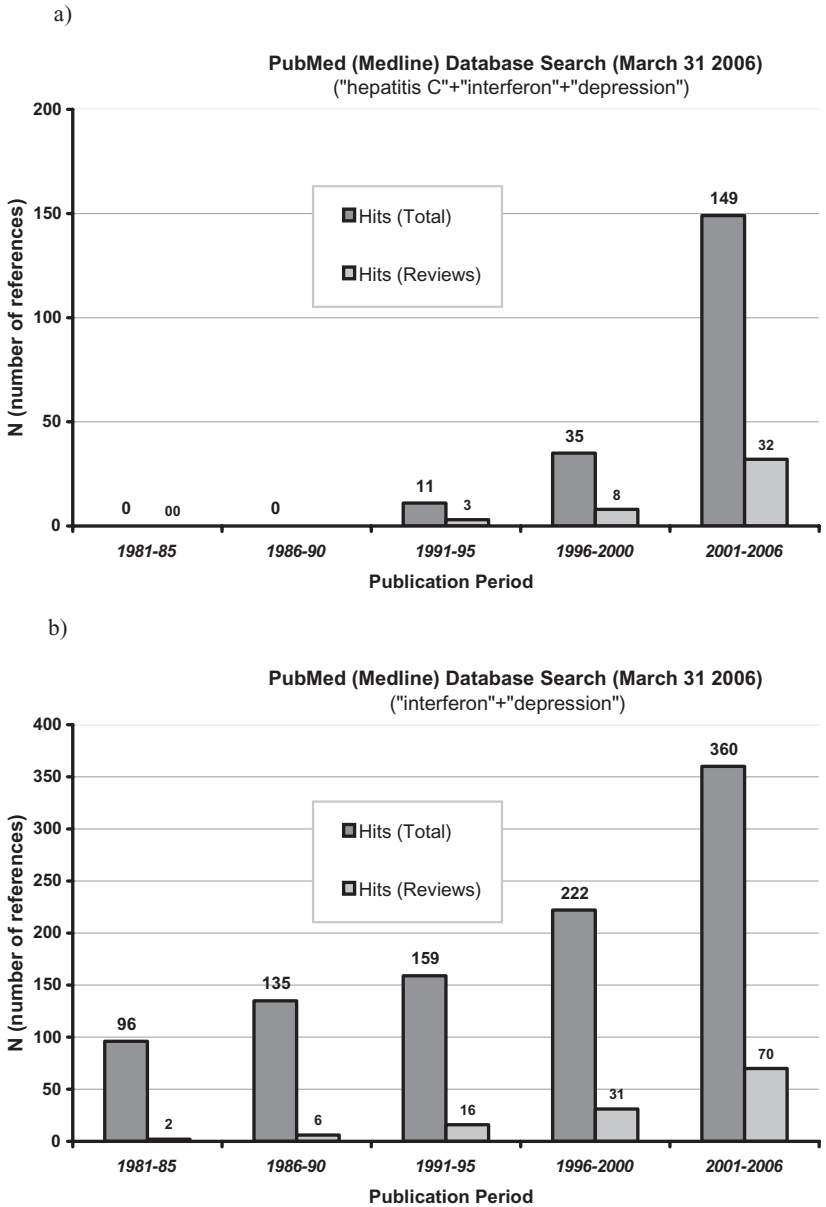

Figure 3. Results from the PubMed/Medline database searches – absolute number of yielded hits depending on the included keywords and the publishing date (deadline: 31 March 2006).

Reports of exceptions are rare and refer to single cases of persisting or worsening of depression. Even suicide attempts following withdrawal from IFN alfa therapy have been reported (Janssen et al., 1994; Rifflet et al., 1998; Nickel et al., 2005). As far as timing and time course of IFN-induced depression is concerned, many authors state that neurovegetative symptoms (e.g. fatigue, psychomotor slowing, changes in sleep and appetite) tend to occur early in treatment and persist, whereas more depression-specific symptoms (e.g. loss of interest or pleasure, depressed mood) develop markedly later during therapy (Capuron et al., 2002; Wichers et al., 2005). However, this cannot be considered a general rule, because there is increasing evidence that

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IFN-induced depression may also occur early, already after 4 weeks of antiviral treatment in some cases (Kraus et al., 2003; Miyaoka et al, 1999).

Several authors also report the induction of manic symptoms by IFN alfa administration (Constant et al., 2005). As irritability is a common adverse neuropsychiatric effect of IFN alfa (Kraus et al., 2003; Raison et al., 2005a), it is not too surprising that several studies confirm that IFN alfa also has the potential of inducing mania (Constant et al., 2005; Strite et al., 1997).

