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Neuropsychiatric Complications of Interferons: Classification, Neurochemical Bases, and Management

PARVIZ MALEK-AHMADI, MD and ROBIN C. HILSABECK, PHD

Department of Neuropsychiatry, School of Medicine, Texas Tech University Health Sciences Center, Lubbock, TX, USA

Background. *Recombinant interferons are widely used for a number of serious illnesses. However, their use is sometimes associated with severe and disabling neuropsychiatric side effects.*

Methods. *A MEDLINE search identified pertinent laboratory investigations, case reports, clinical studies and letters published between 1983 and 2004 in the English language journals. The studies in which interferons were used in combination with other cytokines were excluded.*

Results. *The interferon-associated neuropsychiatric side effects are divided into mood-related symptoms (depression/mania), cognitive impairment (including delirium), psychosis and isolated psychiatric symptoms. Putative neurotransmitters (serotonin and dopamine), hormones (cortisol) and cyokines (interleukin-2 and 6) have been implicated in the pathophysiology of these side effects. Management of neuropsychiatric side effects of interferons ranges from supportive measures, dose reduction, cessation of therapy and the use of appropriate psychotropic agents.*

Conclusions. *Interferon-treated patients should be monitored for mental status changes. There are no controlled studies on pharmacological management of interferon-induced neuropsychiatric side effects. The use of interferons in patients with stable psychiatric disorders is not contraindicated. However, such patients should be closely monitored during the course of treatment with interferons.*

Keywords Interferons, Mood-related symptoms, Cognitive deficits, Psychosis, Neurotransmitters/Cytokines, Management

Interferons (IFNs) are naturally-occurring proteins synthesized by the immune system. Based on their cellular sources, they have been grouped into two main types. Type 1 IFNs (alfa and beta) are acid-stable and produced by leukocytes and fibroblasts. Type 2 IFNs (gamma) are acid-labile and derived from T and natural killer cells (1). Recombinant technology has resulted in availability of several IFNs. They have been utilized for treatment of a number of serious illnesses (2). However, a warning accompanies the information on recombinant IFN alfa (and its subtypes) alerting the healthcare providers and patients to their severe psychiatric side effects (2).

Following a brief review of basic information on IFNs, we describe four groups of IFN-related psychiatric side effects, discuss their proposed underlying mechanisms and review their management.

Address correspondence to Parviz Malek-Ahmadi, Department of Neuropsychiatry, School of Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas 79430-8103. E-mail: parviz.malekahmadi@ttuhsc.edu

Pharmacokinetics of IFNs

Wills has reviewed the pharmacokinetics of IFNs. IFN alfa and its subtypes are eliminated via kidneys. IFN beta and gamma are mostly degraded in the liver (3).

In humans, the plasma half-life for recombinant IFN alfa is four to16 hours. The plasma half-life for IFN beta is one to two hours. A much shorter half-life of 25 to 35 minutes has been reported for IFN gamma. Commonly used pegylated IFN alfa 2a and 2b are bound covalently to polyethylene glycol and have much longer half-lives (2).

Animal studies indicate that IFN alfa penetrates the blood-brain barrier (BBB) in the area where the barrier is deficient (4). In human subjects, recombinant IFNs reach the central nervous

system (CNS) at high concentrations. Mattson et al. (5) in a group of eight patients with bronchogenic carcinoma detected amounts of IFN 35–110 unit (U) /ml in the cerebrospinal fluid (CSF) after intravenous administration of high doses (100–200×10^6 U daily for five days) purified leukocyte IFN (5). Smith et al. (6) studied the distribution of recombinant IFN alfa A in four patients with amyotrophic lateral sclerosis. Utilizing an enzyme-linked immunoassay, intravenous infusion of 18×10^6 U recombinant IFN alfa A yielded serum concentrations of 67–11ng/ml without a measurable concentration in the CSF. In three patients, injection of 50×10^6 of IFN alfa A in approximately one hour resulted in CSF concentrations of 17 to 20 pg/ml.

