

Early Detection of Depressive Symptoms During Treatment With Pegylated Interferon α -2b and Ribavirin in Euthymic Chronic Hepatitis C Patients



P.E. Golstein¹, P. Oswald², M. Dramaix³, J. Mendlewicz², J. Devière¹, and M. Adler¹

¹Gastroenterology, Hôpital Erasme; ²Psychiatry, Hôpital Erasme;

³Biostatistics, Ecole de Santé Publique – Université Libre de Bruxelles, Brussels, Belgium

Introduction

Depressive symptoms are common during therapy with interferon α (IFN) and pegylated interferon α (PegIFN) for chronic hepatitis C (CHC) and may compromise successful treatment because these symptoms jeopardize patient safety (suicidal attempts), decrease treatment adherence, and often necessitate dose reduction or even discontinuation of IFN/PegIFN therapy.

However, depressive symptoms are often recognized late or missed completely because systematic assessment for these symptoms is not performed routinely.

Furthermore, data reporting the incidence of depression in CHC studies with IFN/PegIFN are highly variable (from 0%-44% appearing 1-3 months to 3-6 months after starting therapy) because the designs of these studies are different and often inadequate¹⁻³.

1. Populations are often heterogeneous and include patients with or without pre-existing psychiatric disorders
2. Major depressive disorder (MDD) is often not clearly defined and depressive symptoms are often misclassified as digestive (anorexia, weight loss) or influenza-like (fatigue)
3. Psychometric instruments are different, not systematically used before and during therapy and used by different health care providers with variable methods
4. There are few prospective studies
5. Samples sizes are usually small
6. Assessment of depression is performed at varying time points

Therefore, it is essential to standardise detection of depressive symptoms and MDD during therapy with PegIFN α in patients with CHC and to assess the specific impact of antiviral therapy by studying euthymic patients.

The present study will assess prospectively the early occurrence of MDD in a homogenous population of euthymic treatment-naïve CHC patients, using several validated depression rating scales (DRSs) at regular visits with a psychiatrist throughout therapy.

Objective

- Prospective assessment of the development of MDD in adult treatment-naïve euthymic CHC patients during combination antiviral therapy (PegIFN α -2b 1.5 μ g/kg/week and ribavirin 800-1200 mg/day for 24-48 weeks) using different validated DRSs.

Methods

Population and Inclusion Criteria

- Treatment of CHC in accordance with the current guidelines
 - Treatment-naïve CHC patients, aged between 18 and 65 years old who had elevated ALT levels, were treated with combination therapy for 24 to 48 weeks depending upon HCV genotype
- Inclusion of euthymic patients
 - A 7-item questionnaire was used to screen for psychiatric history (performed by the hepatologist). Psychiatric history was considered negative if all of the following criteria were met:
 1. No history of psychiatric disease (psychosis, bipolar disorder, or MDD)
 2. No history of suicide attempt
 3. No history of hospital admission for psychiatric disease
 4. No current substance abuse or dependence disorder: alcohol; medications; drugs such as cocaine, heroine, amphetamines, and cannabis (intravenous route, inhalation, smoking)
 5. No history of treatment with methadone
 6. No history of treatment with an antidepressant medication more than 4 weeks before inclusion
 7. No long-term treatment (>2 months) with a benzodiazepine at a dose \geq 25 mg/day diazepam equivalent

¹ Abuse implies a recurrent substance use resulting in failure to fulfill major role obligations at work or home and/or continued substance use despite having persistent or recurrent problems caused by the effects of the substance.

² Dependence implies a maladaptive pattern of substance use leading to tolerance (need for markedly increased of the substance and/or diminished effect of continued use of the same amount of the substance) and/or withdrawal. In addition, dependence often implies that the substance is taken large amounts and that important activities are reduced or given up because of substance use.

