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Minimizing the Impact of Neuropsychiatric Effects During Chronic HCV Disease and Treatment

New data are emerging that implicate direct effects of the hepatitis C virus (HCV) on the central nervous system, along with side effects of both peginterferon and ribavirin as causes of multiple symptoms during treatment of HCV. Neuropsychiatric symptoms are of great concern in patients with hepatitis C because they are common, may reduce quality of life, and can limit treatment adherence and effect the outcome of treatment. To improve patient well-being and the likelihood of successful anti-HCV therapy, it is critical that physicians screen patients for neuropsychiatric symptoms and manage these problems and symptoms proactively.

Pre-existing neuropsychiatric symptoms are common in hepatitis C patients. In fact, 35% to 57% of patients with chronic HCV infection may have depression upon

diagnosis or before starting any therapy. Furthermore, new neuropsychiatric symptoms emerge in an additional 30% to 40% of patients receiving peginterferon/ribavirin treatment. Cognitive deficits, particularly those affecting concentration, memory, and psychomotor speed, have been identified in patients with even mild HCV infection as well.

The pathophysiology of these toxic effects of HCV remain poorly defined. One theory is that HCV may infect the brain via macrophage or microglial cells. Another is that toxins may accumulate in the blood secondary to impaired clearance by a cirrhotic liver, causing impaired cognition. Cirrhosis may be predictive of poorer cognitive function due to clinical or subclinical encephalopathy, and progressive hepatic injury in the HCV-infected patient without cirrhosis also may play a role in the development of neurocognitive problems although this

is rarely seen in patients without significant fibrosis and portal hypertension. Antiserotonergic effects of interferon have been proposed as a mechanism in the development of interferon-related depression and may explain why patients symptoms from interferon therapy can be profoundly improved with SSRI type antidepressants.

A recent prospective cohort study found that although only 11% of patients treated with peginterferon/ribavirin met criteria for major depression, yet more than one third developed symptoms of moderate to severe depression during treatment. Whereas interferons are generally known to be associated with psychiatric side effects, this study was one of the first to identify a dose-related association between PEG interferon/ribavirin treatment and depression.

Due to the chronic nature and nonspecific symptoms of HCV infection,

distinguishing the somatic complaints of disease chronicity from a depressive syndrome is a major clinical challenge. Patients with major depression often feel ill, experiencing somatic and/or cognitive symptoms and a perceived state of "brain fog" and other

extreme situations, suicidal ideation or suicide. It is therefore not surprising that depression can have a negative impact on adherence to anti-HCV therapy. Moreover, another prospective cohort study found a correlation between depression symptoms and clear-

remote history of depression may be controversial; but recent studies have shown a benefit and proactive antidepressant therapy is strongly advised in clinical practice, both from this author's clinical experience and from surveys of practitioners who manage

or psychosis, should be referred for expert psychiatric diagnosis and management prior to treatment initiation. Patients with a pre-existing history of bipolar disorder should be monitored closely while receiving interferon therapy, and, whenever possible, treated prophylactically with a mood stabilizer such as olanzapine or quetiapine (lithium or valproic acid can also be considered, with close follow-up). Any patient for whom the medical practitioner is not comfortable starting antidepressant therapy should be referred for clearance before starting anti-HCV treatment, and psychiatric follow-up should continue periodically during therapy.

In summary, neuropsychiatric symptoms are common in HCV-infected patients both at baseline and as side effects of peginterferon therapy. Without appropriate intervention, these symptoms can have serious consequences for the patient and can also limit adherence to, and therefore success of, antiviral therapy. Fortunately, depression and other neuropsychiatric side effects can generally be managed effectively with available pharmacologic therapies, thereby allowing patients to stay on anti-HCV therapy with the best chance of treatment success.

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symptoms that impair the patients functional level. These symptoms can easily be confounded by the presence of a chronic HCV infection. Nonsomatic symptoms of depression may include low self-esteem, feelings of guilt, worthlessness, hopelessness, and in the most severe cases, suicidal ideation. Some depression screening tools-such as the Hospital Anxiety and Depression Scale (HADS)-are geared toward assessment of nonsomatic symptoms of depression, and may be useful in HCV-infected patients who exhibit symptoms of major depression. The Center for Epidemiologic Studies of Depression (CES-D) self-administered scoring sheet also may be useful in an office practice.

The impact of depression on the patient can be significant, causing irritability, fatigue, apathy, lack of concentration, and in

ance of HCV RNA at week 24, even after adjusting for ribavirin dose assignment, genotype, age, antidepressant usage, dose reduction of peginterferon or ribavirin, and knowledge of viral status during treatment. Periodic assessment for depression during treatment is imperative, with expert psychiatric referral provided as needed if signs and symptoms of depression progress during treatment.

Profound improvement can be achieved with antidepressant pharmacotherapy and formal psychotherapy for treatment of depression. There are no placebo-controlled studies evaluating the treatment of interferon-induced depression. An open-label trial of citalopram conducted in 15 patients with HCV infection demonstrated a significantly positive response in interferon-treated patients. Prophylactic therapy in patients with a recent or

HCV treatment. Patients with major depression may also benefit from support groups, but this should not be a replacement for pharmacologic therapy and psychotherapy.

Pharmacologic guidelines for general treatment of neuropsychiatric disorders may offer the best approach to managing depression in the peginterferon-treated patient. These guidelines emphasize individualized selection of an agent, often exploiting the side-effect profile of the various medications available. For example, agents that promote sleep may be most appropriate for patients who have a primary sleep disturbance, whereas patients experiencing fatigue may benefit most from activating agents.

Patients with a history of major depression or significant depressive symptoms including history of suicide attempts, or bipolar disorder

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