In a more recent study, Mackowiak et al. (7) investigated the effects of single subcutaneous injection of IFN beta on cerebral blood flow (CBF) in five patients with multiple sclerosis. Utilizing single photon emission computed tomography (SPECT), the investigators demonstrated increased CBF in the basal ganglia.

IFN Receptors and IFN Signal Transduction

IFN alfa exerts a number of effects in the CNS and is being considered a "neuromodulator" (8). IFN receptors have been identified in the CNS. Type 1 IFNs share the same receptor. IFN gamma binds to a different receptor (1). Type I IFN signal transduction involves Janus kinase (JAK)/signal transducers and activators of transcription (STAT) proteins. Another pathway involves utilization of protein kinase C (1).

IFN alfa also interacts with other types of receptors. In the rat brain, IFN alfa binds to opioid receptors and its effects on electroencephalogram (EEG) is antagonized by naloxone (9). It has been demonstrated that human recombinant IFN alfa inhibits its binding of naloxone to opioid receptors (10). IFN alfa also modulates *N*-methyl-*D*-aspartate (NMDA) receptor response via opioid receptors (11).

NEUROPSYCHIATRIC SIDE EFFECTS OF IFNs

Several reviews on psychiatric side effects (affective and cognitive symptoms) of IFN alfa in patients with chronic hepatitis C (CHC) have been published. In a recent eloquent review, Loftis and Hauser have addressed the prevalence, phenomenology, neurochemistry and treatment of IFN-induced depression (12). However, this article provides a comprehensive review of the subject. We have grouped these side effects into four main categories of: *mood-related symptoms* (depressive/manic), *cognitive deficits*, *psychotic symptoms* and *isolated psychiatric symptoms*.

Mood-related Symptoms

Depressive symptoms are known to be associated with IFN therapy. Suicide attempt and completed suicide have been reported with IFN alfa and beta (1,13–15). A meta-analysis has indicated a frequency of 7% depressive symptoms during the first six months of treatment with IFN alfa 3×10^6 U in patients with CHC. Therapy with higher doses ($>5 \times 10^6$ U) was associated with increased frequency of depressive symptoms (10%) (16). More recent prospective studies, in which the diagnostic criteria and rating scales were utilized to diagnose/quantify IFN-induced depression, have shown a higher frequency of depressive symptoms from 8% to 48 % in patients with CHC (17–25).

Heterogeneity of the patient population, utilization of different instruments, mental states of the patients at initiation of IFN treatment and types of IFN may account for the wide range of frequency. Furthermore, it has been suggested that IFN mood related symptoms do not always conform to specific diagnostic criteria (25,26).

Some IFN-treated patients report minor depressive symptoms two weeks after IFN treatment (27). Therefore, it is important to distinguish these isolated symptoms from a criteria-based IFN-induced depression. It has been suggested that IFN-related depressive symptoms may be linked to ribavirin (28). In a double blind design involving 29 patients with CHC taking 1200 mg ribavirin daily for 12 months, depression was not reported as a side effect (29). However, a multi-center study has shown that the rate of depressive symptoms was higher in patients treated with IFN combined with ribavirin (30). However, pegylated IFN alfa 2a combined with ribavirin is associated with lower incidence of depression (31).

Mania has also been associated with IFN alfa therapy in patients with chronic myelogenous leukemia (CML), melanoma, CHC, and chronic hepatitis B without a history of mania (32–41).

Mania can occur following discontinuation of IFN alfa. Carpiniello et al. (42) have described a patient with chronic hepatitis B who became manic three days after discontinuation of IFN alfa. Progressive depressive symptoms during the fifth week of treatment with IFN alfa necessitated discontinuation of therapy. Another case report has shown occurrence of manic symptoms in a patient with bipolar disorder after discontinuation of IFN alfa (43).

