Care & Counsel II: Helping Patients Stay the Course on Treatment for Hepatitis C

HCV Side Effects Management Handbook

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Dear Colleague:

Clinicians really make a difference in the management of hepatitis C by helping patients understand and gain control of their disease and its treatment. Results of the Care & Counsel II survey, included as an addendum to this handbook, indicate that healthcare providers believe support staff greatly influence treatment outcomes and patient adherence to treatment. Side effect management is a crucial component of the care provided by support staff and one of the primary means by which support staff improve adherence.

We are pleased to provide you with this Care and Counsel II Side Effects Management Handbook, which contains comprehensive information about the side effects of peginterferon/ribavirin combination therapy. Practical recommendations are provided for both prevention and management of these side effects. Strategies include important points for patient education, nonpharmacologic management approaches, and adjuvant therapies that are helpful in alleviating side effects.

You provide an invaluable service to your patients with hepatitis C. We hope you find this handbook to be an equally invaluable reference tool that guides you in your efforts to help patients stay the course of treatment.

Sincerely,

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This handbook is planned and produced as an independent CME activity in accordance with the ACCME Essential Areas and Policies. Projects In Knowledge designates this educational activity for a maximum of 5.25 category 1 credits toward the AMA Physician’s Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

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The Society of Gastroenterology Nurses and Associates has assigned identification number 03-033 to this activity.

This activity is valid for CE credit from June 1, 2003 to May 31, 2005.

There is no fee for this activity.

Successful completion for 5.25 hours of CME credit or 6.4 contact hours of CE credit requires a passing score of 70% or higher on the posttest. Full instructions for submission are included on the posttest at the end of the handbook.

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This activity may include a discussion of therapies that are unapproved for use or investigational, ongoing research, or preliminary data.

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This independent CME/CE activity is supported by an unrestricted educational grant from Schering Hepatitis Innovations.
TARGET AUDIENCE AND LEARNING OBJECTIVES
This activity is designed for nurses and other support professionals who see patients with hepatitis C in a medical setting, and for physicians who lead multidisciplinary treatment teams. Upon completion of this activity, participants should be able to

• Identify necessary parameters needed for measuring side effects and treatment responses

• Review effective management of adverse effects of peginterferon and ribavirin to achieve optimum treatment outcomes

• Expand ways to provide education and support to HCV-infected patients and their families to help them stay the course on treatment
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### Hydration and Diet

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I. Introduction

Remarkable progress has been made in the management of hepatitis C in recent years, and it is now possible to cure more than half of all treated patients. Pegylated interferon has largely replaced standard interferon, and peginterferon/ribavirin combination therapy has become the standard of care. We now have almost 2 years’ worth of experience using peginterferon alfa-2b (Peg-Intron®)—which was approved by the US Food and Drug Administration (FDA) in January 2001 for use as monotherapy and in August 2001 for use in combination with ribavirin (Rebetol®). Clinicians have become increasingly sophisticated in offering personal, individualized therapy to patients infected with hepatitis C virus (HCV). This individualized care includes weight-based dosing, as well as early assessment of response, tailoring of care according to the patient’s histologic findings and HCV genotype, and aggressive monitoring and management of side effects.

Another pegylated interferon product, peginterferon alfa-2a (Pegasys®), was more recently approved by the FDA for use as monotherapy (approved October 2002) or in combination with ribavirin (Copegus™) (approved December 2002). The addition of polyethylene glycol to interferon extends its half-life, produces more favorable pharmacokinetics, increases its biologic/immunologic activity, and allows once-weekly dosing, but the interferon component remains the active biologic agent. The pharmacokinetics of the two peginterferons’ concentrations vary considerably, but similar types of side effects are seen with all interferon alfa–based therapies, and the addition of ribavirin to any of these therapies adds additional ribavirin-specific side effects.

Peginterferon/ribavirin is quite effective, but it is not an easy regimen for patients to complete. Virtually all patients experience side effects. Adherence to treatment clearly has an important impact on treatment outcomes, and clinicians need to take an aggressive approach to keep patients on treatment. Patients need to be prepared for side effects at the initiation of therapy. When side effects do occur, clinicians should take advantage of effective adjunctive therapies to manage them aggressively and help patients stay the course of care. This CME/CE Side Effects Management Handbook is designed to provide you with a comprehensive, logically organized reference tool for managing the side effects of peginterferon/ribavirin in patients with HCV infection. Contained herein you will find practical strategies, including pharmacologic and nonpharmacologic options, for preventing and treating side effects of anti-HCV therapy.
**II. Cardiovascular**

**WARNING:**
Peginterferon must be used with caution in patients with a history of cardiovascular disease (CV). Those patients with a history of myocardial infarction (MI) and/or previous or current arrhythmias should be monitored closely. CV adverse experiences, which include hypotension/hypertension, arrhythmias (including tachycardia: ≥150 beats/min), cardiomyopathy, angina pectoris, and MI have been observed in patients treated with pegylated interferons with or without ribavirin. Patients who have pre-existing cardiac abnormalities should have electrocardiograms (EKGs) administered before antiviral therapy is initiated. Cardiologic consultation should be considered on an individualized basis.

Fatal and nonfatal MIs have been reported in patients with anemia caused by ribavirin. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy and should be monitored appropriately during therapy. If there is any deterioration of CV status, therapy should be suspended or discontinued. Because cardiac disease may be worsened by drug-induced anemia, patients with a history of significant or unstable cardiac disease should not use ribavirin.

**GENERAL CARDIAC EXCLUSION CRITERIA (ANECDOAL)**

- Cardiologist deems patient an unstable candidate for treatment based on CV status
- Prior anthracycline treatment, mediastinal radiation, or high-dose alkylating agents resulting in CV compromise
- Congested heart failure (CHF)
- A history of significant or unstable CV disease

**PRETREATMENT ASSESSMENT**

1. Electrocardiogram (EKG) and/or stress test are indicated for patients with a current or past history of CV disease. Consider EKG for patients ≥50 years of age, regardless of treatment
2. Medical history
3. Past cardiotoxic chemotherapy/medications
4. Past CV history: OBTAIN DOCUMENTATION OF CLEARANCE FROM CARDIOLOGIST IF POSSIBLE
5. Current cardiac medications (including antidiuretic, potassium supplement)
6. Physical assessment
   - Heart rate, rhythm, amplitude
   - Abnormalities (murmurs, gallops, extra heart sounds)
   - Edema
   - Labs: complete blood (CBC), thyroid-stimulating hormone (TSH), chemistry (SMA), serum triglycerides, and serum lipid levels

**RIBAVIRIN DOSE MODIFICATION REQUIREMENTS**

For patients with a history of stable CV disease, a permanent dose reduction is required if the hemoglobin (Hgb) level decreases by ≥2 g/dL during any 4-week period. In addition, if the Hgb remains <12 g/dL after 4 weeks on a reduced dose, the patient should discontinue ribavirin therapy. Please refer to the section on managing hematologic side effects for a discussion on the use of erythropoietin (Procrit®, Epogen®) to manage ribavirin-related anemia.

**CARDIOVASCULAR ADVERSE EFFECTS**

A. **ARRHYTHMIA**

   **Etiologies:** Hemolytic anemia, underlying CV condition, interferons, dehydration, anxiety

   **Treatment:** Symptomatic treatment, repeat EKG, hold treatment

   **Note:** Supraventricular arrhythmias occur rarely and may be correlated with pre-existing conditions and prior therapy with cardiotoxic agents. Controlled by modifying the dose or discontinuing treatment, but may require specific additional therapy.

B. **CHEST PAIN**

   **Etiologies:** Multiple, including hemolytic anemia (10%), underlying CV condition

   **Treatment:** Assess and treat symptoms, assess need for lab work (creatinine phosphokinase [CPK], CBC, troponin, etc), hold treatment, repeat EKG, consider cardiology consultation

C. **HYPOTENSION**

   **Etiologies:** Multiple
Treatment: May require supportive therapy including fluid replacement to maintain intravascular volume. Monitor blood pressure, administration of intravenous (IV) fluids

Note: May occur during or after administration

D. HYPERTENSION

Etiologies: Multiple

Treatment: Monitor blood pressure, initiate treatment if appropriate

E. PERIPHERAL EDEMA

Etiologies: Fluid overload, venous obstruction, heart failure, and capillary leak

Treatment: Monitor electrolytes, elevate extremities, eliminate sports drinks (such as Gatorade®, POWERade®, 10K®, Allsport®) as hydration sources due to high sodium content, daily weight measurement, consider cardiac and renal evaluation

OTHER CONSIDERATIONS

• In patients taking ribavirin, CBC should be monitored at baseline and at weeks 2 and 4 of therapy, then monthly. More frequent monitoring if clinically indicated—for example, CBC should also be measured at week 1 for patients at high risk.

• Patients with hemoglobinopathies (thalassemia, sickle-cell anemia) should not be treated with ribavirin therapy

• Interferon treatment may increase serum triglycerides; hypertriglyceridemia-related diseases are uncommon
III. Contraindications and Cautionary Use

AUTOIMMUNE DISEASE

OVERVIEW

Rarely, development or exacerbation of autoimmune (AI) diseases (eg, thyroiditis, thrombocytopenia, rheumatoid arthritis, interstitial nephritis, myositis, hepatitis, systemic lupus erythematosus (SLE), idiopathic thrombocytopenic purpura, and psoriasis) has been observed in patients treated with interferon alfa. In very rare cases, the event resulted in fatality. The mechanism by which these events develop and their relationship to interferon alfa therapy is not clear. Any patient developing an AI disorder during treatment should be monitored closely and, if appropriate, treatment should be discontinued.

Some immune-mediated diseases strongly associated with HCV infection are sicca syndrome (similar to Sjögren’s syndrome), membranous glomerulonephritis, mixed cryoglobulinemia, and AI hepatitis. HCV is also associated with AI thyroid disease, porphyria cutanea tarda, AI thrombocytopenia, diabetes mellitus (DM), neuropathy, arthritis, lichen planus, idiopathic pulmonary fibrosis, and fibromyalgia. There is also a rare association between HCV and aplastic anemia and lymphoma.

It has been hypothesized that the presence of auto-antibodies in the HCV positive individual may be secondary to a nonspecific upregulation of the cellular immune response. A similar effect occurs with interferon, which diffusely activates the cellular immune system and can initiate new AI diseases in treated patients. Data also suggest that interferon therapy can exacerbate a pre-existing AI process.

Clifford et al conducted a retrospective review of 117 HCV patient records. The charts were reviewed for results of serum AI markers: antinuclear antibodies (ANAs), (SMAs), rheumatoid factor (RF), antimitochondrial antibodies, anti-liver-kidney microsomal (LKM) antibodies, and cryoglobulins. A high prevalence of autoantibody markers was found, especially SMAs (66%) and RF (76%). Overall, there were no differences between the groups (presence or absence of antibody markers) regarding age, sex, severity of HCV, or response to interferon treatment. None of the treated patients developed clinical signs of AI disease.

There are no standardized guidelines for treatment of HCV infection in patients with AI disease. The data suggest that cryoglobulinemia-related symptoms are the only ones improved by interferon treatment, but patients usually relapse after completion of therapy. Interferon therapy may worsen the outcome of other AI processes.
AUTOIMMUNE HEPATITIS

Patients with autoimmune hepatitis (AIH) should not be treated with interferon or ribavirin therapy.

Pathophysiology

AIH is a necro-inflammatory disease, the presentation of which mimics viral hepatitis—varying from asymptomatic to fulminant hepatitis. There is frequent association with other AI disorders, such as insulin-dependent DM, vitiligo, glomerulonephritis, and AI hemolytic anemia. There are two types. Type 1 is most common, generally affecting 30- to 60-year-olds, and is less severe; serum is positive for SMA and/or ANA. Type 2 (rare in the United States) affects primarily adolescent girls and usually is severe; serum is positive for LKM type 1 (LKM1) antibody and liver cytosol antibody type 1 (LC1). Marked hypergammaglobulinemia, especially immunoglobulin G (IgG), is present in both types.

AIH in Hepatitis C

There are reports in the literature of interferon causing an exacerbation of AIH in the HCV-infected patient. Likewise, steroids cause viral concentrations to increase in the HCV patient being treated for AIH. Interferon increases the expression of human leukocyte antigens (HLA) class I and II antigens on liver cells. This results in an exaggerated presentation of these antigens to both helper and cytotoxic lymphocytes, which can lead to an exacerbation of an underlying AI disease process. AIH commonly caused a false positive enzyme immunoassay (EIA) when the first-generation test was administered (a nonspecific test). Fortunately, this problem was resolved with use of EIA-2 and/or recombinant immunoblot assay (RIBA). Cassani et al found 30% of HCV-infected patients to have at least one autoantibody, but their subspecificities are different from those found in the AIH patient (ANA-H, SMA-AA). The HCV-autoantibody positive patient is predominantly female, with more severe biochemical and histologic activity.

An interesting case in point: Bayraktar et al studied 162 patients infected with HCV, and 41 patients with AIH. They found that at baseline both groups had similar rates of ANA (63%) and SMA (65% versus 63%) positivity. Among the 81 HCV-infected patients who were treated with interferon, there were no differences in response rates between patients who had autoantibodies present prior to treatment versus patients who did not (very few patients developed autoantibodies after initiation of treatment). Fifteen interferon-treated patients developed new onset of an AI disease during the course of treatment; only 6/15 had autoantibodies present prior to treatment. Although most required treatment of their new AI disease, none required discontinuation of their interferon therapy. The study found an 18.5% incidence of new-onset AI disease (high compared with a literature review), which was just as likely to occur in individuals without pre-existing autoantibodies. In conclusion, the presence of autoantibodies in HCV-infected patients was unrelated to age or sex, nor did it affect the decision to treat the hepatitis in this study.
Interferon therapy is specifically contraindicated in the individual with AIH and there are no approved treatment guidelines. As noted, immunosuppression causes an increase in viral concentrations, but lowers transaminase levels in the HCV-infected patient. Tran et al recommend that patients affected by both diseases first receive prednisone and azathioprine, reserving interferon for those who fail to respond.

**RHEUMATOID ARTHRITIS**

Rare cases of rheumatoid arthritis have been observed in patients treated with alfa interferons. Any patient developing rheumatoid arthritis should be closely monitored and, if appropriate, treatment should be discontinued.

*Pathophysiology*

The association between rheumatoid arthritis and HCV infection has been well documented. HLA-DR4 histocompatibility antigen is elevated significantly in HCV-infected patients with AI disease, including rheumatoid arthritis. In theory, patients who are genetically predisposed to autoimmunity and who contract hepatitis C can ultimately develop polyarthritis consistent with a rheumatoid arthritis diagnosis. Kessel et al state that 20% to 30% of HCV positive individuals experience clinical manifestations of autoimmunity, while up to 70% are positive for autoantibodies (ANA, RF, anticoagulant, SMA, and LKM antibodies). Also, 2% to 20% of HCV positive patients experience arthritis, and as many as 50% experience arthralgia.

*Rheumatoid Arthritis in Hepatitis C*

The literature documents case reports of patients referred to rheumatology for workup of rheumatic manifestations presumably secondary to rheumatoid arthritis, cryoglobulinemia, or fibromyalgia, only to be subsequently diagnosed with HCV infection. Presentation is often polyarthritis, seropositive for RF. Patients may even fulfill the criteria for rheumatoid arthritis according to the American College of Rheumatology. The literature also recommends that any patient presenting with new onset of polyarthritis should be tested for HCV. Kessel et al conducted a controlled study that determined antikeratin antibody (AKA) to be a statistically significant test to differentiate between true rheumatoid arthritis and HCV-related arthralgias. AKA was detected in 60.6% (20/33) of patients diagnosed with rheumatoid arthritis; AKA was detected in 8% (2/25) of patients with HCV-related polyarthritis (similar to healthy controls). Prior to this study, AKA was considered a well-documented specific marker of rheumatoid arthritis. This article concludes that AKA can be utilized to distinguish between the different processes, so the disease may be treated appropriately. Case studies showed that individuals treated with interferons for various diagnoses developed rheumatoid/arthritic symptoms, which resolved after discontinuation of therapy.

For the patient with an arthritis diagnosis who has subsequently been found to be infected with HCV, the literature discusses treatment with low-dose steroids or nonsteroidal anti-inflammatory drugs (NSAIDs, eg, aspirin, Vioxx, Celebrex, Arthrotec, Naproxen, Motrin, Relafen, Tolectin) (independent of the HCV diagnosis or treatment). Kessel et
al emphasized that HCV-related arthritis treated with steroids or cytotoxic agents can exacerbate HCV, and methotrexate (Trexall®, Mexate-AQ®, Folex®) or hepatotoxic drugs may negatively affect liver function. Therefore, it is important to make an accurate diagnosis and treat accordingly. Patients who developed arthritis secondary to interferon treatment required discontinuation of therapy; some were managed with the addition of NSAIDs.

**PSORIASIS**

There have been reports of interferons, including peginterferons, exacerbating pre-existing psoriasis; therefore, interferon therapy should be used in these patients only if the potential benefit justifies the potential risk. In such cases, treatment should be undertaken in consultation with a dermatologist after the psoriasis is under control.

**Pathophysiology**

Although the exact etiology of psoriasis is unknown, interferon has been implicated in its exacerbation. It has been proposed that “interferon alfa may act as an inducing factor for psoriasis due to activation of the dermal dendrocytes, which produce tumor necrosis factor α. This latter, in turn, induces the expression of adhesion molecules on keratinocytes and endothelial cells, as well as production of transforming growth factor α, which triggers the proliferation of keratinocytes. Psoriatic lesions may appear because the hyperproliferating keratinocytes escape the control mechanisms, due to genetic mutation…..”

It has been established that psoriasis and psoriatic arthritis are associated with HLA class I and II. In the HCV-infected patient, the virus may act as a superantigen, inducing self-reactive T cell clones, which promotes the proliferation of psoriatic lesions. Kapp acknowledges that psoriasis is probably triggered by more than one mechanism, including a genetic predisposition and environmental effects on the immune system.

**Psoriasis: an Overview**

Psoriasis is a recurrent chronic skin disorder that can be limited to a few areas of the skin (mild), or it can be widespread (moderate to severe). Normal skin cells mature in 28 to 30 days and shed from the skin unnoticed. Psoriatic skin cells mature in only 3 to 4 days. They “heap up” and form scaly lesions, which can be painful and pruritic, or can crack and bleed. Psoriasis is slightly more prevalent in women than in men, and appears most often between the ages of 15 and 35 years, although it can happen in infancy or old age. About 2.6% of the US population suffers from psoriasis. Caucasians are at greater risk than African Americans, and there is an increased risk among those with a family history of the disease. Approximately 10% of people with psoriasis also have psoriatic arthritis (PA), which generally affects the hands and feet, but other parts of the body can be involved as well. PA can affect a few joints, or it can be severe and disabling.

There are several forms of psoriasis:
- **Plaque:** Most common; characterized by inflamed skin lesions topped with silvery white scales
- **Guttate:** Characterized by small, dot-like lesions
- **Pustular:** Characterized by pustules and intense scaling
- **Inverse:** Characterized by its appearance in skin folds
• **Erythrodermic:** Characterized by intense erythema, swelling, dead skin exfoliation, and pain

**Psoriasis and Interferon**

In 1993, Garcia-Lora et al\(^\text{14}\) presented the first case study of psoriasis occurring in an HCV-infected patient receiving interferon. Taglione et al\(^\text{19}\) conducted a study that did not support the idea that hepatitis C had a role in the genesis of psoriasis. In addition, there have been interferon-induced cases occurring among the oncologic population, and some reports correlated interferon dose to severity of psoriasis.\(^\text{3,20,21}\) In these cases of concurrent diseases, treatment was generally held, and the psoriasis was treated and resolved. It is unclear whether interferon, the underlying disease, or both cause the genesis or exacerbation of psoriasis; large studies need to be conducted to determine the relationship. Burrows et al\(^\text{22}\) found that treatment of HCV infection with interferon did not exacerbate psoriasis.

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<th>TRIGGERS OF PSORIASIS(^\text{23})</th>
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<tr>
<td>• Genetic predisposition</td>
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<td>• Stress or nervous tension</td>
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<td>• Bacterial or viral infection</td>
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<td>• Lithium (Eskalith(^\text{TM}), Lithobid(^\text{TM}))</td>
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<td>• Chloroquine (Aralen(^\text{TM}))</td>
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<tr>
<td>• Beta blockers (eg, Calan(^\circ), Inderal(^\circ), Isoptin(^\circ), Verelan(^\circ))</td>
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<tr>
<td>• Interferon-induced AI modification</td>
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<tr>
<td>• Illness or injury</td>
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<tr>
<td>• Poison ivy or sunburn</td>
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<tr>
<td>• Overuse of drugs or alcohol</td>
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<tr>
<td>• Use of NSAIDs in those with pre-existing psoriasis</td>
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<td>• HIV/AIDS patients often have severe psoriasis</td>
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**Management\(^\text{23}\)**

1. Diagnosis via skin exam. Occasionally a skin biopsy is done. No specific test is used to diagnose psoriasis.
2. Nails sometimes show signs of psoriasis: may be pitted, discolored, thickened, and crumbly.
3. Affected skin may be reddened and hot to the touch with characteristic lesions.
4. Rule out other causes of a psoriatic flare—even in patients without an apparent family history.
5. Assess patient for pre-existing history of psoriasis; treat carefully.
6. Examine the scalp, knees, elbows, back, buttocks, hands, and feet. Nails, eyebrows, axilla, and anal and genital regions may also be affected. Rarely affects the face, although no area of the skin is exempt.
7. Exacerbation of psoriasis may best be treated with ultraviolet light (UVL)—psoralen (methoxsalen, Oxsoralen\(^\circ\)) and ultraviolet light A (PUVA) or ultraviolet B therapy.
8. The literature cites case studies with conflicting recommendations to either discontinue interferon or treat psoriasis with supportive therapy while the patient completes interferon therapy.
### PHARMACOLOGIC AND OTHER AGENTS

1. **PABA** (para-aminobenzoic acid) for sun-screening properties; treats underlying reaction
2. Topical corticosteroids are used to discourage skin cells from multiplying and control inflammation; short-term use only
3. Keratolytics used in lotion, cream, or ointment (anthralin [Drithocreme®]) to soften scales and skin debris and facilitate removal
4. Keratolytics in shampoo form (anthralin [Dritho-Scalp®]) to treat lesions as above
5. Actiderm skin patch: sometimes applied over psoriasis medications, especially cortisone (Cortone) ointments, to increase efficacy
6. Activated vitamin D3 ointment (calcipotriene [Donovex]); available by prescription for severe forms
7. Methoxsalen (psoralen), a liquid drug, is also widely used
8. Liquid nitrogen for freezing of moderately sized psoriatic lesions
9. Antineoplastic agent used for severe recalcitrant disease
10. Hydroxyurea (Zerit®), cyclosporine (Sandimmune®, Neoral®, Restasis®), and calcitriol (Rocaltrol®) may produce improvement and are under study; all have potentially severe side effects

### GENERAL SUPPORTIVE MEASURES

1. **PUVA** or ultraviolet B therapy to retard the production of new skin cells; anthralin (Drithocreme or Dritho-Scalp) may be used in tandem with UVL (see Pharmacologics table)
2. Lubricants to soften skin (dermatologist will determine/prescribe)
3. Exposure to sunlight; 15 to 30 minutes, but strict avoidance of sunburn, may reduce scaling and erythema
4. Stress-reduction programs
5. Prevention of mechanical injury to skin
6. Instruction to family and significant others that lesions are not communicable
7. Counseling if body image is affected and to help patient adapt to chronic nature of disease
8. Close dermatologic follow-up for complications such as PA or exfoliative psoriatic dermatitis, which can lead to severe disability
SYSTEMIC LUPUS ERYTHEMATOSUS

Rare cases of SLE have been observed in patients treated with alfa interferons. Any patient developing SLE during treatment should be monitored closely and, if appropriate, treatment should be discontinued. SLE itself is a contraindication to interferon therapy.

Pathophysiology

Many patients afflicted with SLE have measurable serum levels of interferon alfa correlating with the amount of disease present, suggesting pathogenesis.24

SLE and Interferon

SLE has been correlated with interferon treatment. Review of the literature revealed many case studies of individuals who were diagnosed with SLE after long-term cancer treatment with interferon (diagnoses varied). The majority of patients had a history of SLE syndrome. Features included myalgia, migratory arthralgia, malar rash, elevated levels of ANA and/or antinative DNA antibodies, hypocomplementemia, lymphopenia, and proteinuria.

Ronnblom et al24 reported a case in which a patient developed SLE during interferon therapy. The patient’s symptoms resolved upon discontinuing interferon, then she relapsed when rechallenged with interferon. Incidentally, tumor regression continued after discontinuation of interferon.25

Another study by Ronnblom et al25 followed 135 patients who were being treated with interferon for malignant carcinoid tumors to assess the development of autoantibodies and/or AI diseases. Only one of the 25 patients who developed an AI disease had SLE. Roughly half of the patients who developed autoantibodies did so after initiation of interferon therapy. Autoimmunity did not affect tumor responses.25

Treatment of the patient who develops SLE while on interferon-based therapy is not specifically addressed in the literature. In the documented case studies, interferon was discontinued to allow the SLE to improve or resolve. However, AI disease is clearly listed as a warning in interferon package inserts. Thus, these patients should be monitored closely.

REFERENCES


Contraindications and Cautionary Use

CARDIOVASCULAR DISEASE

Peginterferon must be used with caution in patients with a history of CV disease. Those patients with a history of MI and/or previous or current arrhythmias should be monitored closely. CV adverse experiences, which include hypotension/hypertension, arrhythmias (including tachycardia: \( \geq 150 \) beats/min.), cardiomyopathy, angina pectoris, and MI have been observed in patients treated with pegylated interferons with or without ribavirin. Patients who have pre-existing cardiac abnormalities should have EKGs administered before antiviral therapy is initiated. Cardiologic consultation should be considered on an individualized basis.

Fatal and nonfatal MIs have been reported in patients with anemia caused by ribavirin. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy and should be monitored appropriately during therapy. If there is any deterioration of CV status, therapy should be suspended or discontinued. Because cardiac disease may be worsened by drug-induced anemia, patients with a history of significant or unstable cardiac disease should not use ribavirin.

**NOTE:** Refer to the “Cardiovascular” section for management information.
Contraindications and Cautionary Use

PREGNANCY

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin (Rebetol® and Copegus™). In addition, ribavirin has a multiple-dose half-life of 12 days, and so it may persist in nonplasma compartments for as long as 6 months. Therefore, ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month posttreatment follow-up period.

RIBAVIRIN

Pregnancy Category X

Ribavirin produced significant embryocidal and/or teratogenic effects in all animal species in which adequate studies have been conducted. Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. Survival of fetuses and offspring was reduced. In conventional embryotoxicity/teratogenicity studies in rats and rabbits, observed no-effect dose levels were well below those for proposed clinical use (0.3 mg/kg/d for both the rat and rabbit; approximately 0.06 times the recommended human 24-hour dose of ribavirin). No maternal toxicity or effects on offspring were observed in a peri/postnatal toxicity study in rats dosed orally at up to 1 mg/kg/d (estimated human equivalent dose of 0.17 mg/kg based on body surface area adjustment for a 60-kg adult; approximately 0.01 times the maximum recommended human 24-hour dose of ribavirin).

Ribavirin is known to accumulate in intracellular components from which it is cleared very slowly. It is not known whether ribavirin contained in sperm will exert a potential teratogenic effect upon fertilization of the ova. In a study in rats, it was concluded that dominant lethality was not induced by ribavirin at doses up to 200 mg/kg for 5 days (estimated human equivalent doses of 7.14–28.6 mg/kg, based on body surface area adjustment for a 60-kg adult; up to 1.7 times the maximum recommended human dose of ribavirin). However, because of the potential human teratogenic effects of ribavirin, male patients should be advised to take every precaution to avoid risk of pregnancy for their female partners.

Women of childbearing potential should not receive ribavirin unless they are using effective contraception (two reliable forms) during the therapy period. In addition,
effective contraception should be utilized for 6 months posttherapy based on a multiple
dose half-life \( t_{1/2} \) of ribavirin of 12 days. Male patients and their female partners must
practice effective contraception (two reliable forms) during treatment with ribavirin and
for the 6-month posttherapy period (eg, 15 half-lives for ribavirin clearance from the
body).

If pregnancy occurs in a patient or partner of a patient during treatment or during the
6 months after treatment cessation, physicians should report such cases by calling
1-800-727-7064 for patients taking peginterferon alfa-2b (Peg- Intron®)/ribavirin
(Rebetol®) or 1-800-526-6367 for patients taking peginterferon alfa-2a
(Pegasys®)/ribavirin (Copegus™).

PEGINTERFERON

Pregnancy Category C

Nonpegylated interferon alfa-2b has been shown to have abortifacient effects in Macaca
mulatta (rhesus monkeys) at 15 and 30 million IU/kg (estimated human equivalent of
5 and 10 million IU/kg, based on body surface area adjustment for a 60-kg adult).
Nonpegylated interferon alfa-2a treatment of pregnant rhesus monkeys at approximately
20 to 500 times the human weekly dose resulted in a statistically significant increase in
abortions; no teratogenic effects were seen in the offspring delivered at term.
Peginterferons should be assumed to also have abortifacient potential. There are no
adequate and well-controlled studies in pregnant women. Peginterferon therapy is to be
used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Peginterferon is recommended for use in fertile women only when they are using
effective contraception during the treatment period.
Contraindications and Cautionary Use

PSYCHIATRIC HISTORY/SUICIDE

Life-threatening or fatal neuropsychiatric events, including suicide, suicidal and homicidal ideation, depression, relapse of drug addiction/overdose, and aggressive behavior have occurred in patients with and without a previous psychiatric disorder during peginterferon treatment and follow-up. Psychoses, hallucinations, bipolar disorders, and mania have been observed in patients treated with alpha interferons. Peginterferon should be used with extreme caution in patients with a history of psychiatric disorders. Patients should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physicians. Providers should monitor all patients for evidence of depression and other psychiatric symptoms. In severe cases, peginterferon/ribavirin should be stopped immediately and psychiatric intervention instituted.

NOTE: Refer to the “Psychologic” section for assessment and management of depression and suicidal ideation.
Contraindications and Cautionary Use

OTHER CONDITIONS

Extra caution should be used when evaluating and considering patients for treatment of HCV infection.

Patients with the following conditions should be identified, and the conditions should be well controlled prior to consideration for therapy:
- Uncontrolled diabetes and thyroid disorders
- Acute alcohol abuse and/or other substance abuse
- Decompensated liver disease
- Pre-existing renal and lung disease
- Ophthalmic disorders
- Hemoglobinopathies

If anti-HCV therapy is undertaken, these patients should be monitored carefully. Some such conditions may be induced or exacerbated by peginterferon/ribavirin. Peginterferon/ribavirin should also be discontinued in the rare case of severe acute hypersensitivity reaction, colitis, or pancreatitis.

In addition, since peginterferon/ribavirin therapy suppresses bone marrow function and can result in severe cytopenias, CBCs should be obtained pretreatment and monitored routinely during therapy. Peginterferon/ribavirin should be used with caution in patients with baseline neutrophil counts <1500 cells/mm$^3$ and with baseline platelet counts <90,000 cells/mm$^3$ or baseline hemoglobin <10 g/dL. Peginterferon/ribavirin should be discontinued, at least temporarily, in patients who develop severe decreases in neutrophil and/or platelet counts. (See “Hematologic” section for management strategies.) The peginterferon alfa-2a package insert includes a warning regarding serious and severe bacterial infections (including some fatalities), some of which are associated with neutropenia. Peginterferon alfa-2a/ribavirin should be discontinued in patients who develop severe infections and appropriate antibiotic therapy should be instituted.

(Some of the conditions listed above are discussed in more details in other sections of this handbook. Please also refer to the package inserts for more information about contraindications and warnings.)
IV. Cutaneous: Oral

CANDIDIASIS

OVERVIEW
Patients receiving treatment for HCV infection may develop oral infections, the most frequent cause of which is fungal, with Candida albicans being the predominating organism. C. albicans is part of the normal flora in 40% to 60% of the population.¹ Risk factors for developing the infection include immunosuppressive therapy, presence of HIV infection, dentures, diabetes, pregnancy, stress, and high doses of prolonged antibiotic therapy.²

Signs and symptoms of oral infections may be minimal. The two most common symptoms are pain and tenderness with possible metallic taste. Other symptoms include oropharyngitis, difficulty eating spicy foods, and taste changes. If signs of odynophagia (painful swallowing) are also present, simultaneous involvement of the esophagus must be assumed, and systemic therapy is necessary.³ Infections appear as cottage-cheese–like to pearly white patches that coat the tongue. The patches may be discolored by food or tobacco and may scrape off easily, thereby revealing ulcerated and sometimes bleeding surfaces.³ Diagnosis is made from a smear taken from a culture using a Gram’s stain; however, the diagnosis is often made by confirming the response to antifungal therapy.¹

PREVENTIVE STRATEGIES
Patients should be instructed to:
1. Maintain good oral hygiene, performing mouth care before and after meals and at bedtime. Gently floss the teeth once daily after brushing.⁴
2. Inspect their mouth daily for patches while on therapy.
3. Maintain good denture care.
4. Maintain a high-protein nutritional diet; avoid a high-carbohydrate diet, especially sugary foods that provide “empty” calories.
5. Avoid alcohol and tobacco.

PREVENTIVE AGENTS (PROPHYLACTIC) FOR CANDIDIASIS

<table>
<thead>
<tr>
<th>ANTIMICROBIAL MOUTH RINSES</th>
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</thead>
<tbody>
<tr>
<td>Chlorhexidine gluconate (Peridex®)</td>
<td>15 mL; rinse three times/d; do not swallow</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>ANTIFUNGALS</th>
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</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>200 mg orally once daily, then 100 mg orally every day (especially in HIV+ patients)</td>
<td></td>
</tr>
</tbody>
</table>
TREATMENT STRATEGIES
Symptomatic patients should be advised to:
1. Brush their teeth within 30 minutes after eating and at bedtime; use a soft-bristle nylon toothbrush and sodium bicarbonate toothpaste with fluoride added; brush the gums, tongue, and top of mouth.
2. Rinse their mouth with 1 oz of saline, saltwater and baking soda, tap water, or 1.5% hydrogen peroxide for 1 to 2 minutes.
3. Avoid foods that are hot, rough, coarse, highly spiced, or acidic.
4. Avoid temperature extremes of food (hot coffee, ice cream).
5. Avoid citrus juices or foods that irritate the mouth and salty foods and drinks, including broth.
6. Avoid lemon and glycerine swabs, as these are drying and irritating.
7. Medicate with antifungal agents and pain medications as directed.
8. Avoid drinking from metallic containers if metallic taste is a problem.

TREATMENT AGENTS FOR CANDIDIASIS

TOPICAL
• Cleanse the mouth before administering the agent. Do not eat or drink for at least 30 minutes after applying.
  • Nystatin oral suspension 500,000 to 2,000,000 units, swish and swallow every 4–6 h
  • Clotrimazole troches 10 mg, five times/d

SYSTEMIC
• Fluconazole 200 mg/d orally/d
• Ketoconazole 200 to 400 mg orally/d
• Amphotericin B 20 mg/d IV for 2 weeks; only as second-line therapy for most adult patients with single organ involvement or candidemia
• Flucytosine Used as salvage in severe disease
• Itraconazole liquid 20 mL orally/d; swish and swallow without food (10 mg/1 mL)

REFERENCES
TASTE CHANGES

PATHOPHYSIOLOGY
Drugs are implicated in taste alterations, much more than is generally appreciated.\(^1\) Drugs that may induce taste alterations include anti-inflammatory agents, antibacterials, antifungals, NSAIDs, antidepressants, antiemetics, and antivirals.

One model used to examine the pathology of taste changes identifies three possible mechanisms for drug-induced taste alterations: interference at the level of the receptor, interruption of neural transmission, and altered central nervous system (CNS) integration. Receptor dysfunction comprises the bulk of drug-related taste changes.\(^1\) Drug injury to the CNS integration is reflected in <5% of all taste pathology. These changes are primarily metabolic in nature. Neural transmission disorders also contribute <5% of the total of drug-related taste pathology.

The effects of interferon on taste probably relate to its action as a suppressor of receptor cell turnover. A wide range of taste sensations are reported by interferon-treated patients, including a decreased threshold for bitter taste, causing a dislike or aversion to beef, pork, chocolate, coffee, or tomatoes; an increased threshold for sweet taste; an increased need for salt on foods; an avoidance of sour foods; and/or a metallic or medicinal taste.\(^2\)

TYPES OF TASTE ALTERATIONS\(^3\)
- **Ageusia**: An absence of taste sensation; often referred to as “mouth blindness.” Patients report that food “has no taste” or “tastes like cardboard.”
- **Dysgeusia**: An altered taste sensation, often perceived as unpleasant. Patients most often comment that their foods/fluids taste “different.” For example, coffee lovers complain of bitter taste and chocolate lovers say the chocolate is too sweet.
- **Hypogeusia**: A decreased taste sensation. Foods with distinct flavors, such as cheeses, sauces, lemon, pizza, and jam, taste bland and lack their pungent or unique flavor.

PREVENTIVE STRATEGIES
Patients should be instructed to:
1. Maintain good oral hygiene; brush teeth before and after meals to keep the mouth clean.
2. Examine the oral cavity daily and report any signs of infection.
3. Avoid tobacco and unpleasant odors, as well as things already known to be unpleasant.
4. Marinate meats to enhance or disguise flavor.

TREATMENT STRATEGIES
Symptomatic patients should be advised to:
1. Identify basic balanced diet requirements and the amount of fluids required daily.
2. Weigh themselves weekly and consult dietitian as needed for counseling.
3. Use supplements between meals if caloric intake is below minimum requirement.
4. Avoid drinking from metallic containers and use plastic utensils to combat metallic tastes.°
5. Eat frequent, small meals rather than three large ones.°
6. Eat meat in the morning (aversions tend to increase during the day; chicken, fish, and cheese are usually well tolerated as protein sources).\(^3\)
7. Avoid hot foods; try cold foods, which may be better tolerated if food odors cause aversions.\(^3\)
8. Add sauces, gravies, fruit sauces; make cream soups with milk.\(^3\)
9. Identify foods subject to aversions and replace them in the diet.
10. Identify the relation between medications and taste changes; adjust eating times accordingly.
11. Change seasonings to compensate for altered sweet/sour threshold.
12. Use hard candies (eg, peppermint) for flavor.°
13. Administer pain medication before meals, if mucositis is present.
14. Prepare foods so as to avoid odors.
15. Reduce urea content of the diet by eating white meats, eggs, and dairy products if a low threshold for bitterness (urea) develops.

In addition, providers should assess the need for a saliva substitute or pilocarpine if xerostomia is present.

<table>
<thead>
<tr>
<th>TREATMENT AGENTS FOR TASTE CHANGES(^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APPETITE STIMULANTS</strong></td>
</tr>
<tr>
<td>Zinc, tabs or lozenges</td>
</tr>
<tr>
<td>Dronabinol</td>
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<tr>
<td>Megestrol acetate</td>
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</tbody>
</table>

**REFERENCES**

CUTANEOUS: ORAL

XEROSTOMIA

PATHOPHYSIOLOGY
Xerostomia (dry mouth) is a symptom that is most frequently associated with reductions of salivary gland output. The most common causes of this decreased output are medications, medical treatments, and systemic disease. More than 500 medications, including interferons, are associated with dry mouth. The major classes of drugs that have been shown to decrease salivary function directly include antidepressants, antihistamines, antihypertensives, decongestants, antipruritics, analgesics, antiemetics, and diuretics. Other causes are ionizing radiation and systemic diseases, such as Sjögren’s syndrome, graft-versus-host disease induced by bone marrow transplantation, poorly controlled DM, thyroid disorders, hepatic disease, dehydration, AI diseases, and depression. Prolonged xerostomia predisposes an individual to oral pathologies, particularly candidiasis and dental caries.

PREVENTIVE STRATEGIES
Providers should first rule out a diagnosis of Sjögren’s syndrome and then advise patients to:
1. Maintain good oral hygiene, performing mouth care before and after meals and at bedtime.
2. Hydrate with clear liquids throughout the day to keep oral tissues moist; avoid sugar-containing fluids.
3. Limit caffeine and alcohol consumption.
4. Use sugarless gums and candies.
5. Humidify environment, especially the bedroom at night, to avoid extreme dryness.
6. Apply moisturizers and emollients to lips.
7. Avoid tobacco, spicy and salty foods, and strong flavorings.
8. Avoid mouth rinses with high alcohol content.

