FREQUENCY OF DEPRESSION;
DURING PEGYLATED INTERFERON THERAPY FOR CHRONIC HEPATITIS C

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ABSTRACT: Combine Pegylated interferon therapy and ribavirin is most commonly used treatment in chronic hepatitis C patients. Along with other complications, different psychiatric disorders are observed during combination therapy including depression. Depression is the major morbidity as it may lead to different destructive ideation including suicide among patients on treatment. We have tried to calculate the frequency of depression along with associated factors in our present study. **Objectives:** To find out the frequency of depression during Pegylated interferon therapy for chronic hepatitis C. **Study Design:** Descriptive study. **Setting:** Liaquat University of Medical & Health Sciences, Jamshoro / Hyderabad **Duration:** The duration of study was six months starting from 01-01-2014 to 31-06-2014. **Methodology:** Two hundred and fifty two cases of chronic hepatitis C on the basis of anti HCV (ELISA) and PCR positive were selected in this study. **Results:** Out of 252 patients, 111 (44%) were males and 141(56%) were females. Most of the patients belonged to 26 to 50 years of age. The duration of treatment was 12 weeks. Two hundred & eight (82.5%) patients had ever married while the remaining 17.5% were unmarried. Out of 106 (42%) depressed patients, 39 (37%) had mild, 31 (29%) had moderate, 20 (19%) had moderately severe and 15 (15%) had severe depression. **Conclusion:** It was observed that depression is a common during combination therapy with Peg interferon and the ribavirin in chronic HCV patients.

Key words: depression, Peg interferon therapy, chronic HCV

INTRODUCTION

Hepatitis C is a hepatic infection which caused by hepatitis C virus (HCV) which is a single standard RNA virus (hepavirus) with properties similar to those of flavivirus. It is difficult for the human immune system to eliminate HCV from body, and infection through HCV typically becomes chronic.

Hepatitis C is a worldwide problem. The HCV is main cause of the acute and the chronic hepatitis. The World Health Organization (WHO) estimates worldwide 170 million cases are infected through hepatitis C virus (HCV). However, the prevalence of HCV infection different worldwide.[1] Prevalence of acute HCV in past dedicate has sharply decreased in the United States. HCV prevalence remains big (approximately 2.7 million Americans), however, because chronic HCV develops approximately 75% of patients acutely infected.[2] Pakistan is among the highest in the world and estimated to

be 4.8%.Although, 10 million people are infected with HCV in Pakistan, and inadequate information reagrding its incedence in different areas of the country.[3] Estmaly 80% cases exposed to chronic HCV infection; 3–11% of those with chronic HCV infection will develop cirrhosis during 20 years, with linked risks of liver failure and hepatocellular carcinoma. All cases having chronic HCV may consider candidates for treatment. Treatment for of chronic hepatitis C is rarely measured less than 70 years of the age with more than mild fibrosis on liver biopsy.[4]

Current recommended treatments contain on combination of pegylated interferon alpha and ribavirin for 24 or 48 weeks, depending on HCV genotype but combination of a conventional ineterferon alpha and ribavirin is also being used due to its low price in this part of the world .The basic aim of therapy is viral elimination. 2nd aim

symptoms reduction and prevention of cirrhosis or HCC. The treatment duration is determined by HCV genotype and response of therapy to virus. Quantitative HCV RNA is utilize to consider the therapeutic response and as guide to treatment discontinuation. The success rate of antiviral treatment in chronic hepatitis C (HCV) has considerably increased during recent years drug adherence remains a difficult problem due to the number and the severity of side effects induced by antiviral therapy.[5]

Systemic side effect occur in 30% to 50 % of cases and include flu like symptoms, fatigue, headache, thyroid dysfunction (hypothyroidism or hyperthrioidism), anorexia, digestive disorder, central nervous system disorder and hematological disorders because of bone marrow dysfunction and anemia. From side effects, symptoms of depression and other neuro-psychiatric are more advances in HCV antiviral therapy and conception and subsequent management effects induced by this treatment should treat more cases through big success.[6,7]

