Education Initiative in Gastroenterology

THE TREATMENT Tx REPORTER℠ GASTROENTEROLOGY

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Part 2 of 4: Treating Hepatitis C in Patients with a History of Depression

Dear Colleague:

With the availability of more effective therapies for chronic hepatitis C, the risk:benefit ratio has shifted, and now favors treatment for more patients. In June 2002, the National Institutes of Health (NIH) convened a Consensus Development Conference at which a nonpartisan panel drawn from institutions across the United States reviewed the state of knowledge on the management of hepatitis C. Arguably, one of the most noteworthy accomplishments of the final statement[1] is to broaden the range of patients who should be considered for treatment of hepatitis C. According to the statement, "All patients with chronic hepatitis C are potential candidates for antiviral therapy." The statement goes on to say that "efforts should be made to increase the availability of the best current treatments" to patients who "have been ineligible for trials because of injection drug use, significant alcohol use, age, and a number of co-morbid medical and neuropsychiatric conditions."

Neuropsychiatric conditions are common among persons infected with hepatitis C virus (HCV). These patients have historically been excluded from treatment for HCV infection because of the increased risk of neuropsychiatric side effects of interferon. The NIH statement opens the door to treating these patients, but provides little guidance on how to do so successfully. In this *Tx Reporter*, Part 2 of the series *Individual Patients, Individualized Care: Confronting the Multiple Challenges of Treating Today's Hepatitis C Patient*, distinguished psychiatrist Charles L. Raison, MD, explains how co-morbid neuropsychiatric conditions can be controlled to allow anti-HCV treatment, and how neuropsychiatric side effects of peginterferon can be prevented or treated in the majority of cases so as to allow for successful completion of peginterferon/ribavirin therapy, even in this high-risk population.

I hope you find this issue and the rest of the series informative and useful as you confront the new challenges of treating today's hepatitis C patients.

Sincerely,

Chair

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Part 2 of a 4-Part Series

Watch Your Mail for the Next Issue!

Inside This Tx REPORTER℠

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Coming soon:

Part 3: Treating Hepatitis C in Substance Abusers

Part 4: Utilizing Support Staff to Expand Patient Services

Now available at www.projectsinknowledge.com:

Part 1: One Size Does Not Fit All: Weight-Based Dosing of Peginterferon alfa-2b and Ribavirin

Part 2: Treating Hepatitis C in Patients with a History of Depression

Learning Objectives

This activity is designed for clinical specialists with a fundamental clinical understanding of assessment, diagnosis, treatment, and ongoing management of patients infected with hepatitis C virus (HCV).

After participating in this activity, the physician should be able to:

- Assess the appropriateness of treatment for a wide range of patient populations, including injection drug users on methadone maintenance therapy and patients with a history of depression
- Tailor treatments to specific patients by adjusting treatment dose according to body weight
- Optimize services and support provided to patients with HCV infection through expanded use of nonphysician clinical staff

CME Information

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This 4-part newsletter series 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 1 category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

Successful completion for 1 hour of CME credit requires a passing score of 70% or higher on the posttest. Full instructions for submission are included on the posttest accompanying this newsletter.

Disclosure

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Schering HEPATITIS INNOVATIONS

Introduction

It has been shown that adherence to the recommended doses and duration of peginterferon/ribavirin therapy, the most effective treatment available for chronic hepatitis C, correlates with successful treatment outcome.[2] However, neuropsychiatric effects are the most common side effects of peginterferon and one of the most common reasons for treatment discontinuation. Fortunately, psychiatric conditions, whether pre-existing or as side effects of peginterferon, do not always need to be treatment limiting, since they are often either preventable or treatable.

