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Cognitive Performance as a Predictor of Hepatic Encephalopathy in Pretransplant Patients With Cirrhosis Receiving Psychoactive Medications: A Prospective Study

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Abstract

Psychiatric disorders and medications may affect the cognitive performance of patients with cirrhosis and complicate the diagnosis and prediction of hepatic encephalopathy (HE). The aim of this study was to study the association of psychoactive medications with cognitive performance and their effects on the ability of tests to predict HE development in patients with cirrhosis referred for transplant evaluation. Cirrhosis details, psychiatric disorders, psychoactive medications, and any history of prior HE were recorded for patients with cirrhosis at 2 transplant centers. Patients were followed until the development of HE. Five cognitive tests—number connection test A (NCT-A), number connection test B, the digit symbol test (DST), the block design test, and the inhibitory control test (ICT)–were administered. A high lure score and a low ICT target score indicated poor performance. The cognitive performances of patients with psychiatric disorders/medications and patients without them were compared. A proportional hazards model was created with the time to HE as the outcome, and it was based on demographics, psychoactive medications, cirrhosis details, and individual cognitive scores. Patients with prior HE and patients without prior HE were then studied separately. One hundred fifty-five patients with a mean age of 57.5 ± 6.2 years and a mean Model for End-Stage Liver Disease (MELD) score of 15.1 ± 6.2 were included [prior HE, 48%; diabetes, 34%; selective serotonin reuptake inhibitors (SSRIs), 32%; opioids, 19%; and antipsychotics, 10%]. Prior HE and antipsychotics (but not opioids or diabetes) were associated with worse cognition. SSRI users had better NCT-A and DST performance. One hundred forty-eight patients were followed for a median of 182.5 days; 58 developed HE at a median of 99 days after inclusion. In the entire group, the model showed that prior HE (hazard ratio =4.13), the MELD score (hazard ratio =1.07), and a high lure score (hazard ratio =1.04) decreased the time to HE, whereas the use of SSRIs (hazard ratio =0.42), a high target score (hazard ratio =0.95), and a high sodium level (hazard ratio =0.89) increased the time to HE.

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Jasmohan S. Bajaj conceptualized this study and was involved in all its aspects. James B. Wade contributed a critical review and drafted the manuscript. Leroy R. Thacker performed the statistical analysis. Douglas M. Heuman, Arun J. Sanyal, Michael Fuchs, R. Todd Stravitz, Richard K. Sterling, H.G., and Velimir Luketic were involved in the data collection and interpretation.

For patients without prior HE, the MELD score (hazard ratio =1.25) and lures (hazard ratio =1.09) predicted the time to HE. Lures (hazard ratio =1.03), targets (hazard ratio =0.96), and sodium (hazard ratio =0.87) were associated with the time to HE in patients with prior HE. In conclusion, cognitive tests (particularly the ICT) remain valid predictors of HE in the face of psychiatric diseases and medications. SSRI use is associated with better cognitive performance and a reduced likelihood of developing HE.

Patients with cirrhosis who have minimal hepatic encephalopathy (HE) and prior HE [which form a spectrum of neurocognitive impairment in cirrhosis (SONIC)] are associated with poor outcomes, especially with respect to future HE development.[1] This cognitive dysfunction is a key component that is linked to everyday functioning and disease prediction in patients with cirrhosis.[2–4] A key concept of SONIC is the treatment of each cognitive test result as a continuum and the prediction of outcomes on the basis of the results. This approach is similar to the cognitive tracking performed for patients with other neurological disorders.[5–8] However, there remain several causes of cognitive dysfunction in patients with cirrhosis apart from HE, such as depression, anxiety, posttraumatic stress disorder (PTSD), and psychosis; their treatment often requires psychoactive drugs.[9,10] The effect of psychoactive drugs on the cognitive performance of patients with cirrhosis is a matter of considerable interest. The quality of life of patients with covert HE has been shown to be impaired in a variety of domains. Psychoactive medications may lead to improvements in mood, alertness, freedom from pain, and other mental functions that contribute to a patient's daily function and quality of life. This leaves questions about the significance of the contributions of these coexisting conditions to the further development of HE episodes in patients being considered for liver transplantation. However, most studies of HE exclude patients on psychoactive medications, who form a large proportion of the pretransplant population.[11]

