**Psychiatric disturbances associated with Interferon therapy for HCV in Sohag Governorate**

**Osama Abdel-Raouf1, HameedMostafa1,AsmaaNaser Mohammad2, Hasan S.Mahmoud3**

**1Department of Neurology and Psychological Medicine, Sohag Faculty of Medicine, Sohag University,2Tropical Medicine and Gastroenterology Department, Sohag Faculty of Medicine, Sohag University,3Tropical Medicine and Gastroenterology Department, Qena Faculty of Medicine, South Valley University, Egypt**

**Abstract**

Background: Psychiatric disturbances in chronic HCV infected patients under treatment by Pegylated-interferon and ribavirin combined therapy (PEG-IFN/Rib)still show worldwide controversy and no sufficient studies address this problem in Upper Egypt.Aim of the study: to detect the pattern and prevalence of psychiatric disturbances in chronic HCV infected (CHC) patientsunderPEG-IFN/Rib and the risk factors for these disturbances. Patients and methods: 167 CHCpatients were recruitedfrom the virology clinic in Sohag University Hospital between November2012 and January 2015; 100 cases of them completed the study. Patients were assessed generally and psychologically before initiation and after 12 weeks of therapy using *Symptom Checklist-90-Revised (SCL-90-R*), The Mini International Neuropsychiatric Interview version 5 (*MINI*), *Hamilton Rating Scale for Depression (HAM-D), Hamilton Anxiety Rating Scale (HAM-A)* , and *The Structured Interview for the Five-Factor Model (SIFFM)* scales.Results: Major depressive disorder (MDD) was the only detected syndrome based on MINI in 35% of cases; but significant subsyndromal depression were detected in further 43% of cases by HAMD, & significant anxiety changes from base lineHAMA results(differences in mean= -4.620±3.902, P<0.001) with further detected significant increase in somatization, interpersonal sensitivity & Hostility by SCL90-R,in addition to depression and anxiety domains. Suicide risks were low, with no case stopped treatment. Age (more elderly), past history and family History of Psychiatric disorders, pre-treatment basal depressive symptoms, anxiety score, somatization score & Hostility scores were a significant predictors for occurrence of MDD.Conclusions:Depression And anxiety are the main disturbances after 12wks of PEG-INF/Rib therapy.Pretreatment screening for depressive symptoms, past & family history of psychiatric illness will help to identify those at high risk of MDD under IFN based therapy for HCV.

**Keywords**:Psychiatric disturbances, depression, HCV, Interferon.

**Introduction**

Chronic HCV infections (CHC) represent a major worldwide public health problem. Approximately 130 to 170 million people infected and they are responsible for a large proportion of liver related deaths, mostly because of HCV-associated hepatocellular carcinoma and cirrhosis[1].Unfortunately, Egypt is considered one of the countries with the highest prevalence [2].Despite the highprevalence of HCV, the level of awareness of HCV is very low, with 78.7% of theEgyptian population having never been tested for HCV infection, and 17.5% of thepopulation have never even heard about hepatitis C [3].Background current treatment combinations for chronic hepatitis C virus infection still include interferon based therapy despite the new therapeutic options available. With variable reports of being associated with a high incidence of adverse effects, psychiatric disturbances are among the most frequent ones and their influence on treatment adherence and effectiveness is controversial [4-6]. The most challenging obstacles for the new treatments are theirvery expensive or high cost that significantly impact the sustainability of healthcaresystems particularly in developing countries[7]. As a result, despite their medicalbenefits, publichealth systems are currently prioritizing interferon (IFN)-free regimens in patients with cirrhosis, liver transplantation,PEG-IFN contraindications, serious psychiatric disorders, andIFN-related serious adverse events in a previous treatment[8]. As a result, IFN-based treatments are still prescribed inclinical practice[4]and interferon is likely to continue as predominant form of treatment available to patients with hepatitis C particularly, in the developing countries [9]. Again PEG-IFN therapy has wide range of side effects [8, 10] of these, Central nervous system-related events are among the most prevalent and significant ones with variable opinion regard termination of therapy based on them[4, 11, 12]. However, theirreal incidence, determinants and effects on treatment compliance, discontinuation of therapy and sustained viral response (SVR) are controversial [13].

**Aim of the study**: To evaluate the psychiatric adverse effects that occur duringPEG-IFN/Ribtherapy for CHC treatment in Upper Egyptian population sample. We also assessed the risk factorsassociated withpsychiatric presentation and their impact ontreatment adherence and treatment response.

**Patients and Methods:**167 chronic HCV patients were recruited from Sohag general hepatology& virology clinics prior to initiating antiviral therapy, of those only 100 cases completed the study (and 67 subjects were excluded; 28 cases were ineligible (9depression, 6current/recently stopped drug abuse, 2GAD, 9 low viraemia, 2 has past history of childhood onset treated epilepsy), 8 cases refuse to participate, 4 cases excluded because of unavailable laboratory results, 26 cases droppedout the 2nd phase evaluation), all were interviewed in the outpatient clinics.Inclusion criteria:age > 18 years old and candidate forIFN therapy. Exclusion criteria:1) current diagnosis of activepsychiatric disorder or during the previous 3 months [detected by the MINI], 2) currently abusing any substances such as alcohol or intravenous drugs, or having abused in the past 12 months. 3) current use of any psychopharmacological medications,4) Any diagnosed medical or neurological conditions associated with significant psychiatric co-morbidity. 5) Cases excluded from IFN treatment e.g; pregnant females.

**Ethical approval**: The study was approved by the local Medical Review Ethics Committee of FacultyofMedicine,Sohag University, Egypt.All participants signed written informed consent.
**Methods:** chronic HCV infected patientswho wereinitiating antiviral therapy with pegylatedinterferon- α (PEG-IFN- α2a:135 mg/week or PEG-IFN- α2b: 120 or 150 mg/week) and oral ribavirin(1000–1200 mg/day) were examined pretreatment (baseline) and after 12 weeks from the beginning oftherapy.

