Hepatitis C, interferon alpha and psychiatric co-morbidity in intravenous drug users (IVDU) : Guidelines for clinical practice

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Abstract

The evidence regarding the co-morbidity of chronic hepatitis C, psychiatric illness and intravenous drug abuse is reviewed from the literature. Also the occurrence and the treatment of psychiatric side effects during treatment with interferon in patients with a history of drug abuse are reviewed.

There is insufficient evidence for a specific hepatitis C induced depression or fatigue, but a direct link between hepatitis C and cerebral dysfunction is not excluded. Immune system activation rather than drug use may explain cerebral symptoms. In HCV positive substance users anxiety and depression are more prevalent than in HCV negative substance users.

During treatment with regular or pegylated (PEG) interferon depression is a frequent side effect (ca 30%) and occurs independently from pre-existing psychiatric disorders or drug abuse. A history of drug abuse per se does not increase the risk of depression as a side effect of interferon treatment. It is extremely important to monitor symptoms of depression in the early weeks of treatment and to start antidepressant treatment as early as possible. Antidepressants should be continued throughout the interferon treatment period.

There are insufficient data to assess these situations in which preventive antidepressant treatment should be started before interferon treatment. Clinical judgement can, however, lead to preventive antidepressant treatment, even at subclinical levels of depression. A cut off score of > 10 on the Beck Depression Inventory before interferon treatment is associated with a higher risk of depression during treatment.

Both selective serotonin reuptake inhibitors and other classes of antidepressants can be used. (Acta gastroenterol. belg., **2005**, 68, **68-80**).

Key words : hepatitis C, interferon, therapy, psychiatry, co morbidity, depression, intravenous drug abuse.

1. Introduction

A wide range of neuropsychiatric problems that may develop in patients with hepatitis (B and) C during treatment with interferon have been described in the last two decades. Several reviews on the topic have been published in recent years (1). Most commonly depression and neuropsychological problems are noted. Also mania and psychosis have been mentioned, but to a far lesser extent.

In most reports, no separate analyses have been made that mention the development of psychiatric symptoms in drug using and non drug using patients. Therefore there is a lack of evidence regarding the occurrence of psychiatric complications in this specific subgroup, whether they use methadone, or whether they are still actively injecting drugs. They constitute, however, a very important subgroup of all patients diagnosed with and treated for chronic hepatitis C, as safety measures have limited the risk of being infected with hepatitis C through blood transfusions, the main route of infection in earlier years (2). We need data about this subgroup as quite often treatment is denied (in up to 70% of HCV + patients) because of (not always evidence based) concerns about e.g. lack of compliance, psychiatric contra-indications, ongoing substance abuse, side effects or re-infection (3-9).

2. Materials and methods

We will **first** review the evidence regarding the co-morbidity of hepatitis C, intravenous drug use (IVDU) and psychiatric symptoms on the basis of a literature search performed on Medline by using the key words hepatitis C, psychiatry, interferon, depression and intravenous drug abuse. From the studies identified in this way further references were used to identify other relevant studies.

We will **also** look at the occurrence of neuropsychiatric symptoms and behavioural problems in drug using patients treated with interferon alpha for hepatitis C, as far as the data allow us to do so.

As there are only few randomised controlled trials that compare the occurrence and the treatment of neuropsychiatric side effects in chronic hepatitis C patients with or without a history of IVDU, all relevant studies were included, even if patient populations were not clearly defined.

We will **then** conclude by formulating some preliminary guidelines regarding the treatment of this specific population.

3. Results

3.1. *The co-morbidity of Hepatitis C, IVDU and psychiatric symptoms*

3.1.1. Hepatitis C and IVDU

Chronic hepatitis C is more common in IVDU than in the general population. Prevalence figures in this

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population vary, but are always significantly higher (46, 9%-90%) than the prevalence in the general population (0, 87%-2, 4%) (10-12). They are similar in Belgium and in other countries. For a review see Matheï *et al.*. in this issue.

3.1.2. IVDU and psychiatric co-morbidity

In general there is a directional discrimination to make in what is called 'dual diagnosis' (the co-occurrence of mental illness and substance abuse). Substance abuse is quite common in psychiatric patients, but psychiatric problems are less common in substance abusers (13).

Merikangas *et al.* (14) point out that the relationship between substance abuse and psychiatric problems may be causal in both directions, and they suggest a shared vulnerability model. More severe problems going from substance use over substance problems to substance dependence are associated with more severe psychopathology.