Addressing Co-morbid Neuropsychiatric Conditions

Many studies demonstrate that psychiatric disturbances, especially depression and anxiety, are more common in patients with medical illnesses than in the healthy population. HCV-infected patients are no exception. In fact, 35% to 57% of all chronic viral hepatitis patients may have depression upon hepatitis diagnosis.[3] Because pre-existing psychiatric symptoms may increase the risk of psychiatric morbidity during interferon-based therapy (Fig. 1), a complete psychiatric history should be taken and any pre-existing psychiatric conditions should be well controlled before treating HCV infection with peginterferon/ribavirin. Standardized screening tools, such as the *Beck Depression Inventory, Hamilton Depression Rating Scale, Hamilton Anxiety Scale,* or *Neurotoxicity Rating Scale* can be used to evaluate patients before starting peginterferon and should be repeated at every visit, especially in patients with a history of psychiatric disturbance. In addition to a history of depression, patients should also be screened for substance abuse, anxiety, panic attacks, and bipolar disorder.

For patients with neuropsychiatric disorders who are motivated to receive treatment for HCV infection, psychiatric treatment should be considered as a prelude to antiviral therapy. A growing literature documents that mood and anxiety disorders in medically ill patients respond well to antidepressant therapy. A well-controlled, double-blind study of melanoma patients demonstrated that the selective serotonin reuptake inhibitor (SSRI) paroxetine, given before initiation of interferon, is superior to placebo in preventing major depression and reducing the need for discontinuing high-dose interferon (Fig. 2).[4]

Addressing Neuropsychiatric Side Effects of Antiviral Therapy

Interferons, including peginterferon, are associated with behavioral side effects, especially depression, anxiety, irritability, fatigue, and cognitive dysfunction. Patients should be evaluated for depression at least every 2 weeks for the first 4 months of interferon-based therapy. Symptoms of interferon-induced depression include depressed mood, fatigue or loss of energy, anorexia, diminished appetite and/or weight loss, insomnia/hypersomnia, psychomotor retardation, inability to concentrate, and diminished interest in pleasurable activities.

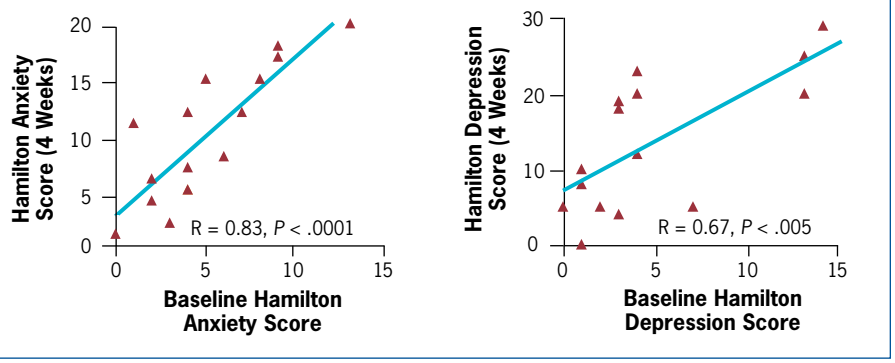

Figure 1. Predicting the Development of Anxiety and Depression in Patients Receiving High-Dose Interferon for Malignant Melanoma. Musselman DL, et al, unpublished data, 2001.

Depression may manifest as treatment-induced fatigue or irritability.

Recent data suggest that antidepressants are effective in treating mild to moderate depression that has developed in patients already receiving peginterferon. Behavioral therapy, support groups, and light regular exercise may also be beneficial. However, in the absence of symptom remission, moderate depression may warrant a reduction in peginterferon dose, and severe depression may require discontinuation of anti-HCV treatment, at least until the depression is controlled.

