

Letters

Novel Treatment Strategies for Depression in Patients With Hepatitis C

TO THE EDITOR: Major depressive disorder and increased depressive symptoms are common in patients with hepatitis C viral infection (HCV), especially during antiviral treatment with interferon-alpha (IFN- α)-based therapies.¹ We read with great interest the case reports by Schaefer et al.,² in which they described three patients with HCV who were treated with tryptophan as either an augmentation strategy or as a monotherapy for depressive symptoms associated with HCV and exposure to IFN- α . By increasing the availability of tryptophan for conversion into serotonin, the authors hypothesized that tryptophan “may have specific antidepressant effects in patients with depression during chronic HCV or during and after antiviral treatment

with IFN- α .” They found that the depressive symptoms improved in all three cases.

Although the possible influence of a placebo effect was not mentioned in the context of these positive outcomes, the results of their case reports are encouraging and support the need for more research to improve the efficacy of current antidepressant treatment strategies.

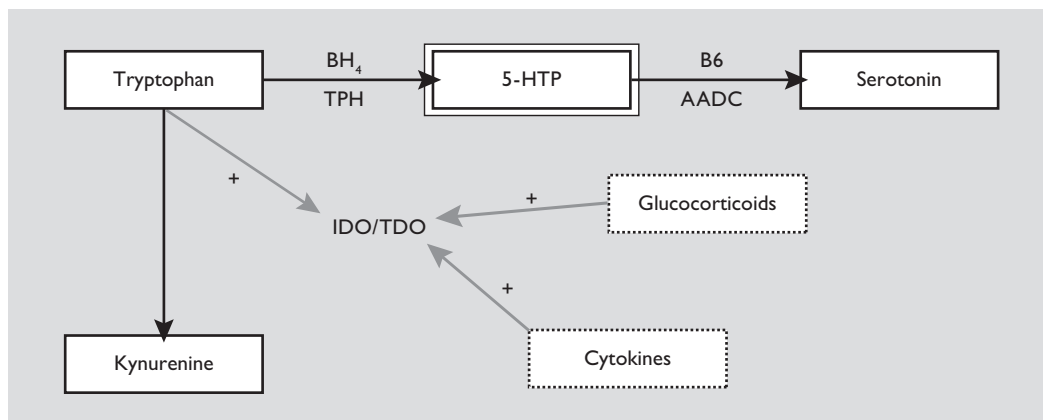
A vast body of literature supports the theory that normal mood depends in part on sufficient serotonin stores. We propose that if the goal of tryptophan supplementation or treatment is ultimately to increase serotonin levels, there may be a more direct approach—one that could additionally avoid the risk of exacerbating IFN-induced production of neurotoxic metabolites, such as kynurenine and quinolinic acid. Thus, an additional consideration in the use of tryptophan for the treat-

ment of depression (particularly during IFN- α therapy) is that tryptophan can regulate its own catabolism via the induction of indoleamine 2,3-dioxygenase (IDO) or tryptophan 2,3-dioxygenase (TDO; see Figure 1).³

At supraphysiologic concentrations, tryptophan increases the activity of TDO five- to sixfold in rat hepatocytes, resulting in a sixfold increase in the production of kynurenine, at the expense of serotonin. (See reviews in Turner and Blackwell, 2005,³ and Turner et al., 2006.⁴) Therefore, increased dietary intake of tryptophan may be an inefficient means of increasing brain serotonin.

A more efficient way of increasing brain serotonin may be to intervene one metabolic step beyond tryptophan by administering 5-hydroxytryptophan (5-HTP), the immediate precursor of serotonin. 5-HTP is hypothesized to normalize serotonin synthesis, which

FIGURE 1. Biochemical Regulation of 5-HTP



The enzymes and cofactors involved in the reactions are listed next to the bold black arrows. The induction of cytokines, a family of proteins that mediate and regulate immunity, inflammation, and hemopoiesis, can modulate the availability of 5-HTP. Proinflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin (IL)-1, IL-2, and IFN- γ affect serotonin metabolism by stimulating or enhancing the stimulation of IDO, which leads to a peripheral depletion of tryptophan, which, in turn, leads to depletion of 5-HTP and serotonin, making less tryptophan available for conversion to 5-HTP and serotonin. Glucocorticoids have also been shown to induce TDO activity, which is important, given that a number of patients with depression have elevated cortisol levels. The arrows and the plus signs indicate increases in the metabolites and enzymes shown.

AADC: aromatic L-amino acid decarboxylase; B6: pyridoxine; BH₄: L-erythro-tetrahydrobiopterin; 5-HTP: L-5-hydroxytryptophan; IDO: indoleamine 2,3-dioxygenase; IFN: interferon; TDO: tryptophan 2,3-dioxygenase; TPH: tryptophan hydroxylase.