Most prevalent (more than depression and anxiety) in the population with substance use disorders are personality disorders. This finding is relevant as was shown by Brooner *et al.* (15-16) who found that intravenous drug users with an antisocial personality disorder shared more needles with more different partners, a risk behaviour for getting (re)infected with hepatitis C. For a summary of the prevalence of the different psychiatric disorders see Table 1 (ref 16-22).

It is also necessary to point out that many intravenous drug users use not only opiates, but several other substances (sedatives, cocaine, alcohol, cannabis …). As these other substance disorders were often seen as exclusion criteria for clinical trials in chronic hepatitis C the results of these trials can not be generalised (23).

3.1.3. Untreated hepatitis C and psychiatric co-morbidity

Johnson *et al.* (24) found more pre-existing depression in drug using patients who were HCV positive than in drug using patients who were HCV negative. Grassi *et al.* (25) found their IVDU hepatitis C patients more anxious than non-infected IVDU. El Sarag *et al.* (26) found all lifetime psychiatric diagnoses including alcohol and drug use to be far more common in hepatitis C positive veterans than in hepatitis C negative veterans.

Depression may exist as a secondary phenomenon (reactive depression due to concerns over one's health status) or may be linked with the well known high rate of depression (and personality disorders) in patients using drugs intravenously.

Wessely *et al.* (27) reviewed the literature on the association between untreated hepatitis C and fatigue and depression. In contrast to many other authors they state that this association is only seen in patients who are aware of their HCV status, those with advanced liver disease and those seen in specialist referral centres. They believe that 'atypical' risk factors such as lack of exercise, demographics and the presence of metabolic and mood disorders exist in hepatitis C as in other physical illnesses and that there is no evidence for a specific hepatitis C depression or fatigue.

There is however some evidence for a direct link between hepatitis C and cerebral dysfunction (28). Forton (29-30) studied the brains of patients with mild hepatitis C by means of proton magnetic-resonance spectroscopy suggesting a biological process (immune system activation) underlying the extrahepatic symptoms. There was no relation with drug use. Also Kramer *et al.* (31) found some evidence for a direct extrahepatic manifestation of hepatitis C by showing that HCV + patients had slight but significant neurocognitive impairment by using P 300 event related potentials, a sensitive electrophysiological test of cognitive processing. The evidence for a direct neurotoxic effect is further supported by the finding of a trend that HIV+/HCV+ have more neuropsychiatric dysfunction than HIV +/HCV- patients (32) even in an end stage of AIDS, where cognitive impairment is already considerable.

In contrast with earlier findings, Dalgard *et al.* (33) found no difference in health related quality of life (HRQOL) (including measures of emotional functioning and mental health) between drug users that were HCV + or HCV-.

In an interesting cross sectional study of 88 both treated and non treated HCV patients, Hauser *et al.* (34) found that the mental component of the SF-36 measuring HRQOL was determined by illness worries and psychiatric co morbidity and not by the severity of liver disease. Also the physical component of the SF-36 was not determined by the severity of the liver disease, but again by the psychiatric co morbidity and medical co morbidities. This underlines the importance of monitoring mental health in these patients before, during and after (interferon) treatment.

Results are summarised in Table 2a (24-26, 35-39).

3.2. *Neuropsychiatric and behavioural problems during treatment with interferon in intravenous drug users with chronic hepatitis C*

3.2.1. Neuropsychiatric side effects

Recent guidelines (40) on the use of screening instruments for depression suggested the Centre for Epidemiologic Studies Depression Scale (CES-D) and Hospital Anxiety and Depression Scale (HADS) as most widely used self report questionnaires (see table 2b, ref 41-52). Neither for these two questionnaires, neither for other instruments has a formal validation process taken place in a population of hepatitis C patients, with or without a history of substance abuse.