- Patients without a psychiatric history underwent further psychiatric evaluation (performed by a psychiatrist)

- MINI: Mini-International Neuropsychiatric Interview is a short, structured, diagnostic interview, developed for DSM-IV and ICD-10 psychiatric disorders, for excluding an active psychiatric illness

- Four DRSs
 - 3 hetero-questionnaires
 - HAM-D (17): Hamilton DRS: 17 items (quotation 0-4)
 - MADRS: Montgomery & Asberg DRS (quotation 0-4)
 - CGI: Clinical Global Impressions (quotation 0-7)
 - 1 self-questionnaire
 - Beck Depression Inventory (BDI), 13 items (quotation 0-3)

- Patients were deemed eligible for study participation if they had no psychiatric disease and if HAM-D and BDI scores were <17 and <18, respectively

Study Design

- Ongoing prospective study conducted in 1 centre (Erasmus Hospital, Free University of Brussels)
- Patients were seen every 2 weeks alternatively by the hepatologist and the psychiatrist
- Depression was regularly assessed throughout therapy by the psychiatrist and by use of DRSs according to the following flow chart (Figure 1)

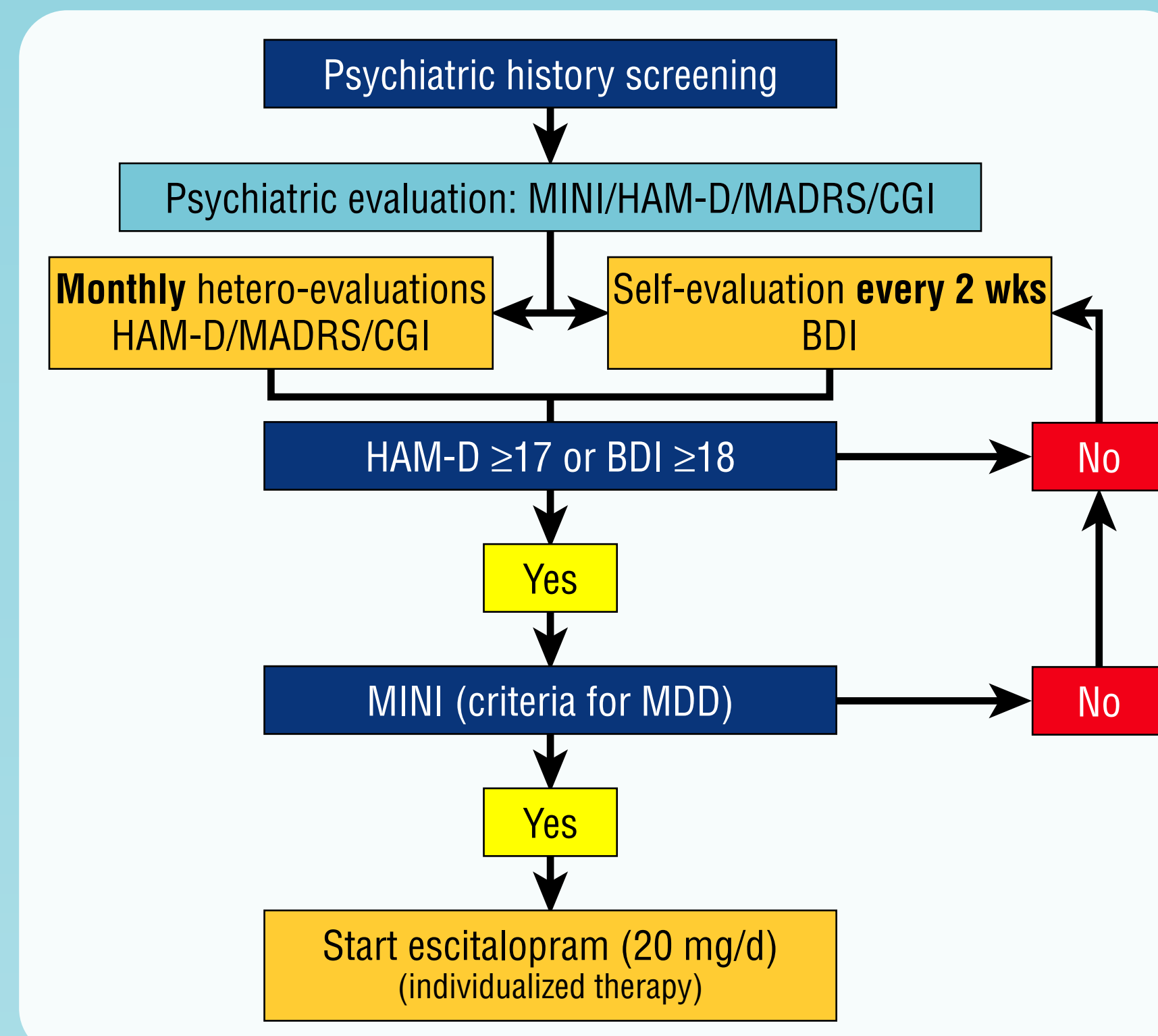


Figure 1. Study Design

Statistics

- Data were analyzed using SPSS version 13.0 software (Chicago, IL) and non-parametric tests were used
- DRS scores were presented as median values. Statistical analyses were performed using the Mann-Whitney test for comparison of baseline DRS scores and the Wilcoxon matched pairs signed rank sum test for comparison of changes in DRS scores. The Fisher exact test was applied for contingency tables analysis

