ORIGINAL ARTICLE

FREQUENCY OF DEPRESSIVE AND ANXIETY SYMPTOMS AMONG PATIENTS ON INTERFERON AND PEGYLATED INTERFERON

Muhammad Waseem Shaikh[1], Farah Ahmad[2*], Gulnaz Shaikh[1], Syed Hasan Danish[2], Kirpal Das Makheja[3], Minhaj A Qidwai[4]

[1]Liaquat University Hospital Jamshoro,
[2]Department of Community Health Sciences , Ziauddin University
[3]Jinnah Postgraduate Medical Centers
[4]College of Physicians and Surgeons Pakistan

ABSTRACT

Background: Chronic Hepatitis C (CHC) is highly prevalent in Pakistan. Current standard treatment is Interferon alpha/ Peginterferon with oral ribavirin. Interferon therapy is associated with development & worsening of depressive symptoms in CHC patients and to determine the frequency of depressive and anxiety symptoms among patients on treatment with interferon/ Pegasus.

Methods: This cross sectional study was conducted at OPD of Liaquat University Hospital Hyderabad during a period of 4 months (from July2013 to October2013). A sample of 120 patients aged 18-60 years, either currently receiving interferon/ Pegasus treatment or had received that treatment during last 12 months was taken. Known cases of anxiety, depression and those suffering from other debilitating co morbid conditions like carcinoma & non-consenting were excluded. Ethical approval was taken from LUH ethical review committee. A Proforma was used to gather the data. The data collected were analyzed using SPSS version 20.0. Mean (±SD) were computed for quantitative variables. Categorical variables (such as gender and outcome variables i.e. anxiety and depressive symptoms) were measured in frequencies and percentages. Stratification was done with regard to age group & gender to see the impact of these on the outcome followed by application of chi-square test with P-value <0.05 taken significant.

Results: Total 120 patients were included in the study & 119 completed the questionnaire. Male patients were 55.5%. Mean age of patients was 32.59 ± 8.56 years (Range: 16-56 years). Primary outcome i-e; frequency of depression & anxiety in patients on interferon were 77.3% & 70.6% respectively. (n=92) had depression. Frequency of depression of almost similar in both genders (77.3% in males & 77.4% in females; p value= 0.584), while anxiety was more in females than males (75% vs 68.2%; p value= 0.273). Both psychiatric symptoms increased with increasing age from 16-26 years to 47-56 years of age (p values = 0.432 & 0.736 respectively). Vast majority (86.6%) were treated with interferon while only 13.4% received the PEGylated interferon therapy. Patients treated with PEGylated interferon had less frequency of depression than those treated with interferon (62.5% vs 79.6%; p value= 0.131).

Conclusion: Depression and anxiety were found to be common in CHC patients who had been or are being treated with antiviral treatment leading to increased risk of morbidity and mortality. Screening for risk of depression, proper education and timely treatment through anti-depressant followed by close monitoring is mandatory to achieve success in antiviral treatment.

KEY WORDS: Hepatitis C, Depressive symptoms, Anxiety, Interferon alpha.

INTRODUCTION

Although about 3% of the world population is reported to be suffering from hepatitis C, the figures are not true representative as many cases remain undiagnosed[1]. Large numbers of patients suffering from chronic hepatitis C (CHC) are being treated with interferon, Pegasus (Pegylated interferon α (pegIFN- α -2b, 1.5mg/kg, weekly, s.c.) and ribavirin (400 mg, b.d.)) because of significant advances in overall improvement in the course of CHC[2]. Interferon, recommended treatment for CHC, is a manufactured drug that mimics the naturally occurring interferon produced as part of the body's immune response to a viral infection. The aim of the drug is to prevent the virus from multiplying and causing further liver damage[3]. However, this treatment is often hampered by severe physical and psychiatric side effects[2, 3]. Interferon and Pegasus are particularly notorious for causing depressive and anxiety symptoms[3, 4]. Chronic Hepatitis C (CHC) patients may be especially prone to develop interferon-induced depression[3-6].