PREVENTIVE AGENTS FOR XEROSTOMIA

MAINTENANCE OF ORAL MOISTURE
Orabalance®
Use after rinsing mouth and after brushing

SALIVA SUBSTITUTES
Moi-Stir®
Use as needed
Xerolube®
Use as needed

SIALOGOGUES (SALIVA PROMOTERS)
Pilocarpine (Salagen®)
5 mg orally three times/d; contraindicated in patients with uncontrolled asthma or narrow-angle glaucoma; use caution with CV disease
**TREATMENT STRATEGIES**

Symptomatic patients should be advised to:

1. Choose moist foods (yogurts, puddings, etc), adding sauces, gravies, and other lubricants to foods whenever possible. Dry foods such as breads, crackers, or dry meats are not well tolerated alone.

2. Use ice chips to keep mouth lubricated and provide comfort.

3. Use topical salivary stimulation methods, such as sugarless mints and gum, but avoid citric acid–containing solutions or foods, such as lemons. Products sweetened with Xylitol may have an antibacterial benefit.

4. Rinse mouth frequently with saline solution.

5. Use fluoride treatment regimen, as recommended by patient’s dentist.

6. Attend to any dental caries that may exist and receive dental check for new-onset caries with prolonged xerostomia.

7. Avoid carbonated beverages, which can be painful to inflamed mucosa.

8. Try saliva replacements for relief of discomfort.

**REFERENCES**


ALOPECIA

PATHOPHYSIOLOGY
Interferon affects the hair follicles and changes the texture of the hair, thereby making it more sensitive to breakage. Hair loss, which has been described as a possible side effect of treatment with interferons, occurs by one of two mechanisms. First, loss via a shearing or friction effect at the scalp level (often during sleep as the hair moves across a pillow) is caused by the weak, brittle nature of hair changes. Second, loss can occur via a spontaneous release of the hair from the follicle, leaving the follicle empty, which is usually seen with vigorous shampooing or brushing. Alopecia is frequently observed when therapy is continued for longer than 3 to 4 months, and is characterized by thinning and slight-to-mild hair loss. It appears to be the most common cutaneous reaction associated with interferon alfa treatment. Alopecia may become more pronounced when interferon is discontinued and may continue for 1 to 3 months. In general, alopecia associated with interferon is reversible. In some patients, hair regrowth occurs during treatment continuation.

Total revealed alopecia is seen more often with high-dose interferon or long-term interferon maintenance therapy. Thinning, often unnoticeable to others, is usually seen during combination therapy with ribavirin or low-dose, short-course interferon. Patches of loss occur unpredictably in some patients.

PREVENTIVE STRATEGIES
Providers should:
1. Educate patients regarding the risk of alopecia, its causes, and management. Inform patients that hair usually regrows, although the new growth may be a different texture; however, in rare cases, hair loss may be permanent.
2. Rule out other etiologies, including a history of alopecia areata, thyroid dysfunction, and other medical conditions, treatment, or medications (eg, chemotherapy, radiation therapy) that may predispose the patient to alopecia.

Patients should be instructed to:
1. Use a wide-toothed comb and/or natural bristle brush; gently comb/brush only once or twice daily.
2. Shampoo less frequently (1–3 times/wk); use conditioner or detangler.
3. Use Nioxin™ or selenium sulfide (Selsun Blue®) shampoo, or Centrum® Complete multivitamin with zinc and selenium.
4. Use vegetable-based henna or vegetable-based hair color (eg, Aveda™, Matrix™) if intent on coloring hair. Avoid use of peroxide-based hair dye or permanent wave solutions while on therapy; their use is not contraindicated, but can accelerate hair loss and hair damage.
5. Pin a silk scarf on pillowcase or buy a satin pillowcase to avoid hair loss through friction or shearing effect.
6. Avoid pressure-based hair items: caps, barrettes, ponytail clips, hair bands.
7. Avoid pulsating showerheads (eg, Waterpik™); these exert too high a PSI and facilitate loss.
8. Avoid/limit use of gels, freezing sprays, mousse; these make hair difficult to comb through.

**TREATMENT STRATEGIES**

Symptomatic patients should be advised to:
1. Cut hair length to decrease hair weight and rate of loss (for progressive thinning in longer, heavier hair).
2. Purchase scarves, wigs, turbans, or caps when total revealed alopecia is anticipated.
3. Complete any hair transplant procedures prior to therapy or continue them after completion of treatment to avoid delayed healing and risk of infection (for patients with pre-existing male pattern baldness).

Providers should, as needed:
1. Provide a prescription for scalp prosthesis or cranial prosthesis (wig) due to treatment-induced alopecia to facilitate insurance/Medicare reimbursement.
2. Refer patients for psychosocial support, such as support groups, and recommend consultation with a cosmetologist or dermatologist (if appropriate) for changed body image issues.
3. Note that drug therapy (minoxidil [Rogaine®]) for hair loss is not efficacious for interferon-related hair loss.

**REFERENCES**

PATHOPHYSIOLOGY

Although occurring less frequently than other cutaneous adverse effects, acute leucocytoclastic vasculitis with possible formation of immune complexes has occasionally been described in patients taking interferon-based therapy.¹ In one patient, it was associated with IgA and C3 deposit on immunofluorescence study. Two reports have been made of vascular injury related to digital ischemic vasculitis of the hand. Angiography showed digital artery occlusion.¹

TREATMENT STRATEGIES

1. Antibiotics as appropriate; may be able to rechallenge on interferon and treat successfully
2. Dermatology consult
3. Treatment discontinuation
4. Resolution of symptoms observed only after interferon withdrawal¹

REFERENCE

Cutaneous: Skin, Hair, and Nails

HYPERSENSITIVITY/ALLERGIC REACTIONS

PATHOPHYSIOLOGY
Hypersensitivity can occur well into therapy with symptoms consisting of swelling at the previous surgical site, hives, pruritus, macular rash, chest tightness, shortness of breath, sneezing, watering eyes, and sore throat. Eosinophils, basophils, and mast cells are all affected by secondary cytokines. Lysis and a release of histamine occur. This release of histamine may cause a hive-like reaction.

TREATMENT STRATEGIES
1. Assess for change in formulation of product given to patient, or whether a different interferon product was used.1
2. Apply topical low-dose hydrocortisone cream to skin.
3. Administer antihistamines (over-the-counter or nonsedating).1
4. Use systemic corticosteroids cautiously as they may inhibit the antiviral activity of interferon alfa.1
5. Hold therapy until the condition resolves.
6. If acute allergic reaction, reinstitute therapy cautiously; dose should be reduced and the patient premedicated with an antihistamine, preferably nonsedating.1 Monitor patient closely. If the reaction occurs late in therapy (delayed reaction) or consists of hives, hold treatment until hives resolve, then resume at 50% dose reduction. If hives recur, terminate treatment.

REFERENCE
Cutaneous: Skin, Hair, and Nails

NAIL DISORDERS

PATHOPHYSIOLOGY
Alterations of the skin and/or nails may be localized, or generalized as a result of the destruction of the basal cells of the epidermis. Reactions can vary considerably in onset, severity, and duration. Nails may become thin, pitted, discolored, thickened, or crumbly, and may peel or break easily. Banding and hyperpigmentation of nail beds are more common in oncology patients receiving chemotherapy than in patients receiving anti-HCV treatment. Psoriasis should be ruled out in patients with HCV infection, since nail changes are a classic sign. Nail changes not associated with AI disease tend to resolve a few months posttreatment.

TREATMENT STRATEGIES
1. Educate patient as to cause, management, and expected resolution.
2. Recommend good diet, hydration, and rest.
3. Assess for impaired nutritional status and/or vitamin deficiency.
4. Recommend that patients protect weak, breakable nails; for example, by limiting the time hands are in water, and wearing gloves for dishwashing and gardening.
5. Recommend nail strengtheners (e.g., Knox gelatin), clear-coat polish, and liquid gel to help decrease splitting and breakage.
6. Treat psoriasis if that is the etiology.
7. Refer to dermatologist in the event of progressive nail loss, bleeding, or infection.

REFERENCE
Cutaneous: Skin, Hair, and Nails

GENERALIZED/INJECTION SITE REACTIONS

PATHOPHYSIOLOGY
Transient and mild cutaneous reactions related to interferon treatment occur in 10% of patients, and these are reported much more frequently than local injection-site reactions. Generalized skin rashes, alopecia, and psoriasis are more common cutaneous reactions associated with interferon.

Possible explanations for this type of skin eruption include:
- Interferon acting as a biologically active substance in the skin (infiltration of skin eruptions with lymphoid CD4 cells)
- The development of an immune complex, which is trapped by the skin and formed by the pre-existing antibody to specific viral antigen, and the antigen being released by the interferon
- The expression of adhesion molecules by the vascular endothelial cells in the skin may result in skin eruptions.

Other factors that must be considered when investigating the etiology of cutaneous reactions include conditions that may predispose a patient to cutaneous ulcerations (eg, allergies, infections, injection-site technique, location, reaction to a drug excipient, injecting drug that is cold, interaction with concomitant medications, and a local reaction to antiseptic used to clean the skin). In cases of cutaneous reaction occurring during treatment with interferon, either alone or in combination with other agents, identification of the etiologic agent may be unclear. Injection-site reactions, induration, or necrosis appear to be extremely rare side effects of standard interferon, but injection-site reactions may be more common with peginterferon. Injection-site reactions usually present as erythema and rarely involve induration at the injection site.

Several theories have been postulated regarding the etiology of cutaneous necrosis or the development of ulcerations at the injection site. Theories include:
- A local immune-mediated inflammatory process in the skin.
- Direct toxic effect of interferon.
- Peri-arterial or intra-arterial injection (congestion disrupting blood flow), with subsequent cutaneous infarction.
- Overproduction of inflammatory cytokines, such as tumor necrosis factor and interleukin-6, in the subcutaneous tissue resulting in hyperpermeability of the cutaneous vasculature.

GENERAL MANAGEMENT STRATEGIES
1. Perform thorough skin assessment at baseline, prior to initiation of therapy, and at regular intervals thereafter. Nurses should instruct patients to monitor their injection sites for the development of erythema and to report this finding immediately.
2. Assess and monitor all patient complaints.\textsuperscript{2} Once erythema is noted, have patients avoid injecting around/at the erythematous area.
3. Pay attention to injection sites, noting reports of unrelieved pain, erythema, discoloration, induration, swelling, or the development of lesions or eruptions.\textsuperscript{2}
4. Be aware that hypersensitivity can develop at any time.
5. Rule out AI and extrahepatic manifestations of hepatitis C, such as porphyria cutanea tarda or lichen planus, as etiology.
6. Rule out coinfection-related skin infections and sequelae.
7. Therapy may need to be discontinued for severe psoriatic flare or due to severe grade 3 skin reaction. In some cases, therapy may be reinstituted on resolution of skin reaction.

**TREATMENT STRATEGIES**

**Pharmacologic Interventions**\textsuperscript{2}

1. Evaluate drug (eg, cloudy color, excipient added to product).
2. Advise patient to make sure injection solution is at room temperature prior to injection and to inject drug more slowly.
3. Assess subcutaneous technique (bevel up, site rotation, etc).
4. Recommend application of cool or warm compresses to site before and after injection or aloe and lidocaine gel as needed. For injection pain: topical analgesics (eg, lidocaine and prilocaine \textsuperscript{[Emla\textsuperscript{®} cream]}), oral analgesics.
5. Give topical povidone-iodine cream (Betadine\textsuperscript{®}) or topical mild corticosteroid creams for rash, reactions, and drug-related pruritus.
6. Premedicate with diphenhydramine (Benadryl\textsuperscript{®}) before peginterferon to decrease potential of an allergic-type reaction. H\textsubscript{1} blockers are better for prevention than treatment. Interferon’s activation of macrophages/neutrophils can lead to degranulation and enzyme release, resulting in lytic action on nearby cells. Basophils/eosinophils are 10% histamine; if lysed, histamine can be released into the system (as seen in hives). A nonsedating antihistamine should ideally be used.
7. Give hydroxyzine (Vistaril\textsuperscript{®}) or naltrexone (Depade\textsuperscript{®}) as needed.
8. Increase dose of oral antihistamine at bedtime if taken for pruritus.
9. Prescribe antibiotics if pruritus is secondary to infection, cellulitis, etc.
10. Assess for use of concomitant medications, herbal therapies, or vitamins that may also cause skin reactions (eg, St. John’s wort may cause photosensitivity).
11. Dose reduction or drug holiday; restart when clear using antihistamine premedication; rechallenges are often successful.

**Nonpharmacologic Interventions**\textsuperscript{2}

Providers should:
1. Assess onset of rash and stress to patient that sun exposure should be limited.
2. Rule out seasonal skin eruptions and AI diseases, eg, psoriasis.
3. Address fluid loss due to fever, nausea/vomiting, diarrhea, and decreased fluid intake.
4. Consult a dermatologist, if needed, to assist in determining cause of reaction, and treatment information.
Patients should be instructed to:

1. Maintain good nutrition, including adequate intake of niacin and vitamin C.
2. Ensure adequate oral hydration; avoid a dry environment and use a humidifier in the bedroom.
3. Wear sun-protective clothing and PABA-free sunscreen when outdoors for extended periods of time.
4. Apply non–alcohol-based emollient creams (Eucerin™, Nivea™) or lotions (Lubriderm™, Alpha Keri™, Nivea™), or cholestyramine (Questran®); usually BID or TID.
5. Add oil at the end of a bath or add a colloidal oatmeal treatment early to the bath (Aveeno™ oatmeal bath soaks or oatmeal bar soap).
6. Take tepid baths, which have an antipruritic effect, probably resulting from capillary vasodilation. Limit to 30 min/d. Use mild soaps, eg, Dove™, Neutrogena™, and Basis.™ Use Oilatum® soap for pruritus.
7. Wash clothing, undergarments, and sheets with mild soaps made for infant clothing (eg, Dreft™).
8. Practice cutaneous stimulation: firm pressure at the site of itching, at a site contralateral to the site of itching, and at acupressure points may break the neural pathway. Rubbing, pressure, and vibration can relieve itching. Avoid scratching.
9. Remove tags from clothing, avoid constrictive garments, or clothing made from wool, synthetics, or harsh fabrics/bedding for pruritus.
10. Avoid soaps and deodorants that contain scents and genital deodorants or bubble baths.
11. Avoid alcohol-based skin lotions or petrolatum (Desitin®) or mineral oil.

REFERENCES

VI. Endocrine

DIABETES BACKGROUND

Type I, or insulin-dependent, DM is present in patients with little or no endogenous insulin secretory capacity. These patients are dependent on injected exogenous insulin therapy for their survival. Type I can occur at any age, but onset occurs predominantly in youth.¹

Type II, or non–insulin-dependent, diabetes mellitus (NIDDM) occurs in patients who retain significant endogenous insulin secreting capacity. Although treatment with insulin may be necessary for the control of hyperglycemia, these patients do not develop ketosis in the absence of insulin therapy and are not dependent on insulin therapy for immediate survival. Onset predominantly occurs after age 40 years.¹

Autoimmunity plays a major role in the etiology of type I diabetes; 90% of patients have demonstrable serum titers of islet cell antibodies or insulin auto-antibodies. Patients with type II diabetes have a 60% incidence of obesity. They have normal or elevated fasting insulin levels, secrete decreased amounts of insulin following meals, and are insulin resistant.¹

INCIDENCE OF DIABETES IN LIVER DISEASE

Chronic liver disease may be associated with diabetes. The liver is involved in carbohydrate metabolism, and as many as 70% of patients with cirrhosis may have impaired glucose tolerance. Hyperinsulinemia, insulin resistance, and hyperglucagonemia (type II) may be a direct consequence of liver disease, especially cirrhosis. In patients with chronic liver disease caused by HCV infection rather than by hepatitis B virus (HBV) infection, the prevalence of diabetes is much higher.²

Type I Diabetes and Hepatitis C

Type I diabetes only rarely develops in patients with HCV infection, whereas type II diabetes is much more prevalent. In a study assessing evidence of AI disease and presence of autoantibodies in 70 HCV-infected patients, all patients with type I diabetes and hepatitis C were positive for one or more markers of pancreatic autoimmunity before treatment with interferon alfa. Furthermore, all had HLA-DR3 and/or HLA-DR4 genetic markers of autoimmune type I diabetes. Treatment with interferon alfa might amplify an already existing AI response against the β cells of the pancreas.³

Type II Diabetes and Hepatitis C

In 45 HCV-infected patients without cirrhosis, 33% were found to have type II diabetes, compared with 5.6% of controls without liver disease and 12% of HBV-infected patients.⁴ HCV-induced liver injury was found to be related to the deterioration of insulin sensitivity and first-phase insulin response. HCV infection was associated with diabetes in many patients, and liver cirrhosis was not the cause of their diabetes.⁴
In an evaluation of glycemic control in 49 HCV-infected patients, 15 had known type II diabetes (NIDDM) and 34 were nondiabetics. In the diabetes group, glycemic control worsened during interferon therapy in five (33.3%). Three of 11 (27.3%) cases formerly managed by diet alone required oral hypoglycemic agents (OHA), one of three formerly managed by OHA required insulin, and a lone insulin patient required intensive insulin therapy/monitoring. In the nondiabetic group, 17 maintained normal glucose levels and 17 had impaired glucose tolerance via fasting blood sugars (FBS).\(^5\)

A threefold increase in incidence of type II diabetes has been found in those with chronic hepatitis C–related disease and cirrhosis, supporting a link between diabetes and HCV infection.\(^6\)

**RISK FACTORS FOR DEVELOPING TYPE II DIABETES\(^6,7\)**
- Positive family history
- Increasing age
- Weight/body mass index
- Male sex
- Severity of liver histology*
- Corticosteroid therapy
*Insulin sensitivity and first-phase insulin secretion are negatively related to liver fibrosis score.\(^8\)

**PATHOPHYSIOLOGY: INTERFERON ALFA AND DIABETES**
Acute treatment with interferon alfa results in an increase in counter-regulatory hormones as well as a hypermetabolic response, leading to insulin resistance. These effects are dose dependent and decrease over time. Accelerated hepatic insulin clearance and a decrease in free fatty acids following interferon treatment can improve glucose tolerance.\(^8\) In a study using \(6 \times 10^{-6}\) U of interferon alfa subcutaneously, three times a week for 4 months, no impairment of glucose homeostasis was observed.\(^8\)

**DIABETES FOLLOWING LIVER TRANSPLANTATION**
Independent predictors of the presence of diabetes 1-year posttransplant*:
- HCV-related liver failure
- Pretransplantation diabetes
- Male sex
*The prevalence of diabetes 1-year-posttransplant in HCV-infected patients was 37%.\(^9\)

**MANAGEMENT STRATEGIES**
1. Pretreatment assessment for occult diabetes or determination of stable blood glucose levels (fasting glucose). If glucose is elevated, measure Hgb A1c and follow-up as in step 2 below.
2. If known diabetic, determine stable glyemic control. Maintain close follow-up with primary care physician and/or endocrinologist. Check Hgb A1c: If \(\geq 8.5\%\), defer treatment until \(\leq 8.5\%\).
3. Before interferon therapy, caution known diabetics regarding compliance with diet, glucose monitoring, and any diabetes medications.
4. Educate patient about signs of hyperglycemia and hypoglycemia (including seizures and coma).
5. Patients may need to increase frequency of Accu-Chek® while on therapy if glucose levels are erratic. Patients should be closely followed by their primary physician or endocrinologist.
6. Providers may need to re-educate patients regarding nutrition and hypoglycemic diet; consider nutritional consult.
7. Endocrinology consult, as needed. Patient may require OHAs or insulin.
8. If patient becomes OHA or insulin dependent, refer to local Certified Diabetes Educator.
9. Measure FBS levels for symptomatic patients.
10. During therapy, document patient’s glycemic control or referral, if necessary.
11. Use peginterferon/ribavirin with caution in patients with predisposition for ketoacidosis.

REFERENCES
WARNING:
Patients with pre-existing thyroid abnormalities whose thyroid function cannot be maintained in the normal range by medication should not be treated with interferon or peginterferon. Therapy should be discontinued for patients developing thyroid abnormalities during treatment whose thyroid function cannot be normalized by medication. Discontinuation of interferon-based therapy has not always reversed thyroid dysfunction occurring during treatment.

PATHOPHYSIOLOGY
The thyroid is a bilobed gland located on either side of the trachea directly above the larynx. It secretes the hormones thyroxine (T₄) and triiodothyronine (T₃). T₄ represents 90% of secreted hormone and T₃ represents 10%. Of T₄, 99.97% is protein bound, with T₃ less strongly protein bound. T₃ and T₄ affect most body tissues by regulating protein, fat, and carbohydrate catabolism as well as metabolism. T₃ and T₄ also regulate CNS development, cardiac rate, and gastrointestinal tract functioning. Thyroid function is regulated by the hypothalamic-pituitary axis. Thyrotropin-releasing hormone (TRH) is released by the hypothalamus, which stimulates the pituitary to secrete TSH. TSH stimulates the thyroid gland to produce T₃ and T₄. T₃ and T₄ circulating levels inhibit release of TSH when sufficient synthesis has occurred. When T₃ and T₄ levels decrease, the pituitary releases TSH. Hypothyroidism results from decreased thyroid gland hormone production and secretion. Primary hypothyroidism results from lower levels of T₃ than T₄. Increased TSH secretion increases T₃ secretion. Secondary hypothyroidism results in decreased synthesis of both hormones. Hyperthyroidism occurs when tissues are exposed to excessive thyroid hormone concentrations. It has multiple causes, some of which are transient and others of which are permanent, ie, Graves’ disease, thyroiditis.

Interferon alfa stimulates production of various cytokines (eg, interferon-gamma [IFN-γ], interleukin-2 [IL-2]) that have direct effects on endocrine cells. As a result, cytokines have been identified as important factors in the pathogenesis of autoimmune endocrinopathies, particularly IFN-γ and IL-2. It is postulated that interferon alfa stimulates production of IFN-γ and IL-2 from thyroid-infiltrating lymphocytes, hence potentiating antithyroid autoimmunity. Specific antithyroid autoantibodies, antithyroid peroxidase, and antithyroglobulin have also been observed in patients on interferon alfa, resulting in an AI thyroiditis. This is generally reversible, but can take up to 18 months to resolve. In some patients, hypothyroidism developed while on treatment may be permanent. Hypothyroidism is more commonly manifested in patients undergoing interferon therapy, with a ratio of hypothyroidism to hyperthyroidism of 2:1 or 3:1. Transient hyperthyroidism followed by persistent hypothyroidism has been reported.

All patients should be counseled prior to initiation of interferon-based therapy that irreversible thyroid disease can occur.
HIGH-RISK PATIENTS
• Women
• Age >40 years
• IL-2 and interferon concomitant therapy
• Pre-existing thyroid disease
• Family history

DIAGNOSTIC TESTS AND INTERPRETATION
1. TSH recommended initially (all patients)
2. If TSH is abnormal, complete thyroid panel including T_4 and free T_3.
   a. High TSH, normal T_4: compensated hypothyroidism
   b. High TSH, low T_4: clinical hypothyroidism
   c. Low TSH, high T_3: hyperthyroidism
3. Consider measuring antithyroid antibodies to rule out AI thyroid disease, such as Hashimoto’s thyroiditis. Antithyroid antibodies: antithyroid peroxides, antithyroglobulin, and antimicrosomal antibodies. Antithyroid autoantibodies are very common in the general population, occurring in about 16% of women. Normal aging increases the number of circulating antibodies; thus, the patient’s health and age must be considered.
4. Note that measuring T_4 alone could lead to missing a diagnosis of compensated hypothyroidism, since the T_4 level could be normal only because the TSH has been stimulating the thyroid into additional production. Compensated hypothyroidism cannot persist for long without progressing to overt hypothyroidism.
5. Note that T_3 is measured, but is less meaningful; may be lower than normal in up to 70% of all hospitalized patients.

<table>
<thead>
<tr>
<th>SYMPTOMS OF HYPOTHYROIDISM¹</th>
<th>SYMPTOMS OF HYPERTHYROIDISM²</th>
</tr>
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<tbody>
<tr>
<td><strong>SUBCLINICAL:</strong></td>
<td><strong>CLINICAL:</strong></td>
</tr>
<tr>
<td>• Easily fatigued</td>
<td>• Declining mental function</td>
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<tr>
<td>• Mood alterations/mild depression</td>
<td>• Increased fatigue</td>
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<tr>
<td>• Inability to lose weight</td>
<td>• Dry skin/myalgias</td>
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<tr>
<td><strong>CLINICAL:</strong></td>
<td>• Constipation</td>
</tr>
<tr>
<td>• Declining mental function</td>
<td>• Irregular/heavy menses</td>
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<tr>
<td>• Increased fatigue</td>
<td>• Pallor, yellow skin tone</td>
</tr>
<tr>
<td>• Dry skin/myalgias</td>
<td>• Hoarseness</td>
</tr>
<tr>
<td>• Constipation</td>
<td>• CHF</td>
</tr>
<tr>
<td>• Irregular/heavy menses</td>
<td>• Increased appetite</td>
</tr>
<tr>
<td>• Pallor, yellow skin tone</td>
<td>• Emotional lability</td>
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<tr>
<td>• Hoarseness</td>
<td>• Weight loss</td>
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<tr>
<td></td>
<td>• Thyroid enlargement</td>
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<tr>
<td></td>
<td>• Infertility</td>
</tr>
<tr>
<td></td>
<td>• Gynecomastia in males</td>
</tr>
<tr>
<td></td>
<td>• Tremors in fingers/hands</td>
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</table>
TREATMENT FOR HYPOTHYROIDISM
1. Check medical history for possible etiology. Two widely used drugs, lithium carbonate (Eskalith®) and amiodarone (Cordarone®, Pacerone®), are known to cause hypothyroidism.
2. Continue anti-HCV therapy while therapy for hypothyroidism is instituted.
3. Thyroid hormone replacement: levothyroxine (Levothroid®, Levoxyl®, Synthroid®, Unithroid™) preferred. Age <50 years: 75–100 µg with 25–50 µg dose adjustment every 2 to 3 weeks. Age >50 years: 25 to 50 µg, increases in 25 µg increments. Do not interchange brands; bioequivalence problems between manufacturers. Peak therapeutic effect: 4 to 6 weeks.
4. Adverse reactions of thyroid hormone replacement:
   a. CNS: nervousness, insomnia, tremor
   b. CV: tachycardia, angina
   c. Gastrointestinal: diarrhea, vomiting
   d. General: weight loss, fever, heat intolerance, menstrual irregularities
5. Recheck thyroid panel in 4 weeks. If there are persistent abnormalities, consider referral to endocrinologist.
6. Be aware that antidiabetic agents may have to be increased when thyroid medications are initiated, and patients taking estrogen (hormone replacement therapy) may need to increase the amount when beginning thyroid medications.

Patients should be instructed to:
1. Take medication at the same time every day to maintain hormone levels. A single morning dose before breakfast decreases the chance of insomnia; tablets may be crushed. Do not adjust the dose.
2. Take iron preparations, antacids, and cholesterol-lowering drugs 4 to 5 hours apart from thyroxine.
3. Notify their healthcare provider of symptoms of intolerance: palpitations, chest pain, anxiety, and sudden increase in size of thyroid gland.
4. Know that symptoms should begin to abate within 2 weeks of therapy initiation.
5. Be aware that thyroid hormone replacement is usually permanent, and they should tell all healthcare providers that they are taking this therapy.
6. Store medications in cool, dark, dry place.
7. Avoid changing dose/brand or discontinuing treatment without physician approval.
8. Limit consumption of high iodine foods (especially kelp preparations), since thyroid medications may increase toxicity to iodine.
9. Inform their radiologist about thyroid medication before any iodine contrast is given for imaging studies.

TREATMENT FOR HYPERTHYROIDISM
1. Upon diagnosis of hyperthyroidism, strongly consider referral to the primary physician and/or endocrinologist.
3. Iodide: Reserved for severe hyperthyroidism following iodine-131 (\(^{131}\text{I}\)) therapy or as preparation for surgery.\(^2\)
4. Beta-adrenergic drugs: Propranolol (Inderal\textsuperscript{®}, Inderide\textsuperscript{®}). Indications: between interval that \(^{131}\text{I}\) therapy becomes effective or prior to surgery.

Patients should be instructed:
1. That medications are generally taken for at least 2 years and should not be abruptly discontinued
2. To contact healthcare professional with first signs of infection or fever
3. That the therapeutic effect of medication is not usually evident for about 3 weeks

THYROID DYSFUNCTION AND HCV INFECTION CONSIDERATIONS
The prevalence of antithyroid antibodies and autoimmune thyroid disease is higher in the HCV-infected population than in control groups.\(^5\) A proportion of patients with antithyroid antibodies will develop clinical thyroid dysfunction. Hypothyroidism is seen more frequently than hyperthyroidism. Hyperthyroidism may transform over time into hypothyroidism. The incidence of antithyroid antibodies and thyroid dysfunction is enhanced by interferon alfa treatment. Thyroid dysfunction is reversible only in a minority of patients following discontinuation of interferon alfa treatment. Antithyroid autoantibodies have a 4.6% to 15% prevalence in untreated HCV-infected patients. Latent AI thyroiditis is more frequent in untreated hepatitis C patients than in controls. Risk factors for developing antithyroid antibodies include\(^5\):
- Age
- Female sex
- Increased TSH levels
- Hypoechogenic pattern of thyroid gland on ultrasound\(^5\)

THYROID DYSFUNCTION IN HCV-INFECTED PATIENTS TREATED WITH INTERFERON ALFA
- Study of 308 patients treated with interferon alfa therapy, including 211 with HCV infection, who underwent thyroid function evaluation before and after interferon\(^6\)
- 14% of patients had antithyroid peroxidase antibodies (ATPO); 3.7% had detectable thyroid dysfunction prior to onset of therapy.\(^6\)
- Interferon alfa led to increase in ATPO in 73% of patients with positive baseline levels; 10.8% of patients developed de novo ATPO.
- Increased prevalence of ATPO following therapy was more frequent in women.\(^6\)
- Patients with high baseline ATPO titers had a higher rate of thyroid dysfunction at end of treatment.
- Six months posttherapy, an increased rate of thyroid dysfunction persisted in 8% of patients.
- 5.8% of euthyroid patients with undetectable ATPO prior to therapy developed thyroid dysfunction; 11/15 developed hypothyroidism and 4/15 hyperthyroidism.
• 15.2% of euthyroid patients with detectable ATPO prior to treatment developed hypothyroidism.
• Six months posttherapy, normal thyroid function was observed in 3/15 patients (20%) who developed hypothyroidism and 4/7 patients who developed hyperthyroidism.
• 3/7 remaining patients who developed hyperthyroidism during treatment progressed to hypothyroidism during follow-up.
• Clinical recommendation: interferon-based therapy can continue unless the patient is symptomatic or unstable.

REFERENCES
VII. Flulike Syndrome

MYALGIA AND ARTHRALGIA

PATHOPHYSIOLOGY

Normal neuromuscular transmission involves depolarization-induced influx of calcium through voltage-dependent, gated channels of the presynaptic nerve terminal. The action takes place at the molecular level, using neurotransmitters, among which are acetylcholine (ACH) and adenosine triphosphate, each stimulating and releasing transmitters at different rates. The calcium stimulates the release of ACH from the presynaptic nerve terminal into the synaptic cleft. ACH binds to ACH receptors and depolarizes the postsynaptic muscle membrane.

It is postulated that interferon interferes with both presynaptic and postsynaptic neuromuscular transmission. Interferon alfa starts the interferon cascade, which can induce, inhibit, or modify several pathways involving the pro-inflammatory cytokines (IFN-γ, IL-1, IL-2, IL-6, IL-8, and tumor necrosis factor [TNF]). Many of the side effects of interferon alfa are said to stem from these interactions. The interactions can also contribute to myalgias/arthralgias seen with interferon. The myalgia caused by interferons related to serotonin may be similar to the myalgia seen in fibromyalgia in addition to the substance P level changes and N-methyl-D-aspartate (NMDA) receptor activity that also accompany that disease. Myalgias of mild to moderate severity that accompany anti-HBV treatment with interferon have also been observed with ribavirin treatment and with other interferon products, such as interferon alfacon-1.

MYALGIA/ARTHRALGIA ETIOLOGY

Myalgia and arthralgia can be caused by a number of widely different conditions, from fibromyalgia to common muscle stress and strain, but the body aches and pains accompanying the flulike symptoms after administration of interferon are fairly predictable. They are usually short-lived and usually diminish with continued drug administration within a few weeks. However, patients on an intermittent regimen may not experience this tachyphylaxis. Severity of myalgia may be dose related, with larger and continuing doses producing more severe and sustained discomfort. Presence or absence of progressively more severe myalgia and arthralgia may also be related to their pre-existence due to HCV infection.

DIFFERENTIAL DIAGNOSES

- AI disorders (new onset or exacerbation), eg, rheumatoid arthritis, lupus, hypothyroidism, etc.
- Fibromyalgia
- Mixed cryoglobulinemia (especially HCV-infected patients)
- Metabolic disorders: decreased Na, Mg, Ca, and glucose levels
- Eosinophilic fasciitis
- Polymyositis
- History of osteoarthritis—patients may be using chondroitin complex or glucosamine supplements

Rare:
- Rhabdomyolysis
- Myasthenia gravis
- Postpolio syndrome
- Guillain-Barré syndrome

LABORATORY TESTS TO CONSIDER
- Urine myoglobulin (intracellular protein secreted into the urine indicating muscle ischemia)
- Creatine kinase
- CPK (soenzymes help to distinguish between cardiac [MB] or skeletal muscle [MM] injury)
- Immunocytochemistry: detects presence of interferon, TNF, and IL-1
- Electrolytes
- ANA

TREATMENT STRATEGIES
(Refer to “Fever” and “Headache” sections)

REFERENCES
Fatigue is a multidimensional condition with several theoretic foundations: physiologic, pathologic, and psychological.\(^1,2\) Fatigue may be a subjective feeling of tiredness, weariness, diminished energy, or temporary loss of physical and emotional energy preventing response to sensory or motor stimuli.\(^3,4\) Moreover, fatigue is often a primary dose-limiting factor that prevents completion of therapy.\(^5\) Fatigue is closely correlated with other conditions, such as sleep disorders, anxiety, agitation, stress, and depression, and continued, unmanaged fatigue can lead to deterioration of physical and mental activities.\(^2\)

**PATHOPHYSIOLOGY**

*Interferon*

Two different types of fatigue are associated with interferon: (1) physical fatigue or weakness that occurs from activation of the interferon cascade and subsequent flulike syndrome\(^6\); and (2) neuroendocrine system fatigue that is associated with neuropsychological fatigue (mental or depressive), that may be accompanied by cognitive (CNS) slowing or decreased performance status that occurs as an effect of these agents.\(^7\) Fatigue accompanying interferon administration is frequently a dose-limiting or treatment-limiting toxicity and may lead to dose reduction in 10% to 49% of all patients.\(^7\)

*Ribavirin*

Ribavirin may cause an acute decrease in Hgb during the first 1 to 2 weeks of administration (a mean Hgb drop of 2.7 g/dL) that can quickly cause a patient to experience acute fatigue. However, this initial fatigue may often progress slowly to chronic fatigue from the same mechanisms stated above. Ribavirin also causes intermittent fatigue when administered to patients infected with HCV.\(^8\)
CONTRIBUTING RISK FACTORS FOR FATIGUE

<table>
<thead>
<tr>
<th>Physiologic</th>
<th>Psychologic/Psychosocial</th>
<th>Treatment/Situational</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anemia (impaired aerobic energy metabolism)</td>
<td>• Sleep disturbances</td>
<td>• Interferon or other bio- or chemotherapy</td>
</tr>
<tr>
<td>• Metabolic disease</td>
<td>• Lack of exercise</td>
<td>• Surgery</td>
</tr>
<tr>
<td>• Cancer</td>
<td>• Anxiety</td>
<td>• Radiation therapy</td>
</tr>
<tr>
<td>• Poor nutritional status</td>
<td>• Depression</td>
<td>• Transplantation</td>
</tr>
<tr>
<td>• Hypermetabolic state (active tumor growth, infection, fever, or surgery)</td>
<td>• Grief, loss</td>
<td>• Dose/timing of administration: interferon</td>
</tr>
<tr>
<td>• Cardiovascular disease</td>
<td>• Social factors/psychosocial stress</td>
<td>• Other medications, eg:</td>
</tr>
<tr>
<td>• Chronic obstructive pulmonary disease</td>
<td>- Divorce</td>
<td>- Antibiotics</td>
</tr>
<tr>
<td>• HIV/HCV co infection</td>
<td>- Work difficulties</td>
<td>- Ribavirin</td>
</tr>
<tr>
<td>• Thyroid or hepatic dysfunction</td>
<td>- Economic status</td>
<td>- Analgesics, sedating antihistamines</td>
</tr>
<tr>
<td>• Weakness</td>
<td>- Lack of social support</td>
<td>- Antihypertensives</td>
</tr>
<tr>
<td>• Chronic pain</td>
<td>• Stress</td>
<td>- Anxiolytics</td>
</tr>
<tr>
<td>• Diagnostic tests</td>
<td>• Environmental influence</td>
<td>- Antidepressants</td>
</tr>
<tr>
<td>(psychologic or physical)</td>
<td></td>
<td>- Sleep agents (long-acting)</td>
</tr>
<tr>
<td>• Anticipatory nausea/vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ethyl alcohol, excess caffeine, nicotine, other addictive substances including illicit drugs</td>
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</tbody>
</table>

TYPES OF FATIGUE

Acute: Normal or expected tiredness characterized by localized, intermittent, or sporadic symptoms; rapid onset; and short duration (days or weeks) that are usually relieved by rest. Chronic: Abnormal or excessive generalized tiredness that is constant or recurrent for at least 1 month and an insidious gradual onset with cumulative effect. Chronic fatigue is not relieved by sleep or rest, and while its cause is unknown, it has a major impact on quality of life (QOL) and ability to maintain compliance with a drug regimen. Fatigue arises following the initial flulike syndrome (FLS) accompanying interferon treatment, but unlike FLS, develops more slowly and may continue to increase with continued therapy.
ASSESSMENT

1. Assess subjective and objective data that may influence fatigue.

2. Elicit patient information about patterns of fatigue: onset, duration, intensity, alleviating or aggravating factors, sleep patterns, impact on QOL, and signs and symptoms.¹

3. Assess subjective and objective symptoms of fatigue, including general appearance, description, attitude, speech, activity, and concentration.³

4. Consider testing extent of fatigue with Pearson-Byars Scale, Fatigue Symptom Checklist, Symptom Distress Scales, Profile of Mood States, Rhoten Fatigue Scale, or other fatigue scales.¹³⁷

5. Review medications: Replace sedating antihistamines and other sedating drugs if possible. Address other drug side effects that cause fatigue or flulike symptoms (nausea/vomiting, anorexia, depression, anemia, diarrhea).

6. Obtain CBC with differential; rule out treatment-induced anemia.

7. Assess laboratory data (TSH, glucose and hormone levels, including electrolytes, alanine aminotransferase/aspartate transaminase [ALT/AST], SMA; serum albumin; and extrahepatic diseases).⁹

8. Determine if pain (or arthralgias and myalgias) awaken patient or if medications are required to prevent awakening.

9. Assess thyroid function.⁴

10. Assess for presence of other risk factors (see Risk Factor table above).

11. Assess timing and extent of exercise schedule. Assess for complaints of dyspnea on exertion or chest pain while exercising.

12. Assess food and fluid intake.

PREVENTIVE STRATEGIES

1. Instruct patient about need for adequate diet, hydration, rest, and exercise and energy conservation; develop patient self-report form.

2. Encourage light exercise program, especially aerobic exercises (eg, walking), to build strength and endurance and to increase patient tolerance and improve pre-existing activity level.

3. Consider education regarding patient-initiated interventions or energy-conservation techniques: resting, “catnapping” (no longer than 20 minutes), alteration of activities; limit standing.