PEG IFN-alpha is strongly linked to depression, anxiety, fatigue and irritability in 30-80% cases. Since success ratio of antiviral treatment of chronic HCV is rising, knowledge regarding side effects through this treatment must should be improve.[7,8]

Depression occurs in estimatly in 60% in HCV-infected individuals however, depression itself is not a contraindication to HCV treatment. There are many methods to assess and follow depression in cases having HCV during treatment with PEG IFN-alpha and ribavirin. Low social support was independently associated with pre-treatment and on-treatment development of depression. Selective serotonin re-uptake inhibitors (SSRIs) have been shown to be effective in treating depression in PEG IFN-treated patients. Citalopram had shown as an excellent option of treatment for patients who developed depression during treatment with PEG IFN for HCV compared to placebo. Depression along with lower socioeconomic status remains a main hurdle to those seeking treatment for HCV

in its early stages, so it enhances the importance of screening and treatment of depression in HCV cases during treatment by the physician. This may increase their attendance to clinics and compliance of treatment which improved response rates and reduction of complications of the disease, mainly cirrhosis and hepatocellular carcinoma.[9]

OBJECTIVES OF STUDY
Chronic hepatitis C is a major health problem worldwide and leading cause of morbidity and mortality. Combination therapy with Pegylated Interferon Alfa and ribavirin is the mainstays of treatment for chronic hepatitis C. Majority of patients develop depressive disorder during combination therapy. The objective of this study was to see the frequency of depression during combination therapy with Pegylated interferon and ribavirin for chronic hepatitis C.

ETHICAL CONSIDERATIONS
Ethical approval for this study was taken from the Ethics Review Committee of Liaquat University of Medical & Health Sciences. Written informed consent was being taken from each participant and they would be free to leave the study whenever they desire.

OPERATIONAL DEFINATION
Depression
Depression is assessed by Primary health questionnaire which is incorporated with DSM IV criteria and a participant with score >5 will be considered as depressed. Depression will be further classified on the following criteria;
o   Mild Depression: score of 5 -9
o   Moderate depression: score of 10-14
o   Moderate severe Depression: score of 15-19
o   Severe Depression: score of 20-27

MATERIAL AND METHODS

Study Design
A Descriptive cross sectional study was conducted at Outpatient Department of Medicine, Liaquat University Hospital Hyderabad in duration of six months from 01-01-2014 t0 31-06-2016 over 252 patients. Sampling technique used was

non-probability consecutive sampling. Inclusion criteria was

ALT levels > 30 u/l, Anti HCV positive patient (by ELISA), HCV RNA detected by any PCR technique before and during treatment, receiving Pegylated Interferon alpha + Ribavirin for 12 weeks and ages between 18 to 60 years in both Sexes (Male/ Female). Exclusion criteria was severe chronic diseases (e.g., cancer, ischemic heart disease, and autoimmune disease), co-infections (hepatitis B virus or human immunodeficiency virus), patients previously treated for hepatitis C / received interferon α and unwilling to participate in the study

DATA COLLECTION PROCEDURE

Patients attending Medial outpatient departments were considered for enrollment in the study. After careful review of inclusion and exclusion criteria suitable patients were selected. A total of 252 patients were enrolled for this study. Participants were interviewed in a quiet room with privacy after taking an informed consent. Hepatitis C was diagnosed on the basis of anti HCV (ELISA) and PCR test. All study participants were seen at 12 weeks of initiation of interferon therapy by using DSM IV criteria. DSM IV was used to measure and compare the frequency of depression among HCV patients during Pegylated interferon and ribavirin therapy. Study variables were

INDEPENDENT/EXPOSURE VARIABLE

Interferon therapy, Socio-demographic characteristics including age, gender, level of education, employment status, history of psychiatric illness and socio-economic status.

DEPENDENT/OUTCOME VARIABLE

Depression.
Taken as a dichotomous variable i.e. Depressed and non-depressed.

DATA ANALYSIS

Data were entered and analyzed in statistical program SPSS version 19.0. Simple frequencies and percentages were calculated for qualitative data such as gender, age (in groups), marital status, socio-economic status, place of residence, employment status, socioeconomic status, level of education and the outcome variable i-e, depression. Mean + SD was calculated for continuous variables like age, weight and score of depression severity.

