REVIEW ARTICLE

Psychiatric Side Effects of Interferon Therapy: Prevalence, Proposed Mechanisms, and Future Directions

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Abstract: **The increasing use of interferon (IFN) in treating a variety of disorders including, malignant melanoma and hepatitis C, has resulted in the identification and increasing concern about the psychiatric side effects that can result from treatment. These effects can occur either shortly after beginning IFN therapy or later as a result of continued treatment. Studies have reported the incidence of later side effects, which include symptoms of depression, anxiety, and occasional suicidal ideation, to be from 0% to 70%. Case studies have demonstrated that pharmacologic interventions are beneficial in reducing iatrogenic psychiatric symptoms while allowing patients to maintain IFN therapy. The present article provides an overview of the psychiatric effects of IFN therapy, the proposed mechanisms of these side effects, and case studies that provide mechanistic support. In addition, limitations of the current literature are provided with suggestions for treating physicians and a discussion of possible future research directions.**

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THE CONTINUED invention of chemical and biologic therapies for medical disorders, such as melanoma, hepatitis C, multiple sclerosis, chronic myelogenous leukemia, and others, has provided physicians with additional avenues in their attempts to provide efficacious treatments. One such biologic intervention, which in its various forms has been approved for use with several medical illnesses, is interferon (IFN).[1] As the use of IFN, and particularly IFN-alfa, has increased, a number of side effects have been identified. When severe, these side effects have resulted in reduction or cessation of IFN therapy. In this article, an overview of the psychiatric side effects is presented after a brief description of IFN. In addition, this article will discuss the proposed reasons for these side effects based on animal models and case studies, identify current limitations in the literature, provide suggestions for physicians to help monitor the development of psychiatric side effects, and suggest avenues of future research.

BACKGROUND OF IFN

IFN is a complex family of proteins that includes three different subspecies, alfa (α), beta (β), and gamma (γ), and acts as part of the body's defense systems to combat foreign materials such as microbes, antigens, viruses, and tumors.[2,3] As such, IFN has both antiviral and antitumor properties that allow it to be used to treat multiple medical conditions. For example, the antiviral activity afforded by IFN in treating hepatitis occurs because of its ability to induce protein synthesis by binding to specific receptors and prevent viral replication.[4,5] In contrast, the antitumor effects can occur by slowing the growth of tumor cells, reducing the availability of essential metabolites, and increasing cell lysis.[2] Finally, IFN can also increase the function of macrophages, natural killer cells, and cytotoxic T cells and even effect cytokine gene expression.[2] Currently, use of IFNα has been approved for use in treatment of hairy cell leukemia, Kaposi's sarcoma in AIDS patients, cutaneous melanoma, and hepatitis C.[2] IFNβ is used in the treatment of multiple sclerosis,[6] and IFNγ is used in the treatment of chronic granulomatous disease.[1]

PREVALENCE OF SIDE EFFECTS

Side effects from IFN treatment fall into two primary categories, constitutional reactions to the initiation of therapy and reactions after repeated high-dose administration. Initial reactions to the medication include chills, fever, fatigue, nausea, vomiting, and malaise that can begin 30 to 120 minutes after IFN treatment and persist for several hours.[7] Continued administration of IFN has resulted in a decrease in the acute flu-like side effects of treatment.[3] Moreover, these side effects are not usually dose-limiting and can be relieved with acetaminophen or anti-inflammatory medications.[1] Although symptoms can occur at any time throughout treatment, it has been reported that 90% of side effects occur within 3 months of starting treatment, with 60% occurring within 1 month, 40% within 2 weeks,

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and 20% within 1 week.[8] Several patient variables, including age, performance status, and underlying disease, have been reported to impact the severity of side effects. Specifically, patients who are younger, have better performance status, and who require lower doses of IFN have reported experiencing fewer side effects.[1]

After several weeks of IFN therapy, individuals may complain of memory loss, depression, cognitive slowing, and reduction in goal-directed behavior.[9] They may also complain of physical side effects, including gastrointestinal toxicity, peripheral neuropathy, cardiac toxicity, and metabolic abnormalities. The majority of these side effects have primarily occurred with elderly patients and seem to be dose-related.[3,7,10] The most important side effect seems to be the continued presence of fatigue associated with long-term IFN therapy and identified as the primary dose-limiting side effect.[1] For the majority of patients, discontinuation of IFN therapy results in remission of side effects in 2 to 3 weeks,[11] although persistent symptoms have been reported up to 3 years after treatment.[12]

In a significant minority of patients, repeated administration of high-dose IFN results in confusion, lethargy, impaired mental state, depression, mania, and, on occasion, suicidality. The prevalence of these side effects ranges from 0% to 70% depending on the study and the side effect reported.[10,12a-16] Table 1 lists recent studies reporting the development of psychiatric side effects, the disease studied, and the dose, duration, schedule, and variety of IFN used.