High variability of reported rates of IFN-induced depression – confounding factors

Reported incidence rates of IFN-induced depression vary widely across studies. This variability might be due to various confounding factors.

First, there is increasing evidence, that incidence and extent of IFN-induced depression are both significantly affected by dose and duration of IFN therapy. Generally, the risk of IFN-induced depression increases with higher doses and longer duration of therapy (Valentine and Meyers, 2005).

Second, the identification of (pre-therapeutic) risk factors of IFN-induced depression has been so far inconclusive and partially contradictory. Nevertheless, data from several studies suggest that the presence and severity of depressive symptoms at the onset of antiviral treatment are of predictive value for the subsequent development of mood disorders (Capuron and Ravaud, 1999; Dieperink et al., 2003; Hauser et al., 2002; Raison et al., 2005b). Therefore, one may speculate that studies with varying incidences of pre-therapeutic depression produce different outcomes with respect to therapy-associated depressive symptoms.

Third, another source of variation across studies may be represented by variably composed study samples (e.g. different proportions of former intravenous drug abusers; varying comorbidities; differences in age, gender and stage of liver disease; differently composed samples with respect to body weight and genetic vulnerabilities to developing [IFN-induced] depression) as well as different regimens (IFN monotherapy versus. combination therapy with ribavirin, standard versus pegylated formulations of IFN alfa). However, as mentioned earlier, we do not expect the latter point to exert a pronounced impact on the incidence or extent of IFN-associated depression in HCV patients (Kraus et al., 2005b; Loftis and Hauser, 2004).

Finally, different methodological approaches of assessing IFN-induced neuropsychiatric side-effects may be responsible for varying results in incidence rates and severity of IFN-induced depression. These approaches refer to, e.g. the choice of applied psychometric instruments and study design and will be discussed in detail in the next section.

Different methodological approaches for the assessment of IFN-induced depression and their potential impact on observed incidence rates

Study design

Rates of IFN alfa-induced depression are usually higher in studies that examine mood disorders and corresponding psychopathological symptoms as a primary study endpoint (Table 2: Reichenberg et al., 2005; Bonaccorso et al., 2002). These studies are usually based on prospective study designs and use depression-specific psychometric instruments. Depression is evaluated as a complex syndrome (including neurovegetative symptoms) and/or depression-specific screening instruments are exploited (Bonaccorso et al., 2002; Kraus et al., 2005b; Kraus et al., 2003; Reichenberg et al., 2005).

In contrast, rates are lower in studies that assessed depression rates retrospectively – especially if the evaluation represents only a part or 'by-product' of a general screening for IFN-induced adverse events (Raison et al., 2005a). This may in part explain the comparably low depression rates reported in early studies in which depression was defined as a single symptom based on patient self-reports during a broad screening for IFN-associated side effects (see Table 2: Davis et al., 1989; McHutchison et al., 1998; Renault et al., 1987).

Interestingly, observed rates of IFN-linked depression appear higher in more recent studies – even when depression represents only a minor aspect of the general screening for adverse events. This tendency may reflect the currently more pronounced awareness of the depression risk in this patient population (Davis et al., 1998; Fried et al., 2002; Hadziyannis et al., 2004, Manns et al., 2001). It should be noted as well in this context that the effects of less pronounced awareness and the use of categorical approaches might be associated to some extent in older studies.

To summarize, there are four main factors that lead to higher observed depression rates: depression as the main study focus, a prospective study design,

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depression-specific psychometric instruments, and, finally, the increasing awareness in recent years with respect to the problem of IFN-induced depression.

Definition of depression – categorical versus symptomatical approaches

Another important consideration in the assessment of IFN-induced depression is its exact definition.

There are different forms of operationalizations of IFN-induced 'depression' in the studies reviewed (Table 2). Basically, we have to distinguish between categorical approaches [e.g. the multidimensional DSM-IV (Table 3) criteria with a possible dichotomous diagnosis of major depressive disorder (MDD) or, e.g. non-standardized doctor-assessments] on the one hand and, on the other hand, symptomatical (scale-based) approaches as far as assessing the extent of depressive symptoms. In parallel, there are self-assessment questionnaires (continuous depression scales) that provide additional cut-off scores for MDD diagnosis (e.g. Zung Self-rating Depressive Scale, ZSRDS; Beck Depressive Inventory, BDI) – this combinatory consideration is, however, only of minor importance in the present review.