Chi-square test was applied after stratification of age, gender, marital status, residence, socio-economic status, employment status & history of psychiatric illness to evaluate the effect modification of frequency of depression by these variables. P value of 0.05 was considered as statistically significant.

RESULTS

To evaluate the frequency of depression in patients of chronic hepatitis C treated through combination therapy with Pegylated interferon and ribavirin, the current study was conducted at the department of Medicine; Liaquat University Hospital Hyderabad taking a sample of 252 patients of chronic hepatitis C. Duration of treatment of all patients was 12 weeks.

The mean ± SD age of patients was 38.03 ± 10.82 years with a range from 17 to 60 years. Mean ± SD weight of patients was 61.38 ± 8.86 Kgs. Minimum weight was 38 Kgs while maximum weight was 82 Kgs. The mean ± SD score of severity of depression in all patients was 11.81 ± 5.11 while the score was 14.74 ± 4.23 among depressed patients with a range of 6-22 points.

Gender distribution of patient showed that there were more females i-e; 56% (n= 141) while the males were 44% (n=111).

Patients belonging to rural areas were 46.4% while 53.6% patients were urban living. Two hundred & eight (82.5%) patients had ever married while the remaining 17.5% were unmarried. Almost half of all patients 48% (n=121) belonged to middle class, 34.5% (n=88) were form poor socio-economic class while only 17.1% (n=43) patients were of upper socio-economic class.

It was noted that nearly 60% patients were either illiterate or had maximum education upto primary

only. Patients with secondary level education were 34.9% while only 6% patients had done graduation or more study. History of psychiatric illness was present in 7.1% patients.

When patient were grouped in different age categories it was seen that more than two thirds i-e 69.8% (n=176) were of age 26-50 years. Only 15.5% & 14.7% were grouped as below 25 years and 51 years & above respectively (Table-I).

The main outcome variable of this study that frequency of depression among patients of chronic hepatitis C treated through combination therapy with Pegylated interferon and ribavirin, was 42.1% (n= 106).

When evaluated for severity of depression it was found that out of total 106 depressed patients, 36.79% (n= 39) had mild depression, 29.25% (n= 31) had moderate depression, 18.87% (n= 20) had moderately severe depression and 15.09% (n= 16) were found to be severely depressed (Figure-2).

When stratified analysis was done to see the effect modification it was significantly noted that females were more depressed (46.8%) as compared to males 36% (P value = 0.056).

Age categorization showed that 26-50 years group patients were highly depressed (47.7%) than other two groups i-e below 25 years and 51 years & above which had depression frequency of 28.2% & 29.7% respectively. The finding was significant (P value = 0.021) (Figure-3).

Further it was also noted that the patients who had history of psychiatric illness had more depression (55.6%) than those did not have any such history (41%) (P value = 0.169).

Marital status also affected the frequency of depression among Hepatitis C patients such that 44.2% of married patients had depression as compared to 31.8% of never married patients. (P value = 0.088).

The study also noted that poor patients were more depressed (45.5%) than patients of middle class (41.3%) & upper class (37.2%) (P value = 0.651).

A non-significant but very interesting finding was noted by the currents study that higher the education higher was prevalence of depression among Hepatitis C patients. It increased from 45% among illiterate to 53.3% among highest education level i-e; Graduation or more (P value = 0.683).

Patients having a government job had least depression prevalence while the businessmen and house wives more most depressed groups when analyzed as per the employment status (P value = 0.222).