As evidenced in Table 1, the variability in the reporting of psychiatric side effects seems to be a result of differences in dosage, disease, and length of treatment.[10,13,18,27,31] An additional variable that may be impacting the identification of psychiatric side effects is the specific way the presence of psychiatric side effects are assessed. Assessment of psychiatric side effects ranges from standardized questionnaires to clinical psychiatric interviews.[13,16,18,24,27,32] Table 2 presents a summary of the various instruments that have been used to identify psychiatric side effects associated with IFN therapy. Weiss[10] noted that the likely result of the inconsistent assessment methods is an underreporting of psychiatric reactions to IFN. She further asserted that depression in particular may not be adequately linked to IFN therapy and may be mistaken for lethargy. As such, the actual rate of depression induced by IFN therapy is unknown.

In addition to identifying psychiatric side effects associated with IFN treatment, studies have also been interested in identifying neuropsychiatric changes and have used neuropsychologic batteries in an attempt to identify these changes. The majority of studies have reported that individuals experience changes in verbal memory, attention, fine motor speed, visual scanning, and executive abilities while undergoing IFN therapy.[16,27,29,33,34] This has led to the suggestion that the observed effects of IFN may be the result of changes that they effect on the frontal lobes.[16,33] However, how this occurs has not been elucidated. Etiologic explanations for the development of psychiatric side effects will be discussed later in the article.

Even if individuals do not meet diagnostic criteria for a disorder, the presence of some diagnostic symptoms during therapy can lead to cessation of treatment. Of these, suicidal ideation and/or attempts, although infrequent, are of greatest concern. Reports of attempted suicide have been reported in individuals with chronic viral hepatitis during IFN treatment.[17] In one report of a woman being treated for hepatitis C, the patient became mildly depressed, exhibited irritability, insomnia, and anxiety, and was subsequently admitted to hospital after setting herself on fire.[23] Janssen et al[17] noted that suicidal attempts frequently follow the development of emotional lability, depression, and apathy, and consistently remit after discontinuation of IFN treatment. They further note, however, that suicidal ideation and attempts are rare, occurring in about one in every 515 patients, according to a survey of 15 hospitals from 10 countries. Interestingly, none of the individuals who developed suicidal ideation, including the aforementioned case, had known psychiatric histories before beginning IFN treatment.

A history or presence of psychiatric symptoms has been considered to be a relative contraindication for using IFN therapy because of the ability of IFN to induce depressive symptoms in normal individuals. As such, little is known about the ability of depressed, anxious, or schizophrenic patients with hepatitis or other diseases to respond positively to IFN treatment. In perhaps the only study that did investigate the ability of IFN to treat patients with premorbid psychiatric illness, Van Thiel et al[22] investigated 31 patients with psychiatric illness and either chronic active hepatitis or chronic persistent hepatitis. Patients had previously been diagnosed with either schizophrenia, depression, or bipolar disorder and were treated with IFN while at the same time maintaining their therapeutic medication. Van Thiel et al[22] concluded that collaboration between psychiatrists and hepatologists allowed 94% of the patients to complete 6 months of IFN therapy. Moreover, the pattern of fatigue experienced by nonpsychiatric patients was identical in that all patients experienced fatigue. None of the patients stopped IFN treatment because of an exacerbation of their psychiatric symptoms. The results from this study suggest that individuals with psychiatric histories and concomitant psychiatric illness can be successfully treated with IFN without an exacerbation of their side effects provided that cooperation between psychiatrist and hepatologist occurs.

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Table 1. Clinical Trials Evaluating the Neuropsychiatric Complications of IFN Therapy