Suicide attempts have been reported with IFN-beta treatment in patients with multiple sclerosis (MS) (44). However, depression as a side effect of IFN beta has been reported with much less frequency. In multi-center studies involving large number of patients with multiple sclerosis, treatment with IFN beta (1a and 1b) was associated with only few cases of depression (45). Recently, Goebel et al. (46) have shown that in patients with MS long-term treatment with IFN beta had no effect on activity of the hypothalamic-pituitary-adrenal (HPA) axis and did not alter the patients' mood states. In another study, IFN beta administered to patients with MS had no significant effect on HPA axis (47).

Cognitive Deficits

In a prospective study involving 10 women with breast cancer, Smedley et al. (48) reported "frank confusion" and inattention in six patients who were treated with leukocyte IFN 20×10^6 U/m^2 daily or 50×10^6 U/m^2 three times a week. By the fourth week, all patients showed diffuse slowing on their EEG recordings. Baseline EEGs in nine patients were normal. The cognitive deficits were resolved in seven to 10 days after discontinuation of therapy.

Talpaz et al. (49) reported insomnia, inattentiveness and impaired memory in six patients with Philadelphia chromosome positive CML treated with recombinant IFN alfa 2a. IFN dose was 5×10^6 U/m^2 of body surface administered daily for four to 14 months. In three patients, cognitive impairment resolved after the dose of IFN was reduced in half. In another patient, symptoms resolved when IFN was discontinued. Two patients exhibited extrapyramidal symptoms.

In a group of 58 patients with CHC treated with IFN alfa 10×10^6 U three times a day or 5×10^6 U daily for four to12 months, three patients (5%) developed delirium. In two patients discontinuation of IFN was necessary. Dose reduction in the third patient resulted in resolution of delirium (50).

Adams et al. (51) studied a group of 11 patients with malignancies treated with "various preparations of interferons." They reported four patients (ages > 60) with pre-existing cerebral palsy who developed delirium within a few days of treatment with recombinant IFN alfa, IFN gamma, human lymphoblastoid IFN and human IFN alfa. Four other patients developed "global cognitive impairment." Two patients taking IFN gamma experienced akathisia and extrapyramidal symptoms. The severity of cognitive impairment resulted in discontinuation of IFN treatment. The authors suggested that a pre-existing CNS lesion is a risk factor for IFN-induced neurotoxicity.

Iaffaioli et al. (52) studied 17 patients with non-Hodgkin's lymphoma treated with 2 to 10×10^6 U/m^2 of recombinant IFN alfa 2b three times a day subcutaneously. Within one month of treatment, eight patients experienced psychomotor retardation.

Meyers et al. (53) reported severe neurotoxicity in seven of nine patients with leptomeningeal metastatic lesions. Partially purified leukocyte IFN (natural IFN alfa) was diluted and administered via a ventricular reservoir. Four patients were given 6 to 9×10^6 U daily. The duration of treatment ranged from 9 to 50 days. Seven patients developed "increasing confusion," and decreased responsiveness to stimuli. In two patients, IFN treatment had to be discontinued. The symptoms were resolved within 7 to 34 days. EEG readings were abnormal in five patients with diffuse slow-wave abnormality in one patient. The remaining four patients did not undergo EEG studies. In addition, some patients experienced extrapyramidal symptoms and seizure.

In some patients, IFN alfa-induced cognitive deficits may persist after discontinuation of IFN. In a retrospective study, Meyers et al. (54) reported IFN-induced cognitive deficits in 10 patients of a group of 14 with various malignancies. The dose of IFN alfa ranged from 3 to 20×10^6 U daily or three times a day for 40 days to three years. Neuropsychological testing was suggestive of "*fronto-subcortical deficit.*" Daily injections were associated with more severe deficit. In two patients, the cognitive deficits persisted up to four and eight months after discontinuation of IFN treatment. However, no baseline testing was performed and the battery was not uniform across patients. Four patients developed extrapyramidal symptoms.

