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Lactulose Treatment for Hepatic Encephalopathy, Gastrointestinal Symptoms, and Health-Related Quality of Life

To the Editor:

We read with great interest the article by Prasad et al.[1] regarding the effect of lactulose therapy on cognitive function and health-related quality of life (HRQOL) in patients with cirrhosis and minimal hepatic encephalopathy. The authors randomly assigned 61 patients with minimal hepatic encephalopathy to receive lactulose treatment or no treatment in a nonblinded fashion. After 3 months of therapy, the lactulose-treated group exhibited significant improvement in cognitive function (measured by means of 6 neuropsychiatric tests) and HRQOL (measured by means of the Sickness Impact profile) compared with the untreated group of patients with minimal hepatic encephalopathy. Thus, this study provides important data supporting the concept that hepatic encephalopathy *per se* is linked to HRQOL impairment in cirrhosis and that lactulose treatment may help improve both cognition and HRQOL in this group of patients.

Several factors have been reported to influence HRQOL in patients with cirrhosis, including cirrhosis severity,[2] cirrhosis-specific symptoms such as muscle cramps and pruritus,[2] hepatic encephalopathy (overt or minimal),[2,3] and psychological factors.[4] Recently, we performed a prospective study evaluating gastrointestinal symptom severity and HRQOL in 128 consecutive patients with liver cirrhosis using validated questionnaires.[5] We found that patients with liver cirrhosis showed increased severity of gastrointestinal symptoms compared with a control population, which was associated with impaired HRQOL. Twenty-nine percent of patients with cirrhosis included in our study were taking lactulose as a treatment for hepatic encephalopathy, and, interestingly, lactulose treatment was found to be independently related to gastrointestinal symptom severity. Daily lactulose use was also negatively related to HRQOL expressed as the physical SF-36 component summary score (biseral correlation coefficient $r = -0.27$; $P < 0.005$).[5]

Lactulose is known to accelerate colonic transit,[6] and, due to a narrow therapeutic window, it can lead to diarrhea. Colonic lactulose fermentation can also induce bloating and abdominal distension.[7] Although lactulose is known to induce gastrointestinal symptoms,[8] this has only rarely resulted in withdrawal of therapy.[9] However, gastrointestinal side effects have only vaguely been reported in clinical trials evaluating the effect of lactulose on hepatic encephalopathy.[10]

In the article by Prasad et al., it is mentioned that none of the patients reported side effects related to lactulose therapy[1] but it is unclear whether patients included were actively evaluated for the occurrence and severity of gastrointestinal symptoms. Although it is unlikely that gastrointestinal symptoms due to lactulose had any significant effect on HRQOL in the patients included in this study,[1] it should be noted that lactulose use as a treatment of hepatic encephalopathy in everyday clinical practice (that is, outside the controlled conditions of a clinical trial) may be implicated in increased gastrointestinal symptom severity and, consequently, reduced HRQOL. Improved physician and patient awareness about the actions of lactulose could potentially help decrease its side effects.

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Should Impaired Liver Function Be Held Responsible for Cognitive Impairment and Poor Health-Related Quality of Life in Alcoholic Cirrhosis?

To the Editor:

In their study in HEPATOLOGY, Prasad et al.[1] showed that lactulose administered to patients with cirrhosis who have minimal hepatic encephalopathy considerably improves cognitive functions and consequently health-related quality of life. In this context, the authors suggested that ammonia plays the key role in the observed cognitive deficits. However, in the description of their sample, approximately 60% of the studied population is reported as having cirrhosis due to alcohol abuse.

It is well established that chronic alcohol abuse produces measurable and often long-lasting cognitive/neuropsychological deficits and morphological brain damage, through the intricate direct and indirect toxic effects of alcohol on the central nervous system,[2] that are independent of liver function impairment[3]; therefore, these deficits should not be attributed primarily to high ammonia levels. It remains an unresolved issue whether these deleterious functional, metabolic, and structural effects are quickly and fully reversible, as recently proposed by various researchers[4,5]; instead, everyday clinical practice and research evidence show that several months or maybe years of abstinence are necessary for the recovery of neurocognitive functions.

Furthermore, the frequent comorbidity of alcohol abuse/dependence with various psychiatric conditions, that is, mood and anxiety disorders, psychotic disorders, and personality disorders,[6] which may at least transiently compromise the mental state and, consequently, a neuropsychological assessment, is a potential influencing factor that needs to be minutely screened for and ruled out before conclusions are reached. For instance, it has been repeatedly reported that 30%-40% of alcohol-dependent individuals fulfill the criteria for a major depressive episode at some time in their lives.[6,7] Moreover, it has been emphasized that there is a complex relationship between alcohol dependence and mood disorders and that the clinical distinction between alcohol-induced and independent major depressive episodes may be difficult to make without the necessary expertise and follow-up assessments.[7] Depression is characterized by, among other things, psychomotor agitation or retardation and impaired concentration and thinking, which cause significant distress and functional impairment. Consequently, depression, especially if untreated, may be heavily implicated in poor mental performance reflected in neuropsychological tests. In addition, there is some recent evidence for continuing subtle neuropsychological impairments even in fully remitted patients with a history of major depressive disorder.[8] Last but not least, we should be reminded that a large proportion of patients suffering from chronic illnesses, in this case serious hepatopathy, are especially prone to developing symptoms of depression that compromise mental functioning and well-being.[9,10]

Therefore, we believe that none of the aforementioned parameters should be underestimated when speculative pathogenetic propositions are advanced regarding cognitive impairment and poor health-related quality of life in patients with alcoholic cirrhosis.

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