4. Help patients improve sleep/wake patterns.

5. Provide strategies to improve nutritional, environmental, or social situation.

6. Suggest reading or engaging in other distracting/relaxing activities.

7. Educate family members; bolster support systems.

TREATMENT STRATEGIES

1. Consider altering timing of administration (eg, give peginterferon in the afternoon or evening).

2. Consider use of psychostimulants for profound fatigue (eg, methylphenidate [Concerta™, Metadate®, Methylin®, Ritalin®], 20 mg PO SR Q AM; rarely, BID).
3. Consider administration of an antidepressant to increase energy levels; bupropion (Wellbutrin XL®) 100 to 400 mg QD in divided doses; and mirtazapine (Remeron®) 15 to 30 mg QHS.
4. For fatigue from emotional stress, counsel regarding possibility of chronic fatigue; offer feedback and encouragement in defining limitations/abilities; supply emotional support by verbal and nonverbal responses; help patient develop effective coping patterns with adequate support systems; prevent or resolve a crisis by utilizing crisis intervention techniques; and/or make appropriate referrals to mental health worker, social worker, or chaplain.
5. Encourage relaxation strategies: music, visual imagery, yoga, visualization, walking, etc.
6. Consider addition of amantadine (Symmetrel®) 100 mg QHS to reduce neuromuscular fatigue.10
7. Consider recommending omega 3 120–180 mg PO QD, vitamin E 800 IU/d, vitamin C 1000 mg/d, and multivitamins. When recommending multivitamins, note that supplements without iron should be used unless the patient is iron deficient.

REFERENCES
Flulike Syndrome

FEVER, CHILLS, AND RIGORS

PATHOPHYSIOLOGY
Fever is a commonplace response to most biologic agents and is strongly dependent on dosage. As part of the FLS associated with interferon, initial fevers of 104°F are not uncommon. The patient’s overall condition, including general health, age, CV status, and potential for infection should be assessed before administering antipyretics. Severity of fever, chills, and rigors abates somewhat as treatment continues and as tachyphylactic response occurs. Flulike symptoms that appeared upon initial administration, first with chills and rigors, followed by fever about an hour later, may recur if dosage is increased.

Fever has come to be viewed as an adaptive mechanism that facilitates body defenses. Many of the cytokines, including the interferons, interleukins, and TNF-α, are endogenous mediators of fever (endogenous pyrogens), although TNF may also be an endogenous antipyretic. These and other mediators of immunity initiate a pathway that raises the thermoregulatory set point of about 98.6°F (37°C) to raise body temperature—a neuro-immunomodulatory reaction. The cytokines within the hypothalamus may initiate fever, but the signals may originate from peripheral nerves within the brain. High fevers (over 104°F) may be induced by the initial dose of interferon, other biologic response modifiers, biologic agents, disease, malignancy, and many other causes. The fever process may be induced via a multipathway mechanism that may have therapeutic value. Thus, controversy still exists as to the wisdom of administering antipyretics to reduce a mild fever.

Interferon alfa modulates fever by changing the body’s release of hypothalamic prostaglandin E2, which may stimulate a neurotransmitterlike substance to raise the temperature set point. Fever is a multiphasic process that is a series of physiologic responses (eg, peripheral vasoconstriction and shivering) and compensatory behavioral responses (eg, adding clothing or changing body position). The stages of fever include:

- **Stage I: Chill or Cold**
  As the body is working to raise the temperature set point, vasoconstriction and shivering (during which the patient feels cold) may occur, which may lead to increased oxygen consumption and tissue catabolism. Other responses include thirst and chills.

- **Stage II: Hot or Plateau**
  The body temperature achieves or exceeds the new set point. Skin is flushed and warm, basal metabolic rate and oxygen demand are elevated, and tachycardia and tachypnea will be experienced. Thirst is common, as are headaches and myalgias. The cause for the fever may be determined and treated, or antipyretics may be administered at this point.
• Stage III: Wet (Defervescence)⁵
  Responses include vasodilation, flushing, and diaphoresis (especially above 38°C), and dehydration.

ASSESSMENT STRATEGIES
1. Educate patients regarding appropriate way to take temperature (e.g., avoid taking temperature immediately after drinking coffee or smoking; keep thermometer in place for adequate time).
2. Investigate infectious causes for development of high fever or fever persisting for more than 48 hours after administration of peginterferon.

PATIENT EDUCATION
Patients should be informed that:
1. Flulike symptoms often accompany biologic therapy and severity may vary.
2. Adaptation or tachyphylaxis usually develops to fever and chills in about 2 to 3 weeks.
3. To ensure adequate hydration, they should drink the equivalent, in fluid ounces per day, of one half their body weight (in lb). For example, a 160-lb person should consume 80 fl oz water/d.
4. Relaxation and guided imagery techniques can minimize discomfort and anxiety.
5. A diary can be used to record fever patterns and other symptoms.
6. They should report to medical personnel any fevers uncontrolled by antipyretics or unrelated to treatment.
7. They should notify medical personnel of “red flags” such as fever >104°F, prolonged rigors, altered mental state, or cyanosis.

TREATMENT STRATEGIES
1. Evening administration (but earlier than at bedtime) of interferon may be helpful in reducing the patient’s awareness of fever and other flulike symptoms, although the patient may experience loss of sleep.² Depending on the timing of symptoms, patients may need to try even earlier administration.
2. Comfort measures (warm blankets, extremity wraps, ice packs) can be helpful.
3. Promote adequate hydration and give IV hydration if needed.
4. Antipyretics may be administered to reduce temperature >101°F and as analgesia, but controversy exists as to their overall effect.¹ Some providers recommend premedicating with these agents and others inform patients to take them as soon as flulike symptoms begin to develop.
   a. Acetaminophen (Tylenol®) 325 to 650 mg Q6H PRN, not to exceed 2 to 3 g/d.
   b. Ibuprofen (Motrin®, Advil®) 200 to 800 mg TID, not to exceed 2400 mg/d, with food.
5. Prednisone is known to limit therapeutic effect and should not be used.⁸
6. Diphenhydramine (Benadryl®) 35 to 50 mg PO is infrequently used in resistant cases as premedication and Q6H PRN.
7. Anti-HCV treatment can be dose reduced or discontinued should fever and other side effects become unmanageable, but patients should be advised that the biologic effects
may be compromised by dose reduction and that the fever may contribute to the therapeutic response.²

REFERENCES
**PATHOPHYSIOLOGY**

Migraines arise from a triggering event that sets off a chain of vascular, muscular, or neurotransmitter responses.\(^1\) The brain chemical serotonin and the trigeminal nerve pathway (site of the nerve responsible for sensation in the face, mouth, and nasal cavity) are the major factors in severe headache (HA). The cerebral cortex responds to emotion or stress (two of the triggers of migraine) by releasing norepinephrine from the adrenal medulla. This causes a release of serotonin from platelets that increases free serotonin concentrations in the plasma. An increased serotonin level causes arterial vasoconstriction (an ischemic event), which may be responsible for the aura experienced by migraineurs.\(^1\) In migraines, serotonin levels rise before onset and decrease during the HA phase. In chronic tension HAs, serotonin levels remain at a constant low. With reduced serotonin levels, an impulse travels along the trigeminal nerve to blood vessels in the meninges. This causes vasodilation in the meninges, which become dilated, inflamed, and swollen; the result is HA or migraine. A vasodilatory effect similar to sepsis is caused by the cytokine interferon that can also produce HA.

Interferon alfa causes disturbances in serotonin levels that are most often associated with HA in patients treated for HCV infection. Patients treated with ribavirin have also experienced HAs.\(^2\)

**STAGES AND CAUSES OF HA, MIGRAINE HA, AND CLUSTER HA**

Common HAs may be caused by stress, tension, anxiety, allergies, constipation, caffeine, eyestrain, hunger, sinus pressure, or muscle tension. However, migraine HA may be caused by a multitude of other triggers.\(^3\) These triggers can include environmental or physiologic factors, sensory stimuli, impending onset of menstruation, foods, and certain drugs, especially those with a vasodilating effect.\(^1\)

Migraine HAs have five distinct phases: prodrome, aura, HA, resolution, and postdrome. The prodrome may begin 24 hours before onset of the actual HA. The aura, which begins about an hour before the HA and lasts 20 to 30 minutes, may cause visual disturbances (flashing lights, moving zigzag lines, and blind spots), or sensory sensations. The HA itself usually starts as a dull pain, then develops into a pulsating, painful sensation—often on only one side of the head, but 40% of patients experience it on both sides, mainly in the temples. It may be felt on any area of the face, head, or neck. Vomiting, nausea, photophobia, and/or phonophobia may accompany the pain. The resolution phase, with cessation of pain and restoration of body homeostasis, usually lasts several hours, frequently during sleep or rest. The last stage is the postdrome, accompanied by a feeling of being drained, tired, and fatigued. Muscles ache, appetite is diminished, and emotions are volatile.\(^1\) Cluster HAs are more severe, and are characterized by their recurring nature. They are accompanied by throbbing, severe pain on one side of the head, tearing
eyes, and nasal congestion. They sometimes occur up to three times per day and may last a few minutes or several hours.

**PREVENTIVE STRATEGIES**

Patients should be instructed to:
1. Establish regular mealtimes, sleep patterns, relaxation, and exercise routines.
2. Eliminate unproductive worry/stress.
3. Avoid caffeine—for withdrawal HA, slowly decrease use.
4. Avoid wide fluctuations in blood glucose by eating smaller, regular meals with snacks.
5. Pre- and 4 hours postinterferon injection, use acetaminophen or an NSAID.
6. Maintain adequate hydration: (consumption equal, in fluid ounces, to one half body weight in pounds; eg, 80 fl oz for a 160-lb person). Limit caffeine to AM, then use decaffeinated products.
7. Identify and avoid dietary triggers. People who suffer from frequent HAs may be reacting to certain foods and food additives, especially wheat, chocolate, sugar, coffee, tea, red wine, alcohol, vinegar and/or marinated foods, citric acid, fermented foods (aged cheese, sour cream, yogurt), monosodium glutamate (MSG), nitrites (contained in hot dogs, bacon, luncheon meats), sulfites (used by restaurants in salad bars).
8. Avoid environmental triggers: fumes, odors, emotional crises, weather/elevation changes.
9. Try eliminating foods containing tyramine and phenylalanine. To determine sensitivity, reintroduce one food at a time and observe which ones produce HA. Phenylalanine is found in aspartame (Equal®, NutraSweet®), MSG, and nitrites. Foods containing tyramine include alcohol, bananas, cheese, chicken, chocolate, citrus fruits, cold cuts, herring, onions, peanut butter, fresh-baked yeast products, sour cream, vinegar, etc. These cause the blood pressure to rise, resulting in HA.
10. Avoid iced or very cold or hot foods or beverages; lukewarm to cool temperatures are less likely to trigger or exacerbate a migraine. Avoid chewing gum and excess salt. Use antiemetics for migraine-induced nausea.
11. Reduce lighting/sound volume since light and sound can be triggers; use earplugs, sunglasses, visors, close blinds, etc.
12. Keep a log to assist in diagnosis and treatment if they experience more than occasional HA for at least 1 to 2 months. Note the time of each HA and describe the pain (throbbing or dull), its severity, location, duration, as well as what relieves/exacerbates the HA.

Providers should:
1. Perform pretreatment assessment of HA/migraine. Candidates for prophylaxis include patients who have predictable attacks, at least three or more attacks per month, or failure of symptomatic therapy. Weaning off HA medications should be attempted after 6 months.
2. Assess date of last eye examination. Also rule out sinusitis; dental causes (eg, temporomandibular joint, bruxism); anemia; hypoglycemia; vertebral misalignment; medications; toxic doses of vitamin A; vitamin B deficiency;
diseases of the ears, nose, and throat; menstrual cycle; or hypertension as etiologies.

3. Administer prophylactic therapy, if warranted (see table).

<table>
<thead>
<tr>
<th>PREVENTIVE AGENTS FOR MIGRAINE HA¹</th>
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<tbody>
<tr>
<td><strong>NSAIDs</strong></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen (Tylenol®)</td>
<td>650 mg BID</td>
</tr>
<tr>
<td>Aspirin (ASA)</td>
<td>Standard dose</td>
</tr>
<tr>
<td>Ibuprofen (Motrin®, Advil®)</td>
<td>300–600 mg TID</td>
</tr>
<tr>
<td>Flurbiprofen (Ansaid®)</td>
<td>200–300 mg/d in divided doses</td>
</tr>
<tr>
<td>Naproxen (Napro syn®)</td>
<td>500 mg BID</td>
</tr>
<tr>
<td><strong>BETA BLOCKERS</strong></td>
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<tr>
<td>Propranolol (Inderal®)</td>
<td>10–20 mg BID initially; gradually increase to 80–240 mg/d</td>
</tr>
<tr>
<td>Timolol (Blocadren®)</td>
<td>10–15 mg BID</td>
</tr>
<tr>
<td><strong>CALCIUM CHANNEL BLOCKERS</strong></td>
<td></td>
</tr>
<tr>
<td>Diltiazem (Cardizem®, Tiazac®)</td>
<td>90–180 mg/d in divided doses</td>
</tr>
<tr>
<td>Nifedipine (Adalat®, Procardia®)</td>
<td>20–30 mg TID</td>
</tr>
<tr>
<td>Verapamil (Calan®, Covera-HSTM,</td>
<td>80 mg TID or QID</td>
</tr>
<tr>
<td>Isoptin®, Verelan®)</td>
<td></td>
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<tr>
<td><strong>ANTIDEPRESSANTS</strong></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline (Elavil®)</td>
<td>25–50 mg QHS, start 10 mg/d, titrate up ~10 mg @1–2 weeks, up to 200 mg/d</td>
</tr>
<tr>
<td>Desipramine (Norpramin®)</td>
<td>50–200 mg; start 10 mg/d, titrate up ~10 mg @1–2 weeks</td>
</tr>
<tr>
<td>Doxepin (Sinequan®)</td>
<td>10–200 mg</td>
</tr>
<tr>
<td>Fluoxetine (Prozac®)</td>
<td>10–20 mg/d</td>
</tr>
<tr>
<td>Imipramine (Tofranil®)</td>
<td>50–200 mg; start 10 mg/d, titrate up ~10 mg @1–2 weeks</td>
</tr>
<tr>
<td>Nortriptyline (Pamelor®, Aventyl®)</td>
<td>10–150 mg</td>
</tr>
<tr>
<td><strong>ANTICONVULSANT</strong></td>
<td></td>
</tr>
<tr>
<td>Valproate (Depakote®, Depakene®)</td>
<td>250 mg BID or TID; average dose is ~1200 mg/d</td>
</tr>
</tbody>
</table>
TREATMENT STRATEGIES

Patients should be instructed to:
1. Practice deep-breathing exercises to increase oxygen.
2. Apply cold compresses (damp, chilled cloth or gel pack) to painful location to constrict blood vessels and ease muscle spasms, or use a heating pad or hot water bottle to relax tense neck or shoulder muscles.
3. For sinus congestion HA, try self-massage to open up the sinuses and ease tension by leaning head forward slightly to encourage sinus drainage. Try application of hot compresses to the sinuses or steam inhalation.
4. Exercise to reduce or eliminate HA/migraine.

Providers should:
1. Rule out anemia.
2. For female patients who are experiencing new onset of HA on newly prescribed oral contraceptives, try switching to a low-estrogen formulation. Oral contraceptives can also cause migraines. Some women with migraines may benefit from using topical progesterone cream (Crinone®).
3. Consider organic causes of HA or poor vertebral alignment (which reduces blood flow to the brain). Determine if flat feet or high heels create vertebral misalignment. Chiropractic adjustment may help.
4. Recommend nonpharmacologic options.³
   a. Music therapy: Water/wind sounds, soothing melodies, light jazz, etc.
   b. Aromatherapy (lavender oil): inhale or apply to temple, sinus area, below nose.
   c. Relaxation exercises/deep breathing especially useful for tension HA; additional oxygen may prevent HA.
   d. Ice, cold compresses.
   e. Acupuncture/accupressure.
5. Administer pharmacologic therapy (see table).
6. Dose-modify peginterferon as needed for HA resistant to other measures.
### SYMPTOMATIC TREATMENT FOR MIGRAINE HA

#### SIMPLE ANALGESICS

- **Acetaminophen (Tylenol®)**
  - 650 mg at onset; repeat Q4H PRN as directed

- **Ibuprofen (Advil®, Motrin®)** or acetaminophen/ASA/caffeine (Excedrin® Migraine)
  - Per manufacturer’s directions; do not exceed. If ineffective, prescription medication

- **ASA**
  - Per manufacturer’s directions

- **ASA-acetaminophen with butalbital** (Phrenilyn®, Sedapap®)
  - 1–2 tablets Q4–6H, maximum: 4

#### NSAIDs

*Note: Narcotic analgesics will be needed for a small percentage of interferon patients.*

- **Ibuprofen (Advil®, Motrin®)**
  - 300–600 mg TID

- **Naproxen (Naprosyn®)**
  - 750 mg initially, 250 mg thereafter; maximum: 1375 mg/d

- **Naproxen sodium (Anaprox®)**
  - 550–750 mg initially; may repeat after 1–2 h

- **Flurbiprofen (Ansaid®)**
  - 200–300 mg/d in divided doses

#### TRIPTAN PREPARATIONS*

- **Sumatriptan (Imitrex®)**
  - 6 mg SC at onset; repeat in 1 h PRN to maximum of 12 mg/24 h

- **Sumatriptan nasal spray**
  - 5, 10, or 20 mg intranasally; repeat in 2 h PRN to maximum of 40 mg/24 h

- **Sumatriptan tablets (25 and 50 mg)**
  - 25 mg at onset or up to 100 mg in single dose; repeat in 2 h PRN to maximum of 300 mg/24 h

- **Naratriptan (Amerge®) tablets**
  - 1 and 2.5 mg; repeat once after 4 h PRN to maximum of 5 mg/24 h

- **Rizatriptan (Maxalt®) Reditabs**
  - 5 and 10 mg, or orally disintegrating tablets 5 and 10 mg (Maxalt-MLT®)
  - 5 or 10 mg at onset; may repeat once after 2 h PRN to maximum of 30 mg/24 h (10-mg dose has greater effect)

- **Zolmitriptan (Zomig®) tablets**
  - 2.5–5 mg at onset; may repeat once after 2 h PRN to maximum of 10 mg/24 h

#### OTHER

- Various antihistamines

#### Prostaglandin inhibitor

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*Triptans (serotonin agonists) are contraindicated in patients with ischemic heart disease, angina pectoris, arrhythmias, previous MI, and/or uncontrolled hypertension. Use with caution with hypercholesterolemia, obesity, diabetes, smokers, or family history of vascular disease.*
REFERENCES
HYDRATION AND DIET

HYDRATION
The possibility of dehydration during treatment for HCV infection exists due to the potential side effects of fever, chills, rigors, diaphoresis (and subsequent insensible fluid loss), diarrhea, nausea/vomiting, anorexia, and diminished fluid intake. Development or exacerbation of diabetes may also contribute to fluid imbalance. Furthermore, cognitive changes may also influence the patient’s ability to take in enough fluids.

It is critical for patients who experience flulike symptoms to maintain adequate hydration as dehydration can contribute to fever. It is estimated that fever increases insensible fluid loss by 10% for each 0.5°C increase in temperature. If the patient goes through several cycles of fever and defervescence, water loss due to dehydration may be considerable.

SIGNS OF DEHYDRATION
• Thirst
• Dry oral mucosa and/or complaints of dry mouth
• Dark urine

Severe/Advanced Dehydration
• Sunken cheeks
• Reduced intraocular pressure
• Pale, cold skin
• Poor skin turgor
• Low cardiac output
• Tachycardia
• Oliguria
• Weight loss
• Dizziness
• Nausea and/or emesis

MANAGEMENT
1. Determine the cause for inadequate fluid intake. Assess history, including medication use, fever, and side effects of treatment.
2. Educate the patient regarding the need to be well hydrated.
3. Determine the optimal intake: Weigh patient, divide weight (in lb) in half and convert into fluid ounces (e.g., a 160-lb person should consume 80 fl oz/d). Plan fluid consumption.
4. Recommend noncaffeinated fluids, including water; sports drinks; juices; Crystal Light™; Kool-Aid® and sugar-free Kool-Aid®; decaffeinated coffee, tea, or soda; and high-protein drinks, such as Ensure®, Boost®, or Carnation Instant Breakfast®. In patients with diarrhea, use supplements with caution; fluids or Carnation® are favored over Ensure®.
5. Advise patients with a history of CHF or hypertension to limit/omit the use of sports drinks due to the high sodium content of these products and risk of retention and fluid overload. If these products are used, dilute to 50% water.
6. Encourage patient to use water bottles or thermal cups with straws: these keep fluids available to sip on all day and are less overwhelming than the “glass-at-a-time” approach. Using a straw increases fluid consumption.
7. Recommend an NSAID (no more than 1200 mg/d) or acetaminophen (Tylenol®; no more than 2 g/d) to manage fever, chills, and diaphoresis that lead to insensible fluid loss. Recommend proton-pump inhibitors, which are effective at preventing chronic NSAID-related endoscopic gastric and duodenal ulcers in patients requiring frequent NSAID use.
8. Check serum electrolytes, turgor, and oral mucosa status as needed.
9. Recommend a multivitamin without iron to replace water-soluble vitamins.

**DIET/NUTRITION**

Maintenance of nutritional status during therapy is of prime importance because anorexia and associated weight loss are common side effects of interferon. Lack of appetite, taste changes, and nausea and emesis may also affect nutrition.

**MANAGEMENT**

1. Assess baseline weight, nutritional status, and dietary intake. Monitor weight throughout therapy.
2. Educate the patient regarding the need for adequate caloric intake.
3. Rule out mucositis as etiology.
4. Advise patients to eat smaller, more frequent meals.
5. Recommend a high-protein/carbohydrate diet. If meat is poorly tolerated, dairy products, beans, and protein powder can be used as protein sources.
6. Promote adequate hydration.
7. Encourage exercise to stimulate appetite.
8. Recommend supplements PRN.
9. Recommend antiemetic use prophylactically and PRN.
10. Recommend cookbooks designed for chemotherapy patients.
11. Treat aphthous ulcers, which may limit eating: (erythromycin ethylsuccinate [E.E.S.® 400] or equivalent) 50 mL + diphenhydramine (Benadryl®) liquid 50 mL + dexamethasone (Decadron®) liquid 50 mL.
12. Use megestrol acetate (Megace®) for significant weight loss, but note that this drug is associated with gynecomastia. Amitriptyline (Elavil®) 25 to 50 mg QHS also stimulates appetite.
13. See “Taste Changes” section if indicated.
14. Consider nutritional consultation, if available.

HEPATITIS DIET
1. Individualize diet recommendations for each patient. Consider other conditions that require special dietary recommendations (e.g., diabetes, steatohepatitis, renal dysfunction, cardiac conditions, etc).
2. Supply patient with food guide pyramid and educate them about the elements of a healthy diet. Hepatitis patients may require additional protein and carbohydrates.
3. Recommend vitamins to replace losses and to aid in liver cell regeneration.
4. Promote adequate fluid intake (fluid ounces equal to one-half body weight in pounds; e.g., a 160-lb person requires 80 fl oz/d).
5. Recommend multiple feedings: frequent meals or snacks increase tolerance.
6. Check iron level. Some physicians advocate limiting iron intake, using only multivitamins without iron, and instructing patients to avoid use of cast-iron skillets, etc. Consider other sources of iron, such as well water.
7. Avoid alcohol.

Note: Magnesium and vitamin B complex deficiencies often exist in these patients. Perform laboratory evaluation for deficiencies and supplement as necessary.

REFERENCES
Gastrointestinal

DIARRHEA

In interferon patients, diarrhea is usually related to dose, but tends to be mild and self-limiting. Ingestion of certain foods, fluids, medications, radiation, or the psychoneuroimmunologic effects of stress, anxiety, or fear are other causes of diarrhea. Also, persistent diarrhea may indicate the presence of systemic bacterial or protozoal infection.

PATHOPHYSIOLOGY
Mitotic arrest of intestinal epithelial crypt cells, followed by superficial necrosis and inflammation of bowel wall, result in production of mucosal factors (leukotrienes, cytokines, free radicals) that stimulate oversecretion of intestinal water and electrolytes. In the gastrointestinal system, the endocrine and paracrine cells, acetylcholine-serotonin-histamine, prostaglandin-releasing cells are affected. This alters the synthesis, release, and metabolism of vasoactive intestinal polypeptides, gastric inhibitory polypeptides, cholecystokinin, neurotensin, motilin, bombesin, and neurotransmitters, resulting in diarrhea.1

ASSESSMENT
1. Obtain history of bowel disease (ie, Crohn’s disease, irritable bowel syndrome, etc).
2. Obtain history of onset and duration of diarrhea, as well as number and composition of stools (watery, bloody, etc).
3. Assess for fever, dizziness, and weakness to rule out sepsis, bowel obstruction, or dehydration.
4. Assess if the patient is on any other medications that could cause diarrhea (eg, antibiotics).
5. Assess dietary intake for diarrhea-enhancing foods and assess for dehydration.
6. Perform stool culture for ova and parasites; check for blood, fecal leukocytes, Clostridium difficile, Salmonella, Escherichia coli, Campylobacter, and infectious colitis.
7. Do abdominal examination, and measure CBC, and electrolytes.

NCI COMMON TOXICITY CRITERIA FOR GRADING SEVERITY OF DIARRHEA

<table>
<thead>
<tr>
<th>W/O Ostomy</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;4 BM</td>
<td>4–6 BM/d or nocturnal stools</td>
<td>≥6 BM, incontinence, or dehydration</td>
<td>ICU or hemodynamic collapse</td>
</tr>
<tr>
<td>W/Ostomy</td>
<td>Mild ↑ in watery, loose BM</td>
<td>Mod ↑; no ADL change</td>
<td>Severe ↑; interfering w/ADL</td>
<td>ICU or hemodynamic collapse</td>
</tr>
</tbody>
</table>
TREATMENT STRATEGIES

Patients should be advised to:

1. Eat small, frequent meals.
2. Maintain adequate hydration (fluid consumption in fluid ounces equal to one-half body weight in pounds; eg, a 160-lb person should drink 80 fl oz/d). For diarrhea, fluids should consist of bouillon, apple juice, grape juice, Gatorade®, weak tepid tea, and gelatin, as well as “flat” caffeine-free carbonated beverages since carbonation may aggravate diarrhea.²
3. Eat foods high in potassium (ie, baked potatoes, halibut, avocados, bananas, and asparagus) if potassium level is low.²
4. Avoid extremely hot or cold foods as they may aggravate diarrhea.²
5. Replace fluids/electrolytes as needed.
6. Eat a low-residue diet, high in protein and calories; avoid fried/greasy foods.² (Individualize fiber intake recommendation.)
7. Avoid milk or milk products, including lactose-containing supplements, if the patient is lactose intolerant.² Temporary lactose intolerance may develop during antiviral therapy. Note: The following foods are usually tolerated: buttermilk, yogurt, processed cheese, and lactose-free dairy substitutes, such as Lactaid® milk, nondairy creamer, Cool Whip®, and soy milk.² Lactose-free supplements, such as Ensure®, may also be considered.
8. Try over-the-counter antidiarrheals, such as bismuth subsalicylate (Pepto-Bismol®), kaolin-pectin (Kaopectate®), or loperamide (Imodium®). If symptoms are not controlled, try diphenoxylate hydrochloride/atropine sulfate (Lomotil®, prescription needed).²
9. Initiate skin care:
   a. Cleanse rectal area with mild soap and warm water after each bowel movement; pat dry.² If very tender to touch, use Peri-care® bottle with warm soapy water and hair dryer on low, cool setting to dry.
10. Sitz baths or sitting in a tub of warm water will help with cleansing and comfort.²
    a. Apply A&D Ointment or zinc oxide (Desitin®) for irritated/broken skin.²

REFERENCES

Gastrointestinal

NAUSEA AND VOMITING

PATHOPHYSIOLOGY
Vomiting is controlled by the nucleus tractus solitarius, referred to as the vomiting center (VC), located in the fourth ventricle in the reticular formation of the medulla, near the centers that regulate CV and respiratory function. Stimulation of the VC by afferent impulses initiates emetic responses. The pathophysiology of nausea is not understood clearly, but is thought to be related to that of vomiting.

Impulses come to the VC from three sources:
1. The chemoreceptor trigger zone (CTZ), located in the area postrema in the brain stem, responds directly to chemical toxins in the blood and spinal fluid.
2. The gastrointestinal tract at the level of the small intestine is the primary location of the serotonin receptors. When stimulated, these receptors send impulses centrally via sympathetic and vagal afferent pathways.
3. Higher cortical centers transmit psychogenic stimuli.

When impulses from any of these trigger points exceed the threshold in the VC, the act of vomiting occurs. The VC receives input via neurotransmitters, such as dopamine and serotonin, from five pathways. Vagal visceral afferents and sympathetic visceral afferents, located in the gastrointestinal tract, are nerve pathways stimulated by gastrointestinal distention, inflammation, irritation, or ischemia caused by chemotherapy or radiotherapy. The CTZ located in the fourth ventricle, is a vascular body with its own blood supply that is sensitive to chemical changes in the blood and cerebrospinal fluid. Vestibular afferents, in the labyrinth of the inner ear, are stimulated by rapidly changing body motions. The cerebral cortex and the limbic system are stimulated by sensory input, and anxiety and pain and are thought to be responsible for the anticipatory nausea/vomiting.

TREATMENT STRATEGIES
Providers should:
1. Assess pretreatment: history of nausea/vomiting, gastrointestinal disorder, eating habits, dietary intake, medications that could exacerbate symptoms (including NSAIDS).
2. Monitor for dehydration, electrolyte imbalance; rehydrate and stabilize electrolytes.
3. Recommend antiemetics—premedicate and PRN use: promethazine (Phenergan®), metoclopramide (Reglan®), ondansetron (Zofran®), dimenhydrinate (Dramamine®), or granisetron (Kytril®).
4. Consider selective serotonin reuptake inhibitors to modulate nausea.
Patients should be instructed to:
1. Take ribavirin with food.
2. Avoid greasy or highly seasoned foods and cooking odors.
3. Allow rest periods with the head and trunk elevated after eating.
4. Consider progressive muscle relaxation, guided imagery, and distraction.
5. Try sea bands, wristbands, acupressure points on wrist and knee, or acupuncture at the ear.
6. Consume flat soda, anything ginger (eg, crystallized ginger, ginger snaps, ginger ale).
7. Exercise.

REFERENCES
Gastrointestinal

CONSTIPATION

PATHOPHYSIOLOGY
Interferon and other cytokines may cause a decrease in gastric motility and emptying, alter intestinal motility, or modify gastric acid secretion. Other primary causes of constipation include dehydration and insufficient bulk or lack of dietary fiber, inadequate fluid and exercise, stress, depression, medications (ie, opioids, tricyclic antidepressants, chemotherapy agents, aluminum antacids, anticholinergics, anticonvulsants, abused laxatives, or enemas), hypercalcemia, hyperkalemia, and myxedema. Mechanical obstruction of the bowel may be caused by fecal impaction, tumor, inflammatory strictures, or barium from contrast studies.

PREVENTIVE STRATEGIES
Patients should be instructed to:
1. Maintain adequate hydration (fluid consumption in fluid ounces equivalent to one-half body weight in pounds; eg, a 160-lb person should drink 80 fl oz/d).
2. Drink fresh fruit juices and warm or hot fluids upon awakening.
3. Increase physical activity as possible.
4. Include fiber in diet; raw fruits and vegetables, whole grain products, prunes, bran.
5. Use stool softener or bulk producers such as docusate sodium (Colace®), Metamucil®, Citrucel®, Benefiber®, or mineral oil. Increase fluid intake with fiber use.
6. Avoid cheese, refined grain products, and other binding foods.
7. Avoid straining at stool.
8. Respond to the urge to defecate.
9. Take time to move bowels at around the same time every day.

TREATMENT STRATEGIES
1. Monitor thyroid function.
2. Recommend dietary interventions (eg, increased fiber).
3. Try over-the-counter agents first.
   a. Milk of magnesia
   b. Correctol®
   c. Ex-Lax®
   d. Peri-Colase®
4. Use laxatives, suppositories, or enemas according to physician order.
   a. Polyethylene glycol (Miralax™) 17 g/d PRN
   b. Lactulose (Kristalose™) 45 to 60 cc PO
   c. Magnesium citrate 8 oz PO
   d. Tegaserod (Zelnorm®) 6 mg PO BID for 4–6 weeks
   e. Bisacodyl (Dulcolax®) suppository 1 by rectum
   f. Fleet® enema 1 by rectum
   g. Bisacodyl (Dulcolax®) 2 to 3 tabs HS-TID
   h. Fleet Phospho-soda® PO
5. Rule out colon cancer, eg, especially in patients >50 years of age or who have a family history of the disease.
6. Consider gastroenterology consult for refractory constipation.

REFERENCES
PATHOPHYSIOLOGY
Anorexia has been demonstrated in mammals after exogenous administration of cytokines, such as interferon. The extent of anorexia seen varies depending on the dose, duration, timing, underlying pathology, and nutritional status of the patient. Cytokine-induced anorexia involves both the peripheral system and the CNS. Cytokines modulate gastrointestinal activities, affect the endocrine system, and exert their effects on the hypothalamus. Cytokines can inhibit appetite by causing a delay in gastric motility and emptying. Cytokine-induced changes can also cause nausea and vomiting. Hormonally, IL-1 may be responsible for alterations in corticotropin-releasing factor, cholecystokinin, glucagon, and insulin. IL-1, interferon, and TNF act directly as well as synergistically on the hypothalamus, altering neurotransmitters (e.g., serotonin) and contributing to taste aversions. These same cytokines can increase the rate of lipolysis, increase serum triglyceride levels, and alter carbohydrate and protein metabolism. Cachexia is a risk with long-term cytokine therapy due to muscle wasting secondary to skeletal muscle protein breakdown.

ASSESSMENT
1. Assess the patient’s current nutritional status.
2. Determine ideal body weight (IBW):
   - Women: Add 100 lb for the first 60 inches of height, 5 lb for each inch over 60 inches, divide by 2.2 to obtain IBW in kilograms (kg).
   - Men: Add 106 lb for the first 60 inches of height, 6 lb for each inch over 60 inches, divide by 2.2 to obtain IBW in kg.
3. Determine caloric needs:
   - Women: Multiply IBW kg calculation x 24 hours x 0.9 calorie = resting needs.
   - Men: Multiply IBW kg calculation x 24 hours x 1.0 calorie = resting needs.
4. Review the patient’s dietary intake diary.
5. Assess for significant weight loss: ≥1–2 lb/wk, 5% weight loss over the past month, and loss of >10% IBW indicate significant weight loss. Assess for signs of anorexia/malnutrition, including hair loss, scaling skin, brittle nails, and impaired skin integrity.
6. Assess serum albumin levels (may be influenced by hydration, infection, position, or activity, and/or decompensated cirrhosis) and electrolytes.
7. Assess transferrin levels (influenced by bone marrow suppression and iron deficiency). Fluctuations in transferrin reflect changes in nutritional state more rapidly than albumin, as it is less affected by factors that affect serum albumin concentrations.
8. Perform CBC and assess for macrocytosis (possible folate or vitamin B₁₂ deficiency).
9. Assess total lymphocyte count. Levels <1200/mm³ suggest nutritional deficiency.
10. Oral cavity examination: rule out oral candida and ulcers, which may contribute to anorexia.

11. Rule out other causes, such as nausea, vomiting, diagnostic studies, biochemical abnormalities, thyroid dysfunction, diarrhea, constipation, lactase deficiency, dysphagia, surgery, tumor presence, mechanical obstruction, chemotherapy, radiation, psychosocial effects (depression, social isolation, fatigue, etc).

12. Monitor thyroid function every 3 months.

PREVENTIVE STRATEGIES
1. Educate the patient regarding anorexia as a potential side effect of interferon and ribavirin and provide suggestions for its management.

2. Determine living conditions: Does the patient have social support, including significant relationships? There is a potential risk for increased malnutrition if patients live alone, prepare their own meals, etc.

3. Suggest packing snacks and fluids in a thermal bag to facilitate eating on the run.

4. Suggest that patients exercise moderately (walking, biking, swimming) on injection days to counter the potential for muscle catabolism with interferon.

TREATMENT STRATEGIES
The management of anorexia for patients on interferon has not been extensively studied. The following interventions may facilitate food intake in those patients experiencing anorexia.

Patients should be instructed to:
1. Increase oral hygiene (avoid smoking if possible).
2. Eat smaller, more frequent meals; small helpings look less overwhelming on smaller plates.
3. Add spices and herbs when experiencing alterations in taste perception. Avoid spicy foods when experiencing nausea.
4. Eat foods chilled or at room temperature rather than hot.
5. Eat foods that are calorically dense, such as peanut butter, granola, and cheese.
6. Consider supplementation with Carnation Instant Breakfast®, Ensure®, Boost®, and instant breakfast bars (watch for iron content, as iron intake should be limited in patients infected with HCV).
7. Consume protein throughout the day. Take advantage of easy sources, such as peanut butter and cold cuts. To boost protein intake, add protein powder and/or powdered milk to cereal, shakes, or any food (1/3 c powdered milk = 80 cal and 8 g protein. The nutritional content of protein powders varies).
8. Avoid carbonated beverages and gas-forming foods, such as broccoli or cabbage, as they may contribute to early satiety.

Providers should:
1. Provide a nutrition consultation to determine optimal diet for the patient.
2. Consider megestrol acetate (Megace®) 800 mg (20 mL)/d via suspension; or 40 mg PO QID as tablets; AM administration preferred. Some evidence suggests that low-dose megestrol acetate may assist with cytokine-induced anorexia. One of its
mechanisms is to inhibit cytokine production and activity. Further research in this area is needed to prevent potential interference with the therapeutic effects of interferon. Availability: suspension 40 mg/mL: less expensive, easier to swallow, increased patient preference versus tablets. Tablets: 20-mg and 40-mg strengths. Average 5 kg weight gain; it may take 4 to 12 weeks to see weight gain.

3. Consider metoclopramide (Reglan®) 10 mg PO before meals and QHS for relief of anorexia, nausea, and early satiety.

4. If other options fail, consider dronabinol (Marinol®): Initially, 2.5 mg PO BID (before lunch, dinner). Range: 2.5 to 20 mg/d. Dronabinol is indicated for treatment of anorexia associated with weight loss in patients with AIDS and for the treatment of nausea and vomiting associated with cancer chemotherapy, but its use has not been studied in patients on interferon. Dronabinol may be problematic for patients with a history of drug abuse, as its active ingredient, synthetic delta9-THC, is a component of Cannabis sativa (marijuana).

5. Consider antidepressants if anorexia is caused by depression.

Note: Although there was initial concern that methylphenidate (Concerta™, Metadate®, Methylin®, Ritalin®) may cause anorexia in patients, a number of studies have shown that patients prescribed methylphenidate for profound depression or fatigue may experience improved appetite from this medication. In one study, 54% of patients experienced appetite stimulation; 13% had minimal improvement in appetite, 29% reported moderate improvement, and 12% were noted to have a marked improvement.

REFERENCES
HUMAN FACTORS RELATED TO HERB SAFETY
1. There is a widespread misconception that anything natural is safe.
2. Specific health conditions can make the individual susceptible to herbal poisoning (HIV, chemotherapy, pregnancy, lactation, poor nutrition status, gender, age).
3. Self-assessment and self-medication are potentially dangerous for persons who do not understand human anatomy and medical conditions.
4. Wildcrafting (gathering herbs in the wild) may result in problems due to incorrect plant identification or contamination.
5. Toxicity may occur due to lack of understanding of appropriate use or dosage, or from long-term use.
6. Use of multiple herbs might result in interactions.
8. Products may be poorly labeled, or patient may purchase products from an unreliable source.
9. There may be variations in the herb/concentration due to storage conditions.
10. There are over 1400 species of herbs and most have not shown true efficacy in clinical trials.
11. Herbal treatments have been protected since 1962 and are not regulated by the US Food and Drug Administration (FDA). They are sold as food products.

BEFORE TAKING HERBAL SUPPLEMENTS
Patients should be instructed:
1. If ill, consult with the healthcare provider.
2. Do not use herbal therapies for serious illness, or in children.
3. Notify healthcare providers of all alternative medicines being used, and inform providers if use is discontinued, since this may affect laboratory values.