From Turner and Blackwell, © 2005.³ Used by permission.

is related to its putative antidepressant properties.^{3,4} Produced commercially by extraction from the seeds of the African plant *Griffonia simplicifolia*, 5-HTP has been used clinically for over 30 years. 5-HTP easily crosses the blood–brain barrier and effectively increases central nervous system (CNS) synthesis of serotonin. Consequently, supplementation with the serotonin precursor 5-HTP should normalize serotonin synthesis despite increased IDO activity.

Although not all studies support a relationship between peripheral serotonin and tryptophan levels and depression, IFN- α therapy is associated with significant decreases in peripheral serotonin levels⁵ and is also known to cause depression in 30% to 40% of patients.¹ This IFN-induced depression has been attributed to the activation of the cytokine network (i.e., IFN- γ) and IDO, resulting, in part, in perturbations of the serotonergic system. To the extent that this is the mechanism for IFN-induced depression, it should be treatable with exogenous 5-HTP.^{3,4} However, most of the clinical trials involving the use of 5-HTP for depression were conducted 20-or-more years ago, and more research is needed to address questions regarding its efficacy and safety in patients with HCV and other chronic liver diseases.

Jennifer M. Loftis, Ph.D.
 Research & Development
 Portland VA Medical Center
 Dept. of Psychiatry
 Oregon Health & Science University
 Portland, OR

Erick H. Turner, M.D.
 Div. of Mental Health and Clinical
 Neurosciences
 Portland VA Medical Center
 Dept. of Psychiatry
 Oregon Health & Science University
 Portland, OR

References

1. Loftis JM, Hauser P: The phenomenology and treatment of interferon-induced depression. *J Affect Disord* 2004; 82:175–190
2. Schaefer M, Winterer J, Sarkar R, et al: Three cases of successful tryptophan addition or monotherapy of hepatitis C and IFN- α -associated mood disorders. *Psychosomatics* 2008; 49:442–446
3. Turner EH, Blackwell AD: 5-Hydroxytryptophan plus SSRIs for interferon-induced depression: synergistic mechanisms for normalizing synaptic serotonin. *Med Hypotheses* 2005; 65:138–144
4. Turner EH, Loftis JM, Blackwell AD: Serotonin a la carte: supplementation with the serotonin precursor 5-hydroxytryptophan. *Pharmacol Ther* 2006; 109:325–338
5. Loftis JM, Morasco BJ, Menasco DJ, et al: Serotonin levels are associated with sustained viral response rates in HCV patients undergoing interferon-based therapy beyond the effects of demographic and disease-related factors. Abstract presented at the 13th International Symposium on Viral Hepatitis and Liver Disease, Washington, DC, March 20–24, 2009

Assessment of Decision-Making Capacity in Patients with Mental Illness

TO THE EDITOR: I read with interest the case report on simple schizophrenia in a patient with breast cancer by Moini and Levenson in the January–February (2009) issue of *Psychosomatics*.¹ We have been involved in similar cases with similar negative outcomes. The authors appropriately emphasize the importance of recognition of this and related psychiatric illness that may interfere with medical treatment so that efforts can be made that might improve adherence and clinical outcome. Assessment of decision-making capacity in patients with mental illness is another relevant issue in this case, and this can present challenging clinical and ethical questions.

The case report describes the poor

decisions made by a woman with simple schizophrenia regarding the treatment of her breast carcinoma. It also describes the positive intent on the part of the treatment team as they tried to compel this patient to acute (immediate) and follow-up oncologic care. It is a sad case, with an unfortunate ending, and it gives rise to the important question: When can we compel someone to involuntary medical treatment, and on what grounds?

The authors report on a patient with schizophrenia, but without hallucinations, delusions, depression, mania, suicidality, delirium, or dementia, who decided against further inpatient cancer treatment and left the hospital against medical advice (AMA). She appeared at first visit to understand the key elements of her medical diagnosis and proposed treatment, and thus was allowed to make the decision to leave the hospital AMA. She re-presented years later with a fungating chest-wall mass and a diagnosis of Stage IV unresectable breast carcinoma.

Looking back, I wonder if one can make an argument for exploring involuntary treatment based on the idea that this patient lacked more nuanced insight into the risks and benefits of treatment, and that this more subtle lack of insight may have had its roots in her psychosis. Although the authors describe no clear finding of a thought disorder, one might argue that her manifest behavior, isolation, homelessness, lack of hygiene, and affective constriction were reflective of some degree of cognitive disorganization that, when brought to bear on her medical illness, adversely affected her decision-making capacity.

Informed-consent doctrine demands that clinicians assess the adequacy of a patient’s insight into the risks and benefits of both proposed