The following investigations were done routinely by physicians in the virology clinic at baseline to all patients: complete blood picture, random blood sugar, kidney and liver functions including prothrombin time, HCV-ab, HBsAg, antinuclear antibody, alpha-feto-protein (AFP), thyroid stimulating antibody, pregnancy test for females, abdominal ultrasonography, liver biopsy, electrocardiography, fundus examination, and quantitative polymerase chain reaction (PCR) for HCV. to assess eligibility for PEG-IFN/Rib therapy and exclude cases with contraindicationsaccording to the guidelines of the National Committee For Control and Prevention of HCV in Egypt.PCR was also obtained 12 weeks after treatment, and all data obtained from these investigations were registered.

**Procedures**: after initial assessment -with hepatologist-167of those considered eligible for treatment by PEG-IFN/Rib were offered to participate. Those accepted started a pre-treatment/basal psychometric assessmentto determine pre-treatment psychological abnormalities.Starting by a semi-structured interview registering socio-demographic and clinical variables.

Psychometric assessments:an interview was done at least twice to: 1) complete the Mini International Neuropsychiatric Interview version 5 (MINI)***[14]***to assess lifetime and currenthistory of psychiatric illness,2) an assessment of current and past use of psychotropic medications, 3)Hamilton rating scale of depression (HAMD) to assess level of depression[15]4) Hamilton anxiety scales (HAMA) to assess level of anxiety[16], 5) Symptoms checklist revised (SCL-90-R)[17] to assess magnitude of psychopathological symptoms and related severity and distress levels, and 6) assessment for personality traits measured by the Structured Interview for the Five-Factor Model (SIFFM)[18, 19].

After 12th weeks of continuous PEG-IFN/Ribtherapy,revaluation of both laboratoryparameters (CBC, LFT, RFT, TSH, HCV viraemia) and psychometric scales for MINI, HAMD, HAMA & SCL90-R.were done for all participants.

**Psychometric scales:**

1. *Symptom Checklist-90-Revised (SCL90-R*)[17]; to measure severity of psychiatric symptoms on a nine primary symptom dimensions and three global indices of distress. can be completed in just 12 to 15 minutes.
2. The Mini International Neuropsychiatric Interview version 5 (MINI)[14];the MINI is a validated interviewer-administered, structured, diagnostic psychiatric interview which follows DSM-IV and the International Classification of Diseases-10 criteria for psychiatric disorders, screening for 17 Axis Idisorders, with brief suicidality and antisocial personality modules.

***3-****Hamilton Rating Scale for Depression (HAM-D)*[15]: Is a 17 item clinician administrated scale that is used to rate theseverity of a patient’s depression . (In qualitative assessment, score of <8 = average; 8-17 = mild depression; 18-24=moderate depression &> 24= severe depression [20])

***4-****Hamilton Anxiety Rating Scale (HAM-A)* :The HAMA[16]is a clinician rated 14-item test that measures the severity ofanxiety symptoms.rank mild if<17, moderate=18:24; severe>24.

***5****-The Structured Interview for the Five-Factor Model (SIFFM)* :A Semi-structured clinical interviews were designed for assessing personality traits based on the five-factor model of personality[18, 19]. The SIFFM is 120 items, assesses the five domains (Extraversion, Agreeableness, Conscientiousness, Neuroticism, and Intellect/Openness) of the NEO-PI-R using 24 items for each domain.It is a clinician rated interview that typically took about an hour to complete.

**Statistical analysis:**

Statistical Package for the Social Sciences (SPSS) v15.0.(SPSS Inc., Chic ago, Illinois, USA)was used for statistical analysis. Student -t- tests and Chi Square/ Fisher’s exact tests were used to test for differences between pre - & post treatment changes in numerical &categorical datarespectively. Continuous data were evaluated with t tests and presented as mean ± S.D. Nominal Logistic regression analysis was performed- taking the results of being depressed or not based on MINI as the dependent factor to estimate the possible predictors or risks of occurrence of depression after 12th weeks of treatment.Two-tailed hypotheses were used with a statistical significance level set at p < 0.05 for all statistical tests.

**Results**

*Sociodemographic Data*

 Table 1 shows the socio-demographicand pre-treatment laboratoryfindings for our patients. The meanage of patients was 38.52 +9.64 years. Mostof the patients were male (70%) and the majority were marriedand live in rural areas. History of Substance abuse only reported in males; with no gender based statistical differences regard education, occupation , residency, and laboratory findings at base line assessment.

*Psychiatric disturbances during antiviral therapy* **(**Table 1: Socio-demographic and medical characteristics of patients who were diagnosed depression or not at the twelve’s week of therapy**).** Thirty five of 100 patients (35%) with chronic viral hepatitis were diagnosed with major depression (MDD) on the twelves’ week of the IFN therapy based on MINI. There were significant differences between the two groups (depressed & non depressed subjects) in mean age. Being more elderly was more likely to cause depression in our study (Table 1). Among our cases (32%) have positive past/lifetime history of psychiatric illnesses & 21% has positive family history of psychiatric illnesses with significant statistical differences (P<0.001 for both) between those who developed depression and those who didn’t. There were no significant differences in gender, residency, marital status, education, and occupation, history of smoking, and history of substance abuse as well as for results of pre-treatment laboratory findings between the patients who developed depression and those who did not.

***Depressive sub-Syndromes***.( Table 2 Comparing the baseline and twelve’s week mean for HAMA & HAMD scores of patients)The mean HAMD scores increased significantly on the twelve’s week of the therapy (14.11 ± 8.17) relative to baseline ones (6.65 ± 3.65) (p < 0 . 001), with high significant statistical differences in the mean of paired sample testing analysis(mean ±SD=-7.480± 5.821).Also based on HAMD; 78% were detected to have positive scores (score >8) in post-treatment evaluation (49% mild, 15% Moderate & 14% severe) with gender distribution showed that female present 29% of mild cases, 67 % of moderate cases & 57% of severe cases respectively with significant statistical differences (P=0.01); that added a further 43% cases with depression not detected by MINI (Subsyndromal).