In studies on depression in this population, several instruments were used (see table 2b). Dieperink *et al.* (53) compared six instruments and found no difference in their ability to identify depression in this population. Golub (39) however found an insufficient

Table 1. — **Psychiatric morbidity in intravenous drug users (IVDU)**

Author	Number of patients (N)	% psychiatric diagnoses	Type of disorder	Comments
Dinwiddie *et al.* 1992 (17)	92 IVDU	Higher rates of alcoholism, depression and personality disorder than control groups	OR for antisocial personality disorder (ASPD) was 21 (95% CI 10.6-41.64) OR for suicide attempt was 8,27 (95% CI 3.30-20.74) OR for depression was 3,02 (95% CI 1.61-5.67)	
Brooner *et al.* 1993 (16)	272 intravenous drug users, 140 on methadone maintenance treatment		44% antisocial personality disorder	Higher chance of HIV + for pts with personality disorder through higher frequency of injecting
Lipsitz *et al.* (1994) (18)	223 intravenous drug users 85 male HIV+ 62 male HIV- 39 female HIV+ 37 female HIV_		26% current depressive disorder	HIV+ men 33% depression vs. HIV- men 16% HIV status less important than intravenous drug use itself
Krausz *et al.* (1998) (19)	350	55% at least one lifetime psychiatric diagnosis (ICD-10)	Psychotic disorders (< 5%) Personality disorders ? Affective disorders (32%)	
Milby *et al.* (1996) (20)	102 patients with substance abuse in methadone maintenance treatment		Anxiety disorder 55% Affective disorder 58%	Veteran sample DSM-IIIR STAI BDI
Frei and Rehm (2002) (21)	Meta-analysis of 3754 opioid addicts (16 studies)		78% at least one lifetime psychiatric diagnosis *Personality disorder 42% *Mood disorder 31% *Anxiety disorder 8%	
Van Thiel *et al.* (2002) (22)	120 recent users of illicit drugs vs. 120 matched controls	44/120 (37%) vs. 21/120 (18%)	Nothing mentioned about different diagnostic categories	Retrospective matched cohort study

correlation between CES-D and BDI to identify depression in a population of young HCV + intravenous drug users and suggested to use both to maximize identification of depression.

Most of the earlier reports on hepatitis C, its treatment with interferon and the occurrence of neuropsychiatric treatment side effects do not mention whether the patients are/were IVDU or not. They usually neither mention the proportion of side effects in IVDU compared with non-IVDU. Dosages of interferon vary between 3 to10 million units per injection subcutaneously. Frequencies of injection vary between 1 (pegylated interferon), 3 and 7 times a week. Duration of treatment is usually 6 or 12 months. Higher dosage seems to lead to more psychiatric complications. The way depression is measured varies from less standardised (chart review, clinical impression) to more standardised (self report questionnaires) to most standardised (structured psychiatric interview). Numbers of patients studied vary between 1 and 11,241. Rates of depression occurring as a side effect of interferon therapy range from 11 to 63% (4, 35, 53-88) but the time of assessment of depression varies widely (measurement of depression every week, every month, every two months…). It seems that interferon induced depression occurs mostly in the early weeks and months of treatment.

Mauss *et al.* (86) could not find a difference in the occurrence of depression as a side effect of pegylated interferon between patients still on methadone maintenance treatment (MMT) and patients that had been off illicit drugs or MMT for more than five years. Van Thiel *et al.* (22) found no difference in side effects during high dose interferon treatment in patients with recent drug use vs. controls. However, no formal assessment of psychiatric symptoms was reported and the need for antidepressant treatment during interferon treatment was not mentioned.

Identifying the patients that are going to be depressed is usually not possible. Capuron *et al.* (88) have tried to predict the development of depression during interferon treatment in a retrospective manner, taking the initial affective state before treatment as a reference. Wichers *et al.* (86) showed that early vegetative symptoms during interferon treatment predict cognitive-depressive changes in a later stage of the interferon treatment. An interesting study by Loftis *et al.* (89) showed that the occurrence of depression during pegylated interferon