FACTS ABOUT HERBS AND SUPPLEMENTS
Alfalfa: contains a chemical that acts as an anticoagulant; has been linked to kidney damage.
Aloe vera gel: used externally for the treatment of burns and wounds. Used in cosmetics, allergy medications. Lethal dose is 1 g/d for several days.
B₆: reduces cell growth; inhibits protein tyrosine kinase. Used for melanoma prevention and neuropathy.
Black cohosh: some indication of relief of hot flashes and improved mood. Large doses cause dizziness, nausea, headaches, stiffness, and trembling. Not safe for persons taking blood pressure medication or those with CV disease.
Borage: contains toxic pyrrolizidine alkaloids.
Calamus: contains carcinogenic cis-isoasarone.
Cayenne: acts as counterirritant for pain relief. Used in arthritis, herpes zoster, toothache, diabetic neuropathy, and musculoskeletal pain. Internally, acts as gastric stimulant. Avoid contact with eyes.

Chamomile: flowers contain an oil believed to have an antispasmodic and anti-inflammatory effect on the gastrointestinal tract. Studies have indicated that it is an effective mouthwash for minor irritation and infections of the mouth and gums. Persons who have allergies to pollen should avoid this herb.

Chaparral: suggested use as an antioxidant, blood purifier, in cancer and acne. Induces liver toxicity: the FDA has found links to acute hepatitis and severe liver damage.

Chondroitin complex: found in cartilage; thought to relieve pain from arthritis.

Coenzyme Q10: a body enzyme that acts in the production of adenosine triphosphate; boosts the immune system, and relieves CHF.

Coltsfoot: contains toxic pyrrolizidine alkaloids.

Comfrey: used externally to reduce the swelling around broken bones. Internal use can cause liver damage due to toxic pyrrolizidine alkaloids. It has been linked to cases of obstructed blood flow from the liver.

Dandelion: considered a liver remedy because it enhances the flow of bile. The leaf is a diuretic comparable to furosemide (Lasix®), but dandelion replenishes potassium and other minerals that are normally depleted by diuretics.

Dogbane: contains toxic cardioglycosides.

Ephedra (ma huang): decongestant, CNS stimulant; might decrease appetite; increases hypertension; causes dry mouth; potential adverse effects include psychosis, stroke, and memory loss. Caffeine potentiates the effect. Ephedra has been blamed for 20 to 30 deaths.

Feverfew: may diminish frequency and severity of migraine headaches.

Folic acid and vitamin B_{12}: downregulate oncogenes; improve appetite and sleep; aid in methyl metabolism.

Foxglove: contains toxic cardioglycosides.

Garlic: some evidence that half a clove per day might lower cholesterol an average of 9%. It decreases clotting, and can interfere with anticoagulants, including warfarin (Coumadin®).

Germander: contains toxic alkaloids with a potential for liver damage; acute hepatitis has been linked to its use.

Ginger: used to aid digestion and prevent nausea due to motion sickness and surgery.

Ginkgo biloba: unsafe for those with bleeding disorder; overdose might induce irritability, restlessness, diarrhea, and vomiting.

Ginseng: interacts with the antidepressant phenelzine (Nardil®) and interferes with some other medications as well; has caused asthma attacks and menstrual changes.

Glucosamine: moderate effect on pain relief and improved mobility. May be as effective as ibuprofen (Advil®, Motrin®). Some evidence to show the slowing progression of cartilage loss in affected joints. May interact with blood-thinning medications and have harmful effects on insulin resistance in type 2 diabetes.

Goldenseal: used as an antibacterial agent in eye drops and for diarrhea.

Guaraná: high in caffeine.
**Herbal Ecstasy**: contains large concentrations of caffeine, ephedra, and other stimulants in amounts that can disrupt the balance of hormones and the CNS; has caused permanent heart damage.

**Jin bu huan**: marketed for insomnia due to pain and stomach ulcers; reported poisoning in children.

**Kava kava**: acts as antagonist to dopamine; induces relaxation/sleep, and decreases anxiety. Anticonvulsant and muscle relaxant; potentiates other CNS depressants. Has been associated with multiple cases of liver toxicity, including liver failure necessitating transplant.

**Licorice**: increases blood pressure in those prone to hypertension, alters electrolytes, and causes pseudoaldosteronism.

**Lobelia**: alkaloid similar to nicotine. In low doses it is an expectorant that works by dilating the bronchial tubes; higher dose can cause slowed respiration, sweating, rapid heart rate, low blood pressure, coma, and death. It is dangerous if combined with nicotine (including the patch or gum).

**Maitake**: studies have shown it possesses antitumor, anti-HIV, antihypertension, antidiabetes, anti-obesity, and antihepatitis activities through enhancement of the immune system. Not only does it seem to improve positive benefits of conventional chemotherapy; it also aids in the amelioration of side effects.

**Melatonin**: hormone. It produces relief of circadian-based sleep disorders. Used for sleep difficulties in the elderly and those with seasonal sleep disorders.

**Melilot**: anticoagulant.

**Milk thistle**: most widely used herb in liver disease. It has anti-oxidant, antifibrotic, and anti-inflammatory properties. It can normalize ALT levels but does not appear to affect hepatitis C viral concentrations; studies are ongoing.

**Mistletoe**: contains alkaloids.

**Pau d’arco**: provides mild antitumor action.

**Pennyroyal**: used to treat coughs and menstrual symptoms (can induce abortions); potentially lethal in large doses.

**Poke root**: unknown contents; fatal in children.

**Pycnogenol**: found in pine-needle extract, grape seeds, and plant oils. It enhances immunity and is used to treat vascular diseases.

**SAM-e**: used to treat mild depression; can cause flatulence, headache, nausea, and diarrhea; do not use with antidepressants.

**Sassafras**: inhibits detoxification enzymes in the liver and increases drug half-life; contains safrole, which is carcinogenic.

**Saw palmetto**: used for prostate enlargement; good only for benign prostatic hyperplasia.

**Senna**: strong stimulant laxative often recommended as diet tea; long-term use might rob the body of vital electrolytes, leading to cardiac arrhythmia.

**Schizandra**: antihepatotoxin, anti-oxidant, nonmutagenic; protects against chemotherapy and radiation.

**St. John’s Wort**: may interact with monoamine oxidase inhibitors. Gastrointestinal irritation has been reported. Photosensitivity characterized by dermatitis and inflammation of mucosal membranes may occur with high levels of intake or prolonged use. Contraindicated with protease inhibitors and nonnucleoside reverse transcriptase inhibitors in HCV/HIV-coinfected patients.
**Tonka beans**: anticoagulant.
**Turmeric**: used as antitumor agent. It increases lymphocyte production and may be hepatotoxic.
**Valerian root**: used as sedative and sleep aid. It reduces nervous tension, stress, anxiety, and restlessness, and may improve sleep quality. Side effects include mild headache or upset stomach. Overdose may cause severe headache, nausea, morning grogginess, and blurry vision. It should not be taken with sedatives.

The most commonly used herbs are: artichoke, black cohosh, boneset, coltsfoot, comfrey, dandelion, fennel, ginseng, licorice, milk thistle, maitake, olive leaf extract, schizandra, St. John’s wort, turmeric.

**HERBAL PRODUCTS WITH SERIOUS TOXIC EFFECTS**
1. Chaparral tea: from leaves and twigs of a desert shrub called the creosote bush; promoted as an anti-oxidant and a pain reliever. It has caused liver failure requiring liver transplant.
2. Some Indian herbal tonics cause lead poisoning.
3. Garlic, ginger, gingko, and feverfew: blood-thinning herbs that counteract or enhance the activity of prescription medication for cardiac problems or bleeding disorder. Combined with aspirin or Coumadin® (warfarin), these herbs could cause excessive bleeding.
5. Comfrey: ingested or used on bruises. It can obstruct blood flow to the liver and is possibly fatal.
6. Kava kava has been associated with multiple cases of liver toxicity, including liver failure necessitating transplant.
7. Lobelia: emetic. At high doses, it causes coma and death. Lesser side effects include tachycardia and tachypnea.
8. Laxatives (eg, senna, cascara, and aloe): can cause potassium loss when used over time. They are particularly dangerous when used with digitalis or prescription diuretics.
10. Ma huang, or ephedra, is an herbal form of the CNS stimulant commonly known as “speed,” and is sold under names such as herbal Ecstasy, Cloud 9, and Ultimate Xphoria. This herb is sold to achieve street-drug “legal highs.” It can cause heart attacks, seizures, psychotic episodes, and death.
PRODUCTS PROMOTED AS CURES FOR ILLNESSES THEY DO NOT CURE
1. Essiac or mistletoe for cancer; pau d’arco tea for cancer and AIDS.
2. Over-the-counter vitamin/amino acids/mineral products: product inserts make unapproved claims related to attention deficit hyperactivity disorder.

HERBAL PRODUCTS THAT ARE FAKE OR HIGHLY CONTAMINATED
1. “The Chomper”: a “cleansing herbal dietary supplement” promoted as an “herbal laxative” and “cleansing” agent to be used as part of a diet regimen. The product is contaminated with digitalis.
2. Plantain leaves (cut or powdered): found in plantain extract, Nature’s Cleanse® tablets, BotaniCleanse® brands, Blessed Herbs, etc. Contaminated with digitalis glycosides.
3. “Siberian ginseng” capsules: capsules labeled as such have been found to contain instead a weed full of male hormone-like chemicals.

VITAMINS
**Vitamin A**: fat-soluble retinoid. It inhibits malignant transformation and builds immune resistance.
**Vitamin B₁**: “thiamine”; enhances immune response and mental attitude, and supports CNS.
**Vitamin B₂**: “riboflavin”; promotes healthy skin, especially in psoriasis, and benefits vision.
**Vitamin B₃**: “niacin”; promotes healthy skin and nerves. Deficiency: headache, depression, and dermatitis.
**Vitamin B₅**: “pantothenic acid”; antioxidant. Deficiency: anemia, fatigue, myalgia, and ataxia.

<table>
<thead>
<tr>
<th>Herbs to Avoid with HCV</th>
<th>Potential Sequelae</th>
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<td>Abnormal liver test</td>
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<td>Chaparral</td>
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<td>Chinese herbs</td>
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<td>Jin bu huan</td>
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<td>Comfrey</td>
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<td>Gentian</td>
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<td>Germander</td>
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<td>Kombucha mushroom</td>
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<td>Lady's mantle</td>
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<td>Life root</td>
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<td>Mistletoe</td>
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<tr>
<td>Senna</td>
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<td>Shark cartilage</td>
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<td>Skullcap</td>
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<td>Valerian</td>
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<td>Hops</td>
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<tr>
<td>Sassafras</td>
<td>Toxicity</td>
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</tbody>
</table>
**Vitamin B₆**: “pyridoxine”; antioxidant. Deficiency: anemia, depression, lethargy, and nervousness.

**Vitamin B₁₂**: involved in immune response. Relieves fatigue, depression, and poor concentration.

**Vitamin C**: antioxidant. It inhibits carcinogen formation and is important in collagen synthesis and glutathione activity.

**Vitamin D**: fat-soluble sunlight vitamin needed for healthy bones, teeth. Deficiency: muscle cramps, psoriasis, etc.

**Vitamin E**: antioxidant/immune stimulant. Alleviates fatigue. Deficiency: anemia, muscle degeneration.

**Vitamin K**: fat soluble, antihemorrhagic; tumor analgesic; cancer inhibitor. Needed for bone loss and cirrhosis.

**Folic acid**: prevents anemia, effective against alcoholism and precancerous lesions.

**MEGAVITAMINS AND ORTHOMOLECULAR THERAPY**
1. Three clinical trials have disproved that megadoses of vitamin C will cure cancer.
2. There is no evidence that megavitamins or orthomolecular therapy is effective in treating any disorder.

**REFERENCES**

**OTHER RESOURCES**
2. Food and Drug Administration: www.fda.gov
3. Health A to Z: www.healthatoz.com
5. NIH Medline Search: www.medscape.com
6. National Council Against Health Fraud: www.ncahf.org
9. Quackwatch: www.quackwatch.com
10. Tufts University: www.altmedicine.com

**HCV NEUTRACEUTICAL WEB SITES**
1. www.spot-x.com/goodstuff.html
2. www.kcweb.com/herb//gotu/htm
IX. Hematologic

ANEMIA

PATHOPHYSIOLOGY
The primary toxicity of ribavirin is hemolytic anemia, which is the premature accelerated destruction of erythrocytes. For most patients treated with combination therapy, the etiology of anemia is “mixed,” incorporating both hemolysis and inhibition of erythroprogenitor cells. Ribavirin is taken into the red blood cells (RBCs), where it is converted to ribavirin triphosphate. Since RBCs lack the enzymes needed to hydrolyze ribavirin triphosphate, it is “trapped” in the RBCs, where it depletes the cells’ adenosine triphosphate (ATP). The resulting ATP deficiency impairs antioxidant defense mechanisms and induces RBC oxidative membrane damage, which causes premature extravascular hemolysis by the reticuloendothelial system.

This is compounded by the bone marrow suppressive effects of interferon. After a single dose of interferon, hemoglobin levels drop along with bone marrow production of erythrocytes, as evidenced by a decrease in reticulocyte count. Erythropoietin production is partly inhibited by interferon, and it takes approximately 1 week for the erythropoietin level to recover. Other conditions may contribute to anemia, including membrane disorders, enzyme deficiencies, and blood loss.

In patients with chronic hepatitis C, anemia is usually defined as a decrease in Hgb level to ≤10 g/dL or either a >2 g/dL or 25% reduction from baseline. The average Hgb decrease during antiviral combination therapy for hepatitis C is 2.7 g/dL. Hgb level generally returns to normal within 7 to 8 weeks of therapy cessation. Most reductions in Hgb level occur within the first 4 weeks of therapy. Cardiac events associated with anemia occur in <10% of patients treated with ribavirin.

PREVENTIVE STRATEGIES
1. Avoid ribavirin in patients with severe cardiac or pulmonary disease who would be unable to tolerate the consequences of hemolytic anemia. Peginterferon monotherapy may be considered for such patients.
2. Monitor blood counts. At baseline, within the first 2 weeks of treatment, at week 4, and monthly during treatment with ribavirin. For patients treated with peginterferon monotherapy, blood counts should be monitored monthly or as clinically indicated. During long-term, low-dose interferon maintenance therapy, measure CBC at week 4 and repeat quarterly or as clinically indicated.

MANAGEMENT STRATEGIES
1. Assess for bleeding.
2. Caution patient about orthostasis and the need to stand slowly; report dizziness.
3. Instruct patient to report onset of shortness of breath or tachycardia.
5. Encourage alternating activity and rest.
7. Advise patients to maintain nutritional status. Check iron level and correct as appropriate. Replace iron, folate, and B₁₂ when necessary.
8. Consider erythropoetin 40,000 IU QW if Hgb falls to <12 g/dL in men or <11 g/dL in women to maintain maximum benefit of the full dose of ribavirin.⁴⁻⁵ Assess response every 2 to 4 weeks and continue at original dose if ≥1 g/dL increase in Hgb level. Dose can be increased in increments of 5000 to 10,000 IU to a maximum of 60,000 IU. Discontinue erythropoetin if no response or if/when Hgb reaches >12 g/dL. Note: Patients with iron deficiency are more likely to develop anemia during ribavirin therapy. Erythropoetin is ineffective in the setting of iron deficiency. Therefore, low iron levels should be corrected prior to erythropoetin therapy.
9. Consider antioxidants (vitamins C 1000 mg/d and E 800 IU/d).⁶
10. See dose modification guidelines in the respective package inserts. Ribavirin dose is typically reduced for patients at normal cardiac risk if Hgb decreases to <10 g/dL or for patients whose Hgb level declines by >2 g/dL. Ribavirin should be discontinued if Hgb level falls to <8.5 g/dL in a patient at normal cardiac risk or <12 g/dL in a patient at high cardiac risk. Dose reduction tends to produce only a small increase in Hgb level. Note: reductions of ribavirin to <80% of the recommended dose are associated with a 50% decrease in chance of early virologic response.

REFERENCES
Neutropenia is the most common hematologic side effect of peginterferon therapy. Neutropenia is defined as an absolute neutrophil count (ANC) of $<1000 \text{/mm}^3$. The ANC is calculated by multiplying the white blood cell (WBC) count by the percentage of bands and segmented neutrophils.\textsuperscript{1} There is a theoretic concern that neutropenia will increase the propensity to develop opportunistic infections. However, peginterferon alfa-2b has been in use for over 2 years, and collective experience has not demonstrated a clinically significant association between neutropenia and infection in patients treated for hepatitis C.

**PATHOPHYSIOLOGY**
Interferon elicits secondary cytokines, such as interleukin-8, which promotes migration of neutrophils to outside the peripheral vascular space and into tissue spaces. There, they become sequestered and reach their nadir.

**THE NATIONAL CANCER INSTITUTE COMMON TOXICITY CRITERIA GRADING FOR NEUTROPENIA\textsuperscript{3}**
- Grade 1: $\geq 1.5 \text{ to } <2.0 \times 10^9/L$ neutrophils
- Grade 2: $\geq 1.0 \text{ to } <1.5 \times 10^9/L$ neutrophils
- Grade 3: $\geq 0.5 \text{ to } <1.0 \times 10^9/L$ neutrophils
- Grade 4: $\geq 0.5 \times 10^9/L$ neutrophils

**PREVENTIVE STRATEGIES**
1. Assess for neutropenia by monitoring the WBC count with differential at baseline and weeks 2 and 4 and then monthly in all patients receiving anti–HCV-treatment. Note: lower neutrophil counts will be recorded if the blood for the CBC is drawn within 24 to 72 hours of peginterferon administration. Consider drawing the CBC 1 to 2 days before peginterferon administration.
2. In the HIV coinfected patient on anti-HCV combination therapy, monitor the WBC/differential biweekly for the first 3 months. After 3 months, monitor WBC/differential monthly and as clinically necessary. A more frequent schedule may be necessary depending on the immune status of the individual patient.
3. Teach patient signs and symptoms of infection (fever, chills, etc) to report to the healthcare provider.\textsuperscript{1}

**TREATMENT STRATEGIES**
1. Consider granulocyte colony-stimulating factor therapy (filgrastim [Neupogen\textsuperscript{®}]) 300 µg SQ once to thrice weekly and then titrated to maintain an ANC $>750/\text{mm}^3$) if ANC is $<1000/\text{mm}^3$ on peginterferon-based therapy. For maximum effect, give at least 24 hours before peginterferon administration. Granulocyte macrophage colony-stimulating factor (sargramostim [Leukine\textsuperscript{®}, Prokine\textsuperscript{®}, Leukomax\textsuperscript{®}]) is also used to treat neutropenic patients.
2. Institute dose reduction/discontinuation guidelines per package inserts. A 50% reduction in peginterferon alfa-2b dose is recommended if WBC becomes <1500/mm$^3$, and both peginterferon and ribavirin should be discontinued if WBC is <1000/mm$^3$. Dose reduction to 135 µg peginterferon alfa-2a is recommended if the neutrophil count is <750/mm$^3$, and treatment should be discontinued if ANC falls below 500/mm$^3$.

3. Monitor for signs of infection; treat appropriately.$^1$

REFERENCES
Thrombocytopenia (an abnormally low platelet count) may be seen in patients treated with interferon. Thrombocytopenia potentially increases the risk of excessive bleeding. Common consequences of thrombocytopenia include easy bruising, ecchymoses, petechiae, hematomas, nose/gum bleeding, prolonged bleeding from venipuncture or invasive procedures, coffee-ground emesis, hemoptysis, hematuria, vaginal/rectal bleeding, gross blood in stools, black tarry/stools, change in vital signs, change in neurologic status (blurred vision, headache, disorientation), occult bleeding in urine and feces, and excessive menses. In patients with advanced liver disease, thrombocytopenia is commonly seen as a consequence of portal hypertension and hypersplenism.

PATHOPHYSIOLOGY
Platelets are fragments of the megakaryocytes produced and released by the bone marrow. In addition to interferon, other factors may affect the number and function of circulating platelets, such as a disease process (eg, cirrhosis), chemotherapy (eg, interferon), some other prescription medications (eg, anticoagulants), and some over-the-counter medications (eg, aspirin). Thrombocytopenia is likely the result of a cytotoxic action on the bone marrow itself, preventing postmitotic cells from completing their maturation in the blood and tissue (bone marrow suppression). If a sudden significant drop in platelet count occurs during interferon therapy, consider ruling out idiopathic thrombocytopenic purpura.

GRADING OF THROMBOCYTOPENIA
Normal: 150,000 to 400,000 platelets/mm³
Mild: 50,000 to 150,000 platelets/mm³
Moderate: 25,000 to 50,000 platelets/mm³
Severe: <25,000 platelets/mm³

PREVENTIVE STRATEGIES
1. Assess for thrombocytopenia by monitoring CBC and platelet count at baseline and at weeks 2 and 4, and then monthly in all patients receiving anti-HCV treatment. Note: lower platelet counts will be recorded when a CBC is obtained within 24 to 72 hours of peginterferon administration. Consider drawing the CBC 1 to 2 days before peginterferon administration.
2. Assess previous or current medications and/or diseases (eg, idiopathic thrombocytopenia) for potential or significant thrombocytopenia.
3. Assess for other factors that may contribute to low platelet count (ie, abnormal hepatic/renal function, sepsis, fever, anticoagulant therapy, aspirin use).
4. Teach patient to report any evidence of spontaneous or excessive bleeding, including petechiae, ecchymoses, hematomas, blood in body excretions, bleeding from body orifices (especially from nose when sneezing), or changes in neurologic functioning.
TREATMENT STRATEGIES

1. Dose modify/hold drug until platelet count recovery, or discontinue per package inserts. Peginterferon alfa-2b dose reduction by half is recommended for platelet count <80,000/mm$^3$, and discontinuation is recommended for platelet count <50,000/mm$^3$. The peginterferon alfa-2a dose should be reduced to 90 µg if the platelet count is <50,000/mm$^3$ and should be discontinued if the platelet count is <25,000/mm$^3$.

2. Consider platelet transfusion (rarely necessary).

Patients should be instructed to:

1. Avoid activities predisposing to trauma or injury.
2. Avoid use of aspirin or aspirin-containing products.
3. Use electric razors rather than blades.
4. Blow nose very gently.
5. Use soft toothbrushes (not electric).
6. Promptly report any difficulties with constipation; avoid straining.
7. Apply continuous pressure for 5 minutes if observable bleeding occurs (ie, knife cut).
8. Observe and immediately report to healthcare provider any bruising, skin problems, blood in urine/stool/emesis, vaginal/rectal bleeding, blurred vision, headache, or disorientation.

REFERENCES

**WARNING:**
Hepatotoxicity, including fatality, has been observed in interferon-treated patients. Any patient developing liver function abnormalities during treatment should be monitored closely, and if appropriate, treatment should be discontinued. When hepatotoxicity occurs, it is usually seen in the first 5 to 6 weeks of treatment.

Interferon-based therapy is contraindicated in patients with decompensated liver disease. There are reports of worsening liver disease, including jaundice, hepatic encephalopathy, hepatic failure, and death following interferon therapy in such patients. Therapy should be discontinued for any patient developing signs and symptoms of liver failure. Patients with a documented rise in aminotransferase levels during interferon therapy should be further evaluated for AIH and drug toxicities.

**ALT/AST ELEVATIONS AND LIVER DISEASE**
Liver diseases themselves may be associated with mild, moderate, or marked elevation of ALT and/or AST levels. Despite moderate aminotransferase elevations being nonspecific, certain liver diseases tend to be associated with either mild or marked ALT elevation.

### DEFINITION OF MILD/MARKED AMINOTRANSFERASES IN LIVER DISEASE

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<thead>
<tr>
<th>Test</th>
<th>Mild*</th>
<th>Moderate</th>
<th>Marked</th>
</tr>
</thead>
<tbody>
<tr>
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<td>&lt;2–3</td>
<td>2–3 to 20</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>&lt;1.5–2</td>
<td>1.5–2 to 5</td>
<td>&gt;5</td>
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</tbody>
</table>

*Numbers in table refer to multiples of the upper limits of normal for the individual enzyme.

### LIVER CONDITIONS ASSOCIATED WITH MILD, ASYMPTOMATIC ELEVATION OF ALT/AST

**Common**
- Fatty liver and NASH (40%–60% of cases)
- Chronic HCV (20%–40% of cases)
- Chronic HBV
- Alcoholic liver disease
- Hemochromatosis

**Uncommon**
- Drug-induced liver disease
- Autoimmune hepatitis
- Alpha₁-antitrypsin deficiency
- Wilson’s disease
- Miscellaneous conditions
LIVER CONDITIONS ASSOCIATED WITH MARKED INCREASE OF ALT/AST

- Acute viral hepatitis
- Drug-induced hepatitis, especially acetaminophen (Tylenol®)/alcohol and antiretroviral therapy
- Hepatic ischemia due to shock or severe right heart failure
- Acute biliary obstruction
- Budd-Chiari syndrome

MANAGEMENT STRATEGIES
1. Monitor liver enzyme levels in accordance with package inserts.
2. If aminotransferase levels flare, reassess for other causes and consider dose reduction or discontinuation of therapy.

REFERENCE
1. American Digestive Health Foundation/American Liver Foundation. Viral Hepatitis Facts: Approach to Elevated Liver Enzymes. HBV087R0.
Hematologic

HYPERTRIGLYCERIDEMIA

Increased triglyceride levels are a rare side effect of interferon-based therapy. Secondary hypertriglyceridemia can be seen with other conditions commonly associated with anti-HCV therapy, including thyroid dysfunction, poorly controlled DM, and nephrotic syndrome.

PATHOPHYSIOLOGY

Serum levels of total triglycerides and cholesterol have been studied in chronic hepatitis patients before, during, and after treatment with interferon. Ruiz-Moreno et al. found no elevations in serum cholesterol during treatment. However, although an uncommon occurrence, a significant increase in total serum triglycerides was observed at the first month of therapy in the treatment groups and remained until the end of therapy. Thereafter, the triglyceride levels returned again to basal values. This was observed with varying schedules and doses of interferon. Moreover, these changes in triglyceride levels were not related to (1) type of interferon, (2) response to therapy, (3) liver disease activity, or (4) the etiologic agent (hepatitis B, C, or D). Fortunately, no hypertriglyceridemia-related disease was observed.

| TRIGLYCERIDE LEVELS (ECOG Scale) |
|----------------------------------|-----------------|-----------------|
| Grade 1 | 401–800 | 338–675 |
| Grade 2 | 801–1600 | 676–1350 |
| Grade 3 | >1601 | >1350 |

PREVENTION STRATEGIES

1. Assess pretreatment risk, and if hyperlipidemia is present, treat underlying cause prior to therapy initiation.
2. Follow serum triglycerides and cholesterol at baseline and monthly in patients with lipid metabolism alteration.
3. Monitor Hgb A1c in diabetic patients monthly and TSH at baseline and quarterly.
   (See also “Endocrine” section.)

TREATMENT STRATEGIES

1. Consider gemfibrozil (Lopid®) 600 mg BID.
2. Consider interferon dose reduction.

REFERENCE

ATAXIA

Ataxia is a very rare side effect in patients with HCV infection at recommended doses of peginterferon/ribavirin. Most incidences of ataxia occur within 2 to 3 weeks of initiation of high-dose interferon and respond well to NSAIDs, safety measures, and prosthetic devices.

PATHOPHYSIOLOGY

Ataxia is a defect in the ability to coordinate muscular movement, especially voluntary muscular movements. The genes encoding cytokines and their receptors are expressed in the CNS under both resting and stimulating conditions. The physiologic effects of interferon therapy on the CNS are probably a consequence of the activation of a complex cascade of secondary cytokines both in the periphery and within the CNS causing a disruption of neuromuscular responses as a result of an inflammatory process. In addition, interferon alfa will stimulate the release of beta interferon, which is well-known to cause ataxia.

ASSESSMENT

1. Assess premorbid functional status.
2. Utilize standardized tools, such as Karnofsky Performance Scale, to assess physical functioning.
3. Obtain a complete medical history regardless of diagnosis and throughout the course of treatment. (If patient is unreliable, obtain history from family or qualified family member.)
4. Perform physical assessment; proposed assessment for ataxia includes observation of rapid initiation of movement, large-muscle and small-muscle coordination, muscle mass and strength, symmetry of movement, and posturing (dorsi-flexing hands during movement indicates strain, weakness, and difficulty coordinating movements).
5. Assess electrolytes, especially sodium and calcium, which are important for neuromuscular communication and strength.
6. Assess and evaluate for myositis; check CPK levels.

TREATMENT STRATEGIES

1. Rule out disease progression, leptomeningeal carcinomatosis, or other conditions that occur in specific age groups (eg, for those >50 years of age: stroke; 30–40 years of age: multiple sclerosis, Huntington’s disease).
2. Make safety the first consideration, particularly if the patient is experiencing confounding muscle weakness and memory/concentration deficits.
3. Recommend NSAIDs.
4. Consider benefit of prosthetic equipment (walker, cane, crutches).
5. Support tolerability until tachyphylaxis occurs.
6. Consider neurologic consult.
7. Consider rehabilitation consult.
8. If patient is unable to control symptoms, consider dose reduction in collaboration with physician. Dose reductions are effective in most cases; however, they must be weighed against the long-term benefit of a full course of optimal-dose therapy.
PERIPHERAL NEUROPATHIES/PARESTHESIAS

PATHOPHYSIOLOGY

Paresthesias are an increase or decrease in sensation as a result of damage to the large-diameter fibers of neural tissues. Cytokines produced in the periphery also can affect the brain through several possible mechanisms:

1. Peripheral cytokines can enter the CNS by crossing the intact blood-brain barrier in areas of a relatively low-pressure gradient, such as circumventricular areas and the hypothalamic region.
2. Peripheral cytokines also transmit signals to the brain via the vagus nerve or other visceral afferent neuronal pathways.
3. Release of IL-1, IL-2, and TNF causes changes in neuromuscular junction endplate activity, motor endplate activity, and stimulation of skeletal muscle fiber.

These effects of interferon correlate with the etiology of peripheral neuropathies, such as paresthesias. Patients with mild, acute neurotoxicity can have severe and progressive residual symptoms. In general, the length of time the patient is treated with interferon is not strongly related to neurotoxicity. More profound paresthesias occur in individuals who have received previous neurotoxic treatment. Symptoms can occur as early as 3 weeks into interferon-based treatment. These effects of interferon therapy may appear and persist months after therapy is completed or discontinued. Peripheral neuropathy can reverse spontaneously or may respond to treatments, as indicated in the “Treatment Strategies” section below.

PREVENTIVE STRATEGIES

1. Perform neurologic assessment prior to anti-HCV treatment, particularly in high-risk individuals, such as those with a history of smoking (including current smokers), or DM.
2. Obtain thorough medical history including history of neurotoxic treatments (which increases risk of interferon-related neurotoxicity) and history of seizure disorder with or without associated Todd’s paralysis. (Interferon can lower seizure threshold and manifest as focal sensory seizures. Therefore, it should be used with caution in patients with seizure disorders.)

TREATMENT STRATEGIES

1. Reduce/eliminate (if possible) use of sedatives, tranquilizers, and antiemetics that may increase toxicity.
2. Encourage standard doses of vitamins, and higher doses if patients have deficiencies.
3. Encourage weight-bearing exercises.
4. Suggest topical application of capsaicin (Zostrix®, Axsain®, Dolorac®, Capsagel®, Capzasin-P®), which works by depleting neuropeptides. Caution: Burning and erythema may occur at application site; use gloves to apply topical ointment and wash.
hands after handling. If burning occurs, use lidocaine (Xylocaine®) for symptomatic relief.

5. Consider pharmacologic therapies (in approximate order of preference):
   a. Low-dose tricyclic antidepressants (amitriptyline [Elavil®] or nortriptyline [Pamelor®, Aventyl®]) or antiprostaglandin, like naproxen (Naprosyn®) 500 mg BID.
   b. Trazodone (Desyrel®) 50 to 400 mg/d. May be better tolerated if entire dose given QHS.
   c. Anticonvulsants: carbidopa-levodopa (Sinemet® CR) 250 mg QHS, gabapentin (Neurontin®) 900 to 3600 mg/d in divided doses with no more than 1200 mg/dose; start low and titrate up.
   d. Steroids, such as prednisone, for burning dysesthesia of hands and feet.3,4
   e. Mexiletine (Mexitil®), a local anesthetic/anti-arrhythmic agent structurally similar to lidocaine (Xylocaine®), but orally active. This agent has been suggested, but is not widely used.
   f. Opioids, avoiding oxycodone (OxyContin®) and fentanyl (Actiq®).

6. For nocturnal “restless legs”: apply warm packs to lower extremities: 15 min on, 15 min off x 4 before bedtime. Also may help to slightly elevate lower extremities. Give trazodone (Desyrel®) in PM.

7. Consult with pain clinic/specialist.

REFERENCES
Concentration and memory loss are common clinical problems for patients taking interferon-based therapy. All patients treated with peginterferon, with or without ribavirin, should be considered at some risk for the development of cognitive side effects.

**PATHOPHYSIOLOGY**

There are multiple mechanisms by which interferon may cause neuropsychiatric side effects, including effects mediated by neuroendocrine, neurotransmitter, and cytokine pathways.\(^1\) Interferon acts as a central dopamine agonist, through an opioid-associated mechanism resulting in psychomotor slowing and cognitive dysfunction defined as: decreased concentration, focus, memory loss, forgetfulness, and dysphoria.\(^1,2\) In addition, alterations of peripheral nonadrenergic receptor levels and serum tryptophan levels have also been observed in patients receiving interferon. Serotonin depletion is responsible for the dementia syndromes associated with cytokine therapy and HIV patients. The hypothesis that disregulation of norepinephrine and serotonin neurotransmitters cause depression-associated cognitive dysfunction was the basis for the development of many antidepressant medications, including tricyclic antidepressants (TCAs) and newer generation selective serotonin reuptake inhibitors (SSRIs).

Special Note: Although combination therapy with peginterferon and ribavirin is associated with neurocognitive fatigue and associated difficulties with concentration, focus, and memory, these symptoms are also clinical manifestations of both HCV and HIV infections and treatment. Since approximately 33\% of all patients with HIV are coinfected with HCV and may be eligible for treatment, clinicians should maintain a high level of suspicion for both diseases in the differential diagnosis when such symptoms are reported.

**ASSESSMENT**

1. Perform baseline assessment and monthly during treatment for the presence of cognitive symptoms utilizing the Center for Epidemiological Studies Depression Scale (CES-D)\(^3\) and/or the Folstein Mini Mental State Examination.
2. Use more comprehensive screening tools (eg, Beck Depression Inventory, Zung Self-Rating Depression Scale, or Profile of Mood States) for more complex situations.\(^1\)
3. Assess family support structure and family’s views on patient’s mood, activity level, and sleep.
4. Assess baseline neurologic status with attention to cerebellar and motor function.
5. Obtain complete medical history, including neurologic history, history of exposure to brain irradiation, and educational experience and success.
6. Perform laboratory evaluation including assessment of electrolytes, liver function, thyroid status, and particularly antithyroid antibodies.
PREVENTIVE STRATEGIES
1. Anticipate symptoms in high-risk populations: patients with previous psychiatric history, mood disorders (bipolar depression), or brain irradiation; co-infection patients; geriatric patients with altered metabolism, pre-existing cognitive deficits, or altered sleep patterns; as well as patients being treated with antidepressants or hypnotics. All should be monitored closely and dose reductions made as needed.
2. Recommend strategies for improving concentration and “staving off symptoms” (eg, doing crossword puzzles, playing card games, doing needlepoint). Advise patients to decrease environmental distractions such as the TV or radio, and to take short naps when fatigued.

TREATMENT STRATEGIES
1. Discuss with patient any mood and cognitive effects as a result of treatment. (There is a significant stigma associated with psychiatric illness and reporting of symptoms.) Do not underestimate the value of reassurance. Include family members/significant others as much as possible.
2. Rule out a differential diagnosis of hydrocephalus, thyroid dysfunction, and HIV opportunistic infection.
3. Evaluate concomitant medications, such as narcotic analgesics, tranquilizers, or sedatives, which may exacerbate cognitive changes.
4. Advise patients to reorganize lifestyle and conserve energy to maintain a reasonable amount of participation in normal activities.
5. Recommend use of reorientation, prompts, or lists.
6. Advise patients to maintain an exercise schedule and participate in concentrating/focusing activities with repetitive actions (ie, gardening, needlepoint).
7. Consider pharmacologic therapy (in approximate order of preference):
   a. Psychostimulants (bupropion [Wellbutrin®] and modafinil [Provigil®]; avoid pemoline [Cylert®]). These agents have amphetamine-like properties, and their indirect dopamine agonist actions may account for their efficacy in the treatment of interferon toxicity. Efficacy has also been cited in adult and pediatric glioma patients, as well as cancer, other chronic illness, depression, and hepatitis patients. Psychostimulants are short acting although sustained-released formulas are available (methylphenidate [Concerta™, MetaDate®, Methylin®, Ritalin®] 20 mg SR; 8-hour duration of action). Caution may be needed in patients with a history of substance abuse. A methylphenidate dose of 2.5 to 20 mg orally/d is recommended for patients receiving interferon therapy. Concern that a patient with HCV infection (and no history of drug abuse) may develop tolerance, dependence, and addiction is not supported by the literature in reviews of methylphenidate use for patients with chronic illness. Remember, as with all medications used, check for drug-drug interactions, and also set firm boundaries for appropriate use.
   b. Opioid antagonist may be used as palliative agent. Naltrexone (ReVia®) 100 mg has been used, but limited study information is available.
   c. Corticosteroids have been used to permit administration of optimum doses of interferon primarily in cancer patients. Caution: Steroids are known to have a mood-elevating effect; however, psychosis and steroid-induced depression can
occur. Therefore, it is imperative to monitor patient on a regular basis (utilization of CES-D self-assessment tool will add validity and reliability to the evaluation).

d. Treatment with TCAs may increase norepinephrine and serotonin levels, but have a sedative effect and become counterproductive in the management of fatigue and aggravate memory dysfunction. TCAs, particularly those with pronounced anticholinergic effects, are less desirable than other treatment options, potentiating cognitive dysfunction related to interferon or cirrhosis. Furthermore, TCAs may be especially problematic for patients with suicidal ideation, given their lethality in overdose.

8. Obtain neuropsychiatric or psychiatric consult.

REFERENCES
INSOMNIA

PATHOPHYSIOLOGY
Insomnia is defined as the prolonged inability to sleep. Cytokines function primarily as communication signals for the immune system, but cytokine receptors are present on many cell types within a variety of organs, including the brain. The cytokine receptor sites located within glial cells, astrocytes, and the brain stem reticular formation result in biochemical and functional changes that affect sleep-inducing substances, such as prostaglandin D₂, factor S, serotonin, and IL-1. It is important to note that insomnia is a common symptom of depression. Significant depletion of serotonin levels will manifest in a variety of CNS symptoms, including depression and insomnia. Insomnia as a result of decreased serotonin levels is seen with interferon therapy.

TYPES OF INSOMNIA
- **Initial**: Difficulty in falling asleep.
- **Intermittent**: Inability to stay asleep.
- **Terminal**: Early morning awakening.

ASSESSMENT
1. Pretreatment assessment of physical, psychological, and psychiatric causes of insomnia.
2. Physical assessment includes the presence or persistence of pain, dyspnea, hypoxia, cough, fever, sweats, pruritus, nocturia, polyuria, diarrhea, or urinary or fecal incontinence.
3. Psychological and psychiatric assessment include the presence or persistence of anxiety, depression, psychosis, mania (common with former or current injection drug users), confusion, or dementia.
4. Assess for the presence of drug-related insomnia: corticosteroids, cocaine, caffeine, xanthines, amphetamines, adverse reaction to diphenhydramine (Benadryl®) or ephedrine (rebound insomnia).
5. Determine if pretreatment and withdrawal of drugs are causing insomnia (benzodiazepines, barbiturates, alcohol, and nicotine).
6. Rule out sleep apnea; sedative agents in patients with untreated apnea can increase sleep disorders and cause nighttime hypoxia.