Rural urban difference was highly significant (P value = 0.003) where 42.2% urban patients were depressed compared to 41.9% rural patients.
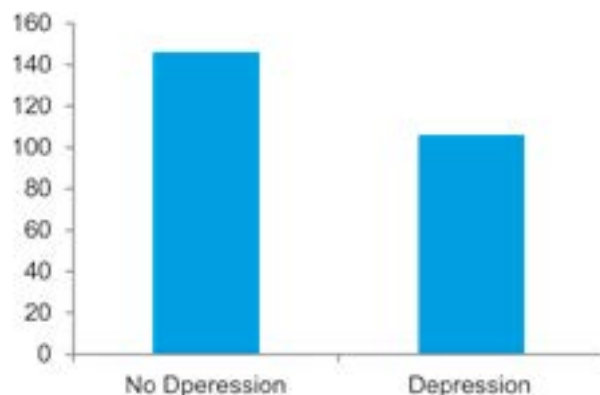

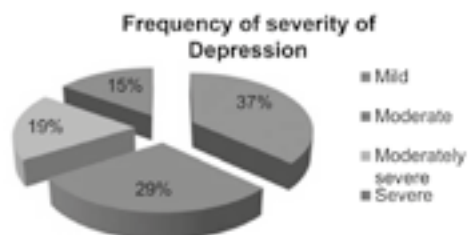**Figure-1. Frequency of depression among chronic hepatitis C treated with combination therapy**

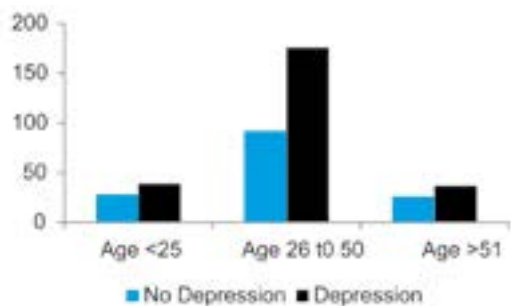**Figure-2. Frequency of Depression according to its severity**

Figure-3. Effect of age on frequency of depression

n= 252	Frequency	Percent
AGE		
Below 25 Years	39	15.5
26-50 Years	176	69.8
51 Years & above	37	14.7
GENDER		
Male	111	44
Female	141	56
RESIDENCE		
Urban	135	53.6
Rural	117	46.4
MARITAL STATUS		
Ever married	208	82.5
Never married	44	17.5
SOCIO-ECONOMIC STATUS		
Upper class	43	17.1
Middle class	121	48
Poor	88	34.9
LEVEL OF EDUCATION		
Higher (Graduate or more)	15	6
Secondary (Matric to Intermediate)	88	34.9
Primary	69	27.4
Illiterate	80	31.7
OCCUPATION		
Business	50	19.8
Government job	29	11.5
Private job	58	23
Job less	48	19
House wife	67	26.6
HISTORY OF ANY PSYCHIATRIC ILLNESS		
Yes	18	7.1
No	234	92.9
Table-I. Descriptive Statistics		

DISCUSSION

Our aim was to see the frequency of depression during combination therapy with Pegylated interferon and ribavarin in Chronic Hepatitis C patients. About 6% of adult and 15% of general population faces an episode of depression in their lives, making it fourth leading cause of disability in world. Chronic diseases are often associated with increase episodic or permanent depression. A WHO study has shown a depressive prevalence of 23% in people with chronic disorders compared with a prevalence of 3.2% of healthy controls.[10] Chronic Hepatitis C patients also exhibit an increased rate of depression with nearly 25% of them affected by major depression compared with 7% of the general public.[10] According to Bruno et al. 46 patients (56.8%) had cur-rent psychiatric disorder among them 23 patients were with major depression and three with distimia.[11] Multiple factors may play their role for this increased prevalence which includes biological and psycho-social reasons. Patients may suffer from neurotoxicity of HCV along with alterations in cerebral metabolism[1] or have fear of disease and its outcome. Lack of knowledge about this disease can also lead to increased rate of depression among patients.[10]

Depression is a major problem observed during therapy with an increase in depression risk to 23% to 44% by interferon-based treatment.[12] Depressive symptoms develop as early as 4 weeks of treatment with its peak at week 24.[13]

In our study we selected 252 patients of chronic hepatitis-C as our sample population and a prevalence of post-therapy depression was found to be 42.1% (n=106). The depression was divided into mild, moderate, moderately severe and severe category based on the intensity felt by patients. The frequency of 42.1% is high but in range of prevalence shown by other studies. The study of Neil Harrison discusses the mechanism of induction of depression by interferon in hepatitis C patient and state a range of 30% to 50% for severe depression in these patients.[14]

Overall rising depression incidence was 0.25 (95%

CI, 0.16 to 0.35) and 0.28 (95% CI, 0.17 to 0.42) at 24 and 48 weeks of treatment, respectively.[15] This high frequency of depression alarm physician to note every behavior change during treatment as it may require reduction in doses of medication or even its cessation.