From the listed studies in Table 2, we can derive that 'earlier studies' (Renault et al., 1987; McHutchison et al., 1998) more frequently and primarily relied on categorical approaches such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (Table 3) or doctor-assessments. Most studies published thereafter – the vast majority (15 of 21) of the listed studies – included at least one psychometric instrument assessing the extent of depressive symptomatology.

Usually, observed incidence rates are lower when a categorical approach (strict DSM criteria for MDD) is chosen (Castera et al., 2002): for example, there are patients that develop clinically meaningful depressive symptoms according to self-assessment questionnaires without meeting the full DSM-IV criteria for major depression (Capuron et al., 2002). The discrepancy between the described approaches becomes obvious for instance in the study by Castera et al. (2002) with incidence rates of 24% [Montgomery–Asberg Depressive Rating Scale (MADRS) scores] versus 12% (MDD according to DSM-III-R criteria).

Consequently, one can conclude that studies using MDD as the main or exclusive criterion for the occurrence of IFN-induced depression may under-estimate clinically relevant depressive symptoms linked to antiviral treatment in CHC (e.g. Horikawa et al., 2003).

Table 3. Criteria for MDD according to DSM-IV (APA, 2000)

Depressed mood and/or loss of interest or pleasure in usual activities
At least five of the following symptoms have to be present for at least two weeks:
– a sad mood for most of the day/most days
– loss of pleasure or interest in usual activities
– sleeping problems
– fatigue
– psychomotor retardation or agitation
– reduced appetite with weight loss (or the converse)
– a negative self-image
– complaints or evidence of difficulty in concentrating (e.g. slowed thinking, indecisiveness)
– recurrent thoughts of death or suicide

Association between varying depression rates and types of psychometric instruments: self-report questionnaires versus clinical rating lists, clinical diagnostic interviews, and other interviews

The studies listed in Table 2 have included written self-report measures, clinical ratings or clinical interviews, or a combination of these approaches. The majority of the cited studies (14 of 21) have included at least one self-report questionnaire. Strengths of these written self-rating scales [e.g. Hospital Anxiety and Depression Scale (HADS), Zigmond and Snaith, 1983; ZSRDS, Zung et al., 1965; Zung et al., 1967a; Zung et al., 1967b; BDI, Beck et al., 1961; Beck et al., 1972; Centre for Epidemiologic Studies' Depression Scale (CES-D), Radloff, 1977] include ease of administration which is important for screening purposes, facilitation of scoring (also by individuals without extensive training), and time-saving administration. Concerning study results, self-rating scales are usually suitable for use in a repeated measure design, and helpful assessing the extent of depressive symptoms – as opposed to diagnostic criteria or categories. However, there are also limitations of written self-report measures such as questionnaires. First, they assess and quantitate depressive symptomatology but they are not able to provide valid diagnoses. Moreover, these instruments are limited by a lack of clear criteria and a tendency towards 'over-diagnosis', i.e. a potentially high percentage of false positive results. Consequently, studies reporting the

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highest depression rates were largely based on written self-report scales (Table 2: e.g. Kraus et al., 2003; Kraus et al., 2005b; Reichenberg et al., 2005).

Association between varying depression rates and the choice of specific self-report questionnaires – the role of specific item pools

Table 2 demonstrates that numerous self-assessment instruments have been used to assess depression during IFN treatment in CHC. It should be noted, however, that none of these instruments (see earlier) has been designed or validated for the use in this special context (HCV patients on antiviral IFN-based therapy). Therefore, in many cases, the choice of applied questionnaires appears arbitrary to some extent – at least, the basis of specific choice has not always been well explained or made transparent.

It is not possible to retrospectively and reliably determine the exact influence of the instruments used (characterized by their respective item pools) on the measured incidence of depression in the cited studies. This would only be possible by prospectively applying different questionnaires (to be compared) within the same study. Nevertheless, we can assume that varying incidence rates across studies may be to some extent due to this variable. Further support for this assumption has been provided by Dieperink et al. (2003) who found intercorrelations between neuropsychiatric measures (e.g. BDI, HAM-D, and ZDSRDS scores) that ranged from r = 0.41 to r = 0.96 before and during IFN alfa treatment. Although the mean overall intercorrelation between different psychometric instruments was high, these findings identify different measures as a putative source of variation with respect to incidence rates of IFN-induced depression.