The a priori hypothesis was that cognitive dysfunction, represented by individual cognitive tests results, could be used to predict the time to the development of HE in patients with cirrhosis referred for transplantation, regardless of coexisting psychoactive medications. Our aims in this study were (1) to determine whether psychoactive medications are associated with cognitive performance in patients with cirrhosis who are referred for consideration of liver transplantation and (2) to determine whether these psychiatric medications affect the ability of cognitive tests to predict the time to HE development.

PATIENTS AND METHODS

All patients with cirrhosis who were referred for evaluation for liver transplantation at the McGuire VA Medical Center and the Virginia Commonwealth University Medical Center between June 2009 and January 2011 and who agreed to participate in this study were included. Only patients whose mini-mental state examination score was >25 at the time of the study were included. The demographics, the reason for the liver transplant referral, the comorbid conditions, and the current medications were recorded. We also recorded prior HE episodes and the use of HE medications such as lactulose and rifaximin. We included patients in the prior HE group only if they had evidence of hospitalizations due to HE or if lactulose and rifaximin were initiated (or the doses were changed) because of clinic and emergency room visits. This was also corroborated by the patients and their family members during interviews. Coexisting cognitive conditions, depression, anxiety, PTSD, and chronic pain treated with opioids were specifically evaluated, and the medications used to treat them were noted. Specifically, the use of antidepressants and anti-anxiety medications [selective serotonin reuptake inhibitors (SSRIs) and others], antipsychotic medications, and opioids was recorded.

The diagnosis of psychiatric problems had been made and confirmed by the patient's primary referring team with diagnostic criteria from *Diagnostic and Statistical Manual of Mental Disorders* (4th edition, text revision), and all these patients were on their psychoactive medications for at least 3 months before the study. None of them had been using alcohol or illicit drugs within 3 months of their evaluation; this was proven by several negative drug and alcohol screens before their testing. All patients had undergone a detailed psychological assessment within a month of the cognitive testing and pretransplant evaluation. The psychological evaluation included an analysis of the control of depression, anxiety, PTSD (according to the *Diagnostic and Statistical Manual of Mental Disorders* criteria), and readiness for transplantation.

Patients then underwent recommended cognitive testing involving a battery of 5 tests administered in a standardized order to limit the impact of sequence effects at the time of testing[12]:

1. Block design test (BDT). Subjects replicate standardized designs with given blocks in a timed manner. The score is based on the designs correctly copied.
2/3. Number connection test A (NCT-A) and number connection test B (NCT-B). Subjects are asked to join the dots between numbers or numbers and letters in a timed fashion, and the number of required seconds is the outcome.
4. Digit symbol test (DST). Subjects are required to copy corresponding figures from a given list within 2 minutes, and the number correctly copied is the result.
5. Inhibitory control test (ICT). This is a 15-minute computerized test. Subjects are instructed to respond to alternating presentations of X and Y on the screen (targets) and to inhibit their responses when X and Y are not alternating (lures).

The BDT tests for visuomotor coordination. The ICT is a validated computerized test of attention, psychomotor speed, response inhibition, and working memory. [13] High BDT, DST, and ICT target scores and low scores on the rest of the tests indicate good cognitive performance. The patients were followed until the (1) development of the next HE episode, (2) transplantation or death, or (c) September 2011 (when follow-up was terminated).