Pavol et al. (55) studied a number of psychometric parameters in 25 patients with CML treated with IFN alfa for one week to 84 months. The weekly dose of IFN alfa ranged from 17 to 77×10^6 U "most often administered subcutaneously. Compared to the control group of 16 patients with CML, the IFN-treated patients demonstrated psychomotor slowing and executive difficulties suggestive of "*mild fronto-subcortical deficit*." In a case report, Moulignier et al. (56) reported emergence of subcortical dementia induced by recombinant IFN alfa.

It has been suggested that the natural IFNs are less likely to cause cognitive deficits. Mapou et al. (57) longitudinally studied a group of asymptomatic human immunodeficiency deficiency virus (HIV) positive patients who were treated with subcutaneous IFN alfa n3 (a natural IFN). The dose ranged from one to 20×10^6 U three times a week for 12 weeks. The investigators did not detect any significant deficit in the domains of attention, psychomotor speed, memory and language. They concluded that natural IFN is less likely to induce cognitive impairment.

Nozaki et al. (58) reviewed 30 case reports (published in Japan) describing 49 patients treated with IFNs. The authors applied standard diagnostic criteria and reported 10 cases of delirium. In most patients, the symptoms commenced within one month of treatment with IFN alfa. Seven patients with delirium showed abnormal EEG although the type of abnormality was not specified. In four patients, repeat EEG normalized after IFN alfa was discontinued. Delirium secondary to IFN beta was not reported.

Several clinical reports have indicated that IFN alfa treatment is associated with slowing of EEG which is suggestive of the CNS effects of IFN alfa (59–63).

A few studies have failed to find cognitive deficits associated with IFN alfa. Caraceni et al. (64) studied 113 patients with melanoma. The patients received IFN alfa 3×10^6 U three times a week for 36 months. Except for anxiety, no cognitive deficit was detected after 12 months. Eight patients developed action tremor. Mayr et al. (65) assessed fourteen patients with myeloproliferative disorders treated with recombinant IFN alfa. The dose of IFN ranged from 10 to 35×10^6 U given weekly. The researchers monitored at the baseline and every three months. Results revealed improved attention and memory. However, in interpreting the results of prospective studies, practice effects should be taken into consideration (66).

In contrast to IFN alfa, no cognitive deficits have been attributed to IFN beta. Liberati et al. (67) assessed attention,

verbal memory and verbal fluency in 21 patients with hematological malignancies treated with IFN beta. No significant changes were found. Again, cognitive assessment of patients may be have been influenced by the practice effect.

IFN-associated Psychosis

In 1991, Bramley et al. (68) reported a patient with metastatic vipoma who experienced "acute paranoid psychosis" after a single first injection of IFN alfa 3×10^6 U. There have been several case reports of IFN alfa-associated psychosis in patients without a history of psychiatric disorders (69–72).

Acute psychotic symptoms also have been reported in a 21-year-old healthy woman who experienced delusions and hallucinations within 10 days following a single injection of 180 μg pegylated IFN alfa. She was treated with antipsychotic agents for two months (73).

In 1996 Fattovich et al. (74) reviewed the adverse effects of IFN alfa in a group of 11,241 patients with chronic viral hepatitis. They reported ten cases (0.09%) of psychosis without a history of psychiatric disorders including substance abuse. The dose of IFN alfa was 3×10^6 U three times a week in nine patients and 6×10^6 U three times a week in one patient. The psychotic symptoms occurred within six to 46 weeks of therapy. IFN alfa was discontinued in all patients. In three patients, the psychotic symptoms resolved. The remaining patients required unspecified psychotropic agents.

In their reports of IFN-related psychiatric disorders, Nozaki et al. (58) reported four patients in whom psychotic symptoms were attributed to IFN alfa 2b. Among the four patients only one had a pre-existing diagnosis of delusional disorder. The interval between the initiation of treatment and the onset of psychosis ranged from one to four months. In three patients, IFN was discontinued. However, all patients were treated with conventional antipsychotics. The authors did not report any psychotic symptoms attributed to IFN beta.

