Reply:

We acknowledge the interest shown by Drs. Kalaityakis and Bjornsson and by Paparrigopoulos and coworkers in our study. We did evaluate for the side effects of lactulose in our patients but none of them reported it. Patients in the treatment arm were explained the mechanism of action of lactulose and were told that for lactulose to be effective it was desirable to titrate their dose to get 2-3 semisoft stools daily. Therefore, it is unlikely that gastrointestinal symptoms (diarrhea) due to lactulose had any significant effect on health-related quality of life (HRQOL) in the patients included in our study.

Several other factors could be responsible for gastrointestinal symptoms and impaired HRQOL in patients with cirrhositic liver. As studied by Kalaityakis et al,[1] Child-Pugh score and gastrointestinal comorbidities such as ulcerative colitis, Crohn's disease and untreated celiac disease could also affect the HRQOL negatively. None of these gastrointestinal co-morbidities were present in our study population. Moreover the majority of patients in our study had Child's A or B cirrhosis and only 13% were in Child's C class. Finally, we agree with Drs. Kalaityakis and Bjornsson that improved patient awareness about the actions of lactulose could potentially help in decreasing its side effects, as has been demonstrated in our study.

In a second letter, Paparrigopoulos and coworkers showed their concern regarding ammonia as a cause for cognitive deficits in our patients with minimal hepatic encephalopathy (MHE), which could be related to chronic abuse of alcohol. Ammonia has been suggested to be a key factor in the pathogenesis of MHE.[2] Additional convincing evidence that ammonia may be responsible for the pathogenesis of this syndrome has come from a study by Minguez and coworkers.[3] This study shows that at least 50% of patients with portal vein thrombosis exhibit impairment of neuropsychological tests associated with high ammonia levels after the administration of glutamine, and abnormalities on magnetic resonance imaging and spectroscopy that are indicative of increased metabolism of ammonia in the brain. Further, cognitive/ neuropsychological deficits improve with treatment modalities that reduce ammonia level, for example, lactulose[4] and probiotics.[5] We did not measure ammonia levels in our patients; therefore, ammonia as pathogenetic mechanism in our patients remains at best speculative.

Chronic alcohol abuse or associated comorbidities, such as mood and anxiety disorders, psychotic disorders and personality disorders may produce cognitive/neuropsychological deficits and may be reversible on abstinence.[6,7] Although we can not totally exclude the long-lasting toxic effect of alcohol leading to neuropsychological deficits in our patients, however, it is unlikely for several reasons. First, a majority of our patients with alcoholic cirrhosis were abstaining from alcohol for a long time; recent literature suggests metabolic and morphological recovery following short- and long-term abstinence.[6,7] Second, the prevalence of MHE (neuropsychological deficits) was not higher in patients with cirrhosis caused by alcohol than in patients whose cirrhosis was not caused by alcohol. Multivariate analysis showed that alcohol etiology was not a factor for poor health-related quality of life or improvement in it following lactulose treatment. Finally, although a detailed psychiatric evaluation was not done by a trained psychiatrist, none of the patients included in this study had known psychiatric illness.

We agree with Paparrigopoulos et al. that a long lasting effect of alcohol on cognitive/neuropsychological deficits and comorbidity with various psychiatric conditions should not be underestimated while speculating pathogenic mechanisms in these patients. Future studies should include detailed psychiatric evaluation of these patients to exclude the effect of undiagnosed psychiatric illnesses such as depression on neuropsychiatric evaluation.

RADHA K. DHIMAN, M.D., D.M., FACG
AJAY DUSEJA, M.D., D.M., FACG
YOGESH K. CHAWLA, M.D., D.M., FACG
Department of Hepatology
Postgraduate Institute of Medical Education & Research
Chandigarh, India

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Hepatitis C Treatment, Subcutaneous Naltrexone Implants, and Methadone Maintenance Treatment

To the Editor:

We read with interest the article by Jeffrey et al. on antiviral treatment of chronic HCV infection in injection drug users who had received subcutaneous naltrexone implants.[1] The authors are to be commended for their efforts in treating a population which does not always receive such a high level of care for liver diseases.

The authors do not provide information on the magnitude, duration, and specific type of injection drug use in their patients. Also, they do not indicate whether their patients are representative of most injection opiate users seen in Australia. Does the clinic where the study was conducted treat all opiate users or only selected groups? It is possible that the patients in this study had not self-administered opiates long enough to develop the well-documented

humoral and cellular immunologic abnormalities seen in more chronic injection drug users.[2] This may be a factor in the high rate of sustained virological response (SVR) to antiviral therapy reported by Jeffrey et al. The accompanying editorial[3] discusses several additional explanations for the high SVR.

The authors propose that subcutaneous naltrexone implants may have advantages over methadone maintenance in modulating the immune response in former opiate users who will receive antiviral therapy. We and others have reported profound immunologic abnormalities in heroin addicts, and others have reported suppression of specific components of the immune response by the short-acting opiate morphine.[2] In chronic maintenance treatment with the long-acting opiate methadone (median duration of treatment: 16 years), we described normalization of several parameters of cellular immunity, including natural killer cell activity.[2,4] Several groups reported satisfactory SVR rates for hepatitis C treatment in former long-term heroin addicts treated with methadone maintenance.[3]

Addiction is a chronic disease. Methadone maintenance treatment has been in clinical use for more than 40 years,[5] has been validated by extensive long-term studies,[6] and has been endorsed by a NIH consensus conference.[7] The articles cited for addiction treatment outcomes of subcutaneous naltrexone implants describe follow-ups of 2 and 13 months, respectively, for 2 impaired physicians[8] and no follow-up of 17 pregnant addicts.[9] Long-term studies of subcutaneous naltrexone implants have been initiated in order to determine the role of this medication in the chronic treatment of addiction.

We look forward to further studies by Jeffrey et al. in patients with addictive diseases. We agree with others who have suggested that expertise in both hepatology and the study of chemical dependency will lead to better outcomes in treatment of persons with addiction and chronic hepatitis C.[10]

DAVID M. NOVICK, M.D.[1,2,3]
MARY JEANNE KREEK, M.D.[1]
[1]*The Rockefeller University, New York, NY*
[2]*Kettering Medical Center, Kettering, OH*
[3]*Wright State University Boonshoft School of Medicine, Dayton, OH*

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