Choosing an Antidepressant

Any antidepressant is likely to be better than none in patients who develop or who are at high risk for interferon-induced depression. All newer antidepressants are generally safe, easy to use, and have mild side effects in most patients (Table 1). A prospective study reported that 79% (11/14) of patients who developed interferon-induced depression were able to complete anti-HCV treatment with concomitant paroxetine treatment.[5] Depression scores declined significantly in all treated patients. Case reports and small case series also suggest efficacy for fluoxetine, sertraline, citalopram, and nefazodone.[6-8] Because several effective options are available, choice of antidepressant should be guided by several criteria: drug-drug interactions, side effects, and speed of onset of action (Table 1). Antidepressant agents that target both norepinephrine and serotonin (eg, venlafaxine, mirtazapine, or SSRIs plus bupropion or desipramine) may be particularly effective and have a rapid onset of action in the treatment of major depression.[9-12]

Many medicines are capable of increasing blood levels of commonly used antidepressants through effects on the cytochrome P450 system in the liver. Because newer antidepressants are nontoxic, these potentially increased blood levels are generally not a clinical problem. However, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) can be lethal when combined with medicines that interact with the P450 system. Thus, TCAs and MAOIs should generally be avoided in patients with medical illnesses that require multiple medications. Venlafaxine, mirtazapine, bupropion, and citalopram have the least risk of drug-drug interactions when used in combination with other medications.

Regardless of which antidepressant is selected, a low initial dose should be used, particularly in patients with anxiety, panic, or somatic manifestations. The dose may then be increased to achieve a therapeutic dose (Table 1). Patients should be informed that it will take 2 to 6 weeks before a response to antidepressants can be expected, and 4 to 8 weeks before a full remission of depressed mood and anxiety is likely.

Case Study

Brad, a 38-year-old investment banker, is diagnosed with HCV infection. He weighs 178 lb. His lab values include an alanine

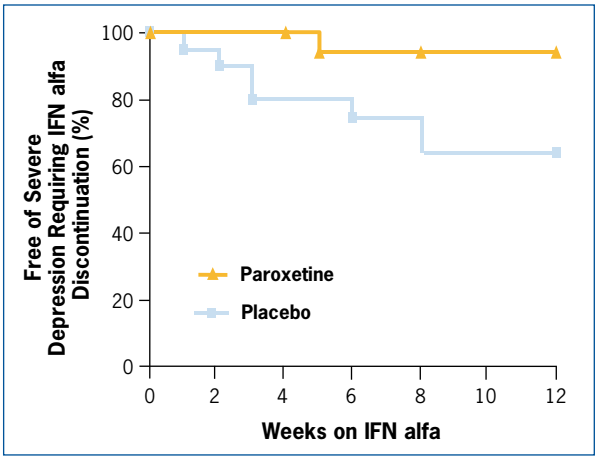

Figure 2. Paroxetine Pretreatment Reduced the Rate of Treatment Discontinuation Due to Severe Depression or Neurotoxicity During First 12 Weeks of Interferon alfa in Patients with Malignant Melanoma.[4] Reprinted with permission from Musselman DL, Lawson DH, Gumnick JF, et al. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med.* 2001;344:961-966.

Table 1. Newer Antidepressants: Dosing and Safety.

Antidepressant*	Starting Dose (mg/d)	Therapeutic Dose (mg/d)	Side Effects	CYP450 Enzyme Inhibitory Potential 1A2	2C	2D6	3A4
Sertraline	25–50	50–200	Anxiety, GI complaints, insomnia, sexual problems, sweating, headaches, weight gain (with long-term use)	0	++	+	+
Fluoxetine	10–20	20–80		0	++	++++	++
Fluvoxamine	100	100–300		++++	++	0	+++
Paroxetine	10–20	20–80		0	0	++++	0
Citalopram	20	20–60		0	0	0	0
Venlafaxine	37.5	75–450	GI complaints, anxiety, sexual problems, sweating, headaches, increased BP (with >150 mg/d)	0	0	0 (metabolite +)	0
Mirtazapine	15–30	15–60	Significant weight gain, somnolence, rare agranulocytosis, no sexual side effects, sleep promoting	0	0	0	0
Nefazodone	50	300–600	Somnolence, nausea, dizziness, very rare fatal liver failure (1 in 300,000), low rate of sexual side effects, sleep promoting	0	0	0	++++
Bupropion†	75	300–450	Anxiety, GI upset, potential for increased seizure risk with HIV protease inhibitors, no sexual side effects	0	0	0/+	0