Isolated IFN-induced Psychiatric Symptoms

Renault et al. (50) reported irritability as one of side effects of therapy with IFN alfa. Homicidal ideations associated with IFN alfa 2b also have been reported (75). Occasionally, affective liability and depersonalization also have been reported with IFN alfa and beta (1,18).

Malaguarnera et al. (18) reported emergence of obsessive-compulsive symptoms during treatment with both natural and recombinant IFNs. Maunder et al. (76) reported symptoms of posttraumatic stress disorder (PTSD) in two patients with CHC treated with IFN alfa. In one patient, IFN therapy activated the symptoms of pre-existing PTSD. In the second patient, IFN therapy was associated with emergence of PTSD symptoms in a patient with a history of trauma. In patients with a history of substance abuse disorder, flashbacks have been reported following treatment with natural IFN alfa (77).

In a large group of patients with CHC, Hosoda et al. (78) described a high frequency of anxiety (100%) and insomnia (76.9%) in IFN-treated patients. They attributed these symptoms to physical side effects of IFN therapy. The investigators did not specify the proportion of patients who met the diagnostic criteria utilized in the study. With respect to IFN beta and gamma, we found only one report in which the use of recombinant IFN gamma (4×10^6 daily for six months) in 51 patients with lung cancer was associated with changes in "mental status" in four patients (79).

SUGGESTED MECHANISMS UNDERLYING NEUROPSYCHIATRIC SIDE EFFECTS OF IFNs

Mood-related Symptoms

The mechanisms underlying IFN-induced depression remain elusive. There is evidence suggesting that depressive symptoms are mediated by deficiency of serotonin in the brain. Werner-Felmayer et al. (80) reported that in human cells IFNs induce indoleamine 2, 3-dioxygenase (IDO). Induction of IDO may shift degradation of tryptophan (from conversion to serotonin) to kynurenine.

IFNs may also decrease serotonergic transmission via other mechanisms. In rats, chronic administration of IFN alfa increases the binding of a selective serotonin receptor agonist to serotonin type 1A receptor (81). In rats single intracerebroventricular injection of IFN alfa reduces serotonin and norepinephrine levels in the frontal cortex (82). IFN alfa also increases the level of serotonin mRNA transporter protein (83). In patients with IFN alfa-induced depression, severity of symptoms are negatively correlated with plasma tryptophan and positively related to plasma interleukin-6 (IL-6) levels (84,85). Furthermore, paroxetine counteracts IFN alfa-induced depletion of tryptophan (86).

The mechanisms underlying IFN mood-related symptoms also may be linked to the effects of IFN alfa on the HPA axis. In a double-blind, placebo-controlled crossover design, controlled study, Cassidy et al. (87) reported a significant increase in serum cortisol and IL-6 levels in a small number of healthy subjects eight hours after subcutaneous administration of IFN alfa. While serotonin deficiency and hyperactivity of the HPA axis have been linked to IFN-induced depression, the mechanism underlying IFN-induced mania is less clear.

It has been suggested that neurotoxicity of IFN alfa is linked to its ability to inhibit cytochrome enzymes 1A2, 2C19 and 2D6. In a group of patients with melanoma, high-dose IFN alfa inhibited the activity of these enzymes which are involved in synthesis and degradation of neurotransmitters (88).

Shuto et al. (89) have shown that chronic administration of IFN alfa inhibits central dopaminergic activity. Asnis at al.

(90) have suggested that a "surge" of dopamine may underlie mania following IFN withdrawal.

Cognitive Impairment

IFNs are capable of stimulating the production of human interleukin-2 (IL-2) (91). In vitro studies have shown that in humans, purified natural human interferon alfa increases the production of IL-2 by mitogenically-stimulated leukocytes (92). Nemni et al. (93) demonstrated that chronic administration of recombinant human IL-2 is associated with neuronal loss in the mice hippocampus. It also has been demonstrated that recombinant IL-2 prevents induction of long-term potentiation in rats (94). Furthermore, recombinant IL-2 decreases potassium-evoked release of acetylcholine in the rat brain (95).