Table 2a. — **Untreated hepatitis C and neuropsychiatric symptoms**

Author	N	Measure	Results	Comments
Johnson *et al.* (1998) (24)	309 drug users currently not in treatment	CES-D	57,2% depression in patients with HCV 48, 2% depression in patients without HCV	High prevalence of depression, (even more so in HCV+ than in HCV- IVDU) compared with normal population
Grassi *et al.* (2002) (25)	62 IVDU and HCV + 76 IVDU and HIV + 152 IVDU and HCV- and HIV -	Brief Symptom Inventory Social Provision Scale Locus of Control Scale Illness behaviour Questionnaire	More obsessive compulsive and phobic anxiety More paranoid ideation and psychoticism higher scores on fighting spirit, hopeless and anxious preoccupation towards illness than HCV +	
El-Serag *et al.* (2002) (26)	22341 HCV + veterans 43267 HCV - veterans	Review of medical files for psychiatric diagnoses 86, 4% had at least one past or present psychiatric, drug- or alcohol related disorder One third had active psychiatric disease,	Life time diagnoses Depression 49, 5% (HCV – 39, 1%) PTSD 33, 5% (HCV – 24, 5%) Psychosis 23, 7% (HCV - 20, 9%) Bipolar disorder 16% (HCV - 12, 6%) Anxiety disorders 40, 8% (HCV - 32, 9%) Alcohol use disorders 77, 6% (HCV - 45%) Drug use disorders 69, 4% (HCV -31, 1%)	
Mulder *et al.* (2000) (35)	63 patients	SCID and SCL-90	26/63 polysubstance abuse 47/63 IVDU 14/63 antisocial personality disorder	
Kraus *et al.* (2000) (36)	113 HCV + currently not receiving interferon 46,9% former IVDU current IVDU was exclusion criterion	Hospital Anxiety and Depression Scale (HADS) State and Trait Anxiety Inventory (STAI) Freiburg Questionnaire on Coping with Illness	22,3% depression 15,2% anxiety	Former IVDU not more depression Former IVDU not more anxious Former IVDU used less distraction and self-revalorisation as coping strategy
Yovtcheva *et al.* (2001) (37)	306 randomly chosen HCV patients	Chart review DSM-IV criteria	38% mood disorders 30% personality disorders 19% post traumatic stress disorder 9% other anxiety disorders 17% psychotic disorder	
Grassi *et al.* (2001) (38)	295 IVDU HIV +/HCV- 13 HIV+/HCV+ 68 HIV -/HCV+ 62 (not on treatment) HIV-/HCV- 152	Suicide probability scale Brief symptom inventory Hospital Anxiety and Depression Scale	High (+/- 30%) scores on suicide risk and psychological symptoms No difference between the groups	
Golub *et al.* (2004) (39)	193 IVDU hepatitis C+	CES-D BDI	44% depression 41,5% depression	Comparison of two depression measures, insufficient correlation, uses both ?

and ribavirin treatment actually predicts a better end of treatment response and sustained viral response compared with the response in patients not developing depression.

(Table 2c was added for your reference)

3.2.2. Compliance

Statements have been made in the past about compliance of patients with (a history of) intravenous drug use as being generally poor. Therefore it was not recommended to start hepatitis C treatment until patients had

Table 2b. — **The use of assessment tools for depression in patients with HCV (and substance abuse)**

Scale	Scoring system	Cut off	comment	Times used in studies in hepatitis C (and drug use)
Centre for Epidemiologic studies Depression Scale (CES-D) (41)	20 items score per item from 0-3	> 16 indicative for depression Golub (2004) cut off > 23 moderate to severe depression	Self administered self report scale	Golub 2004 Sylvestre 2002
Hospital Anxiety and Depression Scale (HADS) (42-43)	14 items (7 on anxiety and 7 on depression	> 16 shows presence of either anxiety or depression	Self administered self report scale	Kraus *et al.* 2003
Beck Depression Inventory (BDI) (44-45)	21 items score per item from 0 to 3	> 19 moderate to severe depression (Golub 2004) > 10 before interferon treatment higher risk to develop depression during interferon treatment	Self administered self report scale	Golub 2004 Dieperink 2003
Zung Self Rating Depression Scale (46)	20 items covering somatic, psychological and affective symptoms	< 50 no depression 50-59 mild depression 60-69 moderate depression > 70 severe depression	Self administered self report scale	Dieperink 2003 Robaeys (?) Gallegos-Orozco 2003 Koskinas 2002
Inventory to diagnose Depression (47)				Dieperink 2003
Positive and Negative Affect Scale (PANAS) (48)				Dieperink 2003
SF-36, measures health related quality of life (49)	36 items 8 dimensions one of which is mental health	0 is worst, 100 is best possible score	Self administered self report scale	Dalgard 2004 Gleason, Yates *et al.* 2002 Gallegos-Orozco 2003
SCL-90 (50)	Multidimensional	Cut off for anger/hostility is > 8	Self administered self report scale	Kraus *et al.* 2003 Gleason, Yates *et al.* 2002
MADRS (Montgomery Asberg Depression Rating Scale) (51)				Wichers 2004
Hamilton Depression Rating Scale (HAM-D) (52)	17 items			Wichers 2004 Gleason, Yates *et al.* 2002 Horikawa *et al.* 2004 Dieperink 2003
Structured Clinical Interview for DSM-IV (SCID)	Psychiatric diagnoses		Structured Clinical Interview	Wichers 2004 Gleason, Yates *et al.* 2002
DSM-IV criteria			Semi structured interview approach	Schaefer 2003 Horikawa *et al.* 2004 Lang 2002 Suzuki *et al.* 2003 El Serag *et al.* 2002

stayed off drugs for 6 or 12 months. Table 3 (22,72, 77,79,87) summarizes data on compliance with hepatitis C treatment in this patient population. Compliance rates vary from 57 to 85%. Data about differences in compliance between patients involved in drug use or MMT and controls are mixed. However, Van Thiel *et al.* (22) report no difference in their study, explaining it by their high rate of follow-up visits and the possibility to contact nursing staff between physician visits.