*Avoid TCAs (amitriptyline, nortriptyline, desipramine, imipramine) and MAOIs, which have a high risk of lethality in overdose, which may occur as a result of interactions with other drugs. †May interact with drugs that affect CYP450 2B6.

aminotransferase level of 80 IU/L, HCV RNA level of 450,000 copies/mL, and HCV genotype 1a. Liver biopsy shows grade 3 inflammation and stage 2 fibrosis. Brad appears anxious during his examination. He reports a history of two major depressive episodes, at ages 26 and 32 years. He has not seen his psychiatrist in the past 3 years and is not currently taking psychotropic medication. His *Beck Depression* and *Anxiety Inventory* scores are mildly elevated.

Brad is started on prophylactic citalopram 20 mg/d. Two weeks later, he begins anti-HCV treatment with peginterferon/ribavirin. Standardized instruments are used every 2 weeks during the first 4 months to monitor for psychiatric side effects. At week 4 of peginterferon/ribavirin, Brad says he has no complaints, except that he is finding it a little harder to concentrate and do his work. At week 8, his wife calls and tells the nurse that Brad is irritable and morose and is not doing his share of the childcare. Brad's HCV RNA level is 3000 copies/mL.

Brad agrees to resume seeing his psychiatrist, who asks him to bring his wife in for a visit within a week of the call. During the visit they discuss Brad's irritability. He is not exhibiting manic symptoms (which can be induced or exacerbated by interferon). Brad is experiencing depressed mood, low energy, and feelings of hopelessness, and displays signs and symptoms of psychomotor retardation. He is not suicidal. The psychiatrist increases his citalopram dose to 40 mg/d. She also recommends counseling, but Brad defers. At the higher dose of citalopram, Brad's irritability and mood improve. He is HCV RNA negative at week 24 of treatment, and he ultimately completes 48 weeks and has a sustained virologic response. He and his wife are planning a second honeymoon to celebrate.

Discussion

Brad's anxiety on examination is a red flag, particularly in light of his history of depressive episodes, that he would be at increased risk for peginterferon-induced psychiatric side effects. This is confirmed by the elevations in *Beck Depression* and *Anxiety Inventory* scores. He was started on a prophylactic antidepressant, which may have minimized the severity of the psychiatric side effects he experienced, and those side effects were ultimately successfully controlled when the citalopram dose was increased. High-risk patients like this one are often best cared for by a multidisciplinary team that includes a psychiatrist who can be involved in ongoing evaluation of the patient and management of any psychiatric symptoms that do occur during anti-HCV therapy. However, when psychiatric care is not readily available or when patients refuse such care, it is often still possible for gastroenterologists to manage psychiatric side effects using newer antidepressants and through careful, regular monitoring and communication with the patient and family. Nurses can play an important role in maintaining contact with the patient via frequent phone calls. In this case study, a patient who previously might have been excluded from treatment based on his psychiatric history and presence of anxiety during baseline examination is able to successfully complete anti-HCV therapy with aggressive monitoring and side effect management, ultimately achieving a sustained virologic response.

Conclusion

In conclusion, although co-morbid psychiatric disorders and psychiatric side effects are common in HCV-infected patients, especially while on peginterferon therapy, effective treatments are available. With close mental health follow-up and careful selection of appropriate management strategies, such effects may not have to interrupt potentially lifesaving therapy in the majority of patients.