TREATMENT STRATEGIES
*Nonpharmacologic*: Providers should determine whether insomnia may be due to anxiety or depression and treat accordingly. They should also advise patients to:
1. Adhere to a sleep hygiene regimen, including regular sleep-wake patterns, and no stimulants.
2. Consider daytime administration of peginterferon injection.
3. Decrease noise and other sensory stimulation at bedtime. Encourage relaxation several hours prior to retiring for the evening (music, reading, crafting, warm bath).
4. Reserve bed for sleeping and sex. Take the television out of the bedroom.
5. Ensure bedroom is a comfortable temperature, neither too warm nor too cool.
6. Decrease fluid intake at bedtime to avoid nocturia. (Hydration during peginterferon/ribavirin therapy is essential; however, hydration requirements should be completed before 6:00 PM).
7. Consider massage or keeping a journal.
8. Develop an appropriate exercise regimen, but avoid strenuous exercise within 4 to 6 hours of bedtime.
9. Modify diet to avoid heavy meals and caffeine at bedtime. Include foods rich in tryptophan (turkey, salmon, warm milk, and eggs) in order to increase plasma free levels of tryptophan, which is a precursor to serotonin.

**Pharmacologic**: (See also “Pharmacologics” table below.)

1. Vitamin B₁₂ and B complex have been helpful in relaxing the patient and promoting deep restful sleep.
2. Inositol (a folic acid analogue) also enhances REM sleep and is often given with the B vitamins in patients with vitamin B deficiency.
3. Diphenhydramine (Benadryl®) 25 to 200 mg QHS. Use with caution in patients with cognitive impairment.
4. Trazodone (Desyrel®) 25 to 400 mg.
5. Hypnotics: zolpidem (Ambien®) 5 to 10 mg is recommended in individuals with hepatic insufficiency. As with all hypnotics, administration is best just before bedtime. Unlike diphenhydramine (Benadryl®), it does not contribute to next day sluggishness in some patients (eg, “the morning after hangover”).
6. Zolpidem (Ambien®) 5 to 10 mg with diphenhydramine (Benadryl®) 25 to 200 mg.
7. Low-dose (7.5–15 mg) mirtazapine (Remeron®). Note: lower doses are more sedating.
8. Benzodiazepines (lorazepam [Ativan®], oxazepam [Serax®], temazepam [Restoril®], and clorazepate [Tranxene®]) can be used for simple sleep disorders because they are safe and effective for at least 1 month of regular use and because they are able to produce a more natural sleep (through less disruption of REM sleep). They are also helpful in increasing the duration of sleep. Note: these drugs may be habit forming.
9. TCAs and serotonin mediators (amitriptyline [Elavil®], nortriptyline [Pamelor®, Aventyl®], and doxepin [Sinequan®]) can be used for depression with concomitant sleeplessness. They have a positive impact on suppression of REM and decrease the number of awakenings from sleep.
10. SSRIs, SNRIs, and serotonin antagonists are first-line treatment for depression associated with insomnia. They generally prevent disruption of the sleep cycle, although a few patients report vivid dreams that disturb sleep.
11. Quetiapine (Seroquel®) 25 to 100 mg. Consider when other options have failed.
## PHARMACOLOGIC AND ALTERNATIVE AGENTS FOR INSOMNIA

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<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Dose and Route</th>
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<td>Ativan®</td>
<td>Lorazepam</td>
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<td>Serax®</td>
<td>Oxazepam</td>
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<td>Temazepam</td>
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<tr>
<td>Tranxene®</td>
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<td>Doxepin</td>
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<td>Prozac®</td>
<td>Fluoxetine</td>
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<td>SSRI</td>
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<td>Mirtazapine</td>
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<td>Wellbutrin® SR</td>
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<td>Desyrel®</td>
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<td>Chamomile tea</td>
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<td>Maypop</td>
<td>Capsule or extract PO</td>
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<td>PO as directed</td>
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<td>Silent Night</td>
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## REFERENCES

PATHOPHYSIOLOGY

Pain is an unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage.¹ There are many reasons that a patient may experience the sensation of pain. Disease, treatment, or lifestyle changes may contribute to pain. Pain affects many patients undergoing therapy for a disease state like hepatitis, cancer, or cardiac or pulmonary disease. Uncontrolled pain can lead to a negative response to therapy, interfere with wound healing, and can interfere with patient treatment adherence.² Pain can lead to depression, social withdrawal, anger, and failure to participate in activities of daily living (ADLs), the treatment plan, and sexual activity. Interferon therapy, with the interaction of the interferon cascade, can cause myalgias, HA, and arthralgias, which can negatively impact patient well-being. Prolonged pain can also interfere with a patient’s role, responsibility, and QOL.¹

1. Pain can be treatment related through the activation of the interferon cascade and the release of IL-8. The patient may experience muscle and fat breakdown resulting in myalgias and arthralgias. The B cell immunity delayed response can cause an exacerbation of arthritic pain. The FLS can cause muscle tightness and HA.

2. Ribavirin-induced anemia can cause chest pain and shortness of breath.

TYPES OF PAIN¹

- **Acute**: Duration is usually <6 months; characterized in intensity as mild-severe; cause is usually known.
- **Chronic**: Duration is usually >6 months; cause may or may not be known. Patient may respond to treatment but pain may not subside after treatment cessation/healing. Intensity described as mild-severe.
- **Somatic**: Most common type of pain; due to the activation of pain receptor fibers located in cutaneous and deep tissue by mechanical, thermal, and chemical stimuli.
- **Visceral**: Due to the activation of pain receptor fibers located in the organs; caused by injury, such as edema, stretching, distention, contraction, ischemia, or chemical irritation.
- **Neuropathic**: Due to injury of the pain fibers at the periphery or can occur at the central level of the spinal cord. Injury can occur from mechanical or metabolic causes, such as spinal cord injury, nerve root compression, or metabolic neuropathy. Neuropathic pain is less responsive to narcotics, but responds better to adjuvant analgesics such as NSAIDs, anticonvulsants, and TCAs.
RISK FACTORS FOR ACUTE AND CHRONIC PAIN

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<tr>
<th>Disease States</th>
<th>Lifestyle Related</th>
<th>Treatment Related</th>
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<tbody>
<tr>
<td>• Anemia</td>
<td>• Overactivity</td>
<td>• Biotherapy, chemotherapy, surgery, radiation therapy, transplant</td>
</tr>
<tr>
<td>• Tumor necrosis</td>
<td>• Underactivity</td>
<td>• AEs and complications related (HA, N/V, chest pain, neuropathies, stomatitis, rash, infection, fibrosis, cough, etc)</td>
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<tr>
<td>• Tumor compression</td>
<td>• Stress</td>
<td></td>
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<tr>
<td>• Chronic pain</td>
<td>• Fear</td>
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<tr>
<td>• Diagnostic tests</td>
<td>• Use of pain for secondary gain</td>
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<tr>
<td>• Tumor progression</td>
<td>• Fatigue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Substance abuse</td>
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</tr>
</tbody>
</table>

ASSESSMENT

1. Assess presence of risk factors for pain.
   a. Disease related
      i. Interferon administration
      ii. Stimulation of pain receptors by edema, effusions, or distention of tissue
      iii. Concurrent diseases, such as arthritis, musculoskeletal disease
   b. Treatment related
      i. Invasive diagnostic and treatment-related procedures (surgery, biopsy)
      ii. Acute complications of therapy: stomatitis, infections, inflammation
      iii. Long-term complications of therapy: myopathies, fibrosis, neuropathies, compression of nerves, nerve damage from surgery or radiation
   c. Lifestyle related
      i. Overactivity—some patients overdo trying to work through the symptoms of the therapy
      ii. Immobility and anxiety or stress related to anti-HCV therapy
      iii. Anxiety related to the change in role and function as a result of the pain and coping with the disease

2. Assess pain using an appropriate assessment tool, such as the 10-point Visual Analog Scale.

3. Assess characteristics of pain; onset, location, duration, quality, frequency, severity, associated symptoms, precipitating, aggravating/alleviating factors.

4. Evaluate types of self-care measures, impact of pain on ADLs and QOL.

TREATMENT STRATEGIES

1. Instruct patients to institute noninvasive measures for pain alleviation, including:
   a. Increase activity, force fluids, and rest if overactive.
   b. Apply heat and cold to area of pain.
   c. Use massage therapy, pressure, relaxation techniques, hypnosis, or guided imagery if needed.
   d. Discuss the pain and other external issues.

2. Administer analgesics
   a. Nonnarcotics: work at peripheral nervous system; use as anti-inflammatory and antipyretic. Good for mild to moderate pain. Examples: aspirin 325 to 650 mg (1–2 standard tablets) Q4H not to exceed 12 tablets in a 24-hour period. Take with food or use enteric coated to decrease GI irritation. Acetaminophen (Tylenol®) 650 mg
Q4H PRN, choline magnesium trisalicylate (Trilasate®) 750 mg TID, ibuprofen (Advil®, Motrin®) 200 to 800 Q6H PRN. New medicines like COX-2 inhibitors have been helpful in patients with arthralgias from interferon.

i. Considerations with NSAIDS: Assess gastrointestinal toxicity, platelet dysfunction, and renal function. NSAIDs have an analgesic ceiling; may need narcotics once the ceiling is reached. Use with caution in patients with thrombocytopenia, coagulopathies, asthma, and/or bleeding ulcers.

b. Narcotics: Opioids work at the level of the CNS; good for moderate-severe pain. Patients with severe migraines may need narcotics. Consider for patients with potential acetaminophen (Tylenol®) toxicity. Examples:

- oxycodone/acetaminophen (Percocet®, Tylox®), meperidine (Demerol®), hydrocodone/acetaminophen (Vicodin®), oxycodone (OxyContin®, OxyIR®, Oxyfast®, Percolone®, Roxicodone™), propoxyphene (Darvon®), and hydromorphone (Dilaudid®). Can use with NSAIDs if all others fail.

i. Considerations for opioids: Use with caution in substance abuse patients. Assess patient sedation, fatigue, nausea/vomiting, urinary retention, constipation, and respiratory depression. Assess for hypo/hypertension, bronchospasm, syncope, pruritus, and uticaria. Seven percent to 10% of patients lack the liver enzyme CYP2D6 needed to activate hydrocodone and codeine; patients who say the medication does not work may lack this enzyme. Medications that impair CYP2D6 (eg, fluoxetine [Prozac®]) may decrease the efficacy of codeine compounds. Oxycodone is not affected by this enzyme.

4. Adjuvant pharmacologic therapy: Antidepressants (good for use with neuropathic pain), anticonvulsants (eg, gabapentin [Neurontin®]), psychostimulants, and tranquilizers.

5. Consider a pain management consultation if these measures are not effective.

REFERENCES
A variety of visual changes can occur among patients treated with interferon-based therapy, including retinal hemorrhage, vision changes, and vision loss.\(^1\) Ophthalmologic toxicity of interferon is usually reversible, but consideration should be given to treatment discontinuation when it occurs. Any patient with ophthalmologic symptoms should be sent for an ophthalmology consult.

**PATHOPHYSIOLOGY**

The underlying pathogenesis of retinopathy associated with interferon is not clear and is probably multifactorial. Lohmann et al\(^2\) reports that although the mechanism of interferon-associated anterior ischemic optic neuropathy is unclear, it is most likely to be linked to an immunologic process. It has been postulated that interferon alfa is able to produce autoantibodies, and subsequently causes deposition of immune complexes in the small retinal or optic nerve arteries. Interferon is also an immunomodulator that stimulates other cytokines, such as various interleukins, and upregulates histocompatibility complex class II proteins. These interleukins can cause an inflammatory reaction of the blood vessels and lead to ischemia. Unfortunately, such ischemia and vision loss may be permanent. The incidence of ophthalmologic complications does not seem to be influenced by the type or dose of interferon. However, there is a reported higher incidence of complications in patients with certain clinical entities, specifically diabetes, hypertension, retinal arterial sclerosis, and anemia.\(^3\) High levels of low-dose lipoprotein cholesterol and atherosclerotic index may also influence the likelihood of the development of retinopathy.\(^3\)

There may be a physiologic relationship between the presence of retinal complications and levels of plasma-activated complement 5 (C5a), which is a known potent intravascular aggregator of granulocytes.\(^4,5\) In specific clinical studies, when retinal hemorrhage occurred, C5a levels were significantly increased. A high C5a level may be an important step in the pathogenesis of retinal capillary infarction, microvascular emboli, hemorrhage, and cotton wool spot formation.

The time of onset after administration is nonspecific, though there are reports of patients with HCV infection who have experienced retinal hemorrhage and/or cotton wool spots early in the course of therapy (ie, within the first 8 weeks).\(^3\) There seems to be no relationship between the incidence of retinopathy and the levels of liver enzymes, but increased incidence is reported in patients after the WBC and the platelet count have reached a nadir. Sudden bilateral visual loss with disc-related field defects and segmental optic disc edema has been reported but is rare. Permanent loss of vision is thought to be a result of closure of the retinal capillaries.

In a Japanese study,\(^6\) 50 patients treated with interferon for chronic HCV, HBV, or renal cell carcinoma were examined for retinal complications. Retinal hemorrhages or cotton
wool spots were observed in 23 patients (46%). Hemorrhage without cotton wool spots was found in 14 patients, cotton wool spots without hemorrhage in 5 patients, and both conditions in 4 patients. These findings were potentially reversible. There was one case of branch retinal artery occlusion and one case with micro-aneurysm. RBC decreased significantly in patients with retinopathy compared with those without retinopathy ($P < .05\%$). In another study, cotton wool spots disappeared after interferon treatment was stopped and they did not return unless interferon therapy was restarted. However, in three cases, the cotton wool spots disappeared despite continued therapy. These cases emphasize the need for careful retinal surveillance of patients treated with interferon to diagnose this potentially reversible retinal ischemia.

Special note: Patients with chronic HCV are known to have circulating immune complexes, and patients with hypertension and/or diabetes have been shown to have damage to endothelial cells, retinal ischemia, and capillary nonperfusion. It may be in this population of patients, in whom this combination of factors exists, that the most severe problems are more likely to be seen.

**BASELINE TESTS RECOMMENDED**
- Ocular examination, including:
  - Photographic documentation
  - Recording of visual evoked responses (VERs)
  - Electroretinograms
  - Visual acuity
  - Visual fields

All healthcare providers should be aware of potential risk to patients treated with interferons. Patients without conditions predisposing to vascular nonperfusion should be followed closely and visual complaints investigated thoroughly. Delayed clinical diagnosis or delays in follow-up of subjective complaints are likely to be associated with poor visual outcomes.

<table>
<thead>
<tr>
<th>COMMON SUBJECTIVE SYMPTOMS*</th>
<th>FREQUENTLY NOTED CLINICAL FINDINGS</th>
<th>FREQUENTLY NOTED CLINICAL FINDINGS</th>
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<tr>
<td>Abnormal vision</td>
<td>Latency in VERs</td>
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<td>Blurred vision</td>
<td>Subconjunctival hemorrhage</td>
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<td>Diplopia</td>
<td>Cotton wool spot formation</td>
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<td>Dry eyes</td>
<td>Retinopathy</td>
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<td>Vision loss</td>
<td>Capillary nonperfusion</td>
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<tr>
<td>Coinfected patients: vision changes, loss</td>
<td>Anterior ischemic optic neuropathy</td>
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<tr>
<td></td>
<td>Rule out CMV retinitis</td>
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</tbody>
</table>

*Patients may be asymptomatic early in treatment.
TREATMENT STRATEGIES\textsuperscript{2,11,13}

1. Discontinue interferon-based therapy. After discontinuation, treatment-associated neurovisual abnormalities may resolve. There are reports of persistent complications, so careful monitoring of patients is required. If the physician elects to resume interferon therapy; advise him/her to obtain a letter of clearance from an ophthalmologist.

2. Obtain a CBC with differential.

3. Consider aspirin and prednisone for anterior ischemic optic neuropathy.

4. Recommend, for local symptomatic relief:
   a. Artificial tears/lubricants
   b. Cool cloths over eyes
   c. Reduced exposure to light: close blinds/drapes, dim lights, use sunglasses

5. Recognize that patients with a history of CMV retinitis will commonly relapse during antiviral therapy.

Special Note:

1. Postliver transplantation symptomatic complications can occur.\textsuperscript{14}

2. Ocular complications have been reported in 2\% of patients with 65\% of these being opportunistic infections such as\textsuperscript{14}:
   a. Herpes viral retinitis
   b. Fungal chorioretinitis
   c. Central retinal vein occlusion
   d. Herpes zoster ophthalmicus
   e. Herpetic keratitis
   f. Cyclosporine retinopathy

3. There are reported clinical trials of interferon alfa-2a for the treatment of choroid neovascularization membranes.\textsuperscript{10}

REFERENCES


XI. Psychologic

DEPRESSION

WARNING (See also “Contraindications” section.)

Severe psychiatric adverse events, including depression and violent behavior (suicides, suicide attempts and suicidal ideations) have occurred during peginterferon/ribavirin or interferon/ribavirin therapy and with interferon monotherapy, both in patients with and without a previous history of psychiatric illness.

Interferon-based therapy should be used with extreme caution in patients with a history of pre-existing psychiatric disorders who report a history of severe depression, and physicians should monitor all patients for evidence of depression. Patients treated with interferon who complain of depression usually describe apathy, cognitive slowing, and fatigue. Some patients report dysphoria at the beginning of treatment and develop flulike symptoms. Others report depression later in treatment, probably because somatic or cognitive symptoms become more pronounced, or more chronic symptoms, such as fatigue, anorexia, myalgia, etc, present themselves. Feelings of helplessness and anhedonia may also be present at this time. Acute onset of dysphoria with suicidal ideation is uncommon, but the clinician must be aware that this may occur. Symptoms consistent with mania may also be seen, and medications used to manage bipolar disease may be beneficial.

Patients who experience moderate depression, including persistent low mood, loss of interest, poor self-image, and/or hopelessness, may benefit from a temporary interferon dose reduction, and should be considered for medical therapy. Patients experiencing severe depression or suicidal ideation should discontinue therapy and be followed closely with appropriate medical management and psychiatric intervention. In general, psychiatric adverse events resolve on cessation of therapy; however, adjunctive psychiatric medications may be required.

PATHOPHYSIOLOGY

While about 6% of the general population is affected by major depression, 35% to 57% of all chronic viral hepatitis patients may have depression upon diagnosis and/or preceding treatment for their disease. Moreover, a number of investigators have reported a correlation between treatment with interferon alfa and depression. Interferon may cause depression by altering neuroendocrine or neurotransmitter functions or by modulating the expression of cytokines or secondary messengers. A brief summary of mechanisms correlated with interferon-induced depression includes:

- Stimulation of the hypothalamic-pituitary-adrenal axis and adrenocorticotrophic hormone oversecretion
- Stimulation of hypothalamic-pituitary-thyroid axis
Alterations of thyroid function, leading to mood and cognitive side effects
Effects on the opioid receptor system; behavior changes are often reversed by opioid antagonists
Neurotoxicity consistent with dopamine antagonism, which increases with long-term interferon use
Effects on serotonin pathway. Patients treated with interferon have altered serum levels of tryptophan (a serotonin precursor), suggesting that serotonin depletion can contribute to depression
Involvement of other cytokines or second-messenger system. Interferon alfa induces production of interleukin-1, which has numerous toxic effects, including dysregulation of hypothalamic neuronal function

OTHER FACTORS THAT MAY CONTRIBUTE TO DEPRESSION

- Uncontrolled pain
- Medications:
  - Steroids and oral contraceptives
  - IFN and IL-2
  - Methyl dopa (Aldoril®, Aldoclor®, Aldomet®)
  - Reserpine (Diutensin®)
  - Barbiturates, nicotine
  - Propranolol (Inderal®)
  - Some antibiotics
    (eg, amphotericin B [Abelcet®, Ambisome®])
  - Some antineoplastics (eg, vincristine [Oncovin®], kinblastine [Velba®], procar bazine [Matulane®], and asparaginase [Elspar®])
  - Metabolic abnormalities:
    - Hypercalcemia
    - Sodium/potassium imbalance
    - Anemia
    - Vitamin B₁₂ or folate deficiency
    - Fever
  - Endocrine abnormalities:
    - Hyper- or hypothyroidism
    - Adrenal insufficiency

SYMPTOMS ASSOCIATED WITH MAJOR DEPRESSIVE SYNDROME

- Depressed mood
- Diminished interest or pleasure in activities
- Significant weight loss/gain or decrease/increase in appetite
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive guilt
- Diminished ability to think or concentrate; indecisiveness
- Recurrent thoughts of death or suicidal ideation

DEPRESSION CLINICAL SCREENING TOOLS

All patients should receive a pretreatment assessment for pre-existing depression or risk factors. Use a standardized tool at baseline and for follow-up.

- CES-D, or Center for Epidemiologic Studies–Depressed Mood Scale (preferred screening tool)
- BDI, or Beck Depression Inventory (good for patients with physical complaints)
- ZSDS, or Zung Self-Rating Depression Scale
PREVENTIVE STRATEGIES
1. Treat/stabilize pre-existing depression before starting anti-HCV therapy.
2. Consider prophylactic antidepressant therapy for those deemed high-risk for depression.
4. Provide positive feedback/reinforcement for proactive side-effect management efforts.
5. Help patient plan and establish regular meal times and sleeping patterns, as well as maintain adequate hygiene. The patient may also benefit from the practice of stress reduction, including relaxation periods.
7. Refer patient to a local hepatitis C support group, if available. Identify a “buddy” or significant other as support. Provide support and educational materials.
8. Encourage patient to recognize and “reroute” negative thinking patterns; eg, use a journal to record thoughts and daily activities.
9. Maintain adequate hydration (consumption in fluid ounces = one half body weight in pounds; eg, a 160-lb person should drink 80 fl oz/d). Limit caffeine, alcohol, and processed-food intake.
10. To increase serotonin production, encourage eating foods high in tryptophan, such as turkey, eggs, milk, salmon, soybeans or soy products, brown rice, legumes, and raw fruits and vegetables. Avoid excess sugar.
11. Limit intake of phenylalanine, which is found in aspartame (Equal™, NutraSweet™), MSG, and nitrates.
12. Patients infected with HCV with history of injection drug addiction: SC injection may trigger feelings of drug hunger, anxiety, depression, or provoke posttraumatic stress disorder. Reassure the patient and arrange for outpatient injection or family member administration.

SAMPLE STUDY—PROPHYLAXIS AGAINST INTERFERON-ALFA–INDUCED DEPRESSION
Title: Paroxetine for the Prevention of Depression Induced by High-Dose Interferon Alfa
Author: Dominique L. Musselman, MD, et al.
Patients: N = 40; malignant melanoma patients receiving standard high-dose interferon (HDI) for melanoma. Two groups were demographically similar.
Design: Double-blind, placebo-controlled, randomization 1:1.
Schema: Paroxetine (Paxil®) versus placebo QD beginning 2 weeks prior to HDI therapy up to and including week 12 of interferon. Two weeks after
initiation of interferon, the dosage of paroxetine could be increased at the
discretion of the study psychiatrist up to four tablets/d (40 mg).

Assessment: Assessment tools included: Hamilton Depression Scale (observer rated),
Carroll Depression Scale (self-reported), Hamilton Anxiety Scale
(observer rated), and Neurotoxicity Rating Scale (self-reported).

Analysis: Intention-to-treat analysis. Log rank tests and Kaplan-Meier plots were
used. Factors included the treatment group (placebo or paroxetine), time
(baseline, weeks 4, 8, 12), and the interactions of the two.

Results: Paroxetine significantly reduced the incidence of major depression among
patients receiving HDI ($P = .04$ by the log-rank test). Symptoms consistent
with a diagnosis of depression occurred in 11% of paroxetine-treated
patients and 45% of placebo-treated patients. In addition, the severity of
depressive symptoms was also reduced ($P < .001$). Five percent of patients
on paroxetine discontinued therapy while 35% of placebo patients
discontinued therapy.

Discussion: In contrast to other studies demonstrating the benefit of treatment of
depression in these patients, this study demonstrates the value of
prophylaxis for patients on HDI. These findings are promising and may
have a significant effect on the ability to keep patients on therapy.

Limitations: Small sample size. The study was limited to the first 12 weeks of
interferon therapy.

Of Note: Two patients assigned to paroxetine were diagnosed with major
depression at screening. Both completed therapy and, by week 12, no
longer had signs of depression.

**TREATMENT STRATEGIES**

1. Assess for past neurologic history, prior brain irradiation, electrolytes, liver function,
   and thyroid status, especially antithyroid antibodies, vitamin B$_{12}$ status, or other risk
   factors/contributing agents.

2. Assess severity of depressed state. Immediately and specifically explore suicidal
   thoughts. Some patients may minimize or deny interferon-induced depression in order
   to continue treatment.

3. Treat depression early and aggressively. Initiate use of an SSRI or other
   antidepressant as appropriate (see “Choosing an Antidepressant” below).

4. Reinforce exercise as an effective antidote to bouts of depression (endorphin
   production).

5. Psychiatric consultation for high CES-D scores. Also see “Indications for Psychiatric
   Consultation” below. A letter of clearance to resume therapy from the patient’s
   psychiatrist is recommended.

6. Some physicians report salvaging “profound” depression patients with 20 mg
   methylphenidate (Concerta™, MetaDate®, Methylin®, Ritalin®) SR PO Q AM or
   another psychostimulant.$^{10}$

7. Interferon treatment can be continued if depression is stable or effectively managed.
   Some clinicians believe in the need to reset the cytokine feedback pathway by
   stopping antiviral therapy, initiating antidepressant therapy, and allowing time for
efficacy, followed by reintroduction of antiviral therapy.
8. If unresponsive to antidepressant therapy, the interferon dose should be decreased. If this does not alleviate depression, interferon should be discontinued either temporarily or permanently, per psychiatrist recommendation.

9. If the depression is severe (suicidal or psychotic) or worsening, discontinue interferon and initiate psychiatric evaluation immediately.

10. When speaking with patients who indicate suicidal ideation by phone, notify the patient’s physician, call 911, and/or remain with patient on the phone until help arrives. See “Suicidal Ideation” section.

11. Consider the risk of having patients transition from depression to mania with antidepressants, even after completion of interferon therapy.¹

**DEPRESSION THERAPIES**

- **SSRIs**: block serotonin receptors on nerve cells in the brain. SSRIs are usually the first antidepressant prescribed when patients initiate therapy.
- **TCAs**: block the norepinephrine and serotonin receptors on nerve cells in the brain. They are associated with more side effects than the SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), and other atypical agents.
- **SNRIs**: affect serotonin and norepinephrine receptors.
- **Atypical**: affect dopamine and norepinephrine (bupropion [Wellbutrin®]) or norepinephrine alone (maprotiline [Ludiomil®]).
- **MAOIs**: block the breakdown of serotonin, epinephrine, and norepinephrine. Use is uncommon in clinical practice because of life-threatening drug and dietary interactions.
- **Opioid antagonists**: naltrexone (ReVia®) has been studied with varying efficacy in resolution of neurotoxic symptoms.
- **Psychostimulants**: indirect dopamine agonist action.
- **Hormone replacement therapy**: adjunct to antidepressant treatment in some postmenopausal women. Should be carefully discussed with patient because it can decrease effect of SSRIs and carries increased risks of other conditions.
- **Electroconvulsive therapy**: indicated for severe pharmacologic/psychotherapy-resistant depression; controversial.
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<th>Generic Name</th>
<th>Brand Name</th>
<th>Average Daily Dose</th>
<th>Sedation</th>
<th>Cardiac Cond. Effects</th>
<th>Anticholin. Effects</th>
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Key: 0, none; ±, equivocal, sporadic; 1, minimal; 2, mild; 3, moderate; 4, strong; 5, severe.
### CHOOSING AN ANTIDEPRESSANT

<table>
<thead>
<tr>
<th>Distressing Symptom</th>
<th>SSRI</th>
<th>TCA</th>
<th>Psychostimulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>+/-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal upset</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid SEs</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>+/-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>+/-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Akathisia</td>
<td>–</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Cognitive/behavioral slowing</td>
<td>+/-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>+/-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Stomatitis/dry mouth</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

### Co-morbid Condition

<table>
<thead>
<tr>
<th>Co-morbid Condition</th>
<th>SSRI</th>
<th>TCA</th>
<th>Psychostimulant</th>
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<tbody>
<tr>
<td>H/O CV disease</td>
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<tr>
<td>H/O CNS dx/seizure</td>
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<td></td>
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<tr>
<td>Hepatic dysfunction</td>
<td>+</td>
<td></td>
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<tr>
<td>Renal dysfunction</td>
<td>+</td>
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<tr>
<td>Glaucoma</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>+</td>
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</tbody>
</table>

### Drug Interactions

<table>
<thead>
<tr>
<th>Drug Interactions</th>
<th>SSRI</th>
<th>TCA</th>
<th>Psychostimulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine (Tagamet®)</td>
<td>√</td>
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<tr>
<td>Digoxin (Digitek®, Lanoxicaps®, Lanoxin®)</td>
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<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Phenytoin (Dilantin®)</td>
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<td></td>
<td>√</td>
</tr>
<tr>
<td>MAOIs</td>
<td>√</td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Warfarin (Coumadin®)</td>
<td>√</td>
<td></td>
<td>√</td>
</tr>
</tbody>
</table>

### Time to Therapeutic Effect

- **SSRI**: 3–6 weeks
- **TCA**: 3–6 weeks
- **Psychostimulant**: 1–4 days

---

**Key:**

- (–) Use of this medication could worsen the symptom/co-morbid disease
- (+) Use of this medication could relieve the symptom/co-morbid disease

---

**Notes**:

1. **Fluoxetine (Prozac®)** is particularly activating, although all SSRIs have the paradoxical effect of hypersomnia. Bupropion (Wellbutrin®) is also somewhat activating.
2. Sedating antidepressants are useful for insomnia, either alone or in addition to another antidepressant. Trazodone (Desyrel®) is often used as a sleep aid in combination with another antidepressant.
3. Antidepressants are useful in treating neuropathic pain. The most studied are TCAs, particularly amitriptyline (Elavil®). Psychostimulants have been used as adjuvant pain medications in conjunction with the opioids.
4. TCAs are least likely to aggravate an existing condition of akathisia, if an antidepressant is needed. SSRIs, although usually the first-line of therapy, can cause akathetic reactions. Benzodiazepines and propranolol (Inderal®) are first-line treatments for akathisia.
5. Sedating antidepressants are most useful for anxious/agitated patients. These include trazodone (Desyrel®), the TCAs, and nefazodone (Serzone®).

6. In general, TCAs and psychostimulants can cause arrhythmias. SSRIs, bupropion (Wellbutrin®), venlafaxine (Effexor®), and nefazodone (Serzone®) are generally less likely to cause cardiovascular problems. Electrocardiograms should be obtained before starting TCA medications, and a cardiologist should be consulted if there is concern of cardiac compromise.

7. Shorter-acting SSRIs (sertraline [Zoloft®] and paroxetine [Paxil®]) are less problematic in those with hepatic dysfunction. Sertraline (Zoloft®), citalopram (Celexa™), and escitalopram (Lexapro™) reportedly have less effect on hepatic cytochrome P-450 enzyme activity; however, the effect of specific drug-to-drug interactions on specific liver enzyme systems for all antidepressants should be considered.

8. Most antidepressant use should take into account renal dysfunction.

9. TCAs are contraindicated in closed-angle glaucoma. Ophthalmologists should be consulted if there is any question of glaucoma.

10. Monoamine oxidase inhibitors (MAOIs) should not be used with meperidine (Demerol®), SSRIs, or TCAs (allow recommended wash-out period).

11. TCAs and MAOIs have a high risk of lethality in overdose, the risk of which is increased if drug interactions occur or restricted foods are consumed with MAOIs. (See also “Serotonin Syndrome” below.) Other classes of agents may be preferable in patients taking multiple medications.

12. Nefazodone (Serzone®) should be avoided in patients with HCV infection since in rare cases it can cause fatal liver failure.

SEROTONIN SYNDROME

- Serotonin syndrome most often occurs in patients taking two or more medications that increase CNS serotonin levels by different mechanisms.
- Causative agents associated with serotonin syndrome include L-tryptophan, MAOIs, and SSRIs. Most cases were reported when MAOIs were used in conjunction with meperidine (Demerol®), tryptophan, dextromethorphan, a TCA, or an SSRI. Always monitor patients taking medications known to cause serotonin syndrome.
- The most common symptoms of serotonin syndrome are mental status changes. Other symptoms include motor abnormalities, cardiovascular changes, gastrointestinal problems, and miscellaneous changes, such as diaphoresis and fever.
- If a patient has serotonin syndrome, the suspected agent(s) should be discontinued. Take supportive measures to reduce hypertension, tachycardia, hyperthermia, and respiratory distress, if these symptoms are present.
- Benzodiazepines are often used to treat serotonin syndrome. Antiserotonergic agents like cyproheptadine (Periactin®), methysergide (Sanseril®), and propranolol (Inderal®) have been used in severe cases.
**DELAYED PSYCHIATRIC EFFECTS: POSTTHERAPY**

Depression, anxiety, mood swings, personality changes, and emotional distance from others may be experienced after treatment concludes, although it is unlikely that these changes are related to interferon. More likely, an underlying or pre-existing condition may elicit these experiences, such as subclinical or masked depression or other psychiatric disorders that come to the surface with therapy or the completion of therapy. Clinicians should consider the psychologic and emotional issues involved in coping with chronic illness and therapy when patients exhibit these tendencies. In addition, the patient’s history, including alcohol or drug abuse, should be considered. The patient’s current social situation and/or denial or suppression of past problems may also be factors in posttherapy experiences of depression, anxiety, etc.

Delayed psychiatric effects posttherapy are sometimes of a physical or physiologic etiology. Consider and evaluate for active substance use; unresolved changes or inflammation of the hypothalamus; organic or electrolyte imbalance; inadequate nutrition or nutritional deficit; worsening chemical imbalance in brain (eg, serotonin production) and undetected cerebral bleed, which may occur during the thrombocytopenic period.

**INDICATIONS FOR PSYCHIATRIC CONSULTATION**

- The physician is uncomfortable treating depression (ie, prominent suicidal tendencies present).
- The patient has a complicated psychiatric history.
- Depressive symptoms treated by the physician are resistant to pharmacologic intervention after 2 to 4 weeks.
• Depressive symptoms worsen rather than improve.
• Side effects of pharmacologic interventions prohibit therapeutic dosing of the antidepressant.
• Symptoms are interfering with the patient’s ability to be cooperative with medical treatment.

REFERENCES
IRRITABILITY/LABILE AFFECT

PATHOPHYSIOLOGY
Use of peginterferon/ribavirin therapy has been associated with personality changes, such as irritability and labile affect. This pattern of personality changes is suggestive of frontal-subcortical dysfunction. The brain dysfunction may be a clinical manifestation of depression. Interferon causes depression by altering neuroendocrine or neurotransmitter functions or by modulating the expression of cytokines. One of several potential mechanisms is altered serum levels of tryptophan (a serotonin precursor), suggesting that serotonin depletion might be responsible for the reported interferon-induced irritability and labile affect.

PREVENTIVE STRATEGIES
1. Assess patients prior to and monthly during treatment for depression utilizing a standardized tool (eg, CES-D).
2. Consider psychiatric evaluation prior to initiating antiviral therapy in patients with a current episode of depression or a history of depression, history of psychiatric hospitalization, history of substance abuse or chemical dependence, family history of depression or suicide attempts, history of posttraumatic stress disorder, or history of violent or abusive behavior.\(^\text{2,3}\)
3. Follow closely patients with concurrent or previous problems with substance or alcohol abuse. Look for relapse of substance abuse or signs of depression.
4. Be aware that some patients may minimize or deny symptoms of irritability and labile affect because of embarrassment or fear of dose reduction or treatment cessation.
5. A high score on the CES-D self-assessment (particularly if the score was low or normal prior to treatment, or if the score is increasing) strongly suggests the need for a psychiatric evaluation.\(^\text{4}\)

TREATMENT STRATEGIES
Patients should be encouraged to:
1. Engage in mild to moderate aerobic and/or anaerobic exercise, as a mechanism to channel anger and irritability.
2. Try meditation/relaxation techniques (yoga, biofeedback, imagery, massage).
3. Maintain good sleep habits (consistent times for sleeping; avoid caffeine; consume tryptophan-containing foods, such as warm milk, turkey, and salmon).
4. Avoid overstimulating environments (crowds, heavy traffic, loud noise).
5. Ensure adequate hydration (consumption in fluid ounces = one half body weight in pounds; eg, a 160-lb person should consume 80 fl oz/d).
6. Enjoy small pleasures (movies, music, friends, pets, laughter, positive reminiscence).
7. Recognize and report warning signs (early detection and intervention are crucial).
Providers should consider:
1. Educating and supporting families to cope with unpredictable, difficult personality changes and mood swings
2. Citalopram (Celexa®), escitalopram (Lexapro®), sertraline (Zoloft®), venlafaxine (Effexor®), and mirtazapine (Remeron®): may offer the added advantage of fewer potential interactions with other medications
3. Nefazodone (Serzone®), bupropion (Wellbutrin®), and venlafaxine (Effexor®): first-line antidepressants that have a sedating effect, reducing irritability and combative behavior
4. Trazodone (Desyrel®): useful adjunct for sleep disturbance and is well tolerated
5. Gabapentin (Neurontin®): may prove useful for mild to moderate irritability or impulsivity in the absence of depressive symptoms. Gabapentin has few significant drug interactions and is not metabolized by the liver.
6. Augmenting strategies combining two antidepressants, dose reductions, or drug holidays: may be beneficial in controlling labile affect and irritability for patients resistant to the above single-drug interventions
7. Referring for psychiatric consultation and/or family counseling
8. Discontinuing treatment if all other alternatives fail

REFERENCES
Psychologic

ANXIETY AND PANIC DISORDER

PATHOPHYSIOLOGY
Anxiety and panic disorder associated with peginterferon/ribavirin may stem from a malfunction of the neurobiologic substances norepinephrine, serotonin, and dopamine, causing excitation of nerve impulses. These neurotransmitters regulate mood, movement, and blood pressure. Gamma-aminobutyric acid inhibits neurotransmission in the brain and is closely associated with benzodiazepine receptors. Theories regarding the cause of the malfunction include chemical excess or deficit, or oversensitivity to chemical cascade.

ANXIETY DISORDER TYPES
Approximately 19.1 million American adults aged 18 to 54 years suffer from anxiety, and approximately 2.4 million suffer from panic disorder. Anxiety appears to affect twice as many women as men. However, psychologists believe that men are less likely to report or even acknowledge having an anxiety disorder, so the disparity between the sexes may not be so wide. Anxiety can be the result of physical or psychological factors, and is categorized as either acute or chronic.

ACUTE\(^2,3\): Manifests as episodes commonly called panic attacks. A panic attack is an instance in which the body’s natural “fight or flight” reaction occurs at the wrong time. This is a complex, involuntary physiologic response, with increased production and release of hormones, especially adrenaline, and norepinephrine. These attacks are abrupt and intense, can occur at any time, and can last from a few seconds up to half an hour, with the patient incorrectly believing they are having a myocardial infarction or stroke. The patient often reports being overwhelmed by a sense of impending disaster or death, hence they are unable to think clearly. Other side effects at this time may include dyspnea; a smothering, claustrophobic sensation; tachycardia; palpitations; chest pain; dizziness; hot flashes and/or chills; trembling; numbness or tingling of the extremities; diaphoresis; nausea; abdominal pain; diarrhea; a feeling of unreality; and a distorted perception of the passage of time. The attacks themselves are unpredictable; some experience one every few weeks, while others report several per day. Many fear having a panic attack while alone or in public, which can lead to social isolation and diminished quality of life.

CHRONIC\(^2,3\): Chronic anxiety is a milder, more generalized form of the disorder. In this instance, patients suffer a vague sense of anxiety most of the time, although the intensity of the feeling does not reach the level of those experiencing a panic attack. Chronic unease, especially in the presence of other people, combined with a tendency to startle easily, is often seen in this type of anxiety. Headaches and chronic fatigue are common complaints among people with this form of anxiety. Although chronic anxiety can begin at any age, onset usually occurs in a person’s 20s or 30s, and appears to run in families. Mitral valve prolapse patients have an increased incidence of this form of anxiety.
Finally, people with chronic anxiety disorder exacerbation often report being under unusual stress and may suffer an occasional panic attack.