3.2.3. Other behavioural problems

Fontana (90) reports a < 5% rate of relapsing in drug abuse in hepatitis C + patients treated with interferon.

Sylvestre (77) mentions one drop out of a sample of methadone maintenance patients on interferon treatment because of alcohol abuse.

Craving for using drugs in patients on methadone can worsen during treatment with interferon (78) and methadone may have to be increased (22,90).

3.3. *Treatment of neuropsychiatric and behavioural problems during treatment with interferon in intravenous drug users with chronic hepatitis C*

Several authors have reported on successful treatment of depression and other neuropsychiatric symptoms in

Table 2c. — **Neuropsychiatric side effects of interferon treatment**

Study	N	Dose of interferon	Assessment	% depressed	Comments
Renault *et al.* 1987 (54) Data collection 1984-1986	58	10mU per 2 days or 5 mU every day	Interview SCL-90	12%	2/58 IVDU, none of them developed psychiatric side effects
Mc Donald *et al.* (1987) (55)	60 (hep B !)	2,5 or 5 or 10 mU 3 × per week	Clinical Interview Schedule (CIS)	63% became 'cases' (mostly, but not only depression)	
Van Thiel *et al.* (1995) (56)	31 consecutive patients	5 mU daily or 3 × per week for 6 months	Clinical interview on a monthly basis	Not mentioned, 29/31 (94%) completed the trial 2 patients had to stop treatment because of mania (causal relationship ?)	20 patients had a history of intravenous drug use
Bourat *et al.* (1995) (57) Data collection 1993	2 patients	3 mU 3 × per week	Clinical examination	One patient had history of polysubstance abuse, interferon stopped because of suicide attempt.	
Taruschio *et al.* 1996 (58)	3 case reports	Not mentioned	Not mentioned	1 psychotic disorder 1 panic attacs 1 depression	
Fattovich *et al.* (1996) (59)	11241 chart review	?	?	2/11241 suicide attempts 10/11241 psychosis depression ?	Prevalence of psychosis and suicide attempts less than in normal population ? Assessment problem ?
Hunt *et al.* 1997 (60)	38/48 hepatitis C patients at a university medical centre	3 mU 3 × per week	HADS, BDI	Depression increased in month 6, anxiety decreased in month 1	Nothing mentioned about prior IVDU
Neri *et al.* 2002 (61)	47 recent heroine abusers after methadone treatment 30 without history of drug abuse	5mU 3 × per week for 12 months	Clinical judgment	3/47 developed severe depression None mentioned in 30 without history of drug abuse	3/47 had to stop INF treatment because of depression
Otsubo *et al.* (1997) (62)	85	?	DSM-IIII-R Hamilton Depression scale	37,3% newly developed depression	
Heeringa *et al.* 1998 (63)	6 patients case series One with a past history or cocaine abuse	Not mentioned for all cases	Clinical examination	Mania, psychosis and depression One suicide	Outcome of case with history of cocaine abuse not known
Malaguarnera *et al.* 1998 (64)	96	3 mU 3 × per week, 4 groups with different types of interferon alpha	Hamilton Depression Scale	79 to 96% after 1 month of treatment 12,5 to 75% after 3 months of treatment 8 to 33% after 6 months of treatment	History of drug use was exclusion criterion but 34% (!) did not know how they were infected
Yates and Gleason 1998 (65)	?	?	?	Substance abuse 36% Depression 28%	
Van Thiel *et al.* 1998 (66)	31 nothing mentioned about IVDU	5mU 3 × per week or daily	Clinical interview	Not mentioned, 100% fatigue	Conclusion is drawn that treatment of psychiatric patients is possible
Pariante 1999 (67)	50 (nothing mentioned about a history of drug abuse)	6-10 mU 3 × per week for 12 months	Non patient version of the Structured clinical interview for DSM-3-R (SCID-NP)	11/50 (22%) developed new psychiatric diagnosis during treatment 3/50 (6%) stopped treatment because of new psychiatric symptoms	Patients with a past psychiatric history or current psychiatric diagnosis not more likely to develop more psychiatric symptoms Current or past drug use not reported