Results

- Patients
 - 28 consecutive CHC patients were screened by a hepatologist and had no psychiatric history
 - Psychiatric evaluation determined that 26 (93%) of those 28 did not have psychiatric disease currently
 - This population represented about one third of treatment-naïve CHC patients who met the criteria for combination therapy in accordance with the current guidelines (normal transaminase levels excluded)
 - Twenty-one patients were included in the analysis; baseline characteristics are presented in Table 1
 - Of these, 18 patients were evaluable (1 dropped out at week 6; 1 treatment ongoing presently at week 6; 1 treatment not yet started)

Table 1. Baseline Characteristics of 21 Euthymic Patients With Chronic Hepatitis C

Age, years (mean \pm SD)	48.8 \pm 10.4
Gender (M/F), n (%)	10 (48) / 11 (52)
Ethnicity, n (%)	
Caucasian	14 (67)
North African	4 (19)
African	3 (14)
HVC genotypes, n (%)	
1	15 (71)
2 and 3	3 (15)
4	3 (14)
Fibrosis (Metavir score), n (%)	
F1	5 (24)
F2	16 (76)
F3-4	0 (0)
Viremia, n (%)	
High (\geq 600,000 IU/ml)	10 (48)
Low (<600,000 IU/ml)	11 (52)
DRS scores, median (range)	
HAM-D	2 (0-7)
MADRS	1 (0-8)
CGI	0 (0-3)
BDI	1 (0-10)

- Five episodes of MDD (28%) occurred during therapy
 - Three early MDD episodes occurred from week 6 to week 18 [genotype 1 (n=2), genotype 4 (n=1)]
 - Two late MDD episodes occurred after week 42 [genotype 1 (n=2)]

The time course of DRS scores in patients in whom developed early MDD is presented in Figure 2

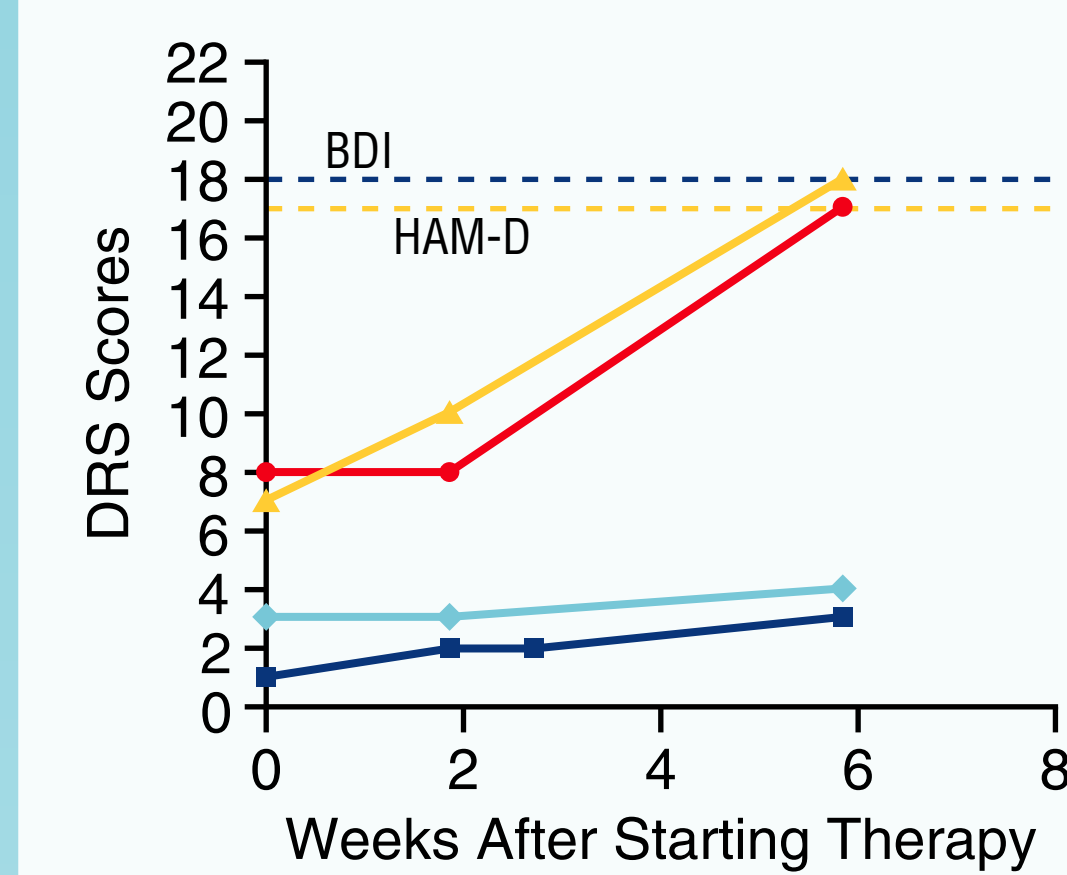
- In patients in whom MDD did not occur during therapy, median DRS scores increased as early as week 2 and reached significance at week 6 for HAM-D and MADRS ($P=0.04^{**}$) and at week 18 ($P=0.02^{**}$) for BDI