Psychotic Symptoms

The mechanism by which IFN alfa may induce psychotic symptoms (in the absence of a history of psychosis) is unclear. In mice, repeated intraperitoneal injections of natural IFN alfa decrease the brain concentration of dopamine suggesting inhibition of the dopaminergic transmission (89). Clinically, akathisia has been reported in patients treated with IFN alfa (96). Sunami et al. (97) reported alleviation of IFN alfa-induced akathisia by the intravenous use of levodopa. There is evidence indicating that decreased activity of the CNS serotonergic system results in hyperactivity of dopaminergic system in the brain (98). A relative hyperdopaminergic state may underlie IFN-associated psychotic symptoms.

Isolated IFN-induced Psychiatric Symptoms

Expression of suicidal or homicidal ideations may indicate the onset of an IFN-induced mood disorder or exacerbation of a pre-existing psychiatric disorder. It is quite possible that in some patients IFN-altered serotonin system results in irritability and aggressive behavior without causing a full-blown disorder.

MANAGEMENT OF IFN NEUROPSYCHIATRIC SIDE EFFECTS

The basic elements of managing psychiatric side effects of IFNs must include educating patients about the side effects and monitoring them closely and regularly. In patients with a prior history of psychiatric disorders, a psychiatric examination prior to initiation of IFN therapy is necessary. Symptomatic patients must be treated with appropriate psychotropic agents. Attention must be paid to abnormal laboratory studies including thyroid function tests and hemogram. EEG studies may be helpful to distinguish IFN-induced delirium or cognitive disorder from IFN-induced depression.

Mood-related Symptoms

Close monitoring of IFN-treated patients should be conducted on a regular basis using clinical interviews and rating scales for mood-related symptoms (99). Discontinuation of IFN may be necessary in severe cases. The symptoms usually resolve within two to four weeks after discontinuation of IFN (100). When they persist, the use of antidepressants should be considered.

There are several case reports and uncontrolled clinical studies advocating the use of antidepressants for treatment of IFN-induced depressive symptoms. However, no controlled study on the efficacy of antidepressants for treatment of IFN-induced depression has been conducted. Nonetheless, when IFN treated patients experience severe depressive symptoms associated with suicidal ideations, the use of antidepressants becomes inevitable.

With a few exceptions, selective serotonin reuptake inhibitors (SSRIs) have been utilized for treatment of IFN-induced depression. Levenson and Fallon (101) first reported the successful use of fluoxetine for treatment of IFN-induced depression in a patient with CHC. There are a number of reports in which SSRIs have been utilized to treat IFN-induced depression. In a retrospective review, Gleason and Yates (102) reported SSRI treatment of five patients with CHC (two with paroxetine and three with sertraline). Four patients who responded to the SSRIs. One of the patients did not tolerate sertraline was successfully treated with imipramine 150 mg daily. Schramm et al. (103) treated 10 patients with CHC and IFN-induced depression. Within two to four weeks, seven patients improved on sertraline 50 mg daily. Kraus et al. (104) treated 14 patients with CHC and IFN-induced depression. The authors utilized paroxetine 20 mg daily which, within four weeks, resulted in improvement in eleven patients who completed IFN therapy. Another member of the SSRI class, citalopram, also has been utilized in a prospective study involving patients with CHC (105).

There are only a few reports on use of non-SSRI antidepressants for treatment of IFN-induced depression. Successful use of nortriptyline has been reported in a single case report (106). Kirkwood et al. (107) have recommended the use of mirtazepine due to its dual action and limited drug interaction. Yoshida et al. (108) described a patient with metastatic renal malignancy and INF-induced depression. His symptoms did not respond to dose reduction and trazodone. He was started on milnacipran (a serotonin/norepinephrine reuptake inhibitor) 75 mg daily, which completely resolved his depressive symptoms. In a single-case report, bupropion has been reported to alleviate IFN-induced depressive symptoms in a patient with CHC (109).