Table 2c. — **Continuation**

Pariante 1999 (68)	60 hep B and C patients 25 with, 35 without prior existing psychiatric diagnosis	6-10 mU 3 × per week for 12 months	HAM-D and STAI	3/25 (12%) developed new psychiatric symptoms that needed to be treated 7/35 (20%) developed new psychiatric symptoms that needed to be treated Not significantly different	Type of psychiatric history not mentioned
Miyaoka *et al.* (1999) (69)	66	6 or 10 mU every day and then for 2 weeks and then 3 × per week	DSM-III-R	21,9% after 4 weeks 38,3% after 12 weeks 27,1% after 24 weeks	
Scalori *et al.* (2000) (70)		3 or 6 mU 3 × per week	MMPI	24,1%	
Schaefer *et al.* (2000) (71) Data collection 1996	1	5mU 3 × per week	Clinical assessment	Patient became psychotic and stayed psychotic even after treatment course was completed	Patient on methadone maintenance
Mulder (2000) (35)	49	3 mU 3 × per week	SCL every month	No increase from baseline	
Backmund *et al.* (2001) (72)	50 current IDU started on treatment during detoxification	6 mU 3 × per week for first twelve weeks, than 3 mU 3 x per week	Clinical assessment	2/50 (4%) treatment stopped by physician because of severe depression 5/50 (10%) mild to moderate depression but continued treatment	Nothing mentioned about treatment of depression as a side effect of interferon treatment
Ho *et al.* (2001) (73)	33	5mU 3 × per week for 6 months	Retrospective chart review Previous IVDU was not considered as psychiatric history if no problems during last 2 years	6/19 (32%) of patients with a psychiatric history developed psychiatric symptoms 2/14 (14%) of patients without a psychiatric history developed psychiatric symptoms One suicide	Veteran population Active substance abuse was exclusion criterion Methadone Maintenance was no exclusion criterion Results difficult to interpret
Jowett (2001) (4) Period 9/1991 –8/1998	237 former IVDU	Dosage ?	?	9/50 (18%) patients who got treatment stopped treatment because of 'profound neutropenia and depression'	30% of appoint-ments were missed Retrospective chart review
Hauser *et al.* (2002) (74)	39	3 mU 3 × per week	SCID, BDI	13/39 (33%) developed major depressive disorder	No difference between previous IVDU and non IVDU Drug use in previous 6 months was exclusion criterion
Pariante (2002) (75)	60 hep B and hepatitis C	6-10 mU 3 × per week for 12 months	DSM-III-R	Increase during treatment in both groups with (n = 25) or without (n = 35) a prior psychiatric history	Current or past drug use not reported separately
Koskinas *et al.* (2002) (76)	38 Hepatitis C 36 hepatitis B	3 mU 3 × per week for 12 months	Zung self rating depression scale	Increase but percentage not reported (Individual scores not used to determine cut off for diagnosis of depression, only means are reported)	No previous psychiatric history. Current or past drug use not reported separately
Sylvestre 2002 (77)	50 IVDU on methadone maintenance treatment	3 mU 3 × per week for 6 or 12 months	CES-D depression scale	31/50 (62%) started new psychiatric medication during treatment (21/31 SSRIs) CES-D before and after treatment not mentioned 70% mentioned depression and irritability as side effect of interferon	16/31 were not taking psychiatric medication before treatment
Bonaccorso *et al.* (2002) (78)	30	3 mU 3 times a week	MADRS DSM-IV	40,7% developed depression by the end of treatment	Current use of substance abuse was exclusion criterion Past history of substance abuse ?