Anxiety and depressive symptoms emanating from treatment with interferon and Pegasus contribute enormously to impaired quality of life[7] and are recognized as a major reason for treatment discontinuation, non-compliance and dose reduction[8,9]. In the trial of Peginterferon alfa-2a (Pegasus) and 2b plus ribavirin, 14% of patients had

Corresponding Author: Farah Ahmad*

to discontinue therapy. The most common adverse events were influenza - like side effects such as fatigue, headache, fever and rigors, which occurred in more than half of the patients, and psychiatric side effects (depression, irritability, and insomnia), which occurred in up to 31% of patients[10]. Depressive and anxiety symptoms may also represent an independent risk factor for poor virologic response[11]. The most common psychiatric side effect of therapy, insomnia is present to some degree in 40% or so of patients. Insomnia can lead to fatigue, headache, irritability, depression, and other side effects and thus worsening the situation. Another very common side effect, irritability is reported in clinical trials in 30% or so of patients, but may be present to a lesser degree in most patients[12].

Significant depressive and anxiety symptoms occur in about 20–60% of patients treated with interferon HCV infection[5, 6, 13]. Hauser et al., reported that depression was found in 38% of patients after 12 weeks of treatment with interferon[5]. A prospective study carried out in Pakistan showed that 37% CHC patients were suffering from depression after 8 weeks of interferon therapy compared to 21% percent at baseline[4].Further, suicidal ideation was detected in all those patients who had severe depression. In a study conducted at Shifa International Hospital, Islamabad from July 2011 to February 2012, depression was present in 27.6% of patients suffering from chronic hepatitis C, 58.6% of those suffering from chronic hepatitis B, and among 37.8% of subjects suffering from neither of the infections[14].

Pakistan being one of the countries in the world where prevalence rate of hepatitis is high (between 2.4% and 6.5%) and hence the use of interferon/Pegasus treatment is also on an increase[15]. Early detection of depressive symptoms may prompt the early treatment of these symptoms as recent open trials also suggest that antidepressant treatment may reduce depression and anxiety during and after anti-viral therapy and thus help improve the quality of life of the patients[16]. Further in patients with uncontrolled depressive disorder treatment for CHC infection with interferon/Pegasus is contraindicated[17].

Given the strong association between interferon/Pegasus treatment and the psychiatric symptoms of depression and anxiety, this study is aimed at the detection of these symptoms in the patients who are receiving or have received the antiviral therapy with interferon/Pegasus.

METHODS

The study was conducted at Outpatient department of Liaquat University Hospital (LUH) Hyderabad during a 4 month period (from July2013 to October2013). Objectives of this cross sectional study were to determine the frequency of depressive and anxiety symptoms among patients on interferon or Pegasus treatment and its relation of age & gender with occurrence of symptoms.

Taking an estimated prevalence of depressive symptoms among patients on interferon therapy @ 20%[8], the calculated sample was approximated to 120. The study included patients aged 18-60 years, either currently receiving interferon/ Pegasus treatment or had received that treatment during last 12 months (records). Diagnosed cases of anxiety and depression and those diagnosed with other debilitating co morbid conditions like carcinoma & non-consenting were excluded. We used ICD-10 criteria to define depression i-e; a state of low mood and aversion to activity. It was labeled present if a patient had any 4 of the following symptoms; loss of interest and enjoyment, reduced energy and decreased activity, reduced concentration, reduced self-esteem, ideas of guilt and unworthiness, pessimistic thoughts, ideas of self-harm/suicidal thoughts, disturbed sleep, diminished appetite. We used ICD-10 criteria to define anxiety also i-e; an unpleasant state of inner turmoil, often accompanied by nervous behavior. It was labeled present if a patient had any 4 of the following symptoms; fearful anticipation, irritability, restlessness, worrying thoughts, dry mouth, frequent or loose motions, constriction in the chest, palpitation, frequent or urgent micturition, tremor, headache, aching muscles, feeling of breathlessness, dizziness & night terror.