Eventually, the disorder can have cumulative effects, such as generalized aches and pains, muscular twitching and stiffness, depression, insomnia, nightmares, early waking, decreased libido, and abnormal feelings of tension with an accompanying inability to relax. Women often report changes in their menstrual cycles and increased premenstrual symptoms. Other sequelae of incorrectly managed anxiety and panic include alcohol and drug abuse, sexual dysfunction, increased physical illness, depression, and suicidal ideation and risk. In individuals with depression, symptoms of anxiety may develop as they begin to have increasing difficulty initiating or completing even the simplest activities of daily living.

### PANIC ATTACK “TRIGGERS”

- Stress; conscious or unconscious
- Certain medications; illegal drugs
- Caffeine-based products and other stimulants
- Poorly controlled pain
- Unfamiliar surroundings/situations
- Withdrawal: ETOH, narcotic/analgesics, sedative/hypnotics
- Certain emotions
- Food allergies/sensitivities
- Crowded environments
- Hypoxia, PE, sepsis, CHF
- Hormone-secreting tumors
- Hereditary link
- Chronic illness
- Hypoglycemia
- Mitral valve prolapse
- Delirium, bleeding
- No apparent cause

### PREVENTIVE STRATEGIES

Providers should:

1. Educate the patient regarding disease, treatment, subcutaneous injection, side effects, and symptom management to allay concerns and anxiety level.
2. Provide contact numbers—office nurse, local hepatitis C support group, and “buddy,” if available.
3. Perform pretreatment assessment for current/past history of anxiety or panic disorder, and/or depression. Consider prescription antidepressants prior to or concomitantly with therapy to prevent progression of the disorder. See “Depression” section for further information.
4. Discuss expectations of therapy including side effects and management, and make specific plans for behavior modification in individuals with prior psychiatric history. This may prevent onset of symptoms or prompt reporting of the development of new symptoms.
5. Involve family members in education and treatment planning to minimize “sick role.”

Patients should be advised to:

1. Reduce or eliminate alcohol, caffeine, nicotine, and other stimulants, and to eat smaller, more frequent meals.
2. Keep a food diary to detect correlation between attacks and foods consumed.
3. Consider stress management/biofeedback interventions, including relaxation exercises and tapes, guided imagery, and meditation. Talking with family or friends can diffuse anxiety.
4. Exercise: walking, swimming, yoga, aerobics, etc. Conversely, assess for and ensure adequate sleep and rest.

**TREATMENT STRATEGIES**

**Nonpharmacologic Management Should Be Attempted Initially**
1. Re-educate patient as necessary regarding hepatitis C, treatment, potential side effects, symptom management, and stimulants and other causes or triggers of panic attacks.
2. Instruct patient how to manage panic attacks: Inhale to a count of four, exhale slowly to a count of four, do nothing to a count of four; repeat until the attack subsides. Patient should remind self that attacks are time-limited and will pass.
3. Obtain psychiatric consultation.
4. Advise the patient to create relaxation times throughout the day and evening, exercise, and limit daily tasks and pressure situations.
5. Be aware that graded exposure may be required to treat panic attacks.
6. Consider withholding interferon-based therapy until the patient is stable, or discontinue per psychiatrist’s recommendation.

**Pharmacologic Interventions**
1. SSRIs: selectively inhibit serotonin uptake and have limited effect on other neurotransmitters. This class of drugs is considered first-line. Initial starting dose is generally lower than that used for depression to minimize exacerbation of anxiety. Dose adjustments are easily tolerated. Generally take several weeks to achieve benefit. Side effects may include nausea, diarrhea, loose stools (sertraline [Zoloft®]), constipation (paroxetine [Paxil®]), insomnia, sedation (minimal and time-limited), headache, dizziness, fatigue, tremor, nervousness and anxiety, sexual dysfunction (30% of patients, men > women), decreased libido, premature ejaculation, and anorgasmia. Advantages include low level of toxicity and decreased lethal effect in overdose.
2. TCAs: various ratios of adrenergic-serotonergic reuptake inhibition. Proven effective. Side effects may include dry mouth, blurred vision, increased intraocular pressure, constipation, urinary retention, weight gain, sexual dysfunction, decreased seizure threshold, and increased toxicity in the elderly and those with suicidal ideation. TCAs generally take 4 to 6 weeks to provide relief of symptoms and can frequently be initiated at the same time as the benzodiazepine with planned taper of the benzodiazepine between 4 and 6 weeks.
3. Dual mechanism antidepressants: block serotonin and norepinephrine. Side effects may include orthostatic hypotension, syncope, tachycardia, arrhythmias, nausea, anorexia, sedation, and confusion. Mirtazapine (Remeron®) may cause agranulocytosis or neutropenia.
4. Midazolam (Versed®) or hydroxyzine (Vistaril®, Atarax®) may be utilized by psychiatrist for acute, severe cases of anxiety or panic on emergency referral.
5. Benzodiazepines: may increase inhibiting effect of gamma-aminobutyric acid and other inhibitory transmitters by binding to receptors in the CNS. Side effects may include drowsiness, dizziness, hypotension, confusion, hypersensitivity, HA, stupor, nausea and vomiting, blood dyscrasias, and jaundice (with hepatic dysfunction); usually beneficial for a limited time period (1 month or less), can be addictive, and withdrawal can lead to seizures and death if not managed carefully. These drugs have high potential for both abuse and resale.

### ANXIOLYTIC AND ALTERNATIVE AGENTS

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Generic Name</th>
<th>Dose and Route</th>
<th>Agent Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xanax®</td>
<td>Alprazolam</td>
<td>0.25–4 mg PO</td>
<td>Benzodiazepine</td>
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<tr>
<td>BuSpar®</td>
<td>Buspirone</td>
<td>15–60 mg PO</td>
<td>Anxiolytic</td>
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<td>Librium®</td>
<td>Chlordiazepoxide</td>
<td>15–100 mg PO</td>
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<td>Klonopin®</td>
<td>Clonazepam</td>
<td>0.25–1 mg PO</td>
<td>Anticonvulsant</td>
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<td>Tranxene®</td>
<td>Clorazepate</td>
<td>15–60 mg PO</td>
<td>Benzodiazepine</td>
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<td>Equanil®</td>
<td>Meprobamate</td>
<td>1200–1600 mg PO</td>
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<td>Valium®</td>
<td>Diazepam</td>
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<td>Doxepin</td>
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<td>TCA</td>
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**NOTE:** See “Depression” section for antidepressant agents and further information.

### ALTERNATIVE THERAPIES

- Chamomile tea
- Passionflower
- Biofeedback
- Relaxation exercises
- Hops, linden
- Motherwort
- Guided imagery
- Valerian root
- Selenium and chromium
- Kava kava
- Exercise
- Yoga or meditation

### REFERENCES

SUICIDAL IDEATION
Suicidal ideation (thoughts about suicide) is a precursor to all other deeds leading to suicide. Suicidal ideation itself is not considered a serious risk factor for completion of suicide, but is a sign of depression and something that should be taken seriously and monitored closely. The risk of suicide attempt increases when suicidal ideation is followed by suicide plans and means.

INTERFERON AND SUICIDAL BEHAVIOR
Depression, suicidal ideation, and suicidal behavior, including suicide attempts and completed suicides, have been reported in association with treatment with alfa interferons. Patients with a pre-existing psychiatric condition, especially depression, or a history of severe psychiatric disorder, need careful evaluation of risks and benefits and diligent monitoring if interferon treatment is indicated. Discontinue interferon therapy in any patient developing severe depression or other psychiatric disorders during treatment.

RIBAVIRIN AND SUICIDAL BEHAVIOR
Severe psychiatric adverse effects, including depression and suicidal behavior (suicidal ideation, suicidal attempts, and suicides) have occurred during both alfa interferon monotherapy, and ribavirin combination therapy, both in patients with and without a previous psychiatric illness. Use with extreme caution in patients with a history of pre-existing psychiatric disorders who report a history of severe depression, and physicians should monitor all patients for evidence of depression. In severe cases, therapy should be stopped and psychiatric intervention sought. In general, adverse effects resolve on cessation of therapy; however, adjunctive psychiatric medications may be required.

DEFINING CHARACTERISTICS/RISK FACTORS
- Presence of suicide plan
- Increasing anxiety levels
- Depression and hopelessness
- Delirium
- Pre-existing psychopathology
- Prior suicide attempts
- Exhaustion
- Fatigue
- Rage/panic states
- Self-destructive behavior
- Active aggressive suicidal acts
- Drug or alcohol abuse

ASSESSMENT AND MANAGEMENT
1. Assess the patient’s understanding of the illness, as well as any present symptoms and their meaning to the patient. Educating patient regarding treatment provides empowerment, increased sense of control, proactive side-effect management...
activities, and decreased fear, anxiety, etc. Asking about suicidal thoughts or feelings does NOT put the thought in a patient’s head or increase risk.

2. Evaluate mental status, including appearance, orientation, cognition, speech, interaction during interview, mood, affect, perceptions, thought processes, thought content, insight, and effectiveness of coping skills. Perform regular depression evaluations (CES-D, other tools, clinical examination). (Also see “Depression” section.)

3. Ensure availability of psychosocial support: family, significant others, local support groups, education, support programs, etc.

4. Improve coping skills.

5. Evaluate need for continued, effective psychopharmacologic agents. Be aware that patients with depression are treated for hepatitis C if their depression is stable and antidepressant medications efficacious. (See “Depression” section.)

6. Determine need for one-to-one supervision.

7. Ask about suicidal ideation, plan, or intent; discontinue interferon-based therapy as appropriate. Discontinue antiviral therapy if suicide attempt is made. Seek appropriate psychiatric intervention.

8. Call 911 and MD with patient reports of suicidal ideation. Maintain contact with patient via phone until help or emergency personnel arrive. Report adverse effects and document for your files.

“SAD PERSONS” SCALE: 10 MAJOR RISK FACTORS OF SUICIDE\(^1,2\)

1. **Sex**: Women make more suicide attempts, but men commit suicide more frequently.
2. **Age**: Patients younger than 19 years and older than 45 years are at greater risk.
3. **Depression**: increases the suicide risk.
4. **Previous attempts**: Suicide rates are higher among people with previous attempts.
5. **Ethanol (alcohol) abuse**: Suicide rates are higher among alcoholics.
6. **Rational thinking loss**: Patients with disorders that impair judgment (eg, psychoses, bipolar disorder) are at risk.
7. **Social support**: Those who lack supportive or meaningful relationships in their lives are at risk.
8. **Organized plan**: The more organized the suicide plan, the greater the risk.
9. **No spouse**: Suicide risk is greater in those who are single, divorced, widowed, or separated.
10. **Sickness**: Suicide rates are higher among people with chronic or debilitating illnesses.

**HOMICIDAL IDEATION**

Be aware of the risk of homicidal ideation. Discontinue interferon-based therapy and refer the patient to a psychiatrist immediately.

**REFERENCES**

XI. Psychologic

DEPRESSION

WARNING (See also “Contraindications” section.)

Severe psychiatric adverse events, including depression and violent behavior (suicides, suicide attempts and suicidal ideations) have occurred during peginterferon/ribavirin or interferon/ribavirin therapy and with interferon monotherapy, both in patients with and without a previous history of psychiatric illness.

Interferon-based therapy should be used with extreme caution in patients with a history of pre-existing psychiatric disorders who report a history of severe depression, and physicians should monitor all patients for evidence of depression. Patients treated with interferon who complain of depression usually describe apathy, cognitive slowing, and fatigue. Some patients report dysphoria at the beginning of treatment and develop flulike symptoms. Others report depression later in treatment, probably because somatic or cognitive symptoms become more pronounced, or more chronic symptoms, such as fatigue, anorexia, myalgia, etc, present themselves. Feelings of helplessness and anhedonia may also be present at this time. Acute onset of dysphoria with suicidal ideation is uncommon, but the clinician must be aware that this may occur. Symptoms consistent with mania may also be seen, and medications used to manage bipolar disease may be beneficial.

Patients who experience moderate depression, including persistent low mood, loss of interest, poor self-image, and/or hopelessness, may benefit from a temporary interferon dose reduction, and should be considered for medical therapy. Patients experiencing severe depression or suicidal ideation should discontinue therapy and be followed closely with appropriate medical management and psychiatric intervention. In general, psychiatric adverse events resolve on cessation of therapy; however, adjunctive psychiatric medications may be required.

PATHOPHYSIOLOGY

While about 6% of the general population is affected by major depression, 35% to 57% of all chronic viral hepatitis patients may have depression upon diagnosis and/or preceding treatment for their disease. Moreover, a number of investigators have reported a correlation between treatment with interferon alfa and depression.

Interferon may cause depression by altering neuroendocrine or neurotransmitter functions or by modulating the expression of cytokines or secondary messengers. A brief summary of mechanisms correlated with interferon-induced depression includes:

- Stimulation of the hypothalamic-pituitary-adrenal axis and adrenocorticotropic hormone oversecretion
- Stimulation of hypothalamic-pituitary-thyroid axis
• Alterations of thyroid function, leading to mood and cognitive side effects
• Effects on the opioid receptor system; behavior changes are often reversed by opioid antagonists
• Neurotoxicity consistent with dopamine antagonism, which increases with long-term interferon use
• Effects on serotonin pathway. Patients treated with interferon have altered serum levels of tryptophan (a serotonin precursor), suggesting that serotonin depletion can contribute to depression
• Involvement of other cytokines or second-messenger system. Interferon alfa induces production of interleukin-1, which has numerous toxic effects, including dysregulation of hypothalamic neuronal function

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<thead>
<tr>
<th>OTHER FACTORS THAT MAY CONTRIBUTE TO DEPRESSION&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Uncontrolled pain</td>
</tr>
<tr>
<td>• Medications:</td>
</tr>
<tr>
<td>- Steroids and oral contraceptives</td>
</tr>
<tr>
<td>- IFN and IL-2</td>
</tr>
<tr>
<td>- Methyldopa (Aldoril&lt;sup&gt;®&lt;/sup&gt;, Aldoclor&lt;sup&gt;®&lt;/sup&gt;, Aldomet&lt;sup&gt;®&lt;/sup&gt;)</td>
</tr>
<tr>
<td>- Reserpine (Diutensin&lt;sup&gt;®&lt;/sup&gt;)</td>
</tr>
<tr>
<td>- Barbiturates, nicotine</td>
</tr>
<tr>
<td>- Propranolol (Inderal&lt;sup&gt;®&lt;/sup&gt;)</td>
</tr>
<tr>
<td>- Some antibiotics</td>
</tr>
<tr>
<td>(eg, amphotericin B [Abelcet&lt;sup&gt;®&lt;/sup&gt;, Ambisome&lt;sup&gt;®&lt;/sup&gt;])</td>
</tr>
<tr>
<td>- Some antineoplastics (eg, vincristine</td>
</tr>
<tr>
<td>[Oncovin&lt;sup&gt;®&lt;/sup&gt;], kinblastine [Velba&lt;sup&gt;®&lt;/sup&gt;],</td>
</tr>
<tr>
<td>procarbazine [Matulane&lt;sup&gt;®&lt;/sup&gt;], and</td>
</tr>
<tr>
<td>asparaginase [Elspar&lt;sup&gt;®&lt;/sup&gt;])</td>
</tr>
<tr>
<td>• Metabolic abnormalities:</td>
</tr>
<tr>
<td>- Hypercalcemia</td>
</tr>
<tr>
<td>- Sodium/potassium imbalance</td>
</tr>
<tr>
<td>- Anemia</td>
</tr>
<tr>
<td>- Vitamin B&lt;sub&gt;12&lt;/sub&gt; or folate deficiency</td>
</tr>
<tr>
<td>- Fever</td>
</tr>
<tr>
<td>• Endocrine abnormalities:</td>
</tr>
<tr>
<td>- Hyper- or hypothyroidism</td>
</tr>
<tr>
<td>- Adrenal insufficiency</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SYMPTOMS ASSOCIATED WITH MAJOR DEPRESSIVE SYNDROME&lt;sup&gt;2,4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Depressed mood</td>
</tr>
<tr>
<td>• Diminished interest or pleasure in activities</td>
</tr>
<tr>
<td>• Significant weight loss/gain or decrease/increase in appetite</td>
</tr>
<tr>
<td>• Insomnia or hypersomnia</td>
</tr>
<tr>
<td>• Psychomotor agitation or retardation</td>
</tr>
<tr>
<td>• Fatigue or loss of energy</td>
</tr>
<tr>
<td>• Feelings of worthlessness or excessive guilt</td>
</tr>
<tr>
<td>• Diminished ability to think or concentrate; indecisiveness</td>
</tr>
<tr>
<td>• Recurrent thoughts of death or suicidal ideation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DEPRESSION CLINICAL SCREENING TOOLS&lt;sup&gt;1,2,4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients should receive a pretreatment assessment for pre-existing depression or risk factors.&lt;sup&gt;5,6&lt;/sup&gt; Use a standardized tool at baseline and for follow-up.</td>
</tr>
<tr>
<td>• CES-D, or Center for Epidemiologic Studies–Depressed Mood Scale (preferred screening tool)</td>
</tr>
<tr>
<td>• BDI, or Beck Depression Inventory (good for patients with physical complaints)</td>
</tr>
<tr>
<td>• ZSDS, or Zung Self-Rating Depression Scale</td>
</tr>
</tbody>
</table>
PREVENTIVE STRATEGIES
1. Treat/stabilize pre-existing depression before starting anti-HCV therapy.
2. Consider prophylactic antidepressant therapy for those deemed high-risk for depression.
4. Provide positive feedback/reinforcement for proactive side-effect management efforts.
5. Help patient plan and establish regular meal times and sleeping patterns, as well as maintain adequate hygiene. The patient may also benefit from the practice of stress reduction, including relaxation periods.
7. Refer patient to a local hepatitis C support group, if available. Identify a “buddy” or significant other as support. Provide support and educational materials.
8. Encourage patient to recognize and “reroute” negative thinking patterns; eg, use a journal to record thoughts and daily activities.
9. Maintain adequate hydration (consumption in fluid ounces = one half body weight in pounds; eg, a 160-lb person should drink 80 fl oz/d). Limit caffeine, alcohol, and processed-food intake.
10. To increase serotonin production, encourage eating foods high in tryptophan, such as turkey, eggs, milk, salmon, soybeans or soy products, brown rice, legumes, and raw fruits and vegetables. Avoid excess sugar.7
11. Limit intake of phenylalanine, which is found in aspartame (Equal™, NutraSweet™), MSG, and nitrates.7
12. Patients infected with HCV with history of injection drug addiction: SC injection may trigger feelings of drug hunger, anxiety, depression, or provoke posttraumatic stress disorder.8 Reassure the patient and arrange for outpatient injection or family member administration.

SAMPLE STUDY—PROPHYLAXIS AGAINST INTERFERON-ALFA–INDUCED DEPRESSION9
Title: Paroxetine for the Prevention of Depression Induced by High-Dose Interferon Alfa
Author: Dominique L. Musselman, MD, et al.
Patients: N = 40; malignant melanoma patients receiving standard high-dose interferon (HDI) for melanoma. Two groups were demographically similar.
Design: Double-blind, placebo-controlled, randomization 1:1.
Schema: Paroxetine (Paxil®) versus placebo QD beginning 2 weeks prior to HDI therapy up to and including week 12 of interferon. Two weeks after
initiation of interferon, the dosage of paroxetine could be increased at the discretion of the study psychiatrist up to four tablets/d (40 mg).

Assessment: Assessment tools included: Hamilton Depression Scale (observer rated), Carroll Depression Scale (self-reported), Hamilton Anxiety Scale (observer rated), and Neurotoxicity Rating Scale (self-reported).

Analysis: Intention-to-treat analysis. Log rank tests and Kaplan-Meier plots were used. Factors included the treatment group (placebo or paroxetine), time (baseline, weeks 4, 8, 12), and the interactions of the two.

Results: Paroxetine significantly reduced the incidence of major depression among patients receiving HDI ($P = .04$ by the log-rank test). Symptoms consistent with a diagnosis of depression occurred in 11% of paroxetine-treated patients and 45% of placebo-treated patients. In addition, the severity of depressive symptoms was also reduced ($P < .001$). Five percent of patients on paroxetine discontinued therapy while 35% of placebo patients discontinued therapy.

Discussion: In contrast to other studies demonstrating the benefit of treatment of depression in these patients, this study demonstrates the value of prophylaxis for patients on HDI. These findings are promising and may have a significant effect on the ability to keep patients on therapy.

Limitations: Small sample size. The study was limited to the first 12 weeks of interferon therapy.

Of Note: Two patients assigned to paroxetine were diagnosed with major depression at screening. Both completed therapy and, by week 12, no longer had signs of depression.

TREATMENT STRATEGIES
1. Assess for past neurologic history, prior brain irradiation, electrolytes, liver function, and thyroid status, especially antithyroid antibodies, vitamin $B_{12}$ status, or other risk factors/contributing agents.
2. Assess severity of depressed state. Immediately and specifically explore suicidal thoughts. Some patients may minimize or deny interferon-induced depression in order to continue treatment.
3. Treat depression early and aggressively. Initiate use of an SSRI or other antidepressant as appropriate (see “Choosing an Antidepressant” below).
4. Reinforce exercise as an effective antidote to bouts of depression (endorphin production).
5. Psychiatric consultation for high CES-D scores. Also see “Indications for Psychiatric Consultation” below. A letter of clearance to resume therapy from the patient’s psychiatrist is recommended.
6. Some physicians report salvaging “profound” depression patients with 20 mg methylphenidate (Concerta™, MetaDate®, Methylin®, Ritalin®) SR PO Q AM or another psychostimulant.$^{10}$
7. Interferon treatment can be continued if depression is stable or effectively managed. Some clinicians believe in the need to reset the cytokine feedback pathway by stopping antiviral therapy, initiating antidepressant therapy, and allowing time for efficacy, followed by reintroduction of antiviral therapy.
8. If unresponsive to antidepressant therapy, the interferon dose should be decreased. If this does not alleviate depression, interferon should be discontinued either temporarily or permanently, per psychiatrist recommendation.

9. If the depression is severe (suicidal or psychotic) or worsening, discontinue interferon and initiate psychiatric evaluation immediately.

10. When speaking with patients who indicate suicidal ideation by phone, notify the patient’s physician, call 911, and/or remain with patient on the phone until help arrives. See “Suicidal Ideation” section.

11. Consider the risk of having patients transition from depression to mania with antidepressants, even after completion of interferon therapy.¹

**DEPRESSION THERAPIES**

- **SSRIs:** block serotonin receptors on nerve cells in the brain. SSRIs are usually the first antidepressant prescribed when patients initiate therapy.

- **TCAs:** block the norepinephrine and serotonin receptors on nerve cells in the brain. They are associated with more side effects than the SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), and other atypical agents.

- **SNRIs:** affect serotonin and norepinephrine receptors.

- **Atypical:** affect dopamine and norepinephrine (buproprion [Wellbutrin®]) or norepinephrine alone (maprotiline [Ludiomil®]).

- **MAOIs:** block the breakdown of serotonin, epinephrine, and norepinephrine. Use is uncommon in clinical practice because of life-threatening drug and dietary interactions.

- **Opioid antagonists:** naltrexone (ReVia®) has been studied with varying efficacy in resolution of neurotoxic symptoms.

- **Psychostimulants:** indirect dopamine agonist action.

- **Hormone replacement therapy:** adjunct to antidepressant treatment in some postmenopausal women. Should be carefully discussed with patient because it can decrease effect of SSRIs and carries increased risks of other conditions.

- **Electroconvulsive therapy:** indicated for severe pharmacologic/psychotherapy-resistant depression; controversial.
## ANTIDEPRESSANT AGENTS

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Average Daily Dose</th>
<th>Sedation</th>
<th>Cardiac Cond. Effects</th>
<th>Anticholin. Effects</th>
<th>Orthostatic Hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>Celexa®</td>
<td>20–40 mg PO</td>
<td>3</td>
<td>±</td>
<td>0</td>
<td>±</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Lexapro®</td>
<td>10–20 mg</td>
<td>3</td>
<td>±</td>
<td>0</td>
<td>±</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Desyrel®</td>
<td>150–400 mg PO</td>
<td>5</td>
<td>±</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Prozac®</td>
<td>20–40 mg PO</td>
<td>±</td>
<td>±</td>
<td>0</td>
<td>±</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Luvox®</td>
<td>50–200 mg PO</td>
<td>±</td>
<td>±</td>
<td>0</td>
<td>±</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Paxil®</td>
<td>20–40 mg PO</td>
<td>1</td>
<td>±</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Zoloft®</td>
<td>75–150 mg PO</td>
<td>±</td>
<td>±</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>TCAs</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Amitriptyline</td>
<td>Elavil®</td>
<td>150–200 mg PO</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>Asendin®</td>
<td>75–150 mg PO</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Anafranil®</td>
<td>150–200 mg PO</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>2</td>
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<tr>
<td>Desipramine</td>
<td>Norpramin®</td>
<td>50–300 mg PO</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Sinequan®</td>
<td>150–200 mg PO</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Imipramine</td>
<td>Tofranil®</td>
<td>150–200 mg PO</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>5</td>
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<tr>
<td>Nortriptyline</td>
<td>Pamelor®</td>
<td>75–100 mg PO</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Protriptyline</td>
<td>Vivactil®</td>
<td>15–40 mg PO</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Trimipramine</td>
<td>Surmontil®</td>
<td>150–200 mg PO</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>3</td>
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<tr>
<td><strong>SNRIs</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mirtazapine</td>
<td>Remeron®</td>
<td>15–45 mg PO</td>
<td>3</td>
<td>±</td>
<td>±</td>
<td>±</td>
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<tr>
<td>Nefazodone</td>
<td>Serzone®</td>
<td>300–600 mg PO</td>
<td>2</td>
<td>±</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Effexor® XR</td>
<td>75–375 mg PO</td>
<td>1</td>
<td>±</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Atypical Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>Wellbutrin®</td>
<td>300–400 mg PO</td>
<td>0</td>
<td>0</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Bupropion SR</td>
<td>Wellbutrin® SR</td>
<td>300–400 mg PO</td>
<td>0</td>
<td>0</td>
<td>±</td>
<td>±</td>
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<tr>
<td>Maprotiline</td>
<td>Ludiomil®</td>
<td>75–150 mg PO</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>4</td>
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<tr>
<td><strong>Psychostimulants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d-amphetamine</td>
<td>Dexedrine®</td>
<td>5–60 mg PO</td>
<td>0</td>
<td>2</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Concerta™, MetaDate®, Methylin®, Ritalin®</td>
<td>20–30 mg PO</td>
<td>0</td>
<td>2</td>
<td>±</td>
<td>±</td>
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<tr>
<td>Pemoline</td>
<td>Cylert®</td>
<td>56.25–75 mg PO</td>
<td>0</td>
<td>2</td>
<td>±</td>
<td>±</td>
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<tr>
<td><strong>Opioid Antagonist</strong></td>
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<tr>
<td>Naltrexone</td>
<td>ReVia®</td>
<td>50 mg PO</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>±</td>
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<tr>
<td><strong>MAOIs – Do not use</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Phenelzine</td>
<td>Nardil®</td>
<td>45–60 mg PO</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>5</td>
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<tr>
<td>Tranylcypromine</td>
<td>Parnate®</td>
<td>30–50 mg PO</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

Key: 0, none; ±, equivocal, sporadic; 1, minimal; 2, mild; 3, moderate; 4, strong; 5, severe.
**CHOOSING AN ANTIDEPRESSANT**

<table>
<thead>
<tr>
<th>Distressing Symptom</th>
<th>SSRI</th>
<th>TCA</th>
<th>Psychostimulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>+/-</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal upset</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Opioid SEs</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>+/–</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Akathisia</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Cognitive/behavioral slowing</td>
<td>+/-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>+/-</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Stomatitis/dry mouth</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

**Co-morbid Condition**

<table>
<thead>
<tr>
<th>Co-morbid Condition</th>
<th>SSRI</th>
<th>TCA</th>
<th>Psychostimulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>H/O CV disease</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H/O CNS dx/seizure</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>+</td>
<td>+</td>
<td></td>
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</tbody>
</table>

**Drug Interactions**

<table>
<thead>
<tr>
<th>Drug Interactions</th>
<th>SSRI</th>
<th>TCA</th>
<th>Psychostimulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine (Tagamet®)</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Digoxin (Digitek®, Lanoxicaps®, Lanoxin®)</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Phenytoin (Dilantin®)</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>MAOIs</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Warfarin (Coumadin®)</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

**Time to Therapeutic Effect**

- 3–6 weeks
- 3–6 weeks
- 1–4 days

Key: (–) Use of this medication could worsen the symptom/co-morbid disease

(+ Use of this medication could relieve the symptom/co-morbid disease

Notes:

1. Fluoxetine (Prozac®) is particularly activating, although all SSRIs have the paradoxical effect of hypersomnia. Bupropion (Wellbutrin®) is also somewhat activating.
2. Sedating antidepressants are useful for insomnia, either alone or in addition to another antidepressant. Trazodone (Desyrel®) is often used as a sleep aid in combination with another antidepressant.
3. Antidepressants are useful in treating neuropathic pain. The most studied are TCAs, particularly amitriptyline (Elavil®). Psychostimulants have been used as adjuvant pain medications in conjunction with the opioids.
4. TCAs are least likely to aggravate an existing condition of akathisia, if an antidepressant is needed. SSRIs, although usually the first-line of therapy, can cause akathitic reactions. Benzodiazepines and propranolol (Inderal®) are first-line treatments for akathisia.
5. Sedating antidepressants are most useful for anxious/agitated patients. These include trazodone (Desyrel®), the TCAs, and nefazodone (Serzone®).

6. In general, TCAs and psychostimulants can cause arrhythmias. SSRIs, bupropion (Wellbutrin®), venlafaxine (Effexor®), and nefazodone (Serzone®) are generally less likely to cause cardiovascular problems. Electrocardiograms should be obtained before starting TCA medications, and a cardiologist should be consulted if there is concern of cardiac compromise.

7. Shorter-acting SSRIs (sertraline [Zoloft®] and paroxetine [Paxil®]) are less problematic in those with hepatic dysfunction. Sertraline (Zoloft®), citalopram (Celexa™), and escitalopram (Lexapro™) reportedly have less effect on hepatic cytochrome P-450 enzyme activity; however, the effect of specific drug-to-drug interactions on specific liver enzyme systems for all antidepressants should be considered.

8. Most antidepressant use should take into account renal dysfunction.

9. TCAs are contraindicated in closed-angle glaucoma. Ophthalmologists should be consulted if there is any question of glaucoma.

10. Monoamine oxidase inhibitors (MAOIs) should not be used with meperidine (Demerol®), SSRIs, or TCAs (allow recommended wash-out period).

11. TCAs and MAOIs have a high risk of lethality in overdose, the risk of which is increased if drug interactions occur or restricted foods are consumed with MAOIs. (See also “Serotonin Syndrome” below.) Other classes of agents may be preferable in patients taking multiple medications.

12. Nefazodone (Serzone®) should be avoided in patients with HCV infection since in rare cases it can cause fatal liver failure.

SEROTONIN SYNDROME\textsuperscript{12}

- Serotonin syndrome most often occurs in patients taking two or more medications that increase CNS serotonin levels by different mechanisms.
- Causative agents associated with serotonin syndrome include L-tryptophan, MAOIs, and SSRIs. Most cases were reported when MAOIs were used in conjunction with meperidine (Demerol®), tryptophan, dextromethorphan, a TCA, or an SSRI. Always monitor patients taking medications known to cause serotonin syndrome.
- The most common symptoms of serotonin syndrome are mental status changes. Other symptoms include motor abnormalities, cardiovascular changes, gastrointestinal problems, and miscellaneous changes, such as diaphoresis and fever.
- If a patient has serotonin syndrome, the suspected agent(s) should be discontinued. Take supportive measures to reduce hypertension, tachycardia, hyperthermia, and respiratory distress, if these symptoms are present.
- Benzodiazepines are often used to treat serotonin syndrome. Antiserotonergic agents like cyproheptadine (Periactin®), methysergide (Sansert®), and propranolol (Inderal®) have been used in severe cases.
DELAYED PSYCHIATRIC EFFECTS: POSTTHERAPY
Depression, anxiety, mood swings, personality changes, and emotional distance from others may be experienced after treatment concludes, although it is unlikely that these changes are related to interferon. More likely, an underlying or pre-existing condition may elicit these experiences, such as subclinical or masked depression or other psychiatric disorders that come to the surface with therapy or the completion of therapy. Clinicians should consider the psychologic and emotional issues involved in coping with chronic illness and therapy when patients exhibit these tendencies. In addition, the patient’s history, including alcohol or drug abuse, should be considered. The patient’s current social situation and/or denial or suppression of past problems may also be factors in posttherapy experiences of depression, anxiety, etc.

Delayed psychiatric effects posttherapy are sometimes of a physical or physiologic etiology. Consider and evaluate for active substance use; unresolved changes or inflammation of the hypothalamus; organic or electrolyte imbalance; inadequate nutrition or nutritional deficit; worsening chemical imbalance in brain (eg, serotonin production) and undetected cerebral bleed, which may occur during the thrombocytopenic period.

INDICATIONS FOR PSYCHIATRIC CONSULTATION
• The physician is uncomfortable treating depression (ie, prominent suicidal tendencies present).
• The patient has a complicated psychiatric history.
• Depressive symptoms treated by the physician are resistant to pharmacologic intervention after 2 to 4 weeks.
• Depressive symptoms worsen rather than improve.
• Side effects of pharmacologic interventions prohibit therapeutic dosing of the antidepressant.
• Symptoms are interfering with the patient’s ability to be cooperative with medical treatment.

REFERENCES
IRRITABILITY/LABILE AFFECT

PATHOPHYSIOLOGY
Use of peginterferon/ribavirin therapy has been associated with personality changes, such as irritability and labile affect. This pattern of personality changes is suggestive of frontal-subcortical dysfunction. The brain dysfunction may be a clinical manifestation of depression. Interferon causes depression by altering neuroendocrine or neurotransmitter functions or by modulating the expression of cytokines. One of several potential mechanisms is altered serum levels of tryptophan (a serotonin precursor), suggesting that serotonin depletion might be responsible for the reported interferon-induced irritability and labile affect.

PREVENTIVE STRATEGIES
1. Assess patients prior to and monthly during treatment for depression utilizing a standardized tool (eg, CES-D).
2. Consider psychiatric evaluation prior to initiating antiviral therapy in patients with a current episode of depression or a history of depression, history of psychiatric hospitalization, history of substance abuse or chemical dependence, family history of depression or suicide attempts, history of posttraumatic stress disorder, or history of violent or abusive behavior.
3. Follow closely patients with concurrent or previous problems with substance or alcohol abuse. Look for relapse of substance abuse or signs of depression.
4. Be aware that some patients may minimize or deny symptoms of irritability and labile affect because of embarrassment or fear of dose reduction or treatment cessation.
5. A high score on the CES-D self-assessment (particularly if the score was low or normal prior to treatment, or if the score is increasing) strongly suggests the need for a psychiatric evaluation.

TREATMENT STRATEGIES
Patients should be encouraged to:
1. Engage in mild to moderate aerobic and/or anaerobic exercise, as a mechanism to channel anger and irritability.
2. Try meditation/relaxation techniques (yoga, biofeedback, imagery, massage).
3. Maintain good sleep habits (consistent times for sleeping; avoid caffeine; consume tryptophan-containing foods, such as warm milk, turkey, and salmon).
4. Avoid overstimulating environments (crowds, heavy traffic, loud noise).
5. Ensure adequate hydration (consumption in fluid ounces = one half body weight in pounds; eg, a 160-lb person should consume 80 fl oz/d).
6. Enjoy small pleasures (movies, music, friends, pets, laughter, positive reminiscence).
7. Recognize and report warning signs (early detection and intervention are crucial).
Providers should consider:

1. Educating and supporting families to cope with unpredictable, difficult personality changes and mood swings
2. Citalopram (Celexa®), escitalopram (Lexapro®), sertraline (Zoloft®), venlafaxine (Effexor®), and mirtazapine (Remeron®): may offer the added advantage of fewer potential interactions with other medications
3. Nefazodone (Serzone®), bupropion (Wellbutrin®), and venlafaxine (Effexor®): first-line antidepressants that have a sedating effect, reducing irritability and combative behavior
4. Trazodone (Desyrel®): useful adjunct for sleep disturbance and is well tolerated
5. Gabapentin (Neurontin®): may prove useful for mild to moderate irritability or impulsivity in the absence of depressive symptoms. Gabapentin has few significant drug interactions and is not metabolized by the liver.
6. Augmenting strategies combining two antidepressants, dose reductions, or drug holidays: may be beneficial in controlling labile affect and irritability for patients resistant to the above single-drug interventions
7. Referring for psychiatric consultation and/or family counseling
8. Discontinuing treatment if all other alternatives fail

REFERENCES

PATHOPHYSIOLOGY
Anxiety and panic disorder associated with peginterferon/ribavirin may stem from a malfunction of the neurobiologic substances norepinephrine, serotonin, and dopamine, causing excitation of nerve impulses. These neurotransmitters regulate mood, movement, and blood pressure. Gamma-aminobutyric acid inhibits neurotransmission in the brain and is closely associated with benzodiazepine receptors. Theories regarding the cause of the malfunction include chemical excess or deficit, or oversensitivity to chemical cascade.

ANXIETY DISORDER TYPES
Approximately 19.1 million American adults aged 18 to 54 years suffer from anxiety, and approximately 2.4 million suffer from panic disorder. Anxiety appears to affect twice as many women as men. However, psychologists believe that men are less likely to report or even acknowledge having an anxiety disorder, so the disparity between the sexes may not be so wide. Anxiety can be the result of physical or psychological factors, and is categorized as either acute or chronic.

ACUTE: Manifests as episodes commonly called panic attacks. A panic attack is an instance in which the body’s natural “fight or flight” reaction occurs at the wrong time. This is a complex, involuntary physiologic response, with increased production and release of hormones, especially adrenaline, and norepinephrine. These attacks are abrupt and intense, can occur at any time, and can last from a few seconds up to half an hour, with the patient incorrectly believing they are having a myocardial infarction or stroke. The patient often reports being overwhelmed by a sense of impending disaster or death, hence they are unable to think clearly. Other side effects at this time may include dyspnea; a smothering, claustrophobic sensation; tachycardia; palpitations; chest pain; dizziness; hot flashes and/or chills; trembling; numbness or tingling of the extremities; diaphoresis; nausea; abdominal pain; diarrhea; a feeling of unreality; and a distorted perception of the passage of time. The attacks themselves are unpredictable; some experience one every few weeks, while others report several per day. Many fear having a panic attack while alone or in public, which can lead to social isolation and diminished quality of life.

CHRONIC: Chronic anxiety is a milder, more generalized form of the disorder. In this instance, patients suffer a vague sense of anxiety most of the time, although the intensity of the feeling does not reach the level of those experiencing a panic attack. Chronic unease, especially in the presence of other people, combined with a tendency to startle easily, is often seen in this type of anxiety. Headaches and chronic fatigue are common complaints among people with this form of anxiety. Although chronic anxiety can begin at any age, onset usually occurs in a person’s 20s or 30s, and appears to run in families. Mitral valve prolapse patients have an increased incidence of this form of anxiety.
Finally, people with chronic anxiety disorder exacerbation often report being under unusual stress and may suffer an occasional panic attack.

Eventually, the disorder can have cumulative effects, such as generalized aches and pains, muscular twitching and stiffness, depression, insomnia, nightmares, early waking, decreased libido, and abnormal feelings of tension with an accompanying inability to relax. Women often report changes in their menstrual cycles and increased premenstrual symptoms. Other sequelae of incorrectly managed anxiety and panic include alcohol and drug abuse, sexual dysfunction, increased physical illness, depression, and suicidal ideation and risk. In individuals with depression, symptoms of anxiety may develop as they begin to have increasing difficulty initiating or completing even the simplest activities of daily living.