An episode of HE was defined as a clinic visit, emergency room visit, or hospital admission with evidence of disorientation that required the initiation or modification of HE-specific therapy in accordance with recent guidelines.[11] The medication profiles of the patients were reviewed again if they suffered another HE episode. We chose HE as the outcome because (1) the transplant outcome is uncertain and depends on the results of the evaluation and the availability of organs, and (2) death is interdependent on the transplant. An episode of HE, therefore, reflects the underlying natural history of each patient, regardless of his or her ultimate listing.

Statistical Analysis

Descriptive statistics were determined for all patients at the baseline, and an analysis of cognitive tests based on the use of individual psychoactive medications, comorbidities, and the severity of cirrhosis was performed with unpaired *t* tests for continuous variables and with Fisher's exact test and the chi-square test for proportions. Results are expressed as means and standard deviations unless otherwise mentioned. A univariate survival analysis of the time to the development of the next HE episode was conducted with Kaplan-Meier estimates, and tests of the equality of survival curves were performed with both log-rank and Wilcoxon test statistics. The major outcome was transplantation, death, or the development of HE. If patients underwent transplantation or died before they developed HE, they were considered to be censored because they may have developed HE but just had not at the time

of transplantation or death; for this group of patients, the time was the length of time from their entry into the study until transplantation or death. If patients developed HE before transplantation or death, they were considered to be uncensored, and the time for this group of patients was the length of time from their entry into the study until they developed HE.

A Cox proportional hazards model was used to examine the impact of demographic, laboratory, and cognitive test results on the development of HE in a multivariate setting. A competing risk analysis for HE development was also performed. The following variables were used: age, educational status, alcoholic etiology of cirrhosis, Model for End-Stage Liver Disease (MELD) score, serum sodium, prior HE, individual raw cognitive test results, SSRIs, antipsychotics, opioids, and other anti-anxiety medications. We also tested this model by including psychoactive drug use and multiple psychoactive drugs as variables instead of the individual medications. We separately approached cognitive dysfunction through individual test results for all 5 tests because this was in keeping with the SONIC model and the intertest correlations were not higher than 0.67. A stepwise model fitting procedure was used: the criterion for entry into the model was $P=0.25$, and the criterion for staying in the model was $P=0.10$. Once a model was finalized, another model with any possible interactions with prior HE was fit to assess whether prior HE had any impact on the other main effect parameter estimates. We then separated the patients into those with prior HE and those without prior HE to evaluate the differences in the prediction of the time to HE development.

This study was approved by the institutional review boards of Virginia Commonwealth University and the McGuire VA Medical Center (Richmond, VA).

RESULTS

One hundred fifty-five patients who were evaluated for liver transplantation were included in this study; the baseline demographics and the comorbid variables are shown in Table 1. None of the patients had evidence of disorientation to time, place, or person or had asterixis at the time of testing. The average mini-mental state examination score was 28 ± 4, and all the patients were able to complete the study procedures.

Almost half of the included patients had prior HE episodes that were controlled with only lactulose or lactulose and rifaximin; 46% were on psychoactive medications, and 25% of all the patients were on psychoactive medications and were being treated for HE (Table 1). Fifty-two patients (34%) had controlled type 2 diabetes. We did not have any patients with chronic neurological conditions such as dementia, brain trauma, or Parkinson’s disease.

Psychiatric Comorbidity and Therapy

The depression and anxiety diagnoses corresponded to the use of medications for these conditions; 4 patients had both diagnoses concurrently. None of the patients had depression at the time of the psychiatric examination that was more than mild according to the Beck Depression Inventory, which was used as part of the transplant psychiatric evaluation (12 patients had mild depression; and the rest scored in the nondepression range). SSRIs were prescribed for depression and anxiety to the majority of the patients (33 patients with depression and 11 patients with anxiety). The remainder of the depressed patients were on tricyclic antidepressants [n =9 (20%)] or trazodone [n =1 (4%)]; 4 more depressed patients were on antipsychotics [risperidone (n =2) or quetiapine (n =2)]. The remainder of the patients with anxiety (40%) were receiving daily benzodiazepine therapy {diazepam [n =6 (32%)] or alprazolam [n =3 (8%)]}. All patients with PTSD were on antipsychotic medications {quetiapine [n =8 (70%)] or risperidone [n =4 (30%)]}, whereas 40% of these patients were also on antidepressant therapy (n =5 for all SSRIs). Rates of benzodiazepine

use were similar between patients with prior HE (n =10) and patients without prior HE (n =7). Patients with chronic pain were taking daily opioids; oxycodone (56%) was being used by the largest proportion, and it was followed by codeine (34%) and methadone (10%).