Some authors have even suggested prophylactic use of SSRIs in patients who are considered for IFN therapy. Hauser et al. (110) reported prophylactic effects of fluoxetine in a patient with malignant melanoma. Musselman et al. (111) reported prophylactic effect of paroxetine in a double-blind, placebo-controlled study involving 40 patients with malignant melanoma. Two weeks before treatment with IFN alfa-2b, half

of the patients were started on paroxetine 20 mg daily. The other half were given placebo. The IFN treatment consisted of 20×10^6 U/m^2 of body surface intravenously administered five days a week for four weeks, followed by 10×10^6 U/m^2 subcutaneously for three days per week for eight weeks. In the placebo group, seven patients discontinued IFN therapy due to severe depression. In the paroxetine group, only one patient was withdrawn from IFN therapy. However, Loftis and Hauser (112) do not recommend prophylactic use of antidepressants and alert clinicians to the risk of hemorrhage in patients with CHC treated with the SSRIs.

After completion of IFN therapy, antidepressants should be cautiously withdrawn. A case report has indicated the recurrence of depressive symptoms within a few days after discontinuation of IFN alfa 2b in a patient without a prior history of mood disorder (113). The literature suggests that IFN-induced depression usually responds to antidepressants. However, it is conceivable that in some cases the severity of depressive symptoms accompanied by suicidal ideations or plan may require the use of electroconvulsive therapy (114).

IFN-induced mania has been treated with antipsychotics, and lithium (30, 37). Howes and McKenzie (38) have reported the use of valproic acid for IFN-induced mania in a patient with CHC. Their patient had a partial response to the combination of olanzapine and clonazepam for six weeks. Adding valproic acid to the combination resulted in remission in two weeks. Greenberg et al. (37) have reported the use of gabapentin for IFN alfa-induced bipolar disorder in two patients with melanoma. There is no controlled data on the use of anti-manic agents in patients with IFN alfa-induced manic symptoms. It is not known whether the resolution of manic symptoms is due to use of anti-manic agents or cessation of IFN alfa therapy.

The choice of an anti-manic agent for treatment of IFN-induced manic symptoms may depend on patient's co-existing illnesses. In patients with hepatic dysfunction, lithium is probably an appropriate choice. IFN alfa can cause extra pyramidal symptoms and akathisia. Therefore when using antidopaminergic agents, there may an increased likelihood of severe extra pyramidal side effects.

Cognitive Impairment

There is much less data on the management of IFN-induced cognitive symptoms. Clinically, the IFN-induced cognitive deficits can be detected by conducting a mental status examination.

The treatment of IFN-induced delirium necessitates suspension of IFN treatment and general management of delirium. Again, atypical antipsychotics or benzodiazepines may be used. Severe cognitive deficits are probably best managed by appropriate dose reduction. It has been suggested that naltrexone may be of potential value in counteracting some of the neurotoxic symptoms (115). The use of cholinesterase inhibitors and NMDA receptor antagonists for IFN induced cognitive deficit has not been studied.

IFN-associated Psychosis

Management of IFN-associated psychotic symptoms includes dose reduction and the use of antipsychotics if the symptoms persist. Toxicological studies may be necessary to rule out substance-induced psychotic symptoms.

Isolated IFN-induced Psychiatric Symptoms

These symptoms may respond to supportive measures. Severe insomnia and anxiety may be alleviated by short-term use of hypnotics and benzodiazepine derivatives. IFN-treated patients who report irritability, insomnia or anxiety must be closely monitored because these symptoms may indicate the onset of an IFN-induced mood disorder.