***Anxiety symptoms:***Although no detected anxiety syndromes after treatment based on MINI results; HAMA results show significant increase in anxiety scoring with high significant statistical differences in the mean of paired sample testing analysis (mean ±SD = -4.62 ± 3.9, P<0.001) table2, and in qualitative assessment- in post treatment evaluation; 85% score in range of mildanxiety (75% of them were males), 12% in range of moderate anxiety (33% males)and 3% severe anxiety (66.6% males) with significant statistical differences(P=0.01) relative to pre-treatment below17 score in all cases.

***Changes in SCL90-R :*** (Figure 1)The mean of SCL90-R showed significant increase for subscore of somatization (**SOM**) (mean± SD=-9.54 ± 6.398, P<0.001), interpersonal sensitivity(**I–S**) (mean±SD= -.050± .18443 , P=0.008), depression(**DEP**) (mean ±SD= -.370 ±.46751 , P<0.001) , anxiety(**ANX**) (mean ±SD=-.403 ± 56755, P=0.001), & Hostility(**HOS**) (mean ±SD=-.126 ±.26709 , P=0.03)following the administration of IFN- α compared withthe levels before the therapy,with correspondent statistically significant increase in mean of Global Severity Index ; Positive Symptom Distress Index and Positive Symptom Total(P<0.001). However Obsessive-Compulsive (**O–C**), Phobic Anxiety (**PHOB**) ; Paranoid Ideation (**PAR**) and Psychoticism(**PSY**)subscoresdidn’t change significantly in the same period.

***Suicide:*** figure 2: suicide risk in our study cases(total & gender differences) after 3 months of PEG-IFN/Rib treatment.overall estimated risk 14%, 9% of low risk (77% of them are females) and 5 % of moderate suicide risk (80% of them are females) with significant statistical differences in gender analysis.

***Treatment Response and Adherence***

48 % of our patient show complete viral clearance (-ve PCR/undetectable viraemia) after 3months of treatment with no statistically significant differences among those with diagnosis of depression relative to non-diagnosed group (table1)

**Predictors and risk factors for psychiatric disturbance under CHC PEG-IFN/Rib therapy:**

The logistic regression model for socio-demographic and pre-treatment laboratory findings was statistically significant, χ2= 59.29, p < 0.001. The model explained 78.0% (Nagelkerke R2) of the variance in cases with IFN induced depression and correctly classified 87.0% of cases. Increasing age (P=0.002) was associated with an increased likelihood of exhibiting psychiatric(MDD) after 3months of IFN therapy, also past history and family History were to found having a high significant predictive abilities (P=0.002, 0.003 respectively) .

**Table 1: Sociodemographic and medical characteristics of patients** .

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **All patients****(No = 100)** | **Cases** **develop MDD** **no (%@)** | **Cases not** **develop MDD****no (%@)** | **Pa value** |
| **Age;**  | **Mean ±SD** | **38.52 ± 9.64**  | **43.34 ± 7.89** | **35.92 ± 9.53** | **0.000** |
| **Gender**  | **Female** | **30 %** | **14 (40%)** | **16 (24.6%)** | **0.11** |
| **Male** | **70 %** | **21 (60%)** | **49 (75.4%)** |
| **Residency**  | **Rural** | **65 %** | **24(68.6%)** | **41(63.1%)** | **0.66** |
| **Urban** | **35 %** | **11(31.4%)** | **24(36.9%)**  |
| **Education**  | **illitrate** | **34 %** | **15 (42.9%)** | **19 (29.2%)** | **0.47** |
| **Basic Educated** | **13 %** | **5 (14.3%)** | **8 (12.3%)** |
| **Secondary school** | **33 %** | **10 (28.6%)** | **23 (35.4%)** |
| **University studies** | **20 %** | **5 (14.3%)** | **15 (23.1%)** |
| **Occupations** | **employee**  | **20%** | **6 (17.1%)** | **14 (21.5%)** | **0.79** |
| **Unemployed** | **80%** | **29 (82.9%)** | **51 (78.5%)** |
| **Marital status**  | **Married** | **61** | **25 (71.4 %)** | **36 (55.4 %)** | **0.18** |
| **Unmarried** | **39** |  **10 (28.6 %)** | **29 (44.6 %)** |
| **Past Hx. of psych dis.**  | **Positive** | **32 %** | **20 (57.1%)** | **12 (16.9%)** | **0.000** |
| **Negative** | **68 %** | **15 (42.9%)** | **53 (83.1%)** |
| **FHx. of psychdis.**  | **Positive** | **21 %** | **16 (45.7%)** | **5 (9.2%)** | **0.000** |
| **Negative** | **79 %** | **20 (54.3%)** | **59 (90.8%)** |
| **Smoking**  | **Positive** | **35 %** | **13 (37.1%)** | **22 (33.8%)** | **0.82** |
| **Negative** | **65 %** | **22 (62.9%)** | **43 (66.2%)** |
| **substance abuseHx** | **Positive** | **17**  | **9 (25.7%)** | **8 (12.3%)** | **0.1** |
| **Negative** | **83** | **26 (74.3%)** | **57 (87.7%)** |
| **#Lab. ,** **Mean ±SD** | **ALT****AST****Bilirubina-FP** | **42.64±30.26****44.38±31.37****0.98 ± 0.59****2.84 ± 0.23** | **46.11 ± 32.40****45.11 ± 31.13****1.18 ± 0.96****3.07 ± 0.68** | **40.43 ± 30.9****43.60 ± 23.5****0.87 ± 0.29****2.35 ± 1.43** | **0.8****0.8****0.14****0.42** |
| **HB****WBCs****Platelet** | **14.8 ± 2.2****7.6 ± 2.65****256 ± 168** | **15.83 ± 0.88****6.76 ± 1.58****216 ± 54.8** | **13.52 ± 1.41****7.81 ± 1.78****288 ± 78.5** | **0.13****0.43****0.65** |
| **TSH** | **1.47± 0.83** | **1.28 ± 0.88** | **1.48 ± 0.95** | **0.31** |
| **# Viraemia** | **(HCV RNA PCR)** | **1054257.16****±3141544.25** | **1146469.46****±2117640.36** | **1004604.38 ±3588465.12** | **0.83** |
| **viral clearance** | **-ve PCR** | **48** | **15 (42.9 %)** | **33 (50.8 %)** | **0.45** |
| **+ve PCR** | **52** | **20 (57.1 %)** | **32 (49.2 %)** |