Cognitive Performance and Comorbid Conditions

Patients receiving SSRIs performed better on the NCT-A and DST than the rest of the patients. When other parameters were input into a multivariate model, SSRI use approached statistical significance for the NCT-A (P =0.06; other significant variables were prior HE, antipsychotics, MELD score, and anxiety with R^2 =20.37) and for the DST (P =0.04; other significant variables were prior HE, age, MELD score, education, antipsychotics, and serum sodium with R^2 = 45.49)

We did not find differences between patients with chronic pain on opioids and the rest of the patients in the individual results of any cognitive test. However, patients on antipsychotic medications, who were mostly suffering from PTSD, performed significantly worse on almost all tests. Prior HE, as expected, was associated with poor performance on most of the cognitive tests (Table 2). There was a significant correlation between the NCT-A (r =0.2, P =0.02), NCT-B (r =0.2, P < 0.01), and DST results (r =0.3, P < 0.01) and the MELD score, but a significant correlation was not found for the other cognitive tests. We did not find any significant differences between any cognitive tests with respect to the diagnosis of diabetes [NCT-A, 46 versus 43 (P =0.53); NCT-B, 135 versus 122 (P = 0.27); DST, 45 versus 48 (P =0.29); BDT, 24 versus 23 (P =0.78); lures, 14 versus 13 (P =0.43); and targets, 90% versus 92% (P =0.27)].

Follow-Up and HE Development

The patients were followed for a median of 182.5 days. Seven patients were lost to follow-up. Fifty-eight of the remaining 148 patients (39%) had an HE episode at a median of 99.0 days after the initial testing. The majority of the patients who had another HE episode had a precipitating factor of sepsis (n =20), upper gastrointestinal bleeding (n =12), noncompliance with HE therapy (n =11), hyponatremia (n =6), or other metabolic disturbances (n =4); the development of HE was spontaneous in the rest. Forty of the patients (27%) underwent endoscopy with sedation during follow-up, but none of the HE episodes were related to that outcome. The medication profile with respect to the psychoactive drugs remained unchanged during the HE episode on follow-up. Twenty-six patients had to be censored at a median of 123.0 days before the development of an HE episode because of death (n =7) or liver transplantation (n = 19). The remaining patients were censored until the last date of follow-up in September 2011. Patients who did not develop HE were followed for significantly longer (mean =361.0 ± 247.8 days, median =281 days) than patients who had developed HE by the time of the study's end (mean =137.6 ± 131.1 days, median =94 days, P < 0.01). All patients remained on similar dosages of these medications throughout the follow-up period, and no dosage effect was seen with any medication with respect to HE development.

There were significant differences in the baseline MELD scores, serum sodium levels, history of prior HE, and cognitive test performances between the patients who had another HE episode and the patients who did not (Table 3). There were no differences with respect to depression, anxiety, PTSD, or psychoactive drug use between the patients who did develop HE and the patients who did not.