A Proforma comprising of the demographic and other relevant information and a check list of the depressive and anxiety symptoms was used to gather the data after taking informed consent. The data collected was analyzed using computer packages SPSS (Statistical Packages of Social Sciences) version 20.0. Mean and standard deviation (SD) were computed for quantitative variables (such as age). Categorical variables (such as gender and outcome variables i.e. anxiety and depressive symptoms) were measured in frequencies and percentages. Stratification was done with regard to age group and gender to see the impact of these variables on the outcome. By using chi square test P-value <0.05 was considered as significant. Approval was taken from the Ethical review committee of LUH Hyderabad.

RESULTS

Total 120 patients were included in the study & 119 completed the questionnaire regarding symptoms of depression and anxiety. Male patients were 55.5% (n=66) while females were 45.5% (n=53). Mean age of patients was 32.59 ± 8.56 years (Range: 16-56 years). Patients of age category 16-26 years were 27.7% (n=33), age category 27-36 years were 43.7% (n=52), age category 37-46 years were 21.8% (n=26) and age category 47-56 were 6.7% (n=8).

General characteristics are given in Table: 1. Patients referred by general practitioner were 37.8% (n=45), 15.1% (n=8) by consultant physician while the rest of patients were either brought by relatives/ themselves or by friends. Only 2.5% (n=3) were diagnosed as having hepatitis C in a hospital when they were admitted for some other illness and were suggested interferon therapy. It was noted that 12.6% (n=15) patients had Hepatitis B, 73.1% (n= 87) had Hepatitis C, while 14.3% (n=17) had both viral infections. More than two thirds (68.1%) were diagnosed within last 6 months and about 57.1% (n=68) had started their treatment within previous 3 months while the rest of patients had started their therapy before this period. Psychiatric symptoms were more in those patients who had received treatment before 3 months period than those who received it with three months period (p value= 0.092).

It was further noted that about a quarter of patients (27.7%; n=33) had one or other psychiatric illness before treatment with interferon and only half of these (n=17) had been treated for that psychiatric illness.

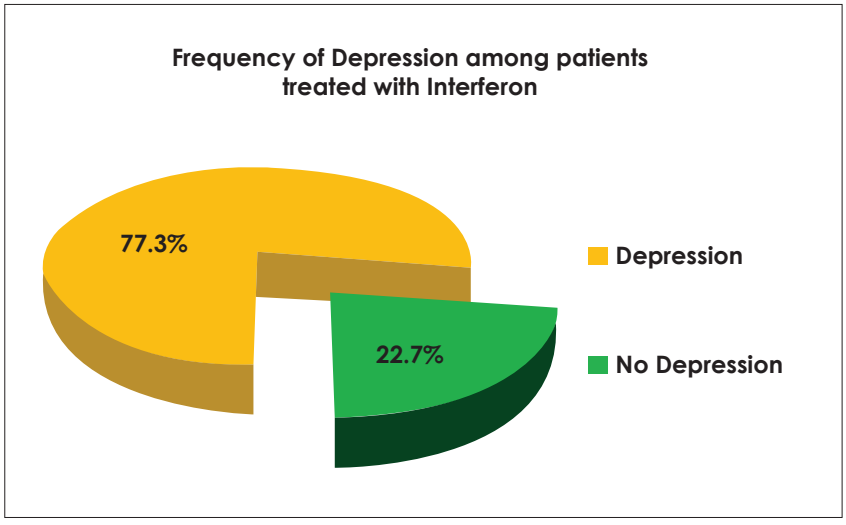
Primary outcome of the study was frequency of depression & anxiety in patients on interferon therapy and the results showed that 77.3% (n=92) had depression (presence of at least 4 symptoms of depression for >2 weeks as per ICD-10) while patients having anxiety (presence of at least 4 symptoms of anxiety for >2 weeks as per ICD-10) were 70.6% (n=84).