**ALT, alanine aminotransferase; AST, aspartate aminotransferase; a-FP, a-feto protein; FBG, fasting blood glucose; HB, hemoglobin;Hx:history; IFN, interferon; INR, international normalization ratio;PHx:PastHistory; FHx:FamilyHistory; TSH: thyroid stimulating hormone; WBC:white blood cell. #pre treatment value, Pa value of significance from anovatable /chi squre results, (%@) % within mini inventory.**

Among psychometric variable model (χ2=87, P<0.001), increased pre-treatment HAMD (P=0.02)& HAMA score (P=0.04), somatization (P=0.04), depression (P=0.02) and hostility (P=0.04) subscores of SCL90-R were associated with an increased likelihood of developing MDD after 12ths’ week of continuous PEG-IFN/Rib therapy in CHC. But changes in other subscales of SCL90-R as well as scores for SIFFM domains show no predictive or significant associations with development of MDD

**TABLE 2; showing changes in psychometric variables for HAMD,HAMA**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **variables** | **Mean** | **SD** | **SE** | **Paired T. test differences** |
| **Mean** | **SD**  | **SE** | **95% CI** | **P** |
| **Upper** | **lower** |
| **HAMD1** | **6.63** | **3.59** | **.36** | **-7.48** | **5.82** | **.58** | **8.64** | **6.33** | **.000** |
| **HAMD2** | **14.11** | **8.17** | **.82** |
| **HAMA1** | **5.48** | **1.80** | **.18** | **-4.62** | **3.90** | **.39** | **5.39** | **3.85** | **.000** |
| **HAMA2** | **10.10** | **4.39** | **.44** |



**SOM.=** Somatization **; O–C** Obsessive-Compulsive**; I–S** Interpersonal Sensitivity **; DEP** Depression **;ANX** Anxiety **; HOS** Hostility**; PHOB** Phobic Anxiety **; PAR** Paranoid Ideation**; PSY ;** Psychoticism; 1 pre-treatment, 2 post treatment.

**Discussion**

In our study, 35% of treated HCV patients developed MDD after 12 weeks of treatment by IFN and ribavirin .That is in agree with majority of both national [13, 21, 22]& international studies[23-27] that reported development of depression in 30-70 % of HCV patient under treatment. None of the Egyptian studies were done in upper Egypt.

Although our results are consistent with the values reported in the literature, the duration of followup, type of scale used, and differences in the study method and samplegroup might cause the incidence rates to vary.

The current study revealed that HAMD and HAMA scores were increased significantly after 12 weeks of treatment. This is in accordance with manyprevious studies which screened for depression and anxiety in HCV patientstreated with IFN and ribavirin.[28-30], with further 43% of cases had subsyndromal depressive symptoms when comparing to MINI results , the majority of depressed cases were in the mild severity in agree with Franzenetal. (2010)[26], with worsening of anxiety symptoms in 15% of our cases after treatment based on HAMA when compared to MINI results of no anxiety syndromes, in agree with [22] but in contrast with others who report a syndromal anxiety disorder[13].

Incurrent studythe detectedsuicide risk was low –in form of suicidal ideation only with no recorded attempts& was not a cause of discontinuation; and was more among female cases.This work agree with majority of other studies that report suicide under HCV treatment[31, 32].low suicide risk is explained by the dominant mild depression associated with IFN-induced depression.

Our study showed that no cases identified to have other psychological disorders other than MDD (based on MINI)in agree with national studies[21, 22].In other studies; those who report psychosis ,delirium, mania & other psychotic disorders [26]presented either a case reports[33-36] or their studies are including patient with psychiatric disorder & present exacerbation of their illness under treatment [13, 37-39].

In this study no cases stopped treatment because of psychiatric adverse effects.Which was in agree with both national[21]& other international studies [39-41]. More over even in studies treating psychiatric patients[39, 42-44]they reported ‘that patients with a pre-existing psychiatric diagnosis can have similar outcomes to patients without mental illness with regard to viral response and treatment interruptions.

However many other studies report variable percentiles & rates of stoppage because of psychiatric adverse effects[42, 45-47].but we noticed that most of studies reported treatment discontinuation either retrospective studies [48] or studies already including psychiatric patients[42], or drug abusers [44, 49]with severe exacerbation of mental states -, or stopped because of non-psychiatric causes [50-52].

Several factors (table 3,4) potentially impact on the development of depression [53]. However, there is no consensus as to whether any of these factors impact on the development of depression in patients taking IFN- a.[11].In our study age, past history of psychiatric illness family history of psychiatric illness & the baseline HAMA scores (*X2=*87.866, *P*<0.036). The baseline HAMD scores(*X2=*87.866, *P*=0.019), SL90-R Depression(*X2=*87.866, *P*=0.021), SCL90-R Somatization (*X2=*87.866, *P*=)&SL90-R hostility(*X2=*87.866, *P*=0.048)were strong predictors foroccurrence of MDD after 12 weeks of treatment.