- Median baseline HAM-D, MADRS, and BDI scores were significantly higher in patients in whom early MDD developed than in patients without MDD throughout therapy (Figure 3)

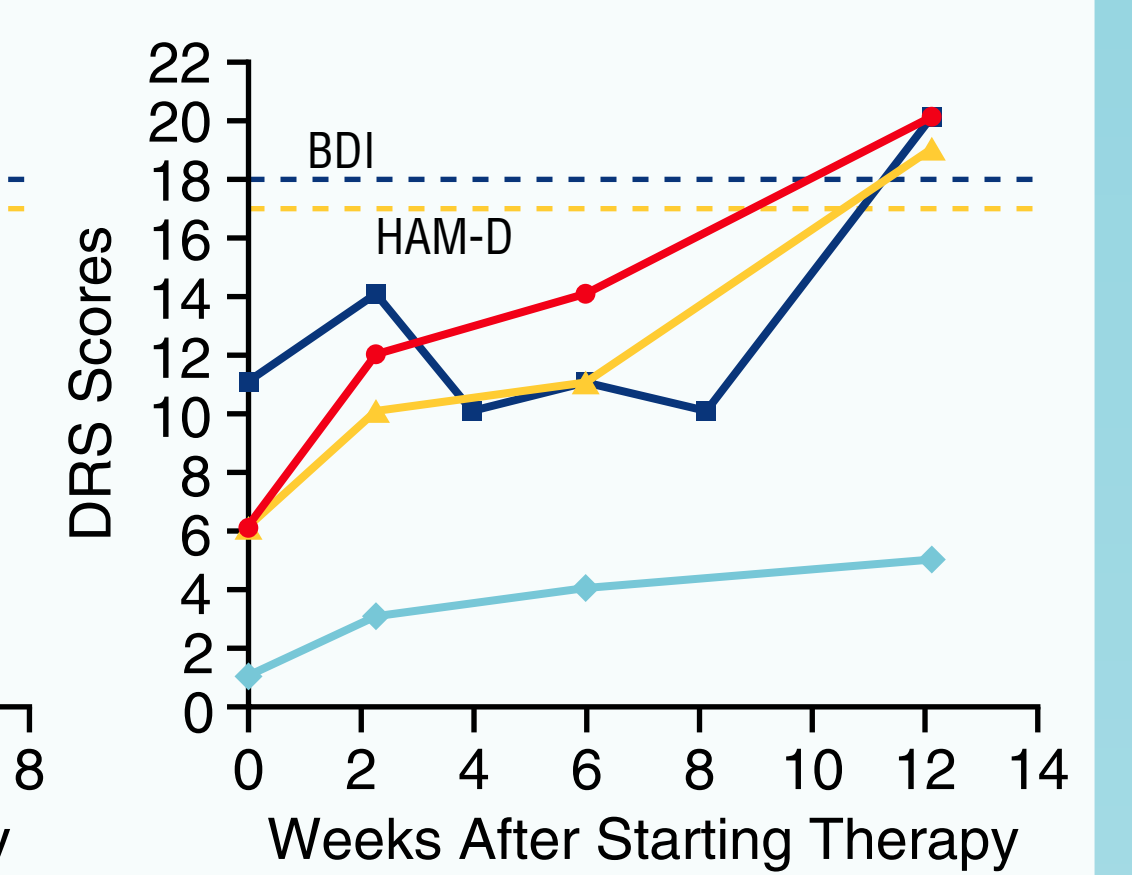
- A baseline HAM-D score \geq 4 or a MADRS score \geq 4 or a BDI score \geq 6 seems to predict the occurrence of early MDD, but these results must be confirmed by the ongoing study (Table 2)