Proposed Predictors of IFN-related Neuropsychiatric Side Effects

Several studies have attempted to identify factors that may predict psychiatric side effects in IFN-treated patients. The review of the literature suggests that IFN-induced cognitive impairment is likely to occur with high-dose therapy and long-term treatment. Patients with pre-existing mood disorder (mania or depression) and CNS lesions are also at risk. Capuron and Ravaud (116) have suggested that patients' pretreatment affective state may predict IFN-induced depression. In a prospective study involving patients with CML pretreatment psychiatric diagnosis was associated with severe psychiatric symptoms during treatment with IFN-alfa 2b (117). A more recent study indicates that sleep difficulties prior to IFN alfa treatment renders patients vulnerable to IFN-induced depression (118).

Other studies have focused on biological factors. Juengling et al. (119) have suggested that prefrontal hypometabolism might be a "predisposing factor" for IFN-induced depression. In a small group of patients with malignant melanoma, cortisol response to acute administration IFN alfa was predictive of IFN induced depression (120). Maes and Bonaccorso (121) have shown that in a small group of patients with CHC, low baseline serum levels of propylendopeptidase (which degrades thyrotropin-releasing hormone) and dipeptyl peptidase IV (which degrades interleukin-1 and -6) predicted higher depressive symptoms during treatment with IFN alfa. In another study, Gochee et al. (122) reported that in a group of 110 patients with CHC the apolipoprotein E $\in$ 4 allele was associated with higher rate of IFN-induced mood-related symptoms.

The Use of IFN in Patients with Pre-existing Psychiatric Disorders

The use of IFNs in stable psychiatric patients is not necessarily contraindicated (37). However, IFN should not be used in unstable patients and patients with suicidal behavior and florid psychotic symptoms. Even in stable patients, it is important to assess the capacity of the patients for understanding the potential side effects of IFN treatment.

Van Thiel et al. (123) described treatment of 31 patients with CHC and co-existing psychiatric disorders. Twenty-nine patients completed treatment with IFN alfa for six months. In another study, Pariante et al. (124) in a prospective design studied 50 patients with CHC who were treated with IFN alfa. The patients with pre-existing anxiety and mood disorders did not have a higher rate of IFN treatment interruption. In another study, Hosoda et al. (78) reported successful completion of treatment with IFN alfa in patients with CHC and a history of psychiatric disorders. The use of interferon alfa in patients with CHC and substance abuse disorder has been a challenge. It has been asserted (without clinical data) that interferons may trigger relapse in patients with CHC who are in remission of substance abuse disorder (125). However, the use of interferon alfa in patients with CHC and coexisting substance abuse disorders or a history of alcohol dependence is not contraindicated (125).

Such patients should be strongly encouraged to enroll in substance abuse programs. In a group of patients with CHC and polysubstance dependence, IFN therapy yielded a sustained virologic response despite a high relapse rate (126). In a prospective study, Schaefer et al. (127) treated 81 patients with CHC with and without preexisting/coexisting psychiatric disorders including former substance abusers and methadone-treated patients. The treatment consisted of IFN alfa 2a three times a week and daily ribavirin. With respect to development of depressive symptoms and virologic response, no significant difference was detected among the subgroup of patients. Mauss et al. (128) conducted a prospective controlled study involving patients with CHC enrolled in methadone maintenance program. The patients were treated with peginterferon alfa 2b and ribavirin. With respect to psychiatric side effects, there was no significant difference between the methadone-treated patients and the control group.

With respect to IFN beta, Göeb et al. (129) have reported delirium (accompanied by psychotic symptoms) in a patient with MS and a history of major depression. However, Feinstein et al. (130) prospectively studied 42 patients with relapsing-remitting MS. Twenty-three patients had a history of mood, anxiety and substance abuse disorders. The use of IFN beta 1b for one year was not associated with an increase in major depression. The investigators concluded that the use of IFN in patients with major depression is not contra indicated.

When patients with preexisting or existing psychiatric disorders are being considered for IFN therapy, a psychiatric evaluation must be conducted prior to initiation of IFN therapy. The patients should be stabilized and residual symptoms must be recognized. Rating scales can help the clinicians to establish a baseline. When patients are stabilized, IFN treatment can be initiated and patients should be closely monitored.

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