In current study, Increasing age increase the likelihood of developing depression(X2=59.29, P=0.002) in agree with others[54] But disagree with [32, 55] who reported Patients significantly younger age in depressed relative to non-depressed patients, further more [22, 23, 53, 56]reported no significant difference in age in depressed cases in relation to those who did not become depressed. This wide variability may be attributed to variability in other socio-demograpic, cultural and economic factors among different studied populations worldwide and may further point to a genetically determined different response to effect of IFN. as mentioned in some studies[57].

|  |
| --- |
| **Table 3: Variables in the Equation in model of sociodemographic variables** |
|  |  | **B** | **Wald** | **Sig.** | **Exp(B)** | **95% C.I.for EXP(B)** |
| **Step 4a** | **age** | **.093** | **9.738** | **.002** | **1.097** | **1.035** | **1.163** |
|  | **FHx Psych** | **-1.815** | **8.680** | **.003** | **.163** | **.049** | **.545** |
|  | **PastHxPsyc** | **-1.744** | **9.790** | **.002** | **.175** | **.059** | **.521** |
|  | **Constant** | **-1.821** | **2.000** | **.157** | **.162** |  |  |

|  |  |
| --- | --- |
| **Table 4: Variables in the Equation in model of pre-treatment psychometric variables** | **95% C.I.for EXP(B)** |
|  |  | **B** | **Wald** | **Sig.** | **Exp(B)** | **Lower** | **Upper** |
| **Step 1a** | **HAMD** | **-.127** | **9.120** | **.019** | **5.881** | **.429** | **1.806** |
|  | **HAMA** | **-.985** | **5.761** | **.036** | **.374** | **.167** | **.835** |
|  | **SCL90R-SOM1** | **8.082** | **2.873** | **.042** | **36.179** | **.089** | **1.182** |
|  | **SCL90R-DEP1** | **3.388** | **2.014** | **.021** | **4.678** | **.001** | **422.005** |
|  | **SCL90R-HOST1** | **5.584** | **3.912** | **.048** | **266.024** | **1.052** | **673.116** |
|  | **Constant** | **-14.217** | **.765** | **.382** | **.000** |  |  |

Past history and family history of psychiatric diseases in our work was highly significantly (X2=59.29, p=0.002&p=0.003 respectively) associated with occurrence of depression in cases under combined therapy and that was in agree with the majority of studies and control trials results[23, 55, 58, 59]. However some studies [54, 60, 61]failed to identify that association.

In current study no association with gender, marital status, educational level, past histoy of substance abuse(X2=59.29,P=0.0.34), smoking, or laboratory parameters at baseline and development of MDD after 12 weeks from treatment. In agree with many studies. Even though there are data which report that being female [58], low educational level [58, 61], substance abuse[43, 55, 62]create a higher risk in terms of the IFNinduced depression.

Women are typically more vulnerable than men to mood and anxiety disorders [53], but in this study Gender was not identified as independent risk factor for depression. That was in agree with [22, 23, 32, 53, 55, 61]. In contrast to others [13, 23, 63, 64] who confirmed female sex as a risk factor for depression. But we noticed that all the latter studies including pretreatment identified psychiatric ill patients which may point to exacerbation or activation of illness in females rather than specific findings.Current data suggests that IFN-MDD may be partially distinct from common forms of MDD that are unique to females.

In psychometric variables; pre-treatment HAMD , HAMA and somatization, depression & hostility subscales of SCL90-R show high predictive abilities in detecting who were more vulnerable to develop MDD, in agree with many studies[53, 58]. However other studies reported no association between basal depressionand development of depression[44].

Little studies have evaluated the effect of personality and personality characters on the outcome after treatment with IFN in HCV. In our studies pre-treatment Neuroticism level/ scores not identified as a Potential premorbid risk factors for IFN-MDD, in agree withMalyszczaketal(2006)[65].But in contrast Lotrichetal. reported that baseline neuroticism was strongly associated with MDD incidence in his work [66].That providing more evidence that IFN induced depression has particular different pathogenic mechanisms different from those of traditional depression and triggered by different risks/ predisposing factors.

There was no association between response to treatment and depression. In agree with other studies.[67]Hypothetically, it was expected that patients who did not respond to treatment will have more depression or anxiety than those who responded to treatment and have viral eradication. That may be explained by that; first, short period between results and our assessment(rapid psychological assessment after 12 weeks of treatment and the patients just know that they did not respond to treatment and some patients were assessed immediately before receiving results of viral clearance. Depression and anxiety might need enough time to develop after the patients know that the virus is not eradicated and they have to stop treatment. Second- for those responding but having depression- it seems that the cerebral effects of chronic HCV infection may be irreversible even after clearance of the virus from the serum[68] evidenced by no change in the brain function and biochemistry according to MRS study after viral clearance[68]. On the other hand, the effect of anxiety or depression on the response to treatment is controversial[13].

There are some limitations for this study. Although it’s reported that the peak incidence of depression between 4-12 week of treatment;[58]There is an obvious need for a more time extended prospective studies specially to determine the effects of different phases of treatment on depression and treatment outcome .

It is recommended to start psychiatric assessment at thebeginning of therapy, to search for early predictors ofdepression. Psychological assessment & comparative studies is needed for those receiving the promising new treatment, A multidisciplinary team should be consulted to develop complexphysical and psychological treatments for patients withCHC .

**References**

**1-**. Zoulim, F., et al., *Hepatitis C virus treatment in the real world: optimising treatment and access to therapies.* Gut, 2015. **64**(11): p. 1824-33.

**2-**. Sarhan, I.I. and C.R. Kamel, *Prevalence of hepatitis C virus seroconversion among hemodialysis patients in Egypt.* Egyptian Liver Journal, 2015. **5**(2): p. 34-39.

**3-**. El-Zanaty, F. and A. Way, *Egypt Demographic and Health Survey 2008*. 2009.

**4**. Masip, M., et al., *Prevalence and detection of neuropsychiatric adverse effects during hepatitis C treatment.* Int J Clin Pharm, 2015.

**5-** Messina, J.P., et al., *Global distribution and prevalence of hepatitis C virus genotypes.* Hepatology, 2015. **61**(1): p. 77-87.

**6-** Hilgenfeldt, E.G., A. Schlachterman, and R.J. Firpi, *Hepatitis C: Treatment of difficult to treat patients.* World J Hepatol, 2015. **7**(15): p. 1953-63.

**7-** Rein, D.B., et al., *The cost-effectiveness, health benefits, and financial costs of new antiviral treatments for hepatitis C virus.* Clin Infect Dis, 2015. **61**(2): p. 157-68.