Model Development for All Subjects With HE as the Outcome

To determine the risk of further HE development, after the significant variables were determined through a univariate analysis, a proportional hazards model was created for the

entire group and then separately for patients with prior HE and patients without prior HE. For the entire group, the significant variables in the regression model were the MELD score, sodium, SSRI use, lures, targets, and prior HE (Table 4). Notably, the remaining cognitive tests did not achieve significance in the regression, but so that their contributions could be tested, they were also added to this model post hoc. The results did not change the underlying predictions, and the likelihood ratios for the model including the variables that were significant on stepwise regression (lures, targets, SSRI use, MELD score, sodium, and prior HE) and the model including the previous 6 variables and 4 additional tests (NCTA, NCT-B, DST, and BDT) did not show significant differences (310.151 – 309.765 =0.38 versus a χ^2 distribution with 4 degrees of freedom, P =0.53). Similarly, to test the effects of any psychoactive medications, we excluded the SSRI variable and evaluated the interaction terms of any psychoactive medications with the MELD score, sodium, prior HE, targets, and lures, and we constructed a test with 5 degrees of freedom to determine whether the parameter estimates were different for patients with any psychoactive medications and patients without any psychoactive medications. The simultaneous test of these interactions was not statistically significant (χ^2 = 1.304, degrees of freedom =5, P =0.93), and this indicated that just the use of any psychoactive medication did not predict HE development in this population. This was also not significant when the number of psychoactive drugs were input as a variable (P = 0.83). To further evaluate the role of prior HE in this prediction, we created an interaction model for prior HE and all 5 remaining variables (lures, targets, sodium, MELD score, and SSRI use). The P value of the interaction test with prior HE was 0.47, and this indicated that there were no significant differences in the slopes of the rest of the variables because of prior HE. The competing risk analysis showed findings similar to those of the proportional hazards model.

Model Development for Patients With Prior HE and Patients Without Prior HE

We then divided the group into patients with prior HE and patients without prior HE, and we studied the proportional hazards models after we arrived at significant variables with a stepwise logistic regression. In the population without prior HE, the only significant variables were the MELD score and lures, and when they were fit into the proportional hazards model, the contributions remained significant. For patients without prior HE, the hazard ratios for the time to developing HE were 1.253 for the MELD score (P < 0.01) and 1.095 for lures (P < 0.01). This model remained unchanged despite the post hoc addition of the other 5 cognitive tests, psychoactive drugs, and serum sodium. For patients who had experienced an HE episode previously, the prediction of further HE depended on a slightly different model. The significant variables were serum sodium, lures, and targets. When they were input into a proportional hazards model, they remained significant, and the hazard ratios for the time to the development of further HE were 1.028 for lures, 0.867 for sodium, and 0.964 for targets in this subgroup.

DISCUSSION

This study shows that SSRIs were associated with better performance on the DST and NCT-B, whereas antipsychotic medications were associated with worse cognitive performance. There was no significant effect of opioid therapy on cognition. As expected, patients with prior HE had worse cognitive performance than patients without prior HE. The follow-up analysis showed that cognitive performance (especially on the ICT) and SSRI use were key determinants of the length of time before a future HE episode and were independent of prior HE, serum sodium, concomitant psychoactive drug use, and the MELD score.

Cognitive dysfunction in patients with cirrhosis has most often been studied in the context of minimal HE and overt HE. The negative consequences that have been studied include a poor health-related quality of life, increases in further HE episodes, a high risk of driving

difficulties, an added fall risk, and, in some studies, a higher mortality rate.[3,14–17] Cognitive function is extremely important in our daily life and is relevant to the patient's comprehension of his or her overall prognosis and socioeconomic status.[3] It has been linked to compliance with medications and clinic visits, readiness for transplantation, and posttransplant functioning, morbidity, and mortality.[18] A comprehensive study of the contributions of cognitive function, regardless of the causes, to the overall natural history of patients is important, therefore, for counseling patients and caregivers.[3,19]