Author	No. of Patients	Disease	Dose, Schedule, Duration, Type of IFN	Side Effects	% of Patients
McDonald et al[13]	40	Chronic hepatitis B	2.5 mu/m^2, tiw, 3-6 mo, recombinant IFNα-A	Fatigue (NR)	
			5 mu/m^2, tiw, 3-6 mo, recombinant IFNα-A	Loss of interest (NR)	
			10 mu/m^2, tiw, 3-6 mo, recombinant IFNα-A	Poor concentration (NR)	
				Anxiety (NR)	
				Depression (NR)	
Janssen et al[17]	3	Hepatitis B	5 mu daily, 3 mo, lymphoblastoid IFN	Irritability, suicidal ideation	
		Hepatitis C	6 mu, tiw, 3 mo, recombinant IFN	Depression, suicidal ideation	
		Hepatitis B	5 mu, daily, 5 mo, recombinant IFN	Depressed, successful suicide	
Renault et al[18]*	58	Hepatitis B	10 mu, every other day, 4 mo, recombinant IFNα	Fatigue	20
		Hepatitis D	5 mu, daily, 4 mo, recombinant IFNα	Psychiatric SE (not specified)	17
		Hepatitis C			
		Autoimmune hepatitis			
Van Thiel et al[19]	29	Hepatitis C	5 mu, tiw, 6 mo, IFNα	Fatigue	100
			5 mu, daily, 6 mo, IFNα		
Levenson & Fallon[20]	1	Hepatitis C	6 mu, NR, 9 mo, IFNα	Depression	
Goldman[21]	1	Hepatitis C	3 mo, tiw, 1 mo, IFNα	Irritable	
				Depression	
Van Thiel et al[22]†	31	Hepatitis C	5 mu, tiw, 6 mo, IFNα	Mania	6
			5 mu, daily, 6 mo, IFN		
Yokoyama et al[8]	2	Hepatitis C	9 mu, tiw, 2 mo, IFNα-2a	Depression	
			NR, tiw, 6 mo, IFNα-2b	Depression, delirium	
Fukunishi et al[23]	1	Hepatitis C	9 mu, daily then tiw, 38 days, natural-type IFNα	Suicide attempt	
				Anxiety	
				Depression	
				Irritability	
Malaguarnera et al[24]	96	Hepatitis C	3 mu, tiw, 6 mo, recombinant IFNα-2a	Depression	100
			3 mu, tiw, 6 mo, recombinant IFNα-2b		
			3 mu, tiw, 6 mo, leukocyte IFNα		
Donnelly et al[25]	143	Melanoma	20 mu/m^2, 5 d/wk, 4 wks, IFNα-2b plus 10 mu/m^2, tiw, 48 wks	Fatigue	96
				Depression	40
Mohr et al[26]	85	Multiple sclerosis	NR, NR, IFNβ-1b	Depression	41
Pavol et al[27]	25	Chronic myclogenous leukemia	17-77 mu, daily, 1 wk-84 mo, IFNα	Depression	50
Iancu et al[28]	1	Chronic myclogenous leukemia	9 mu, daily, 7 mo, IFNα	Euphoric	
				Mania	
Strite et al[29]	2	Chronic myclogenous leukemia	3 mu, every other day, 31 mo, IFNα	Mania	
			NR, NR, 2 yrs, IFNα	Irritable, psychiatric sx	
Valentine et al[30]	9	Chronic myclogenous leukemia	5×10^6 μ/day to 9.8×10^6 μ/day, NR, 1-59 mo, IFNα	Fatigue	88
		Essential thrombocythemia		Irritability	22
				Anxiety	22
				Depression	33
				Confusion & emotional lability	11

Abbreviations: mo, month; mu, million units; NR, not reported; SE, side effects; tiw, three times a week.

*Hepatitis B, 49 patients; hepatitis D, four patients; hepatitis C, four patients; and Autoimmune hepatitis, one patient.

†Study used collaboration with psychiatrist to treat patients.

Nevertheless, given the small sample size and the low dose of IFN used, the results should be interpreted with caution.

Currently, research and clinical case reports have consistently identified the onset of psychologic symptoms during IFN therapy. It is likely that these findings have contributed to the exclusion of individuals with pre-existing psychiatric histories from IFN treatment, despite the preliminary findings that such treatment does not necessarily increase psychiatric symptoms. Although the onset of psychiatric symptoms has been repeatedly documented, what remains

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Table 2. Measure Used to Determine Presence of Psychiatric Side Effects

Author	Measure
Valentine et al[16]	MMPI
Pavol et al[27]	MMPI
Strite et al[29]	MMPI
Renault et al[18]	SCL-90
Malaguarnera et al[24]	Zung Self-Rating Depression Scale
Mapou et al[32]	Beck Depression Inventory, Spielberger State-Trait Anxiety Inventory
McDonald et al[13]	Clinical Interview Schedule General Health Questionnaire

Abbreviations: MMPI, Minnesota Multiphasic Personality Inventory; SCL-90, Symptom Checklist 90.

unknown is why the symptoms develop in the first place. It is possible that some basic risk factors may result in the development of psychiatric side effects (eg, substance abuse, specific disease, and age). It is also possible that a specific disorder or dose of IFN may be responsible for the development of symptoms. The fact that psychiatric side effects have been identified in a variety of diseases and dosages, as well as in patients of varying age and substance abuse history, suggests that the mechanism is neither disease-, dose-, nor behavioral or demographically related. Instead, it is possible that the development of psychiatric side effects results from the action of IFN on basic biologic mechanisms, several of which are presented in the next section.