**8-** EASL, *European Association for Study of the Liver, Recommendations on Treatment of Hepatitis C 2015.* J Hepatol, 2015. **63**(1): p. 199-236.

**9-** Sarwar, S., A.A. Khan, and S. Tarique, *Response Guided Interferon Therapy for Genotype 3 of Chronic Hepatitis C: Compliance and Outcome.* Pak J Med Sci, 2015. **31**(4): p. 843-7.

**10**- Fritz-French, C. and W. Tyor, *Interferon-alpha (IFNalpha) neurotoxicity.* Cytokine Growth Factor Rev, 2012. **23**(1-2): p. 7-14.

11- Smith, K.J., et al., *Risk factors for the development of depression in patients with hepatitis C taking interferon-alpha.* Neuropsychiatr Dis Treat, 2011. **7**: p. 275-92.

**12**- Bota, S., et al., *Severe adverse events during antiviral therapy in hepatitis C virus cirrhotic patients: A systematic review.* World J Hepatol, 2013. **5**(3): p. 120-6.

**13**- Mm, B., et al., *Major depressive disorder and generalized anxiety disorder and response to treatment in hepatitis C patients in Egypt.* Int J Psychiatry Med, 2015. **50**(2): p. 147-62.

**14**- Sheehan, D.V., et al., *The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10.* J Clin Psychiatry, 1998. **59 Suppl 20**: p. 22-33;quiz 34-57.

**15**-Hamilton, M., *A rating scale for depression.* J Neurol Neurosurg Psychiatry, 1960. **23**: p. 56-62.

**16**- Hamilton, M., *The assessment of anxiety states by rating.* Br J Med Psychol, 1959. **32**(1): p. 50-5.

**17**- DERAGOTIS, L.R., *The SCL-90-R: administration, scoring and procedures manual*. 3ed Ed. ed. 1994: Minneapolis, MN: National Computer Systems.

**18-** Widiger, T.A. and T.J. Trull, *Assessment of the five-factor model of personality.* J Pers Assess, 1997. **68**(2): p. 228-50.

**19**-Trull, T.J., T.A. Widiger, and R. Burr, *A structured interview for the assessment of the Five-Factor Model of personality: facet-level relations to the axis II personality disorders.* J Pers, 2001. **69**(2): p. 175-98.

**20-** Zimmerman, M., et al., *Severity classification on the Hamilton Depression Rating Scale.* J Affect Disord, 2013. **150**(2): p. 384-8.

**21-** Elshahawi, H.H., M.M. Hussein, and E.A. Allam, *Depression comorbidity in patients with chronic hepatitis C and its possible relation to treatment outcome.* Middle East Current Psychiatry, 2011. **18**(1): p. 23-28.

**22**- Elsayed, H., et al., *Prospective study of psychiatric side effects during antiviral therapy of chronic hepatitis C in an Egyptian sample.* Middle East Current Psychiatry, 2012. **19**(2): p. 71-77.

**23-** Baranyi, A., et al., *A biopsychosocial model of interferon-alpha-induced depression in patients with chronic hepatitis C infection.* Psychother Psychosom, 2013. **82**(5): p. 332-40.

**24**- Udina, M., et al., *1646 – Genetic risk factors for interferon-induced anxiety (Abstracts of the 21th European Congress of Psychiatry).* European Psychiatry, 2013. **28, Supplement 1**(0): p. 1.

25- Blacklaws, H., A. Gardner, and K. Usher, *Irritability: an underappreciated side effect of interferon treatment for chronic hepatitis C?* J Clin Nurs, 2011. **20**(9-10): p. 1215-24.

**26**- Franzen, P.L., et al., *Poor sleep quality predicts onset of either major depression or subsyndromal depression with irritability during interferon-alpha treatment.* Psychiatry Res, 2010. **177**(1-2): p. 240-5.

**27**- Huckans, M., et al., *A longitudinal study evaluating the effects of interferon-alpha therapy on cognitive and psychiatric function in adults with chronic hepatitis C.* J Psychosom Res, 2015. **78**(2): p. 184-92.

**28**- Majer, M., et al., *IFN-alpha-induced motor slowing is associated with increased depression and fatigue in patients with chronic hepatitis C.* Brain Behav Immun, 2008. **22**(6): p. 870-80.

**29**- Heinze, S., et al., *Depressive mood changes and psychiatric symptoms during 12-month low-dose interferon-alpha treatment in patients with malignant melanoma: results from the multicenter DeCOG trial.* J Immunother, 2010. **33**(1): p. 106-14.

**30**- Huang, Y.W., et al., *Biphasic pattern of depression and its predictors during pegylated interferon-based therapy in chronic hepatitis B and C patients.* Antivir Ther, 2013. **18**(4): p. 567-73.

**31**-Dieperink, E., et al., *Suicidal ideation during interferon-alpha2b and ribavirin treatment of patients with chronic hepatitis C.* Gen Hosp Psychiatry, 2004. **26**(3): p. 237-40.

**32-** Evon, D.M., et al., *Prospective analysis of depression during peginterferon and ribavirin therapy of chronic hepatitis C: results of the Virahep-C study.* Am J Gastroenterol, 2009. **104**(12): p. 2949-58.

**33-**Schafer, M., T. Boetsch, and G. Laakmann, *Psychosis in a methadone-substituted patient during interferon-alpha treatment of hepatitis C.* Addiction, 2000. **95**(7): p. 1101-4.

**34-**Silverman, B.C., A.Y. Kim, and O. Freudenreich, *Interferon-induced psychosis as a "psychiatric contraindication" to hepatitis C treatment: a review and case-based discussion.* Psychosomatics, 2010. **51**(1): p. 1-7.

**35-**Sockalingam, S. and K. Balderson, *Major depressive episode with psychotic features induced by pegylated interferon-alpha-2b and ribavirin treatment.* Int Clin Psychopharmacol, 2005. **20**(5): p. 289-90.