Table 2c. — **Continuation**

Dieperink *et al.* (2003) (53)	42 male veterans	3 mU 3 times a week	Several instruments	23% new cases of depression 48% in total developed new neuropsychiatric symptoms 2 had drug or alcohol relapse during treatment one stopped treatment because of depression and	flu-like symptoms
Half reported life time history of alcohol or illicit drug use but this history did not predict the need for psychiatric treatment during inter-	feron treatment	Schaefer *et al.* (2003) (79) Data collection 1998-2000	16 psychiatric history 21 methadone substitution 21 drug addiction 23 no psychiatric history or no drug history	3 mU 3 times a week	DSM-IV criteria semi-structured interview
Incidence of depression not different in the 4	groups More patients from the psychi-	atric group needed antidepressants during treatment		Close collaboration and frequent follow up could prevent drop out from treat-	ment because of psychiatric side effects
	Suzuki *et al.* (2004) (80)		146		5-10 mU 3 times a week
Hamilton Depression Scale	11,6% Patients with psychiatric history were excluded		Gallegos-Orozco *et al.* (2003) (81)	157	
?	58,6%		Kraus *et al.* (2003) (82) Data collection nov 96-dec	2001	84/104 consecutive patients at clinic for internal medicine
52% infected through IVDU		3 to 5 mU thrice a week			
Hospital anxiety and depression scale		Increase in depression from 15% at baseline tot 35%		Active IVDU was exclusion criterion Prospective controlled study Past IVDU not more depres-	sion during INF treatment
Horikawa *et al.* (2003) (83)	99	6 or 10 mU once a day for 4 weeks, then 3 times a week	Hamilton Rating Scale for Depression	23,2% new cases	Gohier *et al.* (2003) (84)
71		MADRS Ham-A			Van Thiel *et al.* (2003) (22)
120 recent users of illicit drugs vs. 120 matched controls	5 mU once a day for at least one year	No formal assessment of psychiatric symptoms was mentioned	No difference in side effects was mentioned	No formal report on the occurrence of psychiatric side effects	Gochee 2004 (85)

patients treated with interferon (72,77,79). They hint towards the feasibility to treat patients on methadone maintenance treatment and even patients with a relapse of intravenous drug use should not always be denied further treatment. Results from treatment studies are summarized in table 4. In total numerical data are available for 63 patients (from 4 studies) who developed depression during treatment with interferon. Ninety-two percent (58/63) recovered sufficiently to enable them to continue treatment with interferon. All received antidepressants ; in 3 groups they received selective serotonin reuptake inhibitors (SSRI).

Treatment contracts can be used to monitor side effects and improve compliance (97).

Table 3. — **Compliance with interferon in hepatitis C in IVDU**

Study	patients	Compliance rates	comments
Backmund *et al.* (2001) (72)	50 IVDU started on treatment during detoxification	In 10% treatment was stopped because of non-compliance 39/50 did not miss injection until end of treatment 11/50 missed between 3 and 45 of the injections (2 of these still had sustained response)	Compliance measure was defined as sustained response at 24 weeks (determined by loss of detectable HCV rna)
Sylvestre (2002) (77)	50 IVDU on methadone maintenance treatment	39/50 completed treatment	3/11 stopped because of medication side effects 3/11 stopped because of worsening of psychiatric symptoms 3/11 stopped because of decompensating liver disease 1/11 stopped because of alcohol abuse
Schaefer *et al.* (2003) (79)	4 groups Former drug addiction (n = 21) Methadone substitution (n = 21) Psychiatric history (n = 21) No psychiatric history or no drug history (n = 23)	Drop out rates : Former drug addicts 43% Methadone 14% Psychiatric history 18% Control 13%	Drop out rate for the total group was 22% : *somatic 5% *psychiatric :2% *relapse drug/alcohol : 2% *non-compliance : 13%
Van Thiel *et al.* (2003) (22)	120 recent users of illicit drugs vs. 120 matched controls	102/120 (85%) completed study 112/120 (93%) completed study	Frequent follow up visits (monthly) Drug treatment independent from hepatitis C treatment
Mauss *et al.* 2004 (87)	50 patients on methadone maintenance treatment (MMT) 50 controls (> 5 years free of illicit drugs or MMT)	First 8 weeks : MMT 11/50 drop outs Control group 2/50 drop out After 8 weeks no difference	Reason for drop out was patients own request or non-compliance, not due to side effects

Table 4. — **Treatment of neuropsychiatric side effects of interferon treatment in IVDU**