**PANIC ATTACK “TRIGGERS”**

<table>
<thead>
<tr>
<th>• Stress; conscious or unconscious</th>
<th>• Certain emotions</th>
<th>• Chronic illness</th>
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<tbody>
<tr>
<td>• Certain medications; illegal drugs</td>
<td>• Food allergies/sensitivities</td>
<td>• Hypoglycemia</td>
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<td>• Caffeine-based products and other stimulants</td>
<td>• Crowded environments</td>
<td>• Mitral valve prolapse</td>
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<tr>
<td>• Poorly controlled pain</td>
<td>• Hypoxia, PE, sepsis, CHF</td>
<td>• Delirium, bleeding</td>
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<td>• Unfamiliar surroundings/situations</td>
<td>• Hormone-secreting tumors</td>
<td>• No apparent cause</td>
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<tr>
<td>• Withdrawal: ETOH, narcotic/analgesics, sedative/hypnotics</td>
<td>• Hereditary link</td>
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**PREVENTIVE STRATEGIES**

Providers should:
1. Educate the patient regarding disease, treatment, subcutaneous injection, side effects, and symptom management to allay concerns and anxiety level.
2. Provide contact numbers—office nurse, local hepatitis C support group, and “buddy,” if available.
3. Perform pretreatment assessment for current/past history of anxiety or panic disorder, and/or depression. Consider prescription antidepressants prior to or concomitantly with therapy to prevent progression of the disorder. See “Depression” section for further information.
4. Discuss expectations of therapy including side effects and management, and make specific plans for behavior modification in individuals with prior psychiatric history. This may prevent onset of symptoms or prompt reporting of the development of new symptoms.
5. Involve family members in education and treatment planning to minimize “sick role.”

Patients should be advised to:
1. Reduce or eliminate alcohol, caffeine, nicotine, and other stimulants, and to eat smaller, more frequent meals.
2. Keep a food diary to detect correlation between attacks and foods consumed.
3. Consider stress management/biofeedback interventions, including relaxation exercises and tapes, guided imagery, and meditation. Talking with family or friends can diffuse anxiety.
4. Exercise: walking, swimming, yoga, aerobics, etc. Conversely, assess for and ensure adequate sleep and rest.

**TREATMENT STRATEGIES**

*Nonpharmacologic Management Should Be Attempted Initially*

1. Re-educate patient as necessary regarding hepatitis C, treatment, potential side effects, symptom management, and stimulants and other causes or triggers of panic attacks.
2. Instruct patient how to manage panic attacks: Inhale to a count of four, exhale slowly to a count of four, do nothing to a count of four; repeat until the attack subsides. Patient should remind self that attacks are time-limited and will pass.
3. Obtain psychiatric consultation.
4. Advise the patient to create relaxation times throughout the day and evening, exercise, and limit daily tasks and pressure situations.
5. Be aware that graded exposure may be required to treat panic attacks.
6. Consider withholding interferon-based therapy until the patient is stable, or discontinue per psychiatrist’s recommendation.

*Pharmacologic Interventions*

1. SSRIs: selectively inhibit serotonin uptake and have limited effect on other neurotransmitters. This class of drugs is considered first-line. Initial starting dose is generally lower than that used for depression to minimize exacerbation of anxiety. Dose adjustments are easily tolerated. Generally take several weeks to achieve benefit. Side effects may include nausea, diarrhea, loose stools (sertraline \[Zoloft®\]), constipation (paroxetine \[Paxil®\]), insomnia, sedation (minimal and time-limited), headache, dizziness, fatigue, tremor, nervousness and anxiety, sexual dysfunction (30% of patients, men > women), decreased libido, premature ejaculation, and anorgasmia. Advantages include low level of toxicity and decreased lethal effect in overdose.
2. TCAs: various ratios of adrenergic/serotonergic reuptake inhibition. Proven effective. Side effects may include dry mouth, blurred vision, increased intraocular pressure, constipation, urinary retention, weight gain, sexual dysfunction, decreased seizure threshold, and increased toxicity in the elderly and those with suicidal ideation. TCAs generally take 4 to 6 weeks to provide relief of symptoms and can frequently be initiated at the same time as the benzodiazepine with planned taper of the benzodiazepine between 4 and 6 weeks.
3. Dual mechanism antidepressants: block serotonin and norepinephrine. Side effects may include orthostatic hypotension, syncope, tachycardia, arrhythmias, nausea, anorexia, sedation, and confusion. Mirtazapine (Remeron®) may cause agranulocytosis or neutropenia.
4. Midazolam (Versed®) or hydroxyzine (Vistaril®, Atarax®) may be utilized by psychiatrist for acute, severe cases of anxiety or panic on emergency referral.
5. Benzodiazepines: may increase inhibiting effect of gamma-aminobutyric acid and other inhibitory transmitters by binding to receptors in the CNS. Side effects may include drowsiness, dizziness, hypotension, confusion, hypersensitivity, HA, stupor, nausea and vomiting, blood dyscrasias, and jaundice (with hepatic dysfunction); usually beneficial for a limited time period (1 month or less), can be addictive, and withdrawal can lead to seizures and death if not managed carefully. These drugs have high potential for both abuse and resale.

### REFERENCES

Suicidal ideation (thoughts about suicide) is a precursor to all other deeds leading to suicide. Suicidal ideation itself is not considered a serious risk factor for completion of suicide, but is a sign of depression and something that should be taken seriously and monitored closely. The risk of suicide attempt increases when suicidal ideation is followed by suicide plans and means.

INTERFERON AND SUICIDAL BEHAVIOR
Depression, suicidal ideation, and suicidal behavior, including suicide attempts and completed suicides, have been reported in association with treatment with alfa interferons. Patients with a pre-existing psychiatric condition, especially depression, or a history of severe psychiatric disorder, need careful evaluation of risks and benefits and diligent monitoring if interferon treatment is indicated. Discontinue interferon therapy in any patient developing severe depression or other psychiatric disorders during treatment.

RIBAVIRIN AND SUICIDAL BEHAVIOR
Severe psychiatric adverse effects, including depression and suicidal behavior (suicidal ideation, suicidal attempts, and suicides) have occurred during both alfa interferon monotherapy, and ribavirin combination therapy, both in patients with and without a previous psychiatric illness. Use with extreme caution in patients with a history of pre-existing psychiatric disorders who report a history of severe depression, and physicians should monitor all patients for evidence of depression. In severe cases, therapy should be stopped and psychiatric intervention sought. In general, adverse effects resolve on cessation of therapy; however, adjunctive psychiatric medications may be required.

DEFINING CHARACTERISTICS/RISK FACTORS

- Presence of suicide plan
- Increasing anxiety levels
- Depression and hopelessness
- Delirium
- Pre-existing psychopathology
- Prior suicide attempts
- Exhaustion
- Fatigue
- Rage/panic states
- Self-destructive behavior
- Active aggressive suicidal acts
- Drug or alcohol abuse

ASSESSMENT AND MANAGEMENT
1. Assess the patient’s understanding of the illness, as well as any present symptoms and their meaning to the patient. Educating patient regarding treatment provides empowerment, increased sense of control, proactive side-effect management
activities, and decreased fear, anxiety, etc. Asking about suicidal thoughts or feelings does NOT put the thought in a patient’s head or increase risk.

2. Evaluate mental status, including appearance, orientation, cognition, speech, interaction during interview, mood, affect, perceptions, thought processes, thought content, insight, and effectiveness of coping skills. Perform regular depression evaluations (CES-D, other tools, clinical examination). (Also see “Depression” section.)

3. Ensure availability of psychosocial support: family, significant others, local support groups, education, support programs, etc.

4. Improve coping skills.

5. Evaluate need for continued, effective psychopharmacologic agents. Be aware that patients with depression are treated for hepatitis C if their depression is stable and antidepressant medications efficacious. (See “Depression” section.)

6. Determine need for one-to-one supervision.

7. Ask about suicidal ideation, plan, or intent; discontinue interferon-based therapy as appropriate. Discontinue antiviral therapy if suicide attempt is made. Seek appropriate psychiatric intervention.

8. Call 911 and MD with patient reports of suicidal ideation. Maintain contact with patient via phone until help or emergency personnel arrive. Report adverse effects and document for your files.

“SAD PERSONS” SCALE: 10 MAJOR RISK FACTORS OF SUICIDE

1. **Sex:** Women make more suicide attempts, but men commit suicide more frequently.
2. **Age:** Patients younger than 19 years and older than 45 years are at greater risk.
3. **Depression:** increases the suicide risk.
4. **Previous attempts:** Suicide rates are higher among people with previous attempts.
5. **Ethanol (alcohol) abuse:** Suicide rates are higher among alcoholics.
6. **Rational thinking loss:** Patients with disorders that impair judgment (eg, psychoses, bipolar disorder) are at risk.
7. **Social support:** Those who lack supportive or meaningful relationships in their lives are at risk.
8. **Organized plan:** The more organized the suicide plan, the greater the risk.
9. **No spouse:** Suicide risk is greater in those who are single, divorced, widowed, or separated.
10. **Sickness:** Suicide rates are higher among people with chronic or debilitating illnesses.

**HOMICIDAL IDEATION**

Be aware of the risk of homicidal ideation. Discontinue interferon-based therapy and refer the patient to a psychiatrist immediately.

**REFERENCES**

WARNING:
Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, and sarcoidosis, some resulting in respiratory failure and/or patient deaths, may be induced or aggravated by peginterferon or interferon alfa therapy. Recurrence of respiratory failure has been observed with interferon rechallenge. The etiology has yet to be established.
Cough of unexplained etiology can occur in patients receiving interferon or peginterferon alone or in combination with ribavirin. Nonproductive cough is sometimes seen in association with throat irritation accompanying postnasal drip. The cough may be worse at night or may become a nervous cough.

**ASSESSMENT**
Providers should perform physical examination, WBC, chest x-ray, etc, as needed to rule out other possible etiologies before diagnosing cough secondary to peginterferon and/or ribavirin.

**MANAGEMENT STRATEGIES**
Patients should be instructed to:
1. Maintain adequate hydration (consumption in fluid ounces = one half body weight in pounds; eg, a 160-lb person should drink 80 fl oz/d).
2. Humidify air.
3. Use two pillows for sleep.
4. Use a saline nebulizer.
5. Suck on cough drops/hard candy/lozenges.
6. Try Cepacol® spray.
7. Take antihistamines at bedtime.
8. Try expectorants, especially during the day.

Providers should:
1. Follow absolute ANC and CBC with differential.
2. Perform chest x-ray as needed. If x-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient should be closely monitored, and, if appropriate, treatment should be discontinued. Patients who resume interferon treatment should be closely monitored.
3. Administer flu/pneumonia vaccinations if not contraindicated. Administer other vaccinations (eg, hepatitis A and B vaccinations if susceptible) in accordance with Centers for Disease Control and Prevention (CDC) recommendations.
4. Recommend pharmacologic therapies. Consider prescription therapies if over-the-counter agents are not helping.
   a. Dextromethorphan hydrobromide – try before prescribing narcotics
   b. Guaifenesin (Organidin®) with or without codeine; 30 cc as directed around the clock for 2 to 3 days. Guaifenesin can be prescribed in capsule and extended-release forms at 600 mg, 800 mg, 1200 mg

**REFERENCE**
Sinusitis is caused by inflammation of the lining membrane of any sinus, especially one of the paranasal sinuses.\(^1\) It may be acute, caused by the extension of inflammation from the nasal mucosa, or chronic, as a sequela of the acute inflammation, because of incomplete resolution of infection or recurrent acute complications. Symptoms may include postnasal drip, pain, throat irritation, and/or cough. Sinusitis is more common in coinfected patients.

**Treatment Strategies**
1. Adequate hydration (consumption in fluid ounces = one half body weight in pounds; eg, a 160-lb person should drink 80 fl oz/d)
2. Humidifier\(^1\)
3. Oral care with saline gargle\(^1\)
4. Topical decongestant spray\(^1\)
5. Cough drops/hard candy/lozenges
6. Antihistamines
7. Nasal saline spray
8. Antibiotics, if bacterial etiology

**REFERENCE**
Dyspnea, defined as difficult or labored breathing,¹ may be seen as part of pulmonary edema or as part of pulmonary symptoms of unexplained etiology in patients receiving peginterferon/ribavirin. Shortness of breath may occur only on exertion or, in some patients, may be present even at rest. In most cases, dyspnea is secondary to ribavirin-induced anemia.

Pulmonary symptoms, that is, pulmonary infiltrates, pneumonitis, and pneumonia, including fatality, have been observed in patients treated with interferon. The etiology of these pulmonary findings has not been established. Acute serious hypersensitivity reactions (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely in patients on interferon.

It is important to rule out the following:
- Hypersensitivity (wheezing, bronchospasm²) to interferon or other medications patient may be taking
- Pneumonia (infection) or pulmonary infiltrates
- Anemia
- Allergies
- Pulmonary embolism

**MANAGEMENT STRATEGIES**
1. Measure CBC with differential, Hgb, and ANC, and perform chest x-ray, STAT.
   a. If x-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient should be closely monitored, and, if appropriate, treatment should be discontinued. Patients who resume interferon treatment should be closely monitored.
   b. Treat anemia, if present, with epoetin and/or dose reduction (see “Hematologic” section).
2. Prescribe inhalers (eg, albuterol [Proventil®, Ventolin®]), which may relieve dyspnea even in the absence of wheezing.
3. Advise patients to modify ADL and conserve energy. Recommend that patients avoid smoke, sudden inspiration of cold air, allergens, and dust.
4. Hospitalize and administer oxygen as needed.
5. Discontinue interferon immediately if hypersensitivity occurs. Initiate appropriate medical therapy.

**REFERENCES**
HCV infection is common among patients with chronic renal failure. Such patients typically have profound proteinuria, and HCV infection can cause nephrotic syndrome. Although rare, renal lesions, interstitial nephritis, nephrotic syndrome, and acute renal failure have been described in association with interferon therapy for chronic hepatitis C.

The presence of cryoglobulinemia is a characteristic finding of HCV-associated renal disease, with about two-thirds of patients having type II or type III cryoglobulinemia. Patients with cryoglobulinemia often complain of weakness, arthralgia, and purpura. They may also develop Raynaud’s syndrome or leg ulcers. Interferon therapy has been used successfully to treat HCV-associated glomerulonephritis, reducing urinary protein and serum protein, although long-term therapy is often necessary.

**CREATININE CLEARANCE TESTING**
Creatinine is the by-product of muscle energy metabolism. Kidney disorders prevent maximum excretion of creatinine. Creatinine clearance (usually measured in milliliters per minute) is used to estimate the glomerular filtration rate (GFR). The GFR in turn is the standard by which kidney function is assessed. The creatinine clearance test compares levels of creatinine in urine and blood, usually based on a 24-hour urine sample and a blood sample drawn at the end of the 24-hour period.

**In Renal Insufficiency**
- Creatinine clearance is decreased with impaired kidney function, intrinsic renal disease, glomerulonephritis, pyelonephritis, nephrotic syndrome, acute tubular dysfunction, amyloidosis, and hepatic failure.
- Decreased urine creatinine levels are found in hyperthyroidism, anemia, polymyositis, and neurogenic atrophy.
- Increased urine creatinine levels are found in hypothyroidism and early DM.

**Ribavirin in Renal Insufficiency**
Ribavirin mean AUC was threefold greater in patients with creatinine clearance values between 10 and 30 mL/min versus controls with values >90 mL/min. This difference is probably related to the reduction in clearance. Ribavirin should be used with caution in patients with a creatinine clearance <50 mL/min. Ribavirin is not recommended for patients with severe renal impairment or who are receiving hemodialysis. Ribavirin is not removed by hemodialysis.

**Interferon in Renal Insufficiency**
Mild renal effects (ie, asymptomatic and mild proteinuria) have been reported during the first few days of interferon alfa therapy, and may cause fever. Nephrotic syndrome and severe injury are rare.
Interferon is reasonably tolerated in hemodialyzed patients. Small controlled trials have examined the efficacy of interferon therapy for patients with chronic HCV infection who are receiving hemodialysis. Sustained viral response rates range from 20% to 100% with interferon alfa-2b (Intron® A) 3 to 5 million IU SQ TIW for 6 months.

Clearance of interferon is approximately twice as slow in patients on dialysis as it is in patients who are nonuremic. It is possible that reduced renal clearance of interferon results in a higher and more sustained concentration; many patients have experienced severe side effects. Many patients on dialysis have underlying co-morbid conditions such as hypertension, cardiac disease, diabetes, and anemia.

PEGINTERFERON IN RENAL INSUFFICIENCY
Patients with impaired renal function should be closely monitored for signs and symptoms of interferon toxicity and doses should be reduced accordingly. Peginterferon should be used with caution in patients with creatinine clearance <50 mL/min. Chronic renal failure patients on dialysis are difficult to treat. Standard interferons are removed with dialysis, and peginterferon alfa-2b (Peg-Intron®) is partially removed during dialysis. Peginterferon administration should be timed to occur immediately following dialysis treatment to avoid being excessively dialyzed. In patients receiving TIW dialysis, peginterferon should be administered the last day of dialysis for the week. The larger 40-kd peginterferon alfa-2a (Pegasys®) is not removed with dialysis, but dose reduction is recommended.

OTHER MANAGEMENT STRATEGIES/CLINICAL CONSIDERATIONS
• Water-soluble vitamins are depleted with dialysis, and replacement is required. Minerals, such as zinc and magnesium, are also lost. Zinc replacement increases taste sensation and appetite.
• Renal transplant recipients have had responses to interferon therapy with sustained viral clearance. Interferon therapy can be problematic for renal transplant patients because it upregulates the cell surface presentation of class II histocompatibility antigens and therefore may promote allograft rejection. There have been clinical reports of allograft rejection, acute renal failure, and graft loss in conjunction with interferon therapy.

REFERENCES
XIII. Sexual and Reproductive

BREASTFEEDING

According to the CDC, there is no evidence that hepatitis C is transmitted during breastfeeding; therefore, breastfeeding is not contraindicated on the basis of HCV infection alone. However, the CDC recommends advising HCV positive mothers to consider abstaining from breastfeeding if their nipples are cracked or bleeding.

The safety of anti-HCV treatment during breastfeeding has not been clearly determined. In most cases, healthcare providers delay anti-HCV treatment until after weaning has occurred, especially in light of the numerous other stressors that patients confront in the early postpartum period that may affect treatment adherence and outcome.

INTERFERON

It is not known whether interferon is excreted in human milk. However, studies in mice have shown that mouse interferons are excreted into milk. Because of the potential for serious adverse reactions from the drug in nursing infants, a decision should be made whether to discontinue nursing or to discontinue interferon therapy, taking into account the importance of the drug to the mother.

PEGINTERFERONS

Package inserts give no specifics on breastfeeding or nursing mothers, but peginterferons are assumed to have the same potential for adverse reactions as nonpegylated interferon therapy.

RIBAVIRIN

It is not known whether ribavirin is excreted in human milk. Because of the potential for serious adverse reactions from the drug in nursing infants, a decision should be made whether to discontinue nursing or to delay or discontinue ribavirin therapy.
Sexual and Reproductive

MENSTRUAL IRREGULARITIES

Menstrual irregularities and other gynecologic symptoms reported in women treated with interferon-based therapy include amenorrhea, dysmenorrhea, leukorrhea, menorrhagia, pelvic pain, uterine bleeding, and vaginal dryness. Menstrual cycle abnormalities have been observed in studies of nonhuman primates. Decreases in serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon.

MANAGEMENT STRATEGIES

1. Rule out other organic problems or medications that can affect menstruation (eg, oral contraceptives).
2. Perform CBC and check for anemia.
3. Reassure patient that irregularities are a common side effect of treatment.
4. Perform pregnancy test if menstrual irregularities occur.
5. Remind patients to use two effective forms of contraception during treatment.
6. Perform pregnancy testing monthly.
7. If abnormalities persist, refer to gynecologist.
INTERFERON
Interferon alfa is not mutagenic. Interferon has been shown to have abortifacient effects in rhesus monkeys. Interferon therapy should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Interferon (including peginterferon) may impair fertility. Decreases in serum estradiol and progesterone concentrations have been reported in women treated with human leukocyte interferon. Irregular menstrual cycles were observed in cynomolgus monkeys treated with very high doses of peginterferon. Anovulation was suggested by transiently decreased levels of estradiol and progesterone. Peginterferon should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, and therapy is recommended for fertile women only when they are using two forms of effective contraception.

RIBAVIRIN
Ribavirin demonstrated increased incidences of mutation and cell transformation. Significant teratogenic and/or embryocidal effects have been documented with the use of ribavirin in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one twentieth of the recommended human dose of ribavirin.

- In relapsed and naive international and US studies of interferon/ribavirin therapy, pregnancy occurred in 24 patients and/or partners: four out of six women terminated pregnancy, the other two miscarried. Of the 10 partner-pregnancies, one terminated, two were healthy births, three were miscarriages, and four had unknown outcomes.\(^1\)

- Abnormal sperm and testicular degeneration can occur. Total recovery of testicular toxicity occurs after one to two spermatogenesis cycles.

Ribavirin must not be used by women, or their male partners, who are or may become pregnant either during therapy or within 6 months after stopping therapy.

MANAGEMENT STRATEGIES
1. Obtain report of negative pregnancy test immediately prior to initiation of combination therapy.
2. Inform women of childbearing potential and men that they must use effective contraception (at least two reliable forms) during treatment and during the 6-month posttreatment follow-up period. (Some healthcare providers do not recommend additional contraception if the patient is surgically sterilized.) Document this discussion with the patient.
3. Conduct monthly pregnancy tests.
4. REPORT PREGNANCY IF IT OCCURS in a patient or partner of a patient during treatment or during the 6 months after treatment.
   a. For patients taking peginterferon alfa-2b/ribavirin (Peg-Intron®/Rebetol®), call (800) 727-7064.
   b. For patients taking peginterferon alfa-2a/ribavirin (Pegasys®/Copegus™), call (800) 526-6367.

REFERENCE
Reports of sexual dysfunction with interferon, peginterferon, or ribavirin are a rare event. This is most likely due to a lack of sexual assessment, or patients’ reluctance to discuss this topic. However, anecdotal reports indicate that this is a concern for many patients. Decreased libido disproportionately impacts patients with depression.\textsuperscript{1,2} Patients with HCV infection have a higher incidence of depression than in the general population (see “Depression” section). Discussing possible changes in libido and sexual functioning with a patient and offering interventions can result in treatment compliance and improve quality of life.

Piazza et al\textsuperscript{3} described male sexual functioning with long-term interferon therapy. In this study, 18 men with HCV infection receiving 6 million IU TIW of interferon alfa-2a were clinically monitored and questioned about sexual function. Gonadotropin and serum androgen concentrations (follicle-stimulating hormone, luteinizing hormone, total testosterone, free testosterone, androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate, and sex hormone binding globulin) were measured every 3 months. Serum total testosterone and sex binding globulin values decreased slightly at the third month of treatment and then returned to baseline levels. Other measures were essentially unchanged. Twenty-two percent of patients complained of sexual dysfunction (impaired libido, erectile failure, and impaired ejaculation), which was unrelated to any change in serum sex hormones. There was no difference in the serum sex hormones of responders versus nonresponders to therapy. The authors concluded that the sexual dysfunction could be attributed to other side effects of interferon such as asthenia, fatigue, or anxiety, or possibly had a psychologic basis.\textsuperscript{3}

Decreased libido was reported in a few patients enrolled in clinical trials for labeled indications. Decreased concentrations of circulating sex steroids have been demonstrated in men and women treated with interferon alfa. Serum testosterone levels may decrease after interferon alfa use.\textsuperscript{4} In men, decreased testosterone levels have several effects, including functional deterioration of the accessory sex organs; loss of muscle mass, strength, and endurance; and decrease in libido.\textsuperscript{4} In a study of five healthy women given
interferon, levels of follicular-phase estrogen and luteal-phase progesterone were low. Follicle stimulating hormone and luteinizing hormone remained normal. Also, increased prolactin levels could result in diminished androgen or estrogen released.4

**OTHER CAUSES OF SEXUAL DYSFUNCTION**

Sexual dysfunction may be a side effect of antidepressant medications, which are commonly used in patients with HCV infection.2 Disease states such as diabetes and hypertension are associated with sexual dysfunction, and may also potentiate the sexual side effects induced by antidepressants. TCAs have been studied over a long period of time and have resulted in decreased libido, erectile dysfunction (ED), delayed ejaculation, and anorgasmia in males and in dyspareunia, anorgasmia, and lubrication disorders in women.2 Product information sheets for SSRIs; fluoxetine (Prozac®), paroxetine (Paxil®), sertraline (Zoloft®), fluvoxamine (Luvox®), and citalopram (Celexa™) list incidences of ejaculatory dysfunction of 1% to 13%;5 however, actual rates may be considerably higher. Three of the new-agent SSRI/SNRI antidepressants, bupropion (Wellbutrin®), mirtazapine (Remeron®), and nefazodone (Serzone®), claim to have minimal effects on sexual functioning. One survey using the Arizona Sexual Experience Scale questionnaire found that in a sample of 44 patients taking antidepressants, sexual dysfunction developed in 36% of patients taking SSRIs, 29% receiving TCAs, and 14% receiving bupropion (Wellbutrin®) or nefazodone (Serzone®).2

<table>
<thead>
<tr>
<th>CAUSES OF SEXUAL DYSFUNCTION1,6</th>
<th>Both Genders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td>IFN side effects: fatigue, myalgia, arthralgia, N/V</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>Hormone changes and aging</td>
</tr>
<tr>
<td>Vaginal RT/Implants</td>
<td>Fear, anxiety, depression</td>
</tr>
<tr>
<td>H/O gynecologic surgery</td>
<td>Body image and self-esteem</td>
</tr>
<tr>
<td>Postmenopausal changes</td>
<td>Antidepressants</td>
</tr>
<tr>
<td>Estrogen/testosterone</td>
<td>Interferon and other biologic and chemotherapy agents</td>
</tr>
<tr>
<td>fluctuations and deficiency</td>
<td>Other medications: see Table below</td>
</tr>
<tr>
<td>Vaginismus: often a phobic response to trauma</td>
<td>Role and relationship changes</td>
</tr>
<tr>
<td>Clitoral adhesions, tight clitoral hood</td>
<td>Physical changes; response to disease or treatment</td>
</tr>
<tr>
<td>Pubococcygeal muscle weakness or fibrosis</td>
<td>Genitourinary atrophy of aging</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>Cultural and religious issues</td>
</tr>
<tr>
<td>Testosterone decline: aging, CRF, or surgery</td>
<td>Sexuality/anatomy ignorance</td>
</tr>
<tr>
<td>Performance anxiety</td>
<td>Sexual trauma or physical abuse</td>
</tr>
<tr>
<td>Radiation therapy/brachytherapy</td>
<td>Chronic diseases (HTN, DM, BPH, OA, cancer, HCV, etc)</td>
</tr>
<tr>
<td>TURP: “dry” (retrograde) ejaculation and ED</td>
<td>Loss of cognitive function</td>
</tr>
<tr>
<td>Radical cystectomy: ejaculatory and ED</td>
<td>Infidelity, divorce, or loss of significant other</td>
</tr>
<tr>
<td>Orchietomy: ED</td>
<td>Lack of or inadequate foreplay</td>
</tr>
<tr>
<td>Prostate surgery: pelvic nerve damage (demyelination)</td>
<td>Endocrine: hypothyroid, Addison’s, Cushing’s, DM, etc</td>
</tr>
<tr>
<td>Peyronie’s disease</td>
<td>Vascular (ED): leukemia, trauma, sickle cell, hypercoag. states</td>
</tr>
<tr>
<td>Psychologic: anhedonic orgasm: ejaculation without pleasure</td>
<td>Local genital: herpes, STDs, trauma/malformation</td>
</tr>
<tr>
<td></td>
<td>Lower back pain</td>
</tr>
<tr>
<td></td>
<td>Mechanical: hernia, mutilation, or absence</td>
</tr>
</tbody>
</table>
### SEXUAL SIDE EFFECTS OF COMMON PRESCRIPTION MEDICATIONS

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Sexual Side Effect</th>
<th>Drug Name</th>
<th>Sexual Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td><strong>Tricyclics:</strong></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>↓libido, breast swelling, impotence</td>
<td>Amitriptyline</td>
<td>Inhibited ejaculation, impotence</td>
</tr>
<tr>
<td>Thiazides</td>
<td>Impotence</td>
<td>Amoxapine</td>
<td>↓libido, impotence</td>
</tr>
<tr>
<td>Furosemide</td>
<td>None</td>
<td>Desipramine</td>
<td>Inhibited ejaculation</td>
</tr>
<tr>
<td><strong>Centrally acting agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyldopa</td>
<td>↓libido, impotence</td>
<td>Doxepin</td>
<td>Inhibited ejaculation, impotence</td>
</tr>
<tr>
<td>(Aldoclor®, Aldomet®, Aldoril®)</td>
<td></td>
<td>Imipramine</td>
<td>Inhibited ejaculation, impotence</td>
</tr>
<tr>
<td>Clonidine (Catapres®)</td>
<td>Impotence</td>
<td>Maprotiline</td>
<td>Inhibited ejaculation, impotence</td>
</tr>
<tr>
<td>Reserpine (Diutensin®)</td>
<td>↓libido, impotence, depression</td>
<td>Nortriptyline</td>
<td>Inhibited ejaculation</td>
</tr>
<tr>
<td><strong>α-adrenergic blockers</strong></td>
<td></td>
<td>Protriptyline</td>
<td>Inhibited ejaculation, impotence</td>
</tr>
<tr>
<td>Prazosin (Minipress®)</td>
<td>Retrograde ejaculation</td>
<td>(Vivactil®)</td>
<td></td>
</tr>
<tr>
<td>Terazosin (Hytrin®)</td>
<td>Retrograde ejaculation</td>
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<td></td>
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<tr>
<td><strong>β-adrenergic blockers</strong></td>
<td></td>
<td><strong>Atypical agent</strong></td>
<td></td>
</tr>
<tr>
<td>Propranolol (Inderal®)</td>
<td>↓libido, impotence</td>
<td>Trazadone</td>
<td>Priapism</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>↓libido, impotence</td>
<td>(Desyrel®)</td>
<td></td>
</tr>
<tr>
<td><strong>Comb. α and β adrenergic blockers</strong></td>
<td></td>
<td>MAO inhibitors</td>
<td></td>
</tr>
<tr>
<td>Labetalol (Normodyne®)</td>
<td>Inhibited ejaculation</td>
<td>Isocarboxazid</td>
<td>Inhibited ejaculation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Marplan®)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phenelzine</td>
<td>Inhibited ejaculation, ↓libido</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Nardil®)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tranylcypromine</td>
<td>Inhibited ejaculation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Parnate®)</td>
<td></td>
</tr>
<tr>
<td><strong>Nonadrenergic vasodilators</strong></td>
<td></td>
<td><strong>SSRIs</strong></td>
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<tr>
<td>Hydralazine</td>
<td>None</td>
<td>See text under “Other Causes of Sexual Dysfunction”</td>
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<tr>
<td><strong>Sympathetic nerve blockers</strong></td>
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<td><strong>Other</strong></td>
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<tr>
<td>Guanethidine (Ismelin®)</td>
<td>Impotence, retrograde ejaculation</td>
<td>Perphenazine</td>
<td>Inhibited ejaculation</td>
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<tr>
<td></td>
<td></td>
<td>(Trilafon®)</td>
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<tr>
<td><strong>ACE inhibitors</strong></td>
<td></td>
<td>Trifluoperazine</td>
<td>Inhibited ejaculation</td>
</tr>
<tr>
<td>Captopril</td>
<td>None</td>
<td>(Stelazine®)</td>
<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td>None</td>
<td>Thioxanthene</td>
<td>Inhibited ejaculation</td>
</tr>
<tr>
<td>(Lexxel®, Vasotec®)</td>
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<td>(Navane®)</td>
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</tr>
<tr>
<td>Lisinopril</td>
<td>None</td>
<td>Chlorprothixene</td>
<td>Inhibited ejaculation</td>
</tr>
<tr>
<td>(Prinivil®, Prinzide®, Zestril®)</td>
<td></td>
<td>(Taractan®)</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td></td>
<td>Thiothixene</td>
<td>Inhibited ejaculation, impotence</td>
</tr>
<tr>
<td></td>
<td>(Haldol®)</td>
<td></td>
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SEXUAL SIDE EFFECTS OF COMMON PRESCRIPTION MEDICATIONS7-10 (Cont’d)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Sexual Side Effect</th>
<th>Drug Name</th>
<th>Sexual Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotic</td>
<td></td>
<td>Antimania</td>
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<tr>
<td>Thioridazine</td>
<td>Inhibited ejaculation,</td>
<td>Lithium</td>
<td>Possible impotence</td>
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<tr>
<td></td>
<td>↓libido, priapism</td>
<td>(Eskalith®)</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Inhibited ejaculation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Thioridazine®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesoridazine (Serentyl®)</td>
<td>Inhibited ejaculation,</td>
<td>Cimetidine</td>
<td>↓libido, impotence,</td>
</tr>
<tr>
<td></td>
<td>↓libido</td>
<td>(Tagamet®)</td>
<td>gynecomastia</td>
</tr>
<tr>
<td>Phenothiazine</td>
<td>Inhibited ejaculation,</td>
<td>Ranitidine (Zantac®)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>↓libido</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Famotidine (Pepcid®)</td>
<td>None</td>
</tr>
</tbody>
</table>

PLISSIT MODEL OF INTERVENTION

P = Permission giving: Frequently, by just introducing the topic of sexuality, we give patients permission to discuss a topic or ask a question they may have. It also may give them permission to engage in certain sexual activities.

LI = Limited information: Many patients need simple, basic information regarding their illness or have questions regarding normal life development issues.

SS = Specific suggestions: Some patients need more specific suggestions (ie, sexual positioning for comfort).

NOTE: All of the above fall within the scope of nursing practice.

IT = Intensive therapy: Licensed sex therapist/counselor realm. Rape, incest, physical abuse, marital conflict, etc.

MANAGEMENT STRATEGIES1,6

Patients should be advised to:

1. Have sex in a relaxed, tranquil atmosphere. AM intimacy may be more successful, especially if treatment-related fatigue is interfering with sexual activity.
2. Obtain proper rest and nutrition. Prevent/minimize treatment-related side effects.
3. Engage in open and honest communication with partner.
4. Use water-based, soluble vaginal lubricants for dryness and discomfort (ie, Astroglide®, Replens®, K-Y® Jelly, etc).

Healthcare providers should:

1. Determine sexual functioning at baseline and during therapy. Ensure privacy; quiet setting.
2. Assess possible causes of pain or discomfort during sexual activity (ie, position, dryness, osteoarthritis, rheumatoid arthritis, etc).
   a. For patients with a history of osteo/rheumatoid arthritis, assess compliance with arthritis medications; may need to change or titrate as an increase in muscle and/or joint pain may be seen during antiviral therapy.
3. Recommend NSAIDs or acetaminophen (Tylenol®) 30 minutes to 1 hour prior to sexual activity for myalgia- and/or arthralgia-related discomfort.
4. Assess for other causes of symptoms, organic problems, and STDs. Control underlying medical conditions that may contribute to sexual dysfunction (e.g., diabetes, prostate conditions, gynecologic conditions). Evaluate for contributing medications (see Table above). Refer to primary care physician or gynecologist if necessary.

5. For antidepressant-related loss of libido, switch antidepressants, reduce dose, drug holiday, or use adjunctive therapies such as cyproheptadine (Periactin®) and amantadine (Symmetrel®). Men may have less difficulty with orgasm on sertraline (Zoloft®) compared with other SSRIs.

6. Prescribe pharmacologic therapy.
   a. Hydroxyzine (Atarax®, Vistaril®) 10 mg prior to sex to decrease anxiety.
   b. Cyproheptadine (Periactin®) 4 mg about 1 hour prior to sexual activity to treat anorgasmia.
   c. Sildenafil (Viagra®), generally 50 mg (acceptable range: 25–100 mg) taken as needed approximately 1 hour before sexual activity for erectile dysfunction. Should not be used in men for whom sexual activity is inadvisable due to cardiovascular disease.

7. Collaborate with specialized clinical psychologists, sex therapists, and marriage counselors to improve communication and intimacy skills for couples. Identify/refer to local resources and support groups.

OTHER CLINICAL CONSIDERATIONS

1. Assess risk of hepatitis transmission via sexual contact. Counsel patients regarding risk of sexual transmission. The exact mechanism(s) of sexual transmission of hepatitis are still being studied.
   a. Risk increases with number of sexual partners or history of STDs.
   b. Increased risk if sexual trauma (vaginal/anal tears), as in rape or sodomy.
2. Test sexual partners for hepatitis per physician and/or patient and partner request. Periodic testing as appropriate.
3. Caution HCV positive women to abstain or use caution regarding sexual activity during the menstrual cycle. Menstrual flow could theoretically contain significant amounts of HCV.
4. Counsel patients about high risk of transmission with injection drug or cocaine use. Illicit drug or alcohol use may also increase risk of casual sexual activity.
5. Immunize susceptible patients against hepatitis A and B.

REFERENCES


<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACH</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>ADL</td>
<td>Activities of daily living</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse events</td>
</tr>
<tr>
<td>AI</td>
<td>Autoimmune</td>
</tr>
<tr>
<td>AIH</td>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>AKA</td>
<td>Antikeratin antibody</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ANA</td>
<td>Antinuclear antibody</td>
</tr>
<tr>
<td>ANC</td>
<td>Absolute neutrophil count</td>
</tr>
<tr>
<td>ASA</td>
<td>Aspirin</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate transaminase</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>ATPO</td>
<td>Antithyroid peroxidase antibodies</td>
</tr>
<tr>
<td>BPH</td>
<td>Benign prostatic hypertrophy</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete blood (cell) count</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CES-D</td>
<td>Center for Epidemiological Studies Depression Scale</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CPK</td>
<td>Creatinine phosphokinase</td>
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<tr>
<td>CTZ</td>
<td>Chemotherapy trigger zone</td>
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<tr>
<td>CV</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>ECT</td>
<td>Electroconvulsive therapy</td>
</tr>
<tr>
<td>ED</td>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td>EIA</td>
<td>Enzyme immunoassay</td>
</tr>
<tr>
<td>EKG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>FBS</td>
<td>Fasting blood sugar</td>
</tr>
<tr>
<td>FDA</td>
<td>Food &amp; Drug Administration</td>
</tr>
<tr>
<td>FLS</td>
<td>Flulike syndrome</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
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<tr>
<td>HA</td>
<td>Headache</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
</tr>
<tr>
<td>HDI</td>
<td>High-dose interferon</td>
</tr>
<tr>
<td>Hgb</td>
<td>Hemoglobin</td>
</tr>
<tr>
<td>HLA</td>
<td>Human leukocyte antigen</td>
</tr>
<tr>
<td>H/O</td>
<td>History of</td>
</tr>
<tr>
<td>HTN</td>
<td>Hypertension</td>
</tr>
<tr>
<td>IBW</td>
<td>Ideal body weight</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IFN</td>
<td>Interferon</td>
</tr>
<tr>
<td>IgG</td>
<td>Immunoglobulin G</td>
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# Glossary

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>LC1</td>
<td>Liver cytosol antibody type 1</td>
</tr>
<tr>
<td>LKM</td>
<td>Antiliver-kidney microsomal</td>
</tr>
<tr>
<td>LKM1</td>
<td>LKM type 1 antibody</td>
</tr>
<tr>
<td>MAOI</td>
<td>Monoamine oxidase inhibitor</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>MSG</td>
<td>Monosodium glutamate</td>
</tr>
<tr>
<td>NIDDM</td>
<td>Non–insulin-dependent diabetes mellitus</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>NSAID</td>
<td>Nonsteroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>N/V</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>OA</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>OHA</td>
<td>Oral hypoglycemic agent</td>
</tr>
<tr>
<td>PA</td>
<td>Psoriatic arthritis</td>
</tr>
<tr>
<td>PABA</td>
<td>Para-aminobenzoic acid</td>
</tr>
<tr>
<td>PUVA</td>
<td>Psoralen and ultraviolet light A</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RBCs</td>
<td>Red blood cells</td>
</tr>
<tr>
<td>RF</td>
<td>Rheumatoid factor</td>
</tr>
<tr>
<td>RIBA</td>
<td>Recombinant immunoblot assay</td>
</tr>
<tr>
<td>RT</td>
<td>Radiation therapy</td>
</tr>
<tr>
<td>SLE</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>SMA</td>
<td>Smooth muscle antibody</td>
</tr>
<tr>
<td>SNRI</td>
<td>Serotonin and norepinephrine reuptake inhibitor</td>
</tr>
<tr>
<td>SR</td>
<td>Sustained release</td>
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<tr>
<td>SSRIs</td>
<td>Selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>STD</td>
<td>Sexually transmitted disease</td>
</tr>
<tr>
<td>TCA</td>
<td>Tricyclic antidepressant</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor necrosis factor</td>
</tr>
<tr>
<td>TRH</td>
<td>Thyrotropin-releasing hormone</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid-stimulating hormone</td>
</tr>
<tr>
<td>TURP</td>
<td>Transurethral resection of prostate</td>
</tr>
<tr>
<td>UVL</td>
<td>Ultraviolet light</td>
</tr>
<tr>
<td>VC</td>
<td>Vomiting center</td>
</tr>
<tr>
<td>VER</td>
<td>Visual evoked response</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cell</td>
</tr>
</tbody>
</table>
CME/CE Instructions

To receive documentation of your participation in this activity for a total of 5.25 Category I hours of CME credit, or 6.4 contact hours of CE credit, please complete the following steps:

1. Read this handbook.
2. Complete the CME/CE posttest.
3. Complete the CME/CE evaluation survey.
4. Mail or fax your CME/CE posttest and evaluation survey to Projects In Knowledge, Overlook at Great Notch, 150 Clove Road, Little Falls, NJ 07424; fax: 1-973-890-8822.