**36-**Cheng, Y.C., et al., *Prolonged psychosis associated with interferon therapy in a patient with hepatitis C: case study and literature review.* Psychosomatics, 2009. **50**(5): p. 538-42.

**37**-Evon, D.M., et al., *Psychiatric symptoms during interferon treatment for hepatitis C: experiences from a tertiary care hepatology centre.* Aliment Pharmacol Ther, 2008. **27**(11): p. 1071-80.

**38-**Freedman, K. and J. Nathanson, *Interferon-based hepatitis C treatment in patients with pre-existing severe mental illness and substance use disorders.* Expert Rev Anti Infect Ther, 2009. **7**(3): p. 363-76.

**39**-Van Thiel, D.H., et al., *Interferon-alpha can be used successfully in patients with hepatitis C virus-positive chronic hepatitis who have a psychiatric illness.* Eur J Gastroenterol Hepatol, 1995. **7**(2): p. 165-8.

**40-**Pariante, C.M., S. Landau, and B. Carpiniello, *Interferon Alfa–Induced Adverse Effects in Patients with a Psychiatric Diagnosis.* New England Journal of Medicine, 2002. **347**(2): p. 148-149.

**41**-Pariante, C.M., et al., *Treatment with interferon-alpha in patients with chronic hepatitis and mood or anxiety disorders.* Lancet, 1999. **354**(9173): p. 131-2.

**42**-Kuhara, K., et al., *The importance of a prior psychiatric examination in pegylated interferon and ribavirin combination treatment for chronic hepatitis C.* Kurume Med J, 2012. **59**(3-4): p. 39-44.

**43**-Schaefer, M., et al., *Adherence and mental side effects during hepatitis C treatment with interferon alfa and ribavirin in psychiatric risk groups.* Hepatology, 2003. **37**(2): p. 443-51.

**44**-Schaefer, M., et al., *Hepatitis C treatment in "difficult-to-treat" psychiatric patients with pegylated interferon-alpha and ribavirin: response and psychiatric side effects.* Hepatology, 2007. **46**(4): p. 991-8.

**45**-McHutchison, J.G., et al., *Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group.* N Engl J Med, 1998. **339**(21): p. 1485-92.

**46**-Bernstein, D., et al., *Relationship of health-related quality of life to treatment adherence and sustained response in chronic hepatitis C patients.* Hepatology, 2002. **35**(3): p. 704-8.

**47**-Soriano, V., et al., *Premature treatment discontinuation in HIV/HCV-coinfected patients receiving pegylated interferon plus weight-based ribavirin.* Antivir Ther, 2007. **12**(4): p. 469-76.

**48-**Raison, C.L., et al., *Neuropsychiatric Adverse Effects of Interferon-α: Recognition and Management.* CNS drugs, 2005. **19**(2): p. 105-123.

**49-**Van Thiel, D.H., A. Anantharaju, and S. Creech, *Response to treatment of hepatitis C in individuals with a recent history of intravenous drug abuse.* Am J Gastroenterol, 2003. **98**(10): p. 2281-8.

**50**-Espinosa, M., et al., *Pegylated Interferon (Alone or With Ribavirin) for Chronic Hepatitis C in Haemodialysis Population.* Kidney Blood Press Res, 2015. **40**(3): p. 258-65.

**51-** Ahn, S.B., et al., *Efficacy and safety of pegylated interferon base treatment in patients with chronic hepatitis C on dialysis.* Eur J Intern Med, 2015. **26**(4): p. 292-6.

**52**- Rendina, M., et al., *The treatment of chronic hepatitis C with peginterferon alfa-2a (40 kDa) plus ribavirin in haemodialysed patients awaiting renal transplant.* J Hepatol, 2007. **46**(5): p. 768-74.

**53**- Raison, C.L., et al., *Depression during pegylated interferon-alpha plus ribavirin therapy: prevalence and prediction.* J Clin Psychiatry, 2005. **66**(1): p. 41-8.

**54**- Horikawa, N., et al., *Incidence and clinical course of major depression in patients with chronic hepatitis type C undergoing interferon-alpha therapy: a prospective study.* General Hospital Psychiatry, 2003. **25**(1): p. 34-38.

**55**- Castera, L., et al., *Impact on adherence and sustained virological response of psychiatric side effects during peginterferon and ribavirin therapy for chronic hepatitis C.* Aliment Pharmacol Ther, 2006. **24**(8): p. 1223-30.

**56**- Kraus, M.R., et al., *Psychiatric symptoms in patients with chronic hepatitis C receiving interferon alfa-2b therapy.* J Clin Psychiatry, 2003. **64**(6): p. 708-14.

**57-** Birerdinc, A., et al., *Gene expression profiles associated with depression in patients with chronic hepatitis C (CH-C).* Brain Behav, 2012. **2**(5): p. 525-31.

**58**- Udina, M., et al., *Interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis.* J Clin Psychiatry, 2012. **73**(8): p. 1128-38.

**59-**Castellvi, P., et al., *Pegylated interferon and ribavirin-induced depression in chronic hepatitis C: role of personality.* J Clin Psychiatry, 2009. **70**(6): p. 817-28.

**60**-Lotrich, F.E., et al., *Depression following pegylated interferon-alpha: characteristics and vulnerability.* J Psychosom Res, 2007. **63**(2): p. 131-5.

**61**-Martin-Santos, R., et al., *De novo depression and anxiety disorders and influence on adherence during peginterferon-alpha-2a and ribavirin treatment in patients with hepatitis C.* Aliment Pharmacol Ther, 2008. **27**(3): p. 257-65.

**62**-Schaefer, M. and S. Mauss, *Hepatitis C treatment in patients with drug addiction: clinical management of interferon-alpha-associated psychiatric side effects.* Curr Drug Abuse Rev, 2008. **1**(2): p. 177-87.

**63**-Su, K.P., et al., *Phospholipase A2 and cyclooxygenase 2 genes influence the risk of interferon-alpha-induced depression by regulating polyunsaturated fatty acids levels.* Biol Psychiatry, 2010. **67**(6): p. 550-7.