The result of age categorization in our study showed that age group of 26-50 years was highly depressed (47.7%) with a significant P value of 0.021. This finding of the study is similar to other epidemiological studies which uses standard diagnostic criteria. Studies from Blazer, Hughes, & George,1987; Eaton et al 1989; Kramer, German, Anthony, Von Korff, & Skinner, 1985; Myers et al, 1984; Weissman et al 1988 showed decrease prevalence of depression in late age.[16,17,18,19] Similar results are found in other reports based on studies from epidemiological catchment area. The study of Korten & Henderson (2000) also favors our result regarding age categorization. In this study 10641 adult individuals were interviewed and it was concluded that depressive disorder decreases in sex, men and women after the age of 55.[20]

Frequency of depression is also affected by marital status among Hepatitis C patients with 44.2% of married patients having depression with P-value 0.088 as compared to 31.8% of never married patients. This finding of our result contradicts with other studies in which marriages have been shown to have a protective effect over depression and is often recommended for decreasing the symptoms of depression. It is confirmed that marital status having an strong effects on psychological well-being, sustaining shelter perspective. Marital (cohabiting) quality effect association on psychological well-being was significant, while strong effect of marital status remained unchanged after controlling for relationship quality.[21] Marriages are even considered as protective factor for suicide.[22] However, there is a discussion about different effect of marriages on two different sexes. It is generally calculated that marriages are good for men whereas they are bad for women in terms of depression.

Rural urban difference regarding depression in our study was highly significant with P value of 0.003. The urban patients showed a prevalence of 42.2% whereas rural patients showed it to be 41.9%. This finding of our study also contradicts with other studies as most of them show an increased depression among rural population as compared to urban one.[23] In one of such study by Probst JC et al, the unadjusted prevalence of depression was calculated to be significantly higher with P-value 0.0171 among rural than urban populations (6.1% versus 5.2%).[24] Nandi N also find that there is slight but significantly higher prevalence of depression among rural population of India than urban population.[25] However, there are other powerful confounding factors associated with rural/urban location often ignored or misinterpreted in studies such as poverty, joblessness, sex and marital status. In one of such study, when sample was selected controlling for the effects of race, immigration status, working status and marital status, population of rural areas showed a lower prevalence of MDE than those in urban area.[26] And this favors finding of our study.

Our study also noted that poor patients were more depressed (45.5%) than patients of middle class (41.3%) & upper class (37.2%). This result is similar to other studies which shows that low socioeconomic status (SES) is associated with psychiatric disorders especially depression. The discussion of association of depression with socioeconomic status is very important as it reveals social details of the society and their implications for social well-being. National Comorbidity Survey and the Work, Family, and Well-Being Study find out that the association between depression and socioeconomic indicators exists.[27] The study of Taylor, Page, Morreli, Harrison and Carter (2005) also found odds ratio of 1.27 (p <0.05) for expected low and high socioeconomic status telling us that the lower socioeconomic strata is more likely to be depressive than the higher socioeconomic strata.[28]

A non-significant but very interesting finding was noted by the currents study that higher the education higher was prevalence of depression

among Hepatitis C patients. It increased from 45% among illiterate to 53.3% among highest education level i-e; Graduation or more with P value = 0.683. This contradicts with findings by other studies showing education reduces the risks of adult depression. Study conducted by Lin M et al in COPD which is also chronic medical illness, showed that patients with higher education are more likely to be depressed. The association tended to be stronger in well-educated men and women than those less educated was favoring my study.[29]

CONCLUSION

It is concluded that patients of Chronic Hepatitis-C who are on combined therapy with Pegylated interferon and ribavarin developed high frequency of depressive symptoms. It affects nearly half (42%) of the patients with young and female sex showing more vulnerability. Special focus is needed by physician to observe change in mood and other depressive symptoms during treatment as ignorance can lead to fatal outcomes.
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