As with other chronic diseases (e.g. cancer: Trask, 2004), there are specific difficulties in assessing depressive symptoms in the population of patients with chronic HCV infection and IFN therapy. Symptoms of depression are frequently similar to those of the physical illness itself [here: HCV infection, chronic liver disease (Foster et al., 1998; Forton et al., 2006)] or its treatments (here: IFN alfa). Examples for the specific symptoms 'needed' for the diagnosis of depression [e.g. major depression according to DSM-IV criteria (APA, 2000; see also Table 3)] and potentially produced by HCV infection or cytokine administration are: fatigue, weight loss, anhedonia, and psychomotor slowing (neurovegetative symptoms). Additionally, there are IFN-induced adverse events that may overlap with depressive symptoms, such as the development of hypothyroidism that occurs in approximately 12% of IFN-treated HCV patients (Dalgard et al., 2002). The vast majority of studies assessing IFN-induced depression did not, however, address this important methodological issue (Table 2).

One possible approach to deal with this issue consists in including all symptoms (questionnaire items) that usually characterize a depressive disorder (i.e. including neurovegetative symptoms). This 'inclusive' approach has often been used in the assessment of IFN-induced depression (BDI, ZSRDS, CES-D) – with the tendency to over diagnose depression. This is mainly due to the lack of discrimination with respect to the aetiology of the assessed symptoms. A second strategy is to eliminate aetiologically ambiguous symptoms, especially fatigue and weight changes. This is realized, for example, with the use of the HADS (Zigmond and Snaith, 1983), which explicitly excludes somatic or neurovegetative symptoms from the depression subscale. Studies using this instrument (see Table 2: Hunt et al., 1997; Kraus et al., 2005b; Kraus et al., 2003), however, may suffer from the opposite problem of decreased sensitivity but higher specificity (with an increased likelihood of false negatives).

Summary, conclusions, and recommendations

It is widely accepted that therapeutic administration of IFN alfa induces numerous adverse events, including depression and other neuropsychiatric symptoms, cognitive decline as well as fatigue (Angelino and Treisman, 2005; Loftis and Hauser, 2004; Valentine and Meyers, 2005, see also Table 4). Attempted or even successful suicides may occur during IFN alfa therapy. However, the incidence seems to be very low, perhaps not even higher than in untreated patients with CHC or other severe chronic diseases such as cancer (Fattovich et al., 1996; Jonasch et al., 2000; Loftis and Hauser, 2004).

These side effects are attributable to direct or indirect central nervous system (CNS) toxicity. However, results indicating an absence (Mulder et al., 2000) of IFN-induced depression during antiviral HCV treatment or setting the focus on manic (Constant et al., 2005) rather than depressive symptoms have been reported – they represent, however, rare exceptions.

Due to the high variability of IFN-induced depression rates reported across studies, it has become necessary to deliver a systematic overview of methodological

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Table 4. Frequently observed adverse events of peginterferon alfa-2a/b and ribavirin compared with conventional interferon alfa-2b in combination with ribavirin

Reported symptoms	Peginterferon alfa-2a and ribavirin (%) Fried et al. (2002)	Peginterferon alfa-2b and ribavirin (%) Manns et al. (2001)	Peginterferon alfa-2a and ribavirin (%) Hadziyannis et al. (2004)[1]	Interferon alfa-2b and ribavirin (%) Fried et al. (2002)	Interferon alfa-2b and ribavirin (%) Manns et al. (2001)
Fatigue	54	64	48	55	60
Headache	47	62	51	52	58
Pyrexia	43	46	41	56	33
Myalgia	42	56	42	50	50
Rigors	24	48	28	35	41
Insomnia	37	40	35	39	41
Nausea	29	43	32	33	33
Alopecia	28	36	26	34	32
Irritability	24	35	27	28	34
Arthralgia	27	34	26	25	28
Anorexia	21	32	n.a.	22	27
Depression[2]	22	31	21	30	34

[1] Averaged percentages from four treatment subgroups.
[2] Depression assessment: doctors' ratings.

approaches to the assessment of depression linked to cytokine administration. We have tried to accomplish this task by performing literature database searches and by analysing the respective results. Apart from the results of different methodological approaches across studies, our study demonstrated that the issue of IFN-induced depression, especially in CHC, is well recognized and of high scientific interest (see the increase in database search hits over the past years, Figure 3).

Treatment regimens and IFN formulations have changed over the last decade; it is, in our view, however, valid and justified to include studies in this review dealing with both standard and pegylated IFN alfa. Although current pegylated IFN formulations have generally been associated with a more favourable profile of adverse effects (less risk of severe neuropsychiatric side effects) (Rasenack et al., 2003; Valentine and Meyers, 2005), it is apparent that side effects of depression persist (Kraus et al., 2005b; Loftis and Hauser, 2004) and occur in at least 20% of HCV patients receiving treatment with pegylated IFN (Bernstein et al., 2002; Fried et al., 2002; Kraus et al., 2005b; Loftis and Hauser, 2004; Reichenberg et al., 2005). Moreover, clinical experience demonstrates that therapy-induced depression still remains a major problem with the potential danger of therapy discontinuation.