**64**-Pavlovic, Z., et al., *P-519 - Risk factors for depressive symptoms in patients with hepatitis c treated with pegylated interferon alpha therapy.* European Psychiatry, 2012. **27, Supplement 1**: p. 1.

**65-**Malyszczak, K., et al., *[Depressive symptoms during treatment with interferon alpha for HCV infection--preliminary report].* Psychiatr Pol, 2006. **40**(4): p. 799-808.

**66**-Lotrich, F.E., et al., *Risk for depression during interferon-alpha treatment is affected by the serotonin transporter polymorphism.* Biological psychiatry, 2009. **65**(4): p. 344-348.

**67**-Wackernah, R.C., M. Lou, and S.H. Park, *Retrospective chart review to assess the relationship between depression and sustained virological response from interferon treatment for hepatitis C virus.* Clin Ther, 2011. **33**(10): p. 1400-5.

**68**-Pattullo, V., et al., *Influence of hepatitis C virus on neurocognitive function in patients free from other risk factors: validation from therapeutic outcomes.* Liver Int, 2011. **31**(7): p. 1028-38.

**الملخص العربى**

**الاضطرابات النفسية المرتبطة بالانترفيرون كعلاج لفيروس (سي) في محافظة سوهاج**

تعتبر مصر من اعلى البلدان فى معدلات انتشار فيروس التهاب الكبد الوبائي سى فى العالم .وعلى الرغم من التوجه لاستعمال نظام جديد للعلاج عن طريق الفم فى الآونة الأخيرة ، الا ان العلاج بالانترفيرون سوف يستمر لنسبة كبيرة من المرضى – سواء لتكلفة الدواء المرتفعة، أوالقيود الطبية المفروضة لصرفه رغم اعراض علاجات الانترفييرون الجانبية - خاصة النفسية منها والتى ما يزال حولها كثير من الجدل والاختلاف.هدفت الدراسة إلى: قياس معدل حدوث الاضطرابات النفسية في مرضىلتهاب الكبد الوبائي سى عند تلقى العلاج بالانترفيرونوالريبافيرين فى محافظة سوهاج في صعيد مصر- والكشف عن عوامل الخطر المرتبطة بذلك. **منهاجية البحث** : تمت الدراسة فى الفترة من نوفمبر2012 وحتى يناير2015 وشملت 100 من 167 مريض تم معاينتهم على مرحلتين: مرحلة ما قبل العلاج :تم استقصاء التاريخ المرضى وعمل فحص سريرى وعصبى كامل وسحب عينات لاجراء فحوصات الدم واجراء الجزء الاول من القياسات النفسية من خلال تطبيق مقاييس (المقياس الدولى المصغر لقياس الاضرابات النفسية- مقياسى هاميلتون للاكتئاب والقلق- النسخة المختصرة لتقييم السمات الشخصية بناء على نظرية الخواص الخمسةSIFFM.وقائمة فحص الاعراض المنقحة-90 SCL-90-R)– لاستبعاد غير اللائقين والحصول على القياسات الاولية لحساب المتغيرات لاحقا مع العلاج.مرحلة ما بعد العلاج: وهنا يتم مناظرة المرضى مرة اخرى بعد 12 اسبوع من العلاج المستمر بالانترفيرون والريبافيرين ويجرى عليهم نفس التقييمات السريرية والمعملية والنفسية السابقة لدراسة مدى التغير بعد العلاج احصائيا. **النتائج :**- 35٪ من المرضى اصيبوا باكتئاب جسيم (MDD) بعد العلاج بدرجة خطورة خفيفة الى متوسطة الشدة مع افكار انتحارية فى 14% منهم ولكن لا محاولات للانتحار وقد وجد ان حوالى 43% أخرين من مرضانا يعانون اعراض اكتئابية وزيادة 15%فى معدلات القلق ذات دلالة احصائية على مقياسى هاميلتون للاكتاب والقلق ولكن لا تصل بهم الأعراض لتشخيص متلازمة الاكتئاب الجسيم.مع ارتفاعات واضحة فى نتائج بعد العلاج على مقاييس هاميلتون للاكتئاب والقلق ومقياس قائمة الاعراض (خاصة فى مقاييس الاعراض الجسمانية والقلق والاكتئاب ومقياس حساسية التعامل ومقياس العدائية) -و لم يترتب على ظهور اى من الاضرابات او الاعرض ا لنفسية السابقة توقف للعلاج. 48 % من مرضانا لم يتم استكشاف الفيروس لديهم بنهاية الشهر الثالث من العلاج ولم يكن لذلك اى علاقة بظهور الاعراض النفسيةالسابقة.

- ومن بين العوامل الاجتماعية والديموغرافية، تم تحديد وجود ارتباط كبير بين❶سن المريض (خاصة كبار السن)، ❷وجود تاريخ سابق من الأمراض النفسية ❸وتاريخ عائلىللامراض النفسية -والقدرة على التنبؤ بحدوث اكتئاب جسيم في مرضى الالتهاب الكبدى الوبائى تحت العلاج.كما لوحظ ان لوجود اعراض اكتئابية واعراض قلق قبل بدء العلاجقدرة على التنبؤ بحدوث نوبات الاكتئاب الجسيم عند المرضى. **الخلاصة:** تمثل نوبات الاكتئاب الجسيم الاضطراب النفسي الأكثر شيوعا في مرضى فيروس (سي) المزمن تحت العلاج بالأدوية المعتمدة على الانترفيرون بعد 12 اسبوع من العلاج ، ولكن ليس سببا لوقف العلاج. ومن ثم يوصى برصد ومتابعة اعراض الاكتئاب فى هؤلاء المرضى ووجودها قبل العلاج مع العوامل الاخرى فى حال استخدام العلاجات بالانترفيرون ، كما ان هناك حاجة لمزيد من الدراسات لتقييم التأثير الطويل الأجل لذلك العلاج على هؤلاء المرضى وتقييم الآثار السلبية النفسية للعلاج الثلاثي و انواع العلاج الجديدة عن طريق الفم.