In our study, cognition (as assessed by performance on the ICT) and mood disorder therapy with SSRIs independently modulated the time to the development of HE. The protective effect of SSRI use on further HE development may be due to the correction of underlying mood disorders. Previous studies have demonstrated that untreated or suboptimally controlled depression, anxiety, or chronic pain worsen cognition. [20–24] We did not find any dose-response change to SSRIs or any additive effect of additional non-SSRI psychoactive medications on the HE development rate. Therefore, it follows that the control of mood disorders (which left untreated may potentiate cognitive dysfunction) could be protective against further deterioration in the form of HE in patients with cirrhosis. Interestingly, animal studies of brain trauma have demonstrated a neuroprotective effect of SSRIs, which is possibly due to an increase in a brain-derived neurotrophic factor protecting neuroplasticity.[25,26] Although this mechanism was not specifically investigated in this study, it could have afforded protection against further cognitive insults in the patients on SSRIs. We found a trend toward significance for prediction with the NCT-A and DST, despite the addition of other comorbid conditions. Further trials with SSRIs in patients with cirrhosis are required to definitively analyze this effect. In sharp contrast, the effect of antipsychotic medications was most pronounced on tests of psychomotor speed.[27,28] This cognitive profile fits previous studies of antipsychotic medications in patients with PTSD[27,28]; however, the study design could not determine whether this was due to PTSD or antipsychotic use. Antipsychotic use, however, did not affect subsequent HE development. This may have been due to the fact that the individual cognitive test changes were also included in the statistical models. This also brings into focus the concept of brain reserve: it is hypothesized that there is a fixed amount of reserve to cope with changes in brain homeostasis. Thus, with a decline in cognitive reserves, even subtle changes in cortical integrity will precipitate a decline in cognitive ability and neurobehavioral function that is beyond what is expected from the diagnostic findings alone.[29] This is consistent with the finding that in patients with Alzheimer's disease and HE, there is a poor association between cognitive performance and the actual extent of the underlying disease.[30–33] In the current study, the poor performance on cognitive tests (especially the ICT) along with the coexisting medications may have represented an expression of limited reserves, which made the patients more vulnerable to the disorientation associated with HE. It is unlikely that an overdose of these medications in and of itself would have resulted in the next episode because the majority of the precipitating episodes were due to infections and gastrointestinal bleeds.

Our findings confirm previous studies in which patients with hyponatremia and prior HE had a higher likelihood of another HE episode.[4,34] However, we extended previous reports by clarifying the unique contributions of individual cognitive test performances to HE phenomenology (as sought in the SONIC approach) in patients currently on psychoactive medications. These data suggest that the cognitive test results are reflective of the HE continuum. We studied the interactions between test performance and clinical variables without needing to divide the patients into groups (eg, minimal HE and cognitive dysfunction). This approach is useful because it is not dependent on specific definitions of normal and abnormal cognitive performance, which may differ between health care centers. Indeed, the methodology used in this study may be generalizable across other medical populations. We found that despite controlling for obvious factors such as prior HE, MELD

scores, and sodium, performance on the ICT was predictive of the development of HE in models created for the entire group in patients without prior HE and in patients with prior HE. Importantly, these models did not include a significant independent contribution from the remaining standard psychometric tests.

These data suggest that the unique set of cognitive abilities required by the ICT demand underlying activation of specific brain regions intimately associated with HE.[35] The ICT is a challenging test of response inhibition and working memory that has been associated with driving and earning capacity in patients with cirrhosis.[13] This test requires a subject to maintain mental focus for 15 minutes, whereas the remaining 4 cognitive tasks can be completed in just a few minutes.[12,36] The requirement of sustained vigilance and an emphasis on working memory skills makes the ICT particularly sensitive for uncovering cognitive dysfunction in patients with HE in comparison with the other cognitive tests. Alternatively, the correlation of the remaining tests with the underlying severity of cirrhosis could have made their contributions over and above prior HE and the MELD score nonsignificant. Previous studies from our group have shown that a high lure number separates patients without prior HE who have cognitive dysfunction from the rest and represents response disinhibition.[13,37] Amodio et al.[38] showed that as the disease continuum progresses, the accuracy of targets starts to decrease on the ICT, and this indicates a worsening of attention allocation. This was replicated in our results, in which lures were independently predictive of the first HE episode (in addition to the MELD score), whereas targets played a significant role in predicting further HE episodes in patients who had prior HE.