The study evaluated the role of gender and age in occurrence of psychiatric symptoms (depression & anxiety) as additional outcomes in patients being treated with interferon therapy. It was noted that frequency of depression was almost similar in both genders (77.3% in males & 77.4% in females; p value= 0.584), while anxiety was more in females than males (75% vs. 68.2%; p value= 0.273). Age of patients was seen to have an effect on frequency of depression and anxiety in those treated with interferon the frequency of both depression and anxiety among patients treated with interferon therapy. Both psychiatric symptoms increased with increasing age from 16-26 years to 47-56 years of age (p values = 0.432 & 0.736 respectively).

It was important to note that vast majority i-e; 86.6% (n=103) were being treated with interferon while only 13.4% (n=16) received the PEGylated interferon therapy. Patients treated with PEGylated interferon had less frequency of depression than those treated with interferon (62.5% vs. 79.6%; p value= 0.131).

Table1: General characteristics of all patients

Characteristics		Frequency	Percentage
Religion	Muslim	104	87.4
	Hindu	12	10.1
	Christian	3	2.5
Martial Status	Single	21	17.6
	Married	89	74.8
	Widow	5	4.2
	Separated	4	3.4
Education	No formal education	54	45.4
	Primary	31	26.1
	Matriculate	23	19.3
	Graduate	10	8.4
	Mastrers or above	1	0.8
Occupation	Unemoloyed	23	19.3
	Self employed	30	25.2
	Govt job	15	12.6
	Private job	14	11.8
	House wife	21	117.6
	Labour, farmer etc	14	118.8
	Zamindar	2	1.7



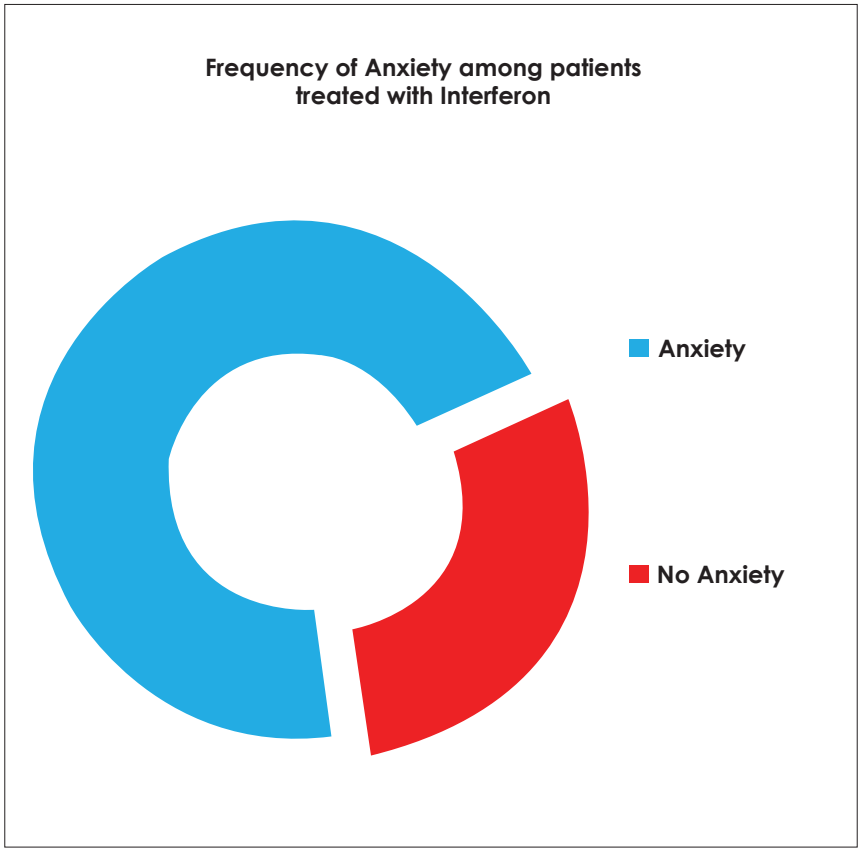


Figure 1: Frequency of depression & anxiety among patients treated with Interferon or Pegasus treatment. P value= 0.584 & 0.273