PROPOSED MECHANISMS FOR SIDE EFFECTS AND SUPPORTING STUDIES

It is widely acknowledged that the specific mechanism responsible for the beneficial effects and, in contrast, the development of psychiatric side effects of IFN is unknown. Because IFN does not readily cross the blood-brain barrier, it is not the direct action of this agent on the brain that is responsible. Despite this, a number of central and peripheral neurochemical and endocrine effects have been proposed based on animal studies and case reports.[21,30] These speculations have fallen into the following categories: opioid-dopamine changes, serotonin depletion, and norepinephrine increases, consistent with the research on the role of neurotransmitters in depression, and effects on thyroid function. Since the 1970s, changes in plasma catecholamine levels in depression have been reported,[35,36] and dopamine, norepinephrine, and serotonin have all been associated with the onset and continuation of depression.

Opioid-Dopamine Changes

Opioids serve as mechanisms for promoting endogenous analgesia and, as a term, describe compounds whose actions can be antagonized by naloxone. Traditionally, opioids have been associated with pain modulation, reward systems, and learning and memory. Although with much less understanding, opioids have also been associated with the modulation of emotion. Evidence from animal studies has reported that when morphine-dependent rats are given naloxone they will demonstrate signs of withdrawal,[37] including psychologic distress, depression, anorexia, and insomnia.[38] These and similar studies have led to the suggestion that depression in humans may be because of underactivity of endogenous opioid systems.[39] In support of this proposition, in the few studies that have looked at opioid activity and affect in humans, inverse correlations between the severity of depression (as defined by clinical ratings) and plasma opioid activity, increased opioid activity in manic episodes when compared with depressive episodes, and lower levels of beta-endorphins in postpartum depression have all been reported.[40-42] Unfortunately, the opposite has also been reported, resulting in equivocal findings as to the specific role of opioids in depression.[43,44] Clarification of this relationship through trials of opioid agonists and antagonists has not been successful, with the one study that used naloxone to treat depression obtaining inconclusive results.[43]

Despite the equivocal nature of the findings, the relationship between IFN, opioids, and depressive side effects has come from evidence that IFNα causes analgesia and catalepsy and also alters naloxone-induced abstinence in rats that are morphine-dependent.[45,46] In addition, amphetamine discrimination studies[47,48] have provided some evidence that IFN may work through an opioid-associated mechanism as a central dopamine agonist. Based on these findings, in an open trial, Valentine et al[16] administered naltrexone to patients being treated with IFNα. They found that individuals who were able to tolerate naltrexone side effects experienced partial or complete relief of neurotoxic side effects (broadly defined as including mood, anxiety, cognitive, and physical problems) based on visual analog ratings scales and clinical assessment. It should be noted, however, that the naltrexone was given to nine patients, with two developing naltrexone side effects requiring discontinuation. Nevertheless, the results provide initial support for the possibility that IFN exerts psychiatric side effects through opioid mechanisms.

Research exploring the role of dopamine in depression has reported that cerebrospinal fluid concentrations of homovanillic acid, a dopamine metabolite, are reduced in some individuals with unipolar or bipolar depression.[38] In addition, elevated plasma dopamine and homovanillic acid have been reported in individuals with psychotic depression.[49] Elevations have also been reported in women with

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psychotic depression when they were compared with women with nonpsychotic depression.[50] A recent study by Hamner and Diammond[51] reported significant correlations between plasma dopamine levels and depression as measured by the Hamilton Rating Scale for Depression, suggesting that plasma dopamine levels may be a reflection of the severity of depression. The relationship between psychoticism and dopamine suggests that plasma levels of dopamine may also be a reflection of the quality of depression.

Bocci[11] suggested that IFN may affect neurotransmitter activity, for example, the disruption of dopamine, thereby resulting in psychiatric disorders that occur through neurotransmitter reductions (eg, depression and bipolar disorder). Support from laboratory studies more specifically suggests that the neurotoxic effects of IFN may result from its action as a dopamine antagonist. The short-term administration of IFN may increase dopamine and reduce depression, similar to drugs like amphetamines and L-dopa. However, the long-term administration may have the opposite effect, decreasing central dopaminergic activity and increasing depressive symptoms.[27] Additionally, reports of tremor and rigidity, extrapyramidal symptoms of depression, in up to 30% of cancer patients exposed to prolonged high doses of IFNα,[52] which may remain after IFN discontinuation,[12,21,52] seem to support the view point that prolonged IFN acts as a dopamine antagonist.