For reasons of conciseness and clarity we did not explicitly list and systematically evaluate the effects of cytokines other than IFN alfa (e.g. IFN-beta, IFN-gamma). Moreover, IFN treatment regimens in other chronic diseases [e.g. malignant melanoma (Musselman et al., 2001; Trask et al., 2004) or multiple sclerosis (Goeb et al., 2005)] were not assessed. However, the authors are aware that studies dealing with different chronic diseases and treatment regimens may contribute to a better general understanding of the side effect profiles produced by cytokine administration.

Important scientific work dealing with the assessment of depression in the medically ill has largely been performed in cancer patients (Trask et al., 2004). There are several results and conclusions that may serve as orientation for the assessment and management of IFN-induced depressive symptoms in HCV patients (e.g. shortcomings of screening instruments). Major research has focused on the identification of optimal cut-off scores for depression in chronic diseases, e.g. in cancer patients (Trask, 2004). The majority of these studies have used the HADS questionnaire in order to identify optimal cut-off scores. Unfortunately, reported results vary widely, and therefore an optimal or optimized cut-off value for patients with chronic diseases cannot be easily transferred to patients with CHC and IFN alfa therapy.

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One has to be aware of the specific issues linked to antiviral treatment in HCV patients: the temporary nature of IFN treatment and priority of not terminating therapy prematurely. Over diagnosis and a higher rate of false positives with respect to MDD would be regarded as minor issues – as opposed to the situation in cancer patients. Regarding the excellent treatment options (Asnis et al., 2005; Kraus et al., 2005a; Kraus et al., 2002; Kraus et al., 2001) of IFN-induced depression, one should aim to reduce 'false negatives' when balancing sensitivity and specificity, which would generally result in lower cut-off scores, regardless of the psychometric instrument used.

In longitudinal studies published up to now, baseline evaluations usually represent a significant part of the produced data (Table 2). However, the term 'baseline' or 'baseline evaluation' has frequently not been clearly defined or standardized. Therefore, there may be many sources for confounding effects such as current patient situation at study entry (e.g. prior therapy failures, motivation for therapy), interval until start of antiviral treatment (days, weeks, or even months before IFN administration). In addition, a close follow-up of long-term treatment of genotype 1 patients has been neglected so far: According to our clinical experience, weeks 24 to 48 are particularly critical with respect to both frequency and extent of neuropsychiatric side-effects.

Moreover, IFN alfa is known to produce thyroid dysfunction in approximately 12% of patients (Dalgard et al., 2002). Consequently, a thorough evaluation of thyroid function should be carried out, if IFN-induced depressive symptoms are detected because the association of hypothyroidism and depression is well known (Dalgard et al., 2002), and both entities display a similar time course of symptoms during antiviral HCV treatment. Of note, however, there is no strict causal relationship between changes in thyroid function and increased depression (Loftis et al., 2004).

Prediction models of IFN-induced depression have been inconclusive so far and therefore unsatisfactory – at present, there are still no pretherapeutic parameters available that reliably predict cytokine-linked depressive symptoms during antiviral treatment of CHC. The only exception is the predictive value of pre-therapeutic depression scores reported in several studies (Loftis and Hauser, 2004). In addition to continuing to search for suitable predictive parameters, one should also focus on the target variable to be predicted: in optimizing the methodological standards of depression assessment in antiviral IFN-based therapy, one may potentially contribute to the improvement of such prediction models that are without any doubt urgently needed.

Finally, we would like to turn to future research regarding the optimization and standardization of depression assessment in the antiviral treatment of CHC.

Certainly, we will need studies that refine diagnostic criteria for depression especially in HCV patients with IFN alfa treatment. Studies examining which symptoms of depression are most frequently seen in HCV patients on antiviral therapy are needed. This goal may be realized by the combination of inclusive and exclusive study approaches as well as the inclusion of both patient self reports and expert ratings.

Based on the result of such research, a step beyond could consist in developing and validating an IFN-specific depression instrument for HCV patients with clearly defined cut-off scores for clinically relevant depression, e.g. indicating the need of selective serotonin reuptake inhibitor (SSRI) intervention. This new combination of subsets of already existing instruments (or newly developed items) should meet the necessary criteria for clinical practice and routine care such as quick and easy administration, few-item structure and easy evaluation, also for non-psychiatrists or non-psychologists.

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