** Wilcoxon match pairs signed rank sum test.

A. MDD at Week 6



B. MDD at Week 12



C. MDD at Week 18

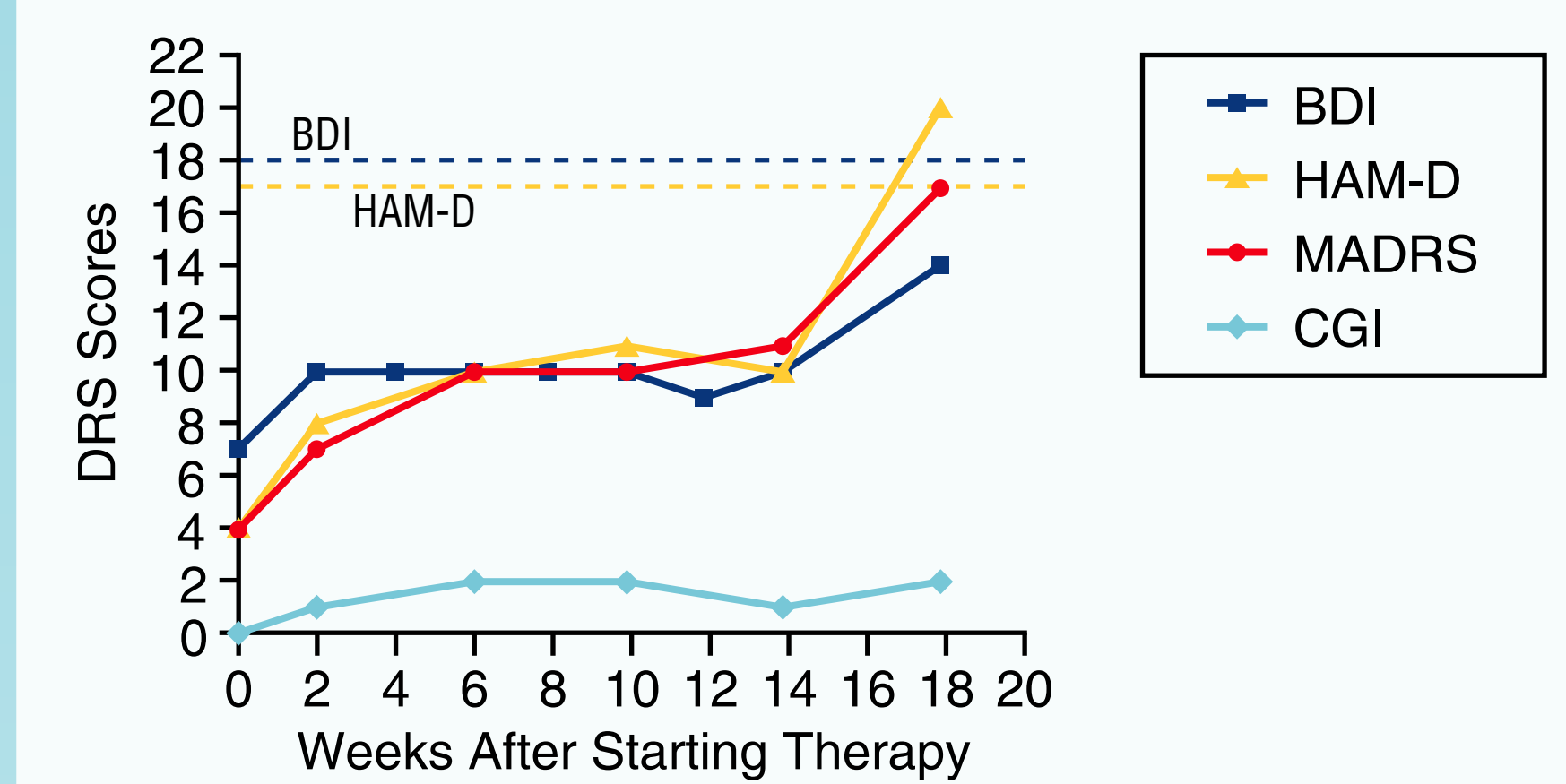


Figure 2. Time Course of DRS Scores in Patients in Whom Early MDD Developed

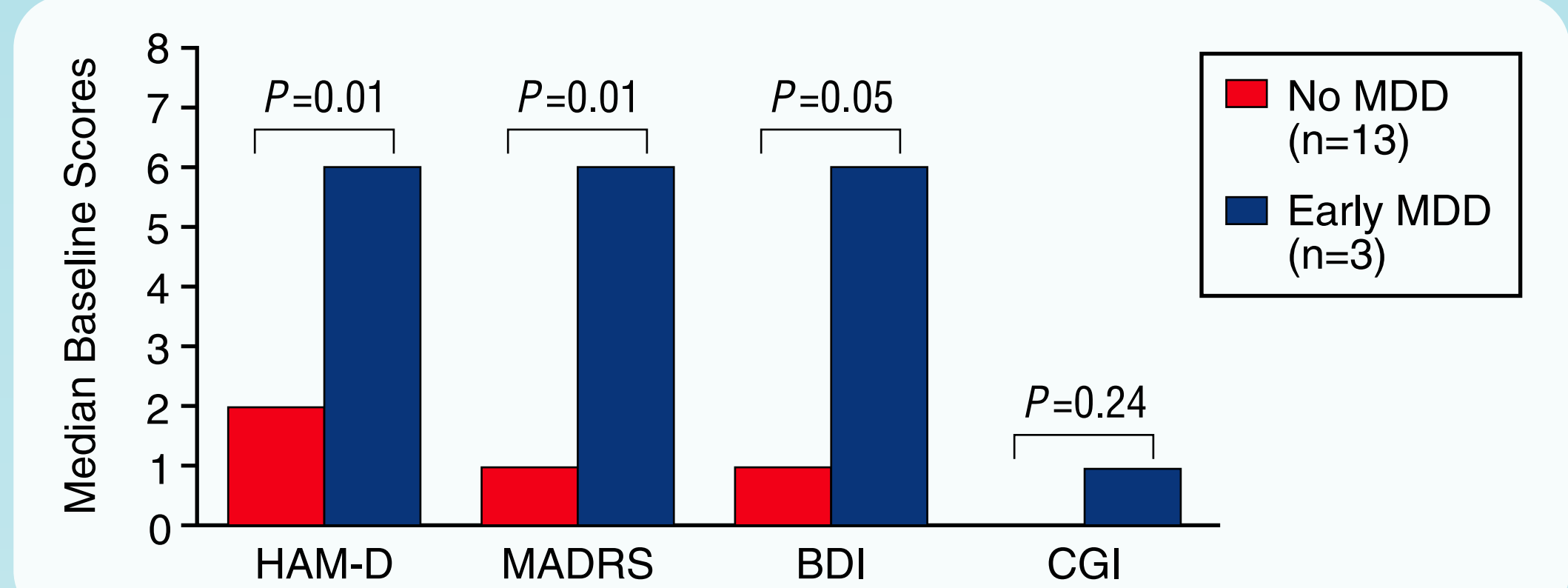


Figure 3. Baseline DRS Scores in Patients Without and With Early MDD

Table 2. Baseline DRS Scores and Early MDD

Baseline Scores (n=16)	Early MDD n (%)	P
HAM-D		
\geq 4 (n=5)	3 (60)	0.018
<4 (n=11)	0 (0)	
MADRS		
\geq 4 (n=5)	3 (60)	0.018
<4 (n=11)	0 (0)	
BDI		
\geq 6 (n=4)	2 (50)	0.13
<6 (n=12)	1 (8)	

5. Conclusions

- There is good agreement between the absence of psychiatric history screened by the gastroenterologist and the absence of psychiatric disorders assessed by the psychiatrist
- MDD develops in a high proportion (28%) of euthymic treatment-naïve patients with chronic hepatitis C during therapy
- In patients in whom MDD does not develop during therapy, the DRS scores increase as early as week 2
- Baseline HAM-D \geq 4 or MADRS \geq 4 or BDI \geq 6 seems to predict early MDD; however, because the number of patients included in this analysis was small, this trend must be confirmed by the ongoing study
- A psychiatric assessment should be performed before starting therapy for CHC, and careful monitoring for MDD development is mandatory throughout therapy for detecting early and late MDD episodes

6. References

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