Study	N	IVDU	Psychiatric treatment	Result	Comment
Gleason and Yates (1999) (92)	5	2/5 polysubstance abuse in remission	1 Sertraline Alprazolam and imipramine 1 Paroxetine	Relapse while taking sertraline after initial result, good result on alprazolam and imipramine Normalisation of mood after 2 weeks	Case series
Schramm *et al.* 2000 (91)	10/13 patients on interferon who became depressed	Nothing mentioned about previous IVDU	Sertraline, 50 mg	10/10 marked improvement	1/13 suicidal and no AD started 2/13 refused AD treatment
Gleason *et al.* (2002) (93)	15	?	Citalopram	13/15 showed > 50% reduction in HAM-D score	
Hauser *et al.* (2002) (74)	13/39 developed new depression	70% past history of drug use	Citalopram (11/13) Fluoxetine (1/13) Bupropion (1/13)	All but one improved, this one patient had to stop INF because of severe depression with psychotic features	Prospective open label treatment study Substance use in last 6 months was exclusion criterion
Sylvestre (2002) (77)	50 IVDU on methadone	All patients	Different antidepressants, mostly SSRIs	Most patients depressive symptoms improved and AD treatment allowed INF treatment to be continued	At the end of 88% of patients were taking ADs
Kraus 2002 (94)	14/121 depressed on interferon	?	Paroxetine 20 mg per day	11/14 better and able to continue treatment	3 had to stop interferon treatment : 1 insufficient response, 1 seizures, 1 nausea

Table 4. — **Continuation**

Lang 2002 (95)	26/52 depressed on interferon	?	?	?	?
Dieperink *et al.* (2003) (53)	15/31 that were not in psychiatric treatment before interferon was started required psychiatric treatment	Half of the patients had a history of drug abuse	Sertraline 50 mg/day	Most patients' depressive symptoms improved and AD treatment allowed INF treatment to be continued	Only male patients Prospective naturalistic study
Schaefer *et al.* 2003 (79)	13/81 developed new depression	No difference between 4 groups	Mostly SSRIs, also mirtazapine, nefazodone and amitriptyline	All patients could complete INF treatment	5/81 admission to psychiatric ward
Horikawa *et al.* 2003 (83)	23/99 became depressed during treatment	Not included	17/22 received sulpiride 150 mg per day 5/22 did not receive sulpiride	Remission rate for sulpiride not different from no treatment In total 13/22 recovered from depression during treatment	1/23 severe depression, treatment was stopped Not randomised
Malek-Ahmadi and Ghandour (2004) (96)	1	?	Bupropion	Improvement in depressive symptoms	Case report
Mauss *et al.* (2004) (87)	50 patients on methadone maintenance treatment (MMT) 50 controls (> 5 years free of illicit drugs or MMT)		Doxepine, paroxetine and citalopram	No formal measurement was performed	No drop outs due to depression

3.4. *Discussion and recommendations*

1. Most treatment studies for chronic hepatitis C have not systematically compared the occurrence of neuropsychiatric symptoms with interferon treatment in patients that were infected through blood transfusion and patients that were infected through IVDU. Assessment of neuropsychiatric symptoms happens in many different ways (different instruments, self-report vs. observer rated, different frequencies of assessment …)

Kraus *et al.* (82) however did not find a correlation between the occurrence of depression during interferon treatment and mode of acquisition of HCV.

Therefore there is currently insufficient evidence to deny treatment of hepatitis C to all (past) intravenous drug users on the basis of these neuropsychiatric symptoms (3).

2. It is not appropriate to use the presence of (past) intravenous drug use as an absolute contra indication for treatment.

It is very appropriate to assess the presence of both psychiatric axis I disorders (depression, psychosis, ongoing opiate and other substance abuse) and psychiatric axis II disorders (personality disorders) before starting treatment, as these are very prevalent (25). The presence of these disorders is linked with risk behaviour and possibly compliance and may predispose for the occurrence of neuropsychiatric symptoms during interferon treatment.

3. It is mandatory to work in an interdisciplinary setting with hepatologists, psychiatrists, specialists in substance use and general practitioners as this allows early detection and treatment and improves adherence (4,72,77).

Different measurement instruments have been used in this population, but no formal validation has taken place.

Pre-existing depression should be treated before starting interferon.

4. When depressive symptoms occur in patients with a history of IVDU, no definitive data exist on the treatment possibilities but there are indications that antidepressants (mainly SSRIs but also antidepressants from other classes) work both in IVDU and non-IVDU hepatitis C patients.

Early vegetative changes may hint towards the development of depression in a later stage of interferon treatment (86).

5. We currently have insufficient data to assess the need to and the situations in which preventive treatment with antidepressants can be started before initiating interferon treatment. However, clinical judgement can lead to preventive treatment with antidepressants, even at (sub) clinical levels of depression (53,88). Also a cut off score of > 10 on Beck's Depression inventory before interferon treatment, possibly predicts the development of depression during interferon treatment (53).

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