The endpoint of this study—the time to HE development— is significant because it can predict mortality, can cumulatively worsen cognitive performance, and can even cast a shadow on posttransplant cognitive recovery.[39–43] The results show that the effects of ICT performance and SSRI use on the time to the next HE episode are independent of prior HE, even when the interaction terms are used. This means that not every patient with prior HE will go on to have another HE episode, and a more nuanced approach to cognitive assessment is needed for this prediction. The abnormalities in ICT performance appear to have been a powerful predictor of future HE in this population, which is representative of a typical pretransplant clinic population (unlike the patients included in previous HE studies). The ICT is available freely for download[44] and can be administered without a psychologist. Therefore, this can be potentially used during the pretransplant testing of patients on psychoactive medications to improve the prognostication even in centers without expertise in psychological testing.[45]

Our study is limited by the inclusion of only patients referred for pretransplant testing, who are mostly vetted to exclude substance abuse, alcoholism, and uncontrolled psychiatric illnesses. However, despite the exclusions, a significant proportion of our patients were on psychoactive drugs. We also cannot infer from the data whether SSRI use will remain protective in patients with cirrhosis and more severe depressive illness.

We have found that specific classes of psychoactive drugs affect cognition differently. SSRIs are associated with improved cognition and protection against HE development, whereas antipsychotic drugs can significantly worsen cognitive performance. Opioids did not have any impact on cognitive performance. These results show that specific cognitive testing, especially with the ICT, can still predict the time to HE development, even in the face of psychoactive drug use, independently of prior HE, MELD scores, and serum sodium and may have additional value beyond what can be readily inferred from a patient's medical history and laboratory values. Further studies evaluating the role of SSRIs in protection against HE development are required.

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Abbreviations

BDT	block design test
DST	digit symbol test
HE	hepatic encephalopathy
ICT	inhibitory control test
MELD	Model for End-Stage Liver Disease
NCT-A	number connection test A
NCT-B	number connection test B
PTSD	posttraumatic stress disorder
SONIC	spectrum of neurocognitive impairment in cirrhosis
SSRI	selective serotonin reuptake inhibitor.

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TABLE 1

Baseline Demographic, Psychiatric, and Medication Profiles of the Patients (n = 155)

Variable	Value
Age (years)	57.5 ± 6.2
Educational status (years)	13.5 ± 2.2
Sex (n)	
Male	101
Female	54
Race (n)	
Caucasian	94
African American	42
Hispanic	15
Other	4
Cirrhosis etiology (n)	
Hepatitis C virus	75
Alcohol	15
Hepatitis C virus and alcohol	27
Nonalcoholic fatty liver disease	25
Other	13
MELD score	15.1 ± 6.2
Serum sodium (mmol/L)	136.6 ± 4.7
Hepatocellular cancer [n (%)]	30 (19.4)
Prior overt HE [n (%)]	75 (48.4)
Diabetes [n (%)]	52 (33.5)
Lactulose at the time of testing [n (%)]	75 (48.4)
Additional rifaximin at the time of testing [n (%)]	35 (22.5)
Psychiatric conditions [n (%)]	
Depression	47 (30.3)
Anxiety	20 (12.9)
PTSD	12 (7.7)
At least 1 psychoactive drug [n (%)]	72 (46.5)
SSRIs	49 (31.6)
Opioids	29 (18.7)
Antipsychotic medications	16 (10.3)
Benzodiazepines	17 (11.0)
Antiseizure medications for pain	2 (1.3)