To date, the findings on the relationship between IFN, opioid-dopamine changes, and depression remain equivocal, and there have been no studies with IFN patients that have specifically looked at the relationship between opioid or dopamine levels specifically and the psychiatric side effects associated with IFN therapy. This lack of findings suggests the ongoing need to develop studies designed to clarify the underlying mechanisms behind the side effects.

Serotonin Depletion

It is now well accepted that a decrease in serotonin is causally related to the onset of depressed mood.[38] One avenue of evidence for this has been research that has looked at CSF levels of the serotonin metabolite 5-hydroxyindoleacetic (5-HIAA) in depressed patients. In several studies of drug-free depressed patients, CSF 5-HIAA levels have been reported to be decreased.[53-55] In addition to lower CSF levels of 5-HIAA, depressed individuals have also been found to have lower levels of plasma-free tryptophan, a serotonin precursor.[56]

Decreases in serum tryptophan levels observed after administration of IFN-α have prompted some researchers to suggest that lowered serotonin levels may be responsible for the psychiatric side effects (especially depression) of IFN therapy.[57] This is consistent with the previously mentioned relationship between serotonin, tryptophan, and depression. If this is the case, then administration of selective serotonin reuptake inhibitors (SSRIs) may reduce the depressive symptoms.

Few studies have been conducted on the administration of an SSRI to treat IFN-induced depression. In one study that addressed this issue, Levenson and Fallon[20] described treatment of a 40-year-old man with hepatitis C who developed depression after treatment with IFNα. His depression was characterized by irritability, hostility, negative thoughts, suicidal ideation, and low energy. Although his symptoms decreased with cessation of IFN therapy, to continue IFN treatment, he was started on fluoxetine in combination with IFN. Depression did not return and fluoxetine was subsequently discontinued after cessation of IFN treatment.

In another study using an SSRI to treat depression associated with IFN therapy, Carpiniello et al[58] reported on an individual with chronic hepatitis B who exhibited symptoms of comorbid depression and panic with agoraphobia during the first month of treatment. Treatment with paroxetine and chlordemethyldiazepam reduced depressive symptoms after 4 weeks and allowed for the continued administration of IFN for 1 year. Interestingly, the abrupt discontinuation of IFN in both of these cases resulted in exhibition of manic symptoms that, when controlled with haloperidol, required reinstatement of paroxetine because of a return of depression.

Although there are currently only two studies that have explicitly treated IFN-induced depression with an SSRI, the positive outcomes suggest that IFN may affect levels of serotonin and subsequently lead to depression. Indeed, Van Thiel et al[19] provided a list of the most commonly used SSRIs for people with hepatitis C, a list that included fluoxetine, sertraline, trazodone, and paroxetine. This suggests that serotonin reuptake inhibitors are used in clinical settings to treat IFN-induced depression despite a lack of controlled clinical trials.

Norepinephrine Increase

The original catecholamine hypothesis asserted that many forms of depression were associated with a deficiency of norepinephrine at important brain adrenergic sites.[59] Investigations of norepinephrine and its metabolite, 3-methoxy-4-hydroxyphenyglycol, conducted in postmortem studies of depressed individuals have been equivocal. Some research shows no changes in plasma and CSF concentrations of norepinephrine or its metabolites,[60,61] whereas others note increased concentrations of 3-methoxy-4-hydroxyphenyglycol in plasma, greater variability of CSF concentrations of

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norepinephrine, and correlations between plasma and CSF levels of norepinephrine in depressed individuals.[38] In the previously mentioned study by Hamner and Diammond,[51] plasma levels of norepinephrine demonstrated a trend toward a significant negative correlation with Hamilton Rating Scale for Depression scores.

There is some evidence that IFNα causes an increase in plasma norepinephrine and a decrease in lymphocyte β2-adrenergic receptors.[62] However, this has only been demonstrated in healthy volunteer test subjects and has not been explored in individuals being treated with IFN therapy. Nonetheless, one case study used tricyclic antidepressants, which have effects on both serotonin and norepinephrine, to treat IFN-induced depression. Goldman[21] reported on a 30-year-old African-American woman with chronic hepatitis C who developed decreased appetite, disrupted sleep, reduced energy, impaired concentration, irritability, anhedonia, and frequent crying after 1 month of IFN therapy. Initiation of nortriptyline reduced symptoms of depression within 2 to 3 weeks and allowed continuation of IFN for the full course of treatment. It has been argued that the Goldman case is not typical in that it did not include systemic side effects of therapy. This led some (ie, Valentine and Meyers[30]) to suggest that the case may have responded better to a less sedating antidepressant (eg, fluoxetine). The symptoms did respond to nortriptyline, however, and the medication also allowed for monitoring of serum levels in a patient with hepatic disease.