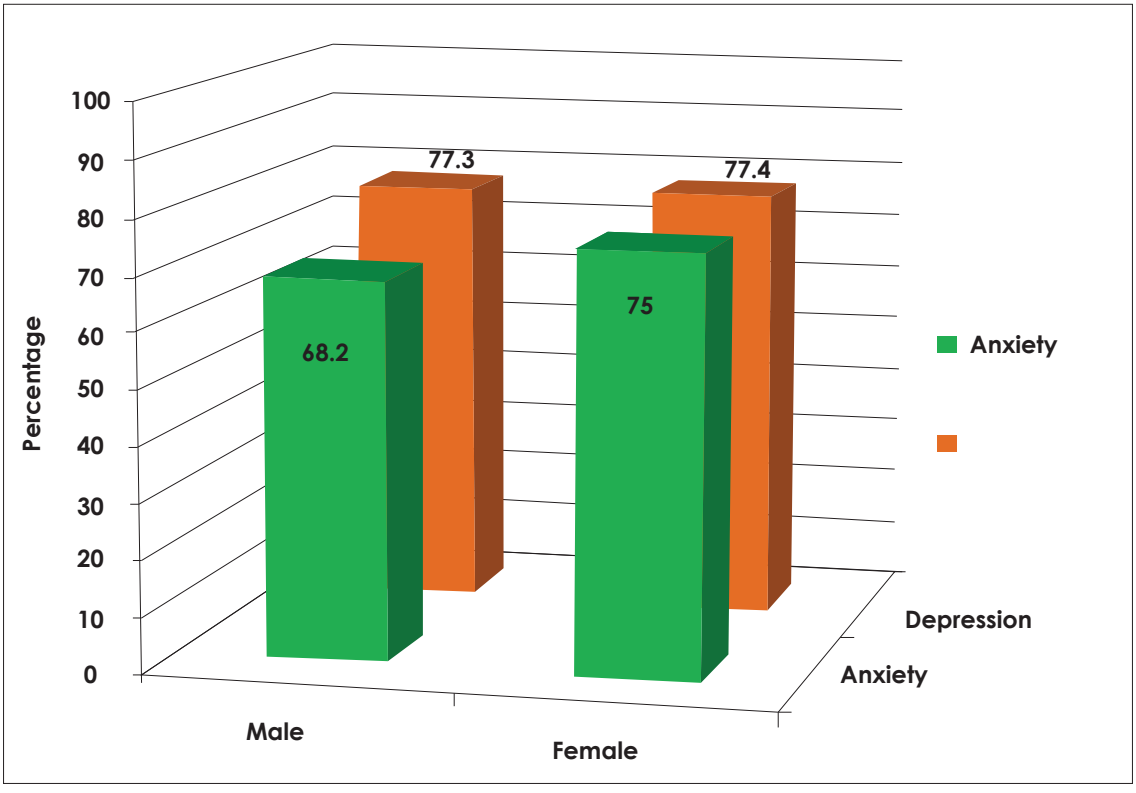


Figure 2: Effect of gender on frequency of depression & anxiety among patients treated with Interferon or Pegasus treatment. P value= 0.584 & 0.273