TABLE 2

Differences in Cognitive Function According to Medication Use and Prior HE

	Prior HE		SSRIs		Opioids		Antipsychotics	
	Yes (n = 75)	**No (n = 80)**	**Yes (n = 49)**	**No (n = 106)**	**Yes (n = 29)**	**No (n = 126)**	**Yes (n = 16)**	**No (n = 139)**
NCT-A (seconds)	49.6 ± 21.8*	39.3 ± 14.3	39.1 ± 15.6*	46.2 ± 20.1	46 ± 21	44 ± 19	53.3 ± 10.6*	43.4 ± 19.4
NCT-B (seconds)	155.8 ± 83.9*	106.2 ± 45.5	115.6 ± 67.6	136.3 ± 73.7	152.4 ± 89.7	125.6 ± 66.7	183.2 ± 53.6*	125.8 ± 71.1
Lures (n)	13.6 ± 7.9	12.8 ± 8.8	12.2 ± 8.8	13.9 ± 8.4	13.6 ± 9.4	13.4 ± 8.3	21.5 ± 10.3*	12.6 ± 7.9
DST score	40.7 ± 12.8*	51.5 ± 13.9	50.2 ± 13.7*	44.3 ± 14.5	44.1 ± 13.5	46.5 ± 14.8	36.7 ± 7.9*	46.8 ± 14.7
BDT score	19.6 ± 11.2*	26.7 ± 13.4	25.6 ± 12.0	22.8 ± 13.2	21.7 ± 12.9	23.9 ± 13.0	18.9 ± 7.9	23.8 ± 13.2
Targets (% right)	88.2 ± 13.1*	93.1 ± 7.4	90.4 ± 13.1	90.5 ± 10.4	89.6 ± 11.7	90.8 ± 10.8	88.8 ± 9.3	90.8 ± 11.0

NOTE: Low values for NCT-A, NCT-B, and lures indicate a good performance; high values for the rest indicate a good performance.

*$P < 0.05$ versus patients not on the particular medication.

TABLE 3

Differences in the Baseline Characteristics of Patients Who Developed HE During Follow-Up and Patients Who Did Not

	HE on Follow-Up (n = 58)	No HE on Follow-Up (n = 90)
Age (years)	58.1 ± 4.8	57.4 ± 7.0
Educational status (years)	13.6 ± 2.3	13.6 ± 2.2
MELD score at testing	17.0 ± 5.9*	13.5 ± 5.7
Serum sodium at testing (mmol/L)	134.6 ± 5.4*	137.7 ± 3.9
Prior HE [n (%)]	44 (76)*	30 (33)
Depression [n (%)]	19 (33)	28 (31)
Anxiety [n (%)]	7 (12)	13 (14)
PTSD [n (%)]	3 (5)	5 (6)
SSRIs [n (%)]	14 (24*)	39 (43)
Opioids [n (%)]	22 (38)	35 (39)
Psychoactive drugs [n (%)]	30 (52)	46 (51)
Worse with higher score		
NCT-A (seconds)	49.3 ± 22.1*	41.1 ± 16.6
NCT-B (seconds)	151.0 ± 78.4*	117.7 ± 65.4
Lures (n)	15.8 ± 8.7*	11.6 ± 7.4
Worse with lower score		
DST score	40.5 ± 14.0*	49.7 ± 13.6
BDT score	20.2 ± 10.6*	25.5 ± 13.7
Targets (% right)	86.6 ± 13.4*	93.0 ± 8.2

NOTE: Patients who had another HE episode were significantly more likely to have a higher MELD score, lower serum sodium levels, and poor performance on all cognitive tests and were less likely to have been treated with SSRI therapy.

*$P < 0.05$.

TABLE 4

Hazard Ratios From a Multivariate Analysis With HE Development as the Outcome

	χ^2	*P* Value	Hazard Ratio (95% Confidence Interval)
MELD score	3.770	0.0522	1.069 (0.999–1.144)
Serum sodium	9.085	0.0025	0.897 (0.835–0.963)
SSRIs	3.741	0.0531	0.419 (0.174–1.012)
Prior HE	13.220	0.0003	4.130 (1.923–8.871)
Targets	10.807	0.0010	0.958 (0.934–0.983)
Lures	4.834	0.0342	1.035 (1.003–1.069)