In addition to nortriptyline, amitriptyline has also been identified as beneficial in the treatment of IFN-induced depression in hepatitis C.[19] Unfortunately, the fact that tricyclic antidepressants interfere with both norepinephrine and serotonin does not allow for clarification of which system is involved in the depressive effects of IFN therapy. Nevertheless, the general effectiveness of both tricyclic antidepressants and SSRIs suggests that both would reduce IFN-induced depression. As such, the specific antidepressant medication used may be a reflection of the specific psychiatric symptoms an individual is experiencing as a result of IFN therapy, as well as the potential antidepressant side effects that the patient wishes to avoid.

Endocrine Dysfunction

Disorders of thyroid function associated with IFNα administration include both hypothyroid and hyperthyroid states.[63,64] Symptoms of hypothyroidism can be confused with depression and can contribute to the fatigue from IFN. The etiology of thyroid dysfunction associated with IFN administration is unclear. IFN therapy has been associated with the development of thyroid autoantibodies, but not all patients who develop autoantibodies manifest clinical thyroid dysfunction.[65] Patients receiving chronic IFN therapy need to be monitored for symptoms of thyroid dysfunction and receive thyroid replacement therapy when indicated. Patients with pre-existing hypothyroidism may need continual adjustments in thyroid replacement therapy while receiving IFN.

Of the studies that reported on the development of psychiatric side effects (Table 1), only three mentioned that they had tested for thyroid function.[30,66,67] Of these, only one specifically stated that no thyroid dysfunction was noted at the time of follow-up. The fact that thyroid function tests were not reported and may not have been completed in these studies allows for the possibility that the observed psychiatric side effects were not the direct result of IFN therapy. Specifically, it is possible that the side effects were the result of changes in endocrine function potentially caused by the IFN treatment but also possibly a result of the specific disease being treated.

Finally, IFNs can stimulate the adrenocorticotropic hormone/cortisol axis, and administration of IFN can result in increases in serum cortisol levels.[63] The effect of chronic IFN administration on adrenal corticol function has not been well evaluated. Although it has recently been suggested that there is a relationship between cortisol and depression in that the administration of antiglucocorticoid medication to individuals with major depression produced antidepressant effects,[68] the authors noted that the results must be interpreted with caution. Therefore, until the specific relationship between cortisol and depression can be identified, not to mention the relation between cortisol and IFN, it is also unclear how a chronic elevation of cortisol would contribute to the neuropsychiatric effects of IFN.

In summary, several hypotheses have been generated to account for the side effects, particularly depression, of IFN therapy, yet the specific mechanism remains unknown. This continues to make it difficult to design strategies to reduce side effects.[1] In addition to those mentioned in the previous sections, there may be others (eg, the actions of other cytokines or neuroendocrine disturbances) that we have not addressed in this article. Elucidating these may provide more information on the effect that IFN has on brain function and mood (for example, the work by Maes et al[69,70]) and may suggest additional forms of intervention, especially as long-term therapy with IFN is used with greater frequency. Nevertheless, the information provided in the aforementioned case reports suggests that there are a variety of medications that might be used to reduce the psychiatric side effects of IFN therapy. Tricyclic antidepressants, SSRIs, naloxone, and antianxiety agents have all been reported to have some benefit in the treatment of side effects without necessitating the need for reduction in IFN dosage. Thus, it

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is possible that appropriate administration of medication may effectively manage the psychiatric side effects (eg, depression and anxiety).[9] In addition to pharmacotherapy, psychotherapy has also been beneficial in treating IFN-induced depression.[26] Unfortunately, the fact that Mohr et al[26] did not specify the exact type of psychotherapy makes replication with other populations difficult. This is just one of the limitations of studies that have looked at psychiatric side effects; limitations that result in the need for future studies.

LIMITATIONS

The literature on the psychiatric effects of IFN therapy has provided insight into the type of problems individuals treated with this biologic agent may experience. Regardless, several limitations are worth noting. Primarily, these include differences in the operational definition of depression, small sample sizes, unclear identification of the etiology of neurotoxicity, and difficulty identifying risk factors for the development of psychiatric side effects.