References

1. National Institutes of Health Consensus Development Conference Statement. Management of Hepatitis C: June 10–12, 2002. Available at: http://consensus.nih.gov. Final statement accessed August 26, 2002.
2. McHutchison JG, Manns M, Patel K, et al. Adherence to combination therapy enhances sustained response in genotype-1–infected patients with chronic hepatitis C. *Gastroenterology*. 2002;123:1061-1069.
3. Zdilar D, Franco-Bronson K, Buchler N, Locala JA, Younossi ZM. Hepatitis C, interferon alfa, and depression. *Hepatology*. 2000;31:1207-1211.
4. Musselman DL, Lawson DH, Gumnick JF, et al. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med*. 2001;344:961-966.
5. Kraus MR, Schafer A, Faller H, Csef H, Scheurlen M. Paroxetine for the treatment of interferon-alpha-induced depression in chronic hepatitis C. *Aliment Pharmacol Ther*. 2002;16:1091-1099.
6. Schramm TM, Lawford BR, Macdonald GA, Cooksley WG. Sertraline treatment of interferon-alfa-induced depressive disorder. *Med J Aust*. 2000;173:359-361.
7. Gleason OC, Yates WR, Isbell MD, Philipsen MA. An open-label trial of citalopram for major depression in patients with hepatitis C. *J Clin Psychiatry*. 2002;63:194-198.
8. Schafer M, Schmidt F, Amann B, Schlosser S, Loeschke K, Grunze H. Adding low-dose antidepressants to interferon alpha treatment for chronic hepatitis C improved psychiatric tolerability in a patient with schizoaffective psychosis. *Neuropsychobiology*. 2000;42(suppl 1):43-45.
9. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry*. 2001;178:234-241.
10. Menza MA, Kaufman KR, Castellanos A. Modafinil augmentation of antidepressant treatment in depression. *J Clin Psychiatry*. 2000;61:378-381.
11. Nierenberg AA. Do some antidepressants work faster than others? *J Clin Psychiatry*. 2001;62(suppl 15):22-25.
12. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med*. 1992;326:1250-1256.

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Education Initiative in Gastroenterology

THE TREATMENT REPORTER℠ GASTROENTEROLOGY

CME Posttest

Individual Patients, Individualized Care: Confronting the Multiple Challenges of Treating Today's Hepatitis C Patient

Part 2 of 4: Treating Hepatitis C in Patients with a History of Depression

CME Instructions

To receive documentation of participation in this four-part CME activity for a total of 1.5 hours of CME credit, please complete the following steps:

1. Read each newsletter carefully.
2. Photocopy and complete the CME posttest included in each of the four parts.
3. **Mail or fax each of the completed posttests to Projects In Knowledge, One Harmon Plaza, Secaucus, NJ 07094; fax: 1-201-617-7333.**
4. After reading the fourth part, complete the CME evaluation survey and mail or fax it together with the final posttest by December 31, 2003, to Projects In Knowledge at the address or the fax number above.

CME Certificate

At the end of the series, Projects In Knowledge will mail you a certificate of completion for this activity if your combined score for all four posttests is 70% or higher. If your combined score is lower than 70%, you will be notified by mail and will be given an opportunity to take a single test covering information from all four parts.

Name _____ Degrees/Credentials _____

Mailing Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

E-mail _____

Please indicate your answers below.

1. Pre-existing anxiety or depression may increase the risk of psychiatric morbidity during interferon-based therapy.

   ❒ True ❒ False

2. In a well-controlled, double-blind study of patients with malignant melanoma, paroxetine given before initiation of high-dose interferon was superior to placebo in:

   a. Preventing major depression
   b. Reducing the need for discontinuation of interferon
   c. Both of the above
   d. None of the above

3. Which of the following antidepressants is associated with a high risk of lethality if blood levels become elevated due interactions with other drugs that utilize the cytochrome P450 pathway?

   a. Fluoxetine b. Amitriptyline c. Mirtazapine d. Venlafaxine

4. Which of the following antidepressants is the least likely to be associated with sexual side effects?

   a. Venlafaxine b. Paroxetine c. Sertraline d. Bupropion

5. A full medical response (ie, remission of depressed mood and anxiety) is expected within 2 to 4 weeks of starting an antidepressant.

   ❒ True ❒ False