CME/CE Certificate

Projects In Knowledge will mail you a certificate of completion for this activity if you score 70% or higher. If you score lower than 70%, you will be notified by mail and given another chance to take the posttest.

Please indicate your answers below (circle one):

1. Contraindications to peginterferon/ribavirin therapy include all of the following except:
   A. Autoimmune hepatitis
   B. Unstable cardiac disease
   C. Depression stabilized on antidepressants
   D. Pregnancy

2. It is important for hepatitis C patients to maintain adequate hydration during treatment. Daily fluid consumption, in fluid ounces, should be equivalent to:
   A. The person’s body weight in pounds
   B. The person’s body weight in kilograms
   C. One half the person’s body weight in pounds
   D. One quarter the person’s body weight in pounds

3. The majority of peginterferon/ribavirin side effects are reversible upon treatment discontinuation, with the exception, in rare cases, of:
   A. Alopecia
   B. Thyroid toxicity
   C. Ophthalmologic toxicity
   D. All of the above

4. Dose reduction may decrease the likelihood of achieving a positive treatment outcome, since adherence to optimal doses for the recommended duration of therapy has been associated with the likelihood of sustained virologic response.
   A. True
   B. False

5. Injection-site reactions usually present as:
   A. Local erythema
   B. Induration at the injection site
   C. Generalized skin rash
   D. Cutaneous lesions/necrosis

6. Hepatitis C patients have an increased incidence of:
   A. Type I diabetes
   B. Type II diabetes

7. Routine laboratory monitoring during anti-HCV treatment should include regular:
   A. CBC with differential
   B. TSH
   C. ALT/AST
   D. All of the above

8. Fatigue, fever, and other flulike symptoms may be improved by administering peginterferon:
   A. In the evening
   B. In the morning
   C. In the midafternoon
   D. None of the above

Please select the most appropriate response to each question.
9. Which of the following is not recommended for patients with nausea/vomiting during peginterferon/ribavirin?
   A. Taking ribavirin with food  
   B. Standard antiemetics  
   C. Nonsteroidal anti-inflammatory drugs  
   D. Selective serotonin reuptake inhibitors

10. Which of the following herbs is associated with hepatotoxicity?
   A. Ginger  
   B. Dandelion  
   C. Milk thistle  
   D. Jin Bu Huan

11. If hemoglobin decreased from 14 to 11 g/dL in a male patient after 4 weeks of therapy, which of the following would be the preferred management option?
   A. No change; continue treatment and monitoring  
   B. Initiate epoetin 40,000 IU QW  
   C. Dose reduce ribavirin  
   D. Discontinue treatment

12. Assessment for cognitive side effects should include baseline and regular evaluation using a standardized instrument (eg, CES-D or Folstein Mini Mental State Examination) during anti-HCV treatment.
   A. True  
   B. False

13. Family members should be discouraged from attending patient appointments because their anxiety about the patient’s condition generally distracts the patient from appropriate education and care.
   A. True  
   B. False

14. Evaluation of side effects should generally include consideration of:
   A. Psychosocial and risk factors  
   B. Co-morbid diseases  
   C. Concurrent medications  
   D. All of the above

15. Psychiatric side effects of peginterferon/ribavirin occur only in patients with a history of psychiatric illness or pre-existing condition at baseline.
   A. True  
   B. False

16. Which of the following antidepressants has a strong sedating effect?
   A. Bupropion  
   B. Trazodone  
   C. Fluoxetine  
   D. Venlafaxine  
   E. All of the above  
   F. None of the above

17. Blood count and chest x-ray should be ordered immediately for patients with dyspnea or other poorly controlled respiratory symptoms while on peginterferon/ribavirin.
   A. True  
   B. False

18. Patients on hemodialysis should not be treated with:
   A. Standard interferon alphas  
   B. Pegylated interferons  
   C. Ribavirin  
   D. Any of the above

19. A patient who wishes to become pregnant must be advised to wait until at least 1 month after cessation of peginterferon/ribavirin therapy.
   A. True  
   B. False

20. Sexual dysfunction in patients on peginterferon/ribavirin may be a result of:
   A. Effects of antiviral therapies on hormone levels  
   B. Other side effects of peginterferon/ribavirin (eg. fatigue, flulike symptoms, pain)  
   C. Side effects of adjunctive therapies used in the treatment of peginterferon/ribavirin side effects (eg. antidepressants)  
   D. Other physical or psychological conditions  
   E. All of the above
Instructions

Please complete this survey, along with the CME/CE Posttest, and mail or fax (both sides) to Projects In Knowledge, Overlook at Great Notch, 150 Clove Road, Little Falls, NJ 07424; fax: 1-973-890-8822.

1. Please rate the extent to which you achieved the learning objectives:

- Identify necessary parameters needed for measuring side effects and treatment responses
- Review effective management of adverse effects of peginterferon and ribavirin to achieve optimum treatment outcomes
- Expand ways to provide education and support to HCV-infected patients and their families to help them stay the course on treatment

2. How well do the objectives above relate to the goal of this activity?

The goal of this activity is to help clinical professionals enhance HCV-infected patients’ adherence to therapy by effectively managing side effects.

3. How effective were the teaching/learning resources used in this activity?

4. Please rate the overall value of this enduring material:

5. Course was free from commercial bias:

If you “Disagree” or “Strongly Disagree,” why?

6. Please rate the level of the material presented:

7. Please list any changes in your practice that you would consider making as a result of participating in this activity:

8. Please rate your interest in self-directed or distance learning in the following formats:

- Audioconference
- Videoconference
- Enduring materials (audiocassettes, videotapes, monographs)
- Internet (online discussions with experts, educational activities)
- Multimedia (online, CD-ROM)

9. Please tell us how long it took you to complete this course:

10. Please list topics and/or experts you would find interesting and professionally relevant for future CME activities:

11. Follow-up: As part of our ongoing continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our CME courses on professional practice. Please indicate your willingness to participate in such a survey:

❑ Yes, I would be interested in participating in a follow-up survey. ❑ No, I’m not interested in participating in a follow-up survey.

Additional comments about this activity:
The content of Care and Counsel II: Helping Patients Stay the Course on Treatment for Hepatitis C was developed during a meeting of a large distinguished panel of clinical professionals who are engaged in hepatitis C research or who manage HCV-infected patients. Specialties included hepatologists, gastroenterologists, nurse practitioners, physician assistants, and other support staff.

At this meeting, several formats and techniques were used to gather information and establish consensus recommendations on difficult management issues. Small-group discussions were conducted to develop the side effect management chapters of this Handbook. In addition, consensus on issues of side effect management and overall care provided to hepatitis C patients by support staff was based on a written survey that included questions regarding demographics and practice perspectives. These questions were prepared by Projects In Knowledge with input from the Care and Counsel II faculty. This survey instrument was chosen in order to prevent individual responses from being influenced by those of other participants. Eighty experts participated in this comprehensive paper-based survey.

Completed surveys were submitted at the close of the meeting or by mail shortly thereafter. The majority of the survey questions utilized a visual analog scale from 1 to 5 (eg, from “strongly disagree” to “strongly agree” or “least important” to “most important”). The mean rating for each option was calculated. Survey results, provided here, give an enlightening picture of the extensive role played by support staff in caring for patients with hepatitis C, as well as a picture of the current standard of care in the management of this important disease.
I. DEMOGRAPHIC INFORMATION

1. In what region of the US do you work? (n = 78)

<table>
<thead>
<tr>
<th>Region</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northeast</td>
<td>31%</td>
</tr>
<tr>
<td>Midwest</td>
<td>24%</td>
</tr>
<tr>
<td>Southeast</td>
<td>14%</td>
</tr>
<tr>
<td>Southwest</td>
<td>13%</td>
</tr>
<tr>
<td>South</td>
<td>10%</td>
</tr>
<tr>
<td>Northwest</td>
<td>6%</td>
</tr>
<tr>
<td>Rocky Mtns.</td>
<td>1%</td>
</tr>
</tbody>
</table>

2. How many years have you been seeing patients with hepatitis C? (n = 78) mean = 4; median = 3 years

3. What is the nature of the practice in which you work? (n = 82*)

<table>
<thead>
<tr>
<th>Practice Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specialty group practice</td>
<td>49%</td>
</tr>
<tr>
<td>Academic, predominantly clinical</td>
<td>13%</td>
</tr>
<tr>
<td>Government facilities</td>
<td>11%</td>
</tr>
<tr>
<td>Multispecialty group practice</td>
<td>10%</td>
</tr>
<tr>
<td>Private solo practice</td>
<td>7%</td>
</tr>
<tr>
<td>Academic, predominantly research</td>
<td>5%</td>
</tr>
<tr>
<td>Academic, administrative &amp; clinical</td>
<td>4%</td>
</tr>
<tr>
<td>HMO staff provider</td>
<td>1%</td>
</tr>
</tbody>
</table>

4. How would you best describe the practice? (n = 75)

<table>
<thead>
<tr>
<th>Practice Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>General gastroenterology/hepatology</td>
<td>69%</td>
</tr>
<tr>
<td>Predominantly hepatology</td>
<td>19%</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>9%</td>
</tr>
<tr>
<td>Other:</td>
<td>3%</td>
</tr>
</tbody>
</table>

   - Hepatitis C patients only
   - Internal medicine

5. How many patients with the following have you seen in the past 6 months? (n = 74)
   a. HCV infection: mean = 186; median = 100 patients
   b. HCV/HIV coinfection: mean = 24; median = 5 patients

*Some survey respondents selected more than one option; hence, n, which denotes the number of responses, may be greater than the total number of respondents (n = 80).
6. What percentage of your HCV-infected patient population is: \( n = 76 \)

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>62%</td>
</tr>
<tr>
<td>Black or African American</td>
<td>17%</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>12%</td>
</tr>
<tr>
<td>Asian</td>
<td>4%</td>
</tr>
<tr>
<td>Other:</td>
<td>3%</td>
</tr>
<tr>
<td>• African (Egyptian)</td>
<td></td>
</tr>
<tr>
<td>• European</td>
<td></td>
</tr>
<tr>
<td>• Russian</td>
<td></td>
</tr>
<tr>
<td>• Middle Eastern/Arabic</td>
<td></td>
</tr>
<tr>
<td>• South American</td>
<td></td>
</tr>
<tr>
<td>• Mediterranean</td>
<td></td>
</tr>
<tr>
<td>Native American</td>
<td>2%</td>
</tr>
</tbody>
</table>

7. Based on the last 12 months, would you say that the number of patients with HCV infection you are seeing is: \( n = 74 \)

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing</td>
<td>85%</td>
</tr>
<tr>
<td>Remaining the same</td>
<td>12%</td>
</tr>
<tr>
<td>Decreasing</td>
<td>3%</td>
</tr>
</tbody>
</table>

8. What percentage of the patients with hepatitis C you currently see are: \( n = 72 \)

<table>
<thead>
<tr>
<th>Status</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naive</td>
<td>64%</td>
</tr>
<tr>
<td>Nonresponders to interferon/ribavirin</td>
<td>15%</td>
</tr>
<tr>
<td>Nonresponders to interferon</td>
<td>12%</td>
</tr>
<tr>
<td>Relapsers to interferon/ribavirin</td>
<td>6%</td>
</tr>
<tr>
<td>Relapsers to interferon</td>
<td>1%</td>
</tr>
<tr>
<td>Relapsers to peginterferon/ribavirin</td>
<td>1%</td>
</tr>
<tr>
<td>Nonresponders to peginterferon/ribavirin</td>
<td>0%</td>
</tr>
</tbody>
</table>

9. How many MDs are at your place of work? \( n = 72 \) Mean = 7; median = 4 MDs

10. How many of the following support staff at your place of work deal directly with hepatitis C patients? \( n = 71 \)

<table>
<thead>
<tr>
<th>Staff Type</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAs</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>NPs</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nurses</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Administrative staff</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Medical assistant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pharmacist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Insurance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Psychiatrist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Social worker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Research coordinator</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CTAs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
II. PRACTICE PERSPECTIVES

1. Who performs the following tasks in your practice? (n = 80)

<table>
<thead>
<tr>
<th>Task</th>
<th>MD (%)</th>
<th>NP (%)</th>
<th>PA (%)</th>
<th>Nurse (%)</th>
<th>Other (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Meet with new consults</td>
<td>80</td>
<td>45</td>
<td>38</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>b. HCV risk assessment</td>
<td>74</td>
<td>50</td>
<td>43</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>c. Take patient history</td>
<td>78</td>
<td>55</td>
<td>45</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>d. Perform physical examination</td>
<td>73</td>
<td>55</td>
<td>44</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>e. Set up treatment/plan of care</td>
<td>63</td>
<td>51</td>
<td>41</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>f. Monitoring and follow-up</td>
<td>53</td>
<td>56</td>
<td>45</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>g. Patient education about hepatitis C</td>
<td>44</td>
<td>56</td>
<td>45</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>h. Patient education about treatment options</td>
<td>60</td>
<td>54</td>
<td>41</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>i. Patient education about self-injection</td>
<td>10</td>
<td>49</td>
<td>34</td>
<td>48</td>
<td>8</td>
</tr>
<tr>
<td>j. Patient education about side effects</td>
<td>41</td>
<td>54</td>
<td>43</td>
<td>41</td>
<td>4</td>
</tr>
<tr>
<td>k. Patient education about lab results</td>
<td>45</td>
<td>53</td>
<td>43</td>
<td>35</td>
<td>4</td>
</tr>
<tr>
<td>l. Study coordination</td>
<td>23</td>
<td>29</td>
<td>25</td>
<td>34</td>
<td>10</td>
</tr>
<tr>
<td>m. Collecting/compiling research data</td>
<td>21</td>
<td>24</td>
<td>25</td>
<td>34</td>
<td>14</td>
</tr>
<tr>
<td>n. Annual hepatocellular carcinoma screening</td>
<td>64</td>
<td>44</td>
<td>38</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>

2. Are there other tasks related to management of HCV infection that are commonly performed by support staff? (n = 44)

- Drawing of blood – MA
- Storing medication – MA
- Obtaining insurance approval/authorization/drug coverage – MA, nurse
- Giving injections – MA
- Telephone inquiry – office staff, nurse, NP
- Calling/renewing medications – nurse
- Lab appointments – nurse, NP
- Collecting lab results – nurse, secretary
- Charting flow sheets
- Scheduling classes for group treatment education and adherence counseling
- Disability or FMLA forms
- Disease reporting to public health
- Interface with PCPs to recommend management follow-up
- Clinic and research coordination
- General office or administrative tasks
- Community education workshops, family counseling
- Data collection and storage/maintaining folders – MA
- Patient support, phone assessment, management of side effects – nurse
- Psychiatric consultation – RN, MSN
- Psychiatric evaluation – social worker

3. Please indicate the degree of autonomy in which support staff perform the tasks that you checked off in question 1 or listed in question 2. (1 = complete supervision to 5 = full autonomy [ie, no direct supervision of individual care but physician is available and/or signs off]) (n = 78)

<table>
<thead>
<tr>
<th>Task</th>
<th>MD</th>
<th>NP</th>
<th>PA</th>
<th>Nurse</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. NPs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. PAs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. Nurses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A. NPs
B. PAs
C. Nurses

Complete Supervision

Full Autonomy

A
B
C

2.9
4.4
4.4

4.4
4. Please rate the extent to which each of the following factors impacts treatment outcomes in the care of HCV-infected patients in your practice. (1 = no impact to 5 = strong impact) \((n = 78)\)

- A. Patient motivation
- B. Lack of social support for patients
- C. Opportunities for ongoing hepatitis C education for support staff
- D. Level of support staff training specific to hepatitis C
- E. MD interest
- F. Patient acceptance of care by support staff (vs MD)
- G. Economic level of patient population
- H. Availability of transportation/access to care
- I. Lack of time for clinical care
- J. Differences between support staff and MD regarding messages to be conveyed to patients
- K. Insufficient reimbursement for support staff functions

<table>
<thead>
<tr>
<th>Factor</th>
<th>Impact Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Patient motivation</td>
<td>4.5</td>
</tr>
<tr>
<td>B. Lack of social support for patients</td>
<td>3.9</td>
</tr>
<tr>
<td>C. Opportunities for ongoing hepatitis C</td>
<td>3.8</td>
</tr>
<tr>
<td>D. Level of support staff training specific to hepatitis C</td>
<td>3.5</td>
</tr>
<tr>
<td>E. MD interest</td>
<td>3.4</td>
</tr>
<tr>
<td>F. Patient acceptance of care by support staff (vs MD)</td>
<td>3.3</td>
</tr>
<tr>
<td>G. Economic level of patient population</td>
<td>3.1</td>
</tr>
<tr>
<td>H. Availability of transportation/access to care</td>
<td>2.9</td>
</tr>
<tr>
<td>I. Lack of time for clinical care</td>
<td>2.9</td>
</tr>
<tr>
<td>J. Differences between support staff and MD regarding messages to be conveyed to patients</td>
<td>2.8</td>
</tr>
<tr>
<td>K. Insufficient reimbursement for support staff functions</td>
<td>2.7</td>
</tr>
</tbody>
</table>

5. To what extent do you think the following factors affect patient adherence to therapy? (1 = no effect to 5 = great effect) \((n = 80)\)

- A. Patient belief in treatment
- B. Patient education
- C. Active IVDU or alcohol abuse
- D. Active psychiatric disease
- E. Adherence to visits
- F. Provider experience
- G. Side effects
- H. Family education
- I. Social supports
- J. Disease stage
- K. Inactive IVDU
- L. Gender
- M. Race

<table>
<thead>
<tr>
<th>Factor</th>
<th>Impact Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Patient belief in treatment</td>
<td>4.7</td>
</tr>
<tr>
<td>B. Patient education</td>
<td>4.7</td>
</tr>
<tr>
<td>C. Active IVDU or alcohol abuse</td>
<td>4.6</td>
</tr>
<tr>
<td>D. Active psychiatric disease</td>
<td>4.4</td>
</tr>
<tr>
<td>E. Adherence to visits</td>
<td>4.4</td>
</tr>
<tr>
<td>F. Provider experience</td>
<td>4.3</td>
</tr>
<tr>
<td>G. Side effects</td>
<td>4.3</td>
</tr>
<tr>
<td>H. Family education</td>
<td>4.1</td>
</tr>
<tr>
<td>I. Social supports</td>
<td>4.1</td>
</tr>
<tr>
<td>J. Disease stage</td>
<td>2.5</td>
</tr>
<tr>
<td>K. Inactive IVDU</td>
<td>3.4</td>
</tr>
<tr>
<td>L. Gender</td>
<td>2.0</td>
</tr>
<tr>
<td>M. Race</td>
<td>1.9</td>
</tr>
</tbody>
</table>

6. How much impact do you think support staff have on patient adherence? (1 = no impact to 5 = tremendous impact) \((n = 78)\)

<table>
<thead>
<tr>
<th>Impact Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Impact</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
</tbody>
</table>
7. What percentage of the HCV-infected patients seen where you work are being treated for HCV infection?  
\((n = 76)\)

8. At the place where you work, which of the following is recommended as first-line therapy for treatment-naive patients with HCV genotype 1?  
\((n = 76)\)

9. At the place where you work, which of the following is recommended as first-line therapy for treatment-naive patients with HCV genotype 2/3?  
\((n = 78)\)
10. Assuming on-treatment response, what duration of treatment is used for genotype 2/3 infections? \( n = 78 \)

![](chart)

11. On a scale of 1 = strongly disagree to 5 = strongly agree, rate your level of agreement with each of the following statements, based on your own clinical experience and observations: \( n = 80 \)

<table>
<thead>
<tr>
<th>Statement</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Weight-based dosing of peginterferon/ribavirin increases efficacy for heavy patients compared with fixed dosing.</td>
<td>4.8</td>
</tr>
<tr>
<td>B. Calculation of the dose of peginterferon and ribavirin based on body weight is quick and simple to perform.</td>
<td>4.7</td>
</tr>
<tr>
<td>C. Weight-based dosing of peginterferon/ribavirin improves treatment safety for lighter patients.</td>
<td>4.7</td>
</tr>
<tr>
<td>D. Patients learn to administer weight-based doses of peginterferon as quickly and easily as they do fixed doses.</td>
<td>4.1</td>
</tr>
</tbody>
</table>

12. How frequently do you or your MD provide patients with the following regarding injections? (1 = never to 5 = always) \( n = 77 \)

<table>
<thead>
<tr>
<th>Instruction</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Instructions on safety and storage</td>
<td>4.8</td>
</tr>
<tr>
<td>B. Explanation of self-administration techniques</td>
<td>4.7</td>
</tr>
<tr>
<td>C. Demonstration of good injection technique</td>
<td>4.7</td>
</tr>
<tr>
<td>D. Illustrated guidelines</td>
<td>4.6</td>
</tr>
<tr>
<td>E. Troubleshooting</td>
<td>4.6</td>
</tr>
<tr>
<td>F. Instructions on calculating and preparing the dose</td>
<td>4.5</td>
</tr>
<tr>
<td>G. Injection sheet</td>
<td>4.3</td>
</tr>
<tr>
<td>H. Supervision of return demonstration</td>
<td>4.3</td>
</tr>
</tbody>
</table>

13a. At your place of work, the first HCV RNA measurement after starting therapy is made at week: \( n = 78 \)

<table>
<thead>
<tr>
<th>Time</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>8%</td>
</tr>
<tr>
<td>Week 8</td>
<td>5%</td>
</tr>
<tr>
<td>Week 12</td>
<td>71%</td>
</tr>
<tr>
<td>Week 24</td>
<td>14%</td>
</tr>
<tr>
<td>Other*</td>
<td>3%</td>
</tr>
</tbody>
</table>

* 12 weeks for genotype 1, 1 month for genotype 2/3 (2); 12 weeks for genotype 1, 24 weeks for genotype 2/3
13b. Treatment response is based on HCV RNA level at week: \((n = 79)\)

<table>
<thead>
<tr>
<th>Time</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>0%</td>
</tr>
<tr>
<td>Week 8</td>
<td>1%</td>
</tr>
<tr>
<td>Week 12</td>
<td>35%</td>
</tr>
<tr>
<td>Week 24</td>
<td>53%</td>
</tr>
<tr>
<td>Week 48</td>
<td>4%</td>
</tr>
<tr>
<td>Other*</td>
<td>5%</td>
</tr>
</tbody>
</table>

14. For a patient with stage 3/4 fibrosis who has had a <2-log decline in HCV RNA at week 12, do you: \((n = 74)\)

- 73% Discontinue the initial treatment regimen but switch to maintenance therapy
- 14% Continue a full course of treatment because of its potential histologic benefit
- 8% Continue to week 24 and reassess virologic response then
- 5% Discontinue treatment

15. What percentage of nonresponders to interferon/ribavirin seen at your place of work has received treatment with peginterferon/ribavirin combination therapy (PEG IFN/RBV)? \((n = 79)\)

- Not re-treated with PEG IFN/RBV: 38.7%
- Re-treated with PEG IFN/RBV: 61.3%

- Not re-treated with PEG IFN/RBV: 25%
- Re-treated with PEG IFN/RBV: 75%

* 12 or 24 weeks (2); 24 or 48 weeks depending on genotype; 12, 24, or 48 weeks; 6 months posttreatment; SVR at week 24 posttreatment
16. Do you or your MD encourage patients to get involved in patient support programs? (1 = rarely to 5 = always) \( (n = 79) \)

![Bar chart showing the response distribution for Q16.](image)

17. Please list support programs that have helped you in managing hepatitis C patients: \( (n = 67) \)

- Be In Charge (34)
- American Liver Foundation local support groups (27)
- Community Support Group (14)
- Hepatitis C classes (7)
- Commitment to Care (5)
- Hepatitis Web sites and Listserve (5)
- Hospital support group (4)
- VA support group (4)
- Pegassist (4)
- Care and Counsel (3)
- Drug representatives (2)
- None available locally

18. Please rate the extent to which the following conditions are considered contraindications to anti-HCV therapy in your practice: (1 = never to 5 = always) \( (n = 78) \)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. History of significant or unstable CV disease</td>
<td>4.4</td>
</tr>
<tr>
<td>B. CHF (NYHA &gt; class 2)</td>
<td>4.0</td>
</tr>
<tr>
<td>C. Pre-existing history of depression with suicide attempt</td>
<td>4.0</td>
</tr>
<tr>
<td>D. Autoimmune hepatitis</td>
<td>3.9</td>
</tr>
<tr>
<td>E. Cardiovascular compromise due to prior treatment with cancer agents</td>
<td>3.8</td>
</tr>
<tr>
<td>F. Arrhythmias requiring medication</td>
<td>2.1</td>
</tr>
<tr>
<td>G. Other autoimmune disorder</td>
<td>1.8</td>
</tr>
<tr>
<td>H. Pre-existing history of depression</td>
<td>1.8</td>
</tr>
<tr>
<td>I. Diabetes</td>
<td></td>
</tr>
<tr>
<td>J. Thyroid abnormalities controlled on medication</td>
<td></td>
</tr>
</tbody>
</table>
19. How likely are you to recommend each of the following for a patient with oral candidiasis? (1 = very unlikely to 5 = very likely) \( (n = 76) \)

A. Topical nystatin (Mycostatin®, Nilstat®, Nystex® Ointment, Pedi Dri® Topical Powder)
B. Topical clotrimazole troches (Mycelex®)
C. Fluconazole (Diflucan®)
D. Ketoconazole (Nizoral®)
E. Amphotericin B (Abelcet®, AmBisome®, Amphotec®)
F. Flucytosine (Ancobon®)

![Graph showing ratings](image)

20. How likely are you to recommend each of the following for a patient with mucositis? (1 = very unlikely to 5 = very likely) \( (n = 74) \)

A. Acetaminophen
B. NSAID for pain
C. Saline solution mouth rinse
D. Topical lidocaine
E. Combination solution containing calcium carbonate, diphenhydramine with alcohol, and lidocaine 2%
F. Coating agent (Orabase, Benzocaine, Oratect)
G. Baking soda solution mouth rinse
H. Chlorhexidine mouth rinse
I. Topical dyclonine hydrochloride

![Graph showing ratings](image)

21. How likely are you to recommend each of the following for a patient with an allergic reaction during treatment? (1 = very unlikely to 5 = very likely) \( (n = 79) \)

A. Oral antihistamine administration
B. Hydrocortisone skin cream
C. Reinstitution of anti-HCV treatment when condition abates, with prophylactic antihistamine
D. Treatment discontinuation
E. Systemic corticosteroids

![Graph showing ratings](image)
22. How likely are you to recommend each of the following for a patient with an injection-site reaction? (1 = very unlikely to 5 = very likely) (n = 79)

A. Cool or warm compresses after injection
B. Increased oral hydration
C. Room temperature injection
D. Non-alcohol-based emollient creams or lotions
E. Topical Betadine cream or corticosteroid cream
F. Sun-protective clothing and sunscreen
G. Oil or colloidal oatmeal baths or soaps
H. Slower injection
I. Diphenhydramine premedication
J. Oral analgesics
K. Aloe and xylocaine gel
L. Topical analgesics
M. Laundry detergents made for infants
N. Dermatology consult
O. Niacin or vitamin C
P. Hydroxyzine or naltrexone
Q. Cutaneous stimulation
R. Drug holiday

23. How beneficial are each of the following strategies in reducing fatigue? (1 = not helpful to 5 = very helpful) (n = 79)

A. Counseling/emotional support
B. Relaxation strategies
C. Altering timing of peginterferon administration
D. Antidepressants
E. Psychostimulants (eg, methylphenidate, modafinil)
F. Peginterferon dose reduction

24. What agent do you most commonly recommend for headache in patients receiving anti-HCV therapy?

a. Prophylaxis:

**OTC Analgesics/Migraine Medications**
- Acetaminophen (Tylenol®, Excedrin®): 31/71 44%
- Ibuprofen (Motrin®, Advil®, Nuprin®): 20/71 28%
- NSAIDs (nonsteroidal anti-inflammatory drugs): 16/71 23%
- Naproxen (Aleve®): 5/71 7%

**Fluids/Hydrants**
- Fluid intake (water): 9/71 13%

**Beta-blocker**
- Propranol hydrochloride (Inderal®): 2/71 3%
25. How likely are you to recommend each of the following nonpharmacologic strategies for headache relief? (1 = very unlikely to 5 = very likely) (n = 80)

A. Relaxation exercises/deep breathing
B. Ice/cold compresses
C. Music therapy
D. Aromatherapy
E. Accupuncture/accupressure
F. Natural progesterone cream
G. Herbal therapies

26. How often do you provide your patients with information about recommended: (1 = never to 5 = always) (n = 80)

A. Hydration
B. Diet
27. In patients with diarrhea, how often do you: (1 = never to 5 = always) \( (n = 79) \)

- A. Obtain history of onset/duration of diarrhea
- B. Obtain description of number/composition of stools
- C. Assess dietary intake for diarrhea-enhancing foods
- D. Obtain history of bowel disease
- E. Assess for fever, dizziness, weakness to rule out sepsis, bowel obstruction, or dehydration
- F. Advise patients to drink at least 3000 mL fluid/day
- G. Assess for other medications that could cause diarrhea
- H. Advise patients to eat small, frequent meals
- I. Recommend OTC products such as Pepto-Bismol®, Kaopectate®, or Imodium®
- J. Advise patients to eat foods high in potassium if potassium level is low
- K. Advise patients to avoid lactose-containing foods and supplements
- L. Recommend rectal-area skin care
- M. Perform stool culture for O&P or check for blood/fecal leukocytes, C difficile, Salmonella, E coli, Campylobacter, infectious colitis
- N. Advise patients to eat low-residue diet
- O. Recommend prescription products such as Lomotil®
- P. Advise patients to avoid hot or cold foods

28. In patients with nausea/vomiting, how often do you: (1 = never to 5 = always) \( (n = 79) \)

- A. Assess history, eating habits, dietary intake, and medications that could exacerbate symptoms
- B. Monitor for and correct dehydration and electrolyte imbalance
- C. Advise patients to avoid greasy or highly seasoned foods
- D. Recommend premedication and PRN use of antiemetics
- E. Recommend foods/drinks containing ginger
- F. Recommend rest periods with head and trunk elevated after eating
- G. Recommend exercise
- H. Recommend flat soda
- I. Recommend progressive muscle relaxation, guided imagery, or distraction
- J. Recommend SSRIs
- K. Recommend benzodiazepines
- L. Recommend sea bands, wrist bands, acupressure on wrist/knee/ear
- M. Advise patients to eat foods that contain tryptophan (eg, turkey)
29. Which if any of the following do you recommend for nausea/vomiting: \((n = 80)\)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prochlorperazine (Compazine®)</td>
<td>68%</td>
</tr>
<tr>
<td>Metoclopramide (Reglan®)</td>
<td>46%</td>
</tr>
<tr>
<td>Ondansetron (Zofran®)</td>
<td>46%</td>
</tr>
<tr>
<td>Dronabinol (Marinol®)</td>
<td>15%</td>
</tr>
<tr>
<td>Granisetron (Kytril®)</td>
<td>6%</td>
</tr>
</tbody>
</table>

30. Please rate the extent to which the following strategies for managing peginterferon-related anorxia are helpful in men and in women. \((1 = \text{very unhelpful} \, \text{to} \, 5 = \text{very helpful})\) \((n = 77)\)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smaller, more frequent meals</td>
<td>4.4</td>
<td>4.6</td>
</tr>
<tr>
<td>Nutritional supplements</td>
<td>4.1</td>
<td>4.1</td>
</tr>
<tr>
<td>Eating calorically dense foods</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Increased protein consumption</td>
<td>3.7</td>
<td>3.7</td>
</tr>
<tr>
<td>Avoidance of carbonated and gas-producing foods</td>
<td>3.5</td>
<td>3.6</td>
</tr>
<tr>
<td>Nutrition consult</td>
<td>3.3</td>
<td>3.5</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>3.1</td>
<td>3.2</td>
</tr>
<tr>
<td>Increased oral hygiene</td>
<td>3.0</td>
<td>3.1</td>
</tr>
<tr>
<td>Eating foods chilled or room temperature</td>
<td>2.7</td>
<td>2.8</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Adding spices/herbs to food</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Dronabinol</td>
<td>2.2</td>
<td>2.0</td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td>2.1</td>
<td>2.2</td>
</tr>
</tbody>
</table>

31. For management of hematologic side effects, how likely are you to: \((1 = \text{very unlikely} \, \text{to} \, 5 = \text{very likely})\) \((n = 75)\)

A. Initiate epoetin for anemia, without dose reduction/treatment discontinuation

B. Initiate G-CSF for neutropenia, without dose reduction/treatment discontinuation

C. Initiate epoetin for anemia, in conjunction with dose reduction/treatment discontinuation

D. Initiate G-CSF for neutropenia in conjunction with dose reduction/treatment discontinuation

E. Dose reduce/discontinue therapy according to the PI, without use of growth factors
32. Please rate the degree of benefit of each of the following in treating impaired concentration or memory loss in patients receiving anti-HCV therapy (rating 1 = no benefit to 5 = great benefit) \((n = 69)\)

A. SSRIs  
B. Psychostimulants (eg, methylphenidate, modafinil)  
C. Tricyclic antidepressants  
D. Opioid antagonists  
E. Corticosteroids

<table>
<thead>
<tr>
<th></th>
<th>No Benefit</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Great Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>1.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

33. Please rate the degree of benefit of each of the following in treating irritability or depression in patients receiving anti-HCV therapy (rating 1 = no benefit to 5 = great benefit) \((n = 75)\)

<table>
<thead>
<tr>
<th></th>
<th>Irritability</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep</td>
<td>4.5</td>
<td>3.9</td>
</tr>
<tr>
<td>Mild to moderate exercise</td>
<td>4.2</td>
<td>4.3</td>
</tr>
<tr>
<td>Paroxetine (Paxil®)</td>
<td>4.2</td>
<td>4.3</td>
</tr>
<tr>
<td>Adequate hydration</td>
<td>4.2</td>
<td>4.2</td>
</tr>
<tr>
<td>Avoidance of overstimulating environments</td>
<td>4.2 3.5</td>
<td></td>
</tr>
<tr>
<td>Meditation/relaxation techniques</td>
<td>4.1 3.9</td>
<td></td>
</tr>
<tr>
<td>Citalopram (Celexa™)</td>
<td>4.1</td>
<td>4.3</td>
</tr>
<tr>
<td>Small pleasures (eg, movies, music, friends, pets)</td>
<td>3.9 4.2</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine (Effexor®)</td>
<td>3.9</td>
<td>4.2</td>
</tr>
<tr>
<td>Sertraline (Zoloft®)</td>
<td>3.8</td>
<td>4.2</td>
</tr>
<tr>
<td>Fluoxetine (Prozac®)</td>
<td>3.7</td>
<td>4.0</td>
</tr>
<tr>
<td>Bupropion (Wellbutrin®)</td>
<td>3.5</td>
<td>3.9</td>
</tr>
<tr>
<td>Support groups</td>
<td>3.5</td>
<td>3.6</td>
</tr>
<tr>
<td>Mirtazapine (Remeron®)</td>
<td>3.4</td>
<td>3.5</td>
</tr>
<tr>
<td>Trazodone (Desyrel®)</td>
<td>3.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Cognitive-behavioral therapy</td>
<td>3.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Fluvoxamine (Luvox®)</td>
<td>3.1</td>
<td>3.0</td>
</tr>
<tr>
<td>Nefazodone (Serzone®)</td>
<td>2.7</td>
<td>2.8</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>2.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>2.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Foods high in tryptophan</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>Aromatherapy</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Drug holidays</td>
<td>2.1</td>
<td>2.0</td>
</tr>
<tr>
<td>Herbal therapies</td>
<td>1.7</td>
<td>1.7</td>
</tr>
</tbody>
</table>
34. Please rate how familiar you are with each of the following depression screening tools (1 = not at all familiar to 5 = very familiar) and how commonly you use each of the following tools to screen for depression in HCV-infected patients (1 = never to 5 = always). In the last column, please indicate whether there are any specific subgroups of patients for whom you are most likely to use each tool. \( n = 75 \)

<table>
<thead>
<tr>
<th>Screening Tool</th>
<th>How Familiar?</th>
<th>How Commonly used?</th>
<th>Applicable Population (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Center for Epidemiologic Studies–Depressed Mood Scale (CES-D)</td>
<td>3.3</td>
<td>3.2</td>
<td>• All HCV+ pts (15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Pts with a history of depression (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• VA patients</td>
</tr>
<tr>
<td>Beck Depression Inventory (BDI)</td>
<td>3.1</td>
<td>2.2</td>
<td>• All HCV+ pts (7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Pts with a history of depression (5)</td>
</tr>
<tr>
<td>Zung Self-Rating Depression Scale (ZSDS)</td>
<td>1.6</td>
<td>1.3</td>
<td>• All HCV+ pts</td>
</tr>
<tr>
<td>Hospital Anxiety and Depression Scale (HADS)</td>
<td>1.4</td>
<td>1.2</td>
<td>• All HCV+ pts</td>
</tr>
<tr>
<td>Psychological Distress Inventory (PDI)</td>
<td>1.5</td>
<td>1.3</td>
<td>• All HCV+ pts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Restricted to psychological consultation</td>
</tr>
<tr>
<td>Brief Symptom Inventory (BSI)</td>
<td>1.6</td>
<td>1.5</td>
<td>• All HCV+ pts for 6 weeks therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Used by some psych consultants</td>
</tr>
<tr>
<td>Montgomery-Asberg Depression Rating Scale (MADRS)</td>
<td>1.3</td>
<td>1.1</td>
<td>• All HCV+ pts</td>
</tr>
<tr>
<td>Neurotoxicity Rating Scale (NRS)</td>
<td>1.3</td>
<td>1.2</td>
<td>• All HCV+ pts</td>
</tr>
<tr>
<td>Other:</td>
<td>5.0</td>
<td>3.0</td>
<td>• All new pts</td>
</tr>
<tr>
<td>• Coping Skills Inventory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Assessment designed by myself</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

35. \( n = 77 \)

a. How common do you believe sexual dysfunction is among men taking peginterferon/ribavirin? (1 = very rare to 5 = very common) 3.5

b. How common do you believe sexual dysfunction is among women taking peginterferon/ribavirin? (1 = very rare to 5 = very common) 3.2

c. How likely are you to ask men receiving anti-HCV treatment about sexual dysfunction? (1 = very unlikely to 5 = very likely) 3.4

d. How likely are you to ask women receiving anti-HCV treatment about sexual dysfunction? (1 = very unlikely to 5 = very likely) 3.1

e. How often do you prescribe medications (eg, sildenafil citrate [Viagra®]) for patients who experience sexual dysfunction while on anti-HCV therapy? (1 = never to 5 = always) 2.7
36. Support groups
a. Do men attend support groups as frequently as women? \((n = 72)\)

- No: 51%
- Yes: 49%

b. Are support groups more helpful for? \((n = 69)\)

- Women: 86%
- Men: 3%
- Both, equally: 12%

- Women: 86%
- Older Patients: 8%
- Younger Patients: 6%
- Both, equally: 86%

d. Are support groups helpful for family members? \((n = 71)\)

- Yes: 100%

- No: 7%

- No: 7%
- Yes: 93%