Depression is a construct that is capable of being defined differently by different individuals. Following a *Diagnostic and Statistical Manual IV* approach, a diagnosis of depression requires that the individual exhibit five of nine symptoms over a 2-week period, during which one of the symptoms is either depressed mood or loss of interest or pleasure.[71] Alternatively, measures of depression range from those that have diagnostic properties (eg, Diagnostic Interview Schedule and Structured Clinical Interview for *Diagnostic and Statistical Manual IV*) to those that are reliable and valid measurements of depressed mood (eg, Minnesota Multiphasic Personality Inventory, Beck Depression Inventory, and Brief Symptom Inventory) but that are not diagnostic in nature. It should be noted that caution needs to be exercised when using some of these measures with medically ill individuals (eg, Beck Depression Inventory) because there is a tendency within the measure to increase depression scores because of the endorsement of somatic items. The potential result is a spurious increase in depression solely because of somatic items.[66] As such, some researchers have started to use measures that do not include somatic items in their assessment of depression. In contrast to defining depressed status through measurements of depressed mood, some researchers have defined depression through patient description, labeling depression as patient reports that range from fatigue, apathy, and mental slowing to severe dysphoria, helplessness, and anhedonia.[9] Given this discrepancy, one limitation to accurately determining how many individuals actually suffer from depression while on IFN therapy comes from the different definitions and methods used by researchers to define depression.

Another limitation comes from the small sample sizes included in studies. The majority of studies are case reports, providing clinical descriptions of anywhere from one to three patients. Others are open-label drug studies that also use small numbers of patients (ie, nine in the Mohr et al[26] study). Although case studies allow for information that may be useful to individuals to be rapidly disseminated, when it comes to treating symptoms of depression and other psychiatric side effects, the frequent result of such small sizes are idiosyncratic interventions and professional preferences. This is most clearly observed in the discussion between Goldman[21] and Valentine and Meyers[30] over the use of fluoxetine versus nortriptyline. Unfortunately, although such case studies provide insight into an important problem, they are inadequate in serving as clinical studies in the efficacy of one pharmacologic intervention over another. Whereas the widespread use of case studies may be a reflection of the lack of individuals with some diseases being treated with IFN because of prevalence (eg, malignant melanoma) or to the strictness of clinical protocols (ie, the exclusion of patients with previous psychiatric histories), the use of IFN with some populations occurs with enough frequency to move away from case studies and into a priori experiments. In particular, increasing numbers of hepatitis patients are being treated with IFN. This represents not only a population with a sufficient number of subjects but one that may also have a priori psychiatric illness or increased risk of developing psychiatric side effects.

An additional limitation to studies that attempt to identify the reasons for psychiatric side effects is the fact that the specific mechanism responsible for the beneficial effects of IFN is unknown. As such, studies that try to identify reasons for neuropsychiatric disorders in patients undergoing therapy with IFN do so by looking at a third variable. Specifically, knowledge of what causes depression is used to infer that IFN affects similar systems. Although the speculations for such neurotoxicity lie primarily in the serotonin, norepinephrine, and dopamine/opioid systems, no definitive evidence has been produced to clearly identify one as the principal mechanism. Moreover, the possibility remains that a combination of these systems may be responsible for the effects, a possibility that is important in developing rational treatment protocols. Clearly further research is needed to clarify this issue.

Finally, the issue remains as to why some people develop IFN-induced neurotoxicity and psychiatric side effects when others do not. Although a number of risk factors have been identified that increase the risk of developing side effects such as increased age, duration, and dosage of IFN, these have not consistently predicted who develops symptoms and who does not. As such, a number of risk factors

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need to be evaluated. For example, a percentage of individuals with hepatitis C have significant substance abuse histories, which are historically related to mood disorders. Perhaps a history of past substance abuse is predictive of who develops psychiatric symptoms. Identifying accurate predictors of who will develop psychiatric effects is perhaps more important than determining how many individuals develop side effects.

SUGGESTIONS FOR TREATING PHYSICIANS

Given the aforementioned literature, it is almost certain that individuals treated with IFN will experience fatigue and possibly psychiatric side effects such as depression and anxiety. For treating physicians, being able to identify these symptoms early increases the opportunity to treat the side effects and help patients complete IFN therapy. Various assessment procedures, ranging from self-rating scales (eg, Beck Depression Inventory, Profile of Mood States) to clinician ratings based on psychiatric interviews, have been recommended for identifying side effects.[9] To identify side effects, it is important that any measure be reliable in identifying psychiatric symptoms yet brief enough to be completed within 15 minutes. This effectively rules out psychiatric interviews. More appropriate are the self-report scales, which balance internal and external validity, are easy and quick to implement, and identify psychiatric side effects. The identification of significant side effects should prompt a referral to a psychologist or psychiatrist who specializes in the relationship between physical disorders and the psychologic consequences (eg, a psychologist who specializes in behavioral medicine).

Several questionnaire measures meet the criteria of accuracy, reliability, and brevity. The Symptom Checklist-90-R[67] and its shortened form, the 53-item Brief Symptom Inventory,[72,73] both assess for the presence of psychiatric symptoms and take between 5 and 15 minutes to complete. The questionnaires ask the patient to report how distressed they were by the following questions during the past week. Individual items are answered on a 0 (not at all distressed) to 4 (extremely distressed) scale and are summed into one of nine clinical scales (eg, depression, somatization, paranoid ideation, and so on) and three summary scales. Principle among the summary scales is the General Severity Index, which provides the most sensitive measure of overall distress. The Brief Symptom Inventory is standardized using area T scores, with a mean of 50 and a SD of 10. For clinical purposes, a T score greater than 70 is representative of distress significantly high enough to warrant intervention.

The Beck Depression Inventory,[74] the Hospital Anxiety and Depression Scale (HADS)[75] and the Spielberger State Trait Anxiety Inventory[76] are all short (21, 14, and 40 items, respectively) self-administered questionnaires with good reliability and validity. Each has cutoff scores representing significant distress. The Beck Depression Inventory specifically assesses for the presence of depression and has been criticized for the inclusion of somatic symptoms of depression that may be present in many medical patients and may spuriously increase the reporting of depression. To that end, the HADS is more effective because it does not include the somatic symptoms. The HADS is also additionally helpful in that it assesses both anxiety and depression. For the assessment of anxiety alone, the Spielberger State Trait Anxiety Inventory assesses both dispositional and transient anxiety. This could be beneficial in determining whether anxiety is increasing during treatment.

Table 3. Short Self-Administered Questionnaires and Cutoff Scores

Measure	Cutoff Score
SCL-90-R	50 = Normal distress
	60 = Moderate distress
	70 = Severe distress
BSI	50 = Normal distress
	60 = Moderate distress
	70 = Severe distress
BDI	21 for clinical purposes
HADS	10 on either scale
STAI	40 on either the state or trait scale

Abbreviations: SCL-90-R, Symptom Checklist 90-Revised; BSI, Brief Symptom Inventory; BDI, Beck Depression Inventory; STAI, State Trait Anxiety Inventory.

Regardless of which measure is chosen, it is important to administer the questionnaire before the patient begins IFN to obtain a baseline measure of functioning. Given that the majority of psychiatric side effects develop during the first 3 months,[8] administering the questionnaire monthly during this time should provide the greatest opportunity for identifying changes. Valentine et al[9] suggested that longitudinal markers of distress should be obtained at baseline (pretreatment) and routinely every 3 months. As discussed below, this length of time may be too long. A referral to a psychologist or psychiatrist would be appropriate when scores pass the criteria for significant distress. Table 3 lists the measures and their cutoff scores for determining mild, moderate, and severe distress.

FUTURE DIRECTIONS FOR RESEARCH

The 3-month period between assessments suggested by Valentine et al[9] may actually be too long a time between assessments. Specifically, different diseases frequently have IFN protocols of various dosages. For example, a higher dose of IFN is used in melanoma in comparison with

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hepatitis C. Given that a percentage of individuals report increased emotional distress during the first month, a 3-month assessment timetable may miss the increase in depression. In ongoing, separate studies by Trask and colleagues with hepatitis C and melanoma patients, emotional distress is being assessed on a monthly basis. As a result of this schedule, increases in emotional distress have been observed after 1 month of treatment, with additional increases in the second month.

The identification of significant increases in emotional distress from baseline during the first month of IFN therapy strongly argues for the need to provide appropriate adjuvant treatment to combat this distress. Although it has already been mentioned that several pharmacologic agents seem efficacious in treating side effects, there is a lack of prospective studies that do not allow for the systematic exploration of the efficacy of one method over another.[77] Moreover, the viability of psychologic interventions has not been tested. If the onset of psychiatric side effects is looked at from a behavioral perspective, they seem to occur as a result of increased fatigue resulting from IFN therapy. The functional impairment (eg, social withdrawal, job absenteeism, somnambulism, and reduction in physical activities[7]) that occurs with continued therapy is consistent with the behavioral theory of depression. This theory states that a reduction in physical activities and withdrawal place the individual at increased risk for depression and will eventually lead to depression should the pattern continue.[78] Given this possibility, future research needs to be conducted that compares different interventions, both pharmacologic and psychologic. Identification of useful interventions may allow prophylactic use of psychopharmacologic or psychotherapeutic interventions that begin concomitant with IFN therapy.

Thus, future studies on IFN need to focus on (1) determining the underlying mechanisms responsible for the development of psychiatric side effects, (2) identifying variables that discriminate those who develop psychiatric side effects from those that don't, and (3) developing viable treatments that can subsequently be used in conjunction with IFN therapy. As Valentine et al[9] pointed out, the relationship between past psychiatric history, family history, current psychologic stressors, and available antidepressant medication needs to be determined.

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