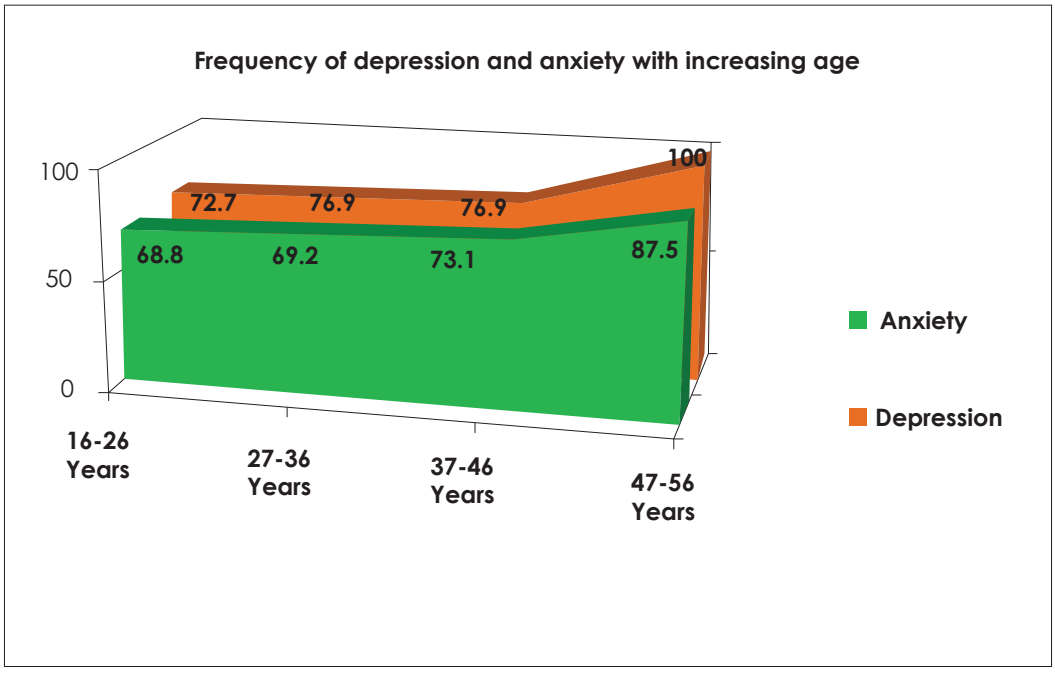


Figure 3: Effect of age on frequency of Depression & anxiety among patients treated with Interferon or Pegasus treatment. P value= 0.432 & 0.735

DISCUSSION

According to the WHO statistics, there are 3 to 4 million newly infected cases of HCV each year and of these at least 85% become chronically infected and about 70% develop CHC[18]. It is estimated that five out of every six people HCV infected are undiagnosed and under-treated and which causes further morbidity & mortality[1,3-6,19]while only 1 to 2% of HCV infected people are currently receiving internationally recognized and recommended therapy. Interferon & Pegasus prevent the virus from multiplying and causing further liver damage[2,4,6] but are associated with psychiatric side effects such as depression and anxiety[7-9,11,20]. These are two critical conditions which negatively affect patients' functional health, were found to be very strongly associated with decline in ability to work, self-perceived health, quality of life and well-being. These symptoms caused by antiviral therapy are usually reversed back to normal within 24 weeks of completion of antiviral therapy[7,21].Interferon-alpha (IFN-alpha) induced depression is a major limitation for the treatment of chronic hepatitis C, especially for patients with psychiatric disorders[6].

The current study assessed the magnitude of burden of depression and anxiety caused by interferon therapy and its variation as per gender and age. We found that depression & anxiety symptoms were quite common in CHC patients on interferon therapy. More than three fourths (77.3%) had depression while about 70.6% patients had anxiety. Commonest depressive symptoms found in our patients were depressed mood, loss of interest and enjoyment, reduced energy, decreased activity, disturbed sleep &commonest anxiety symptoms were diminished appetite and irritability, worrying thoughts, dry mouth, tremor, headache and aching muscles. Although male patients were slightly more (55%) than females (45%) in our study, we noted that depression was almost equal in both genders (77.3% males & 77.4% females; p value= 0.584), while anxiety was more frequent in females than males (75% vs. 68.2%; p value= 0.273). The results were contrary to previous studies documenting male predominance [6,7,13]

Raison CL, et al.,[13] Self-Rating Depression Scale (SDS) in 162 HCV-infected patients at baseline and after 4, 8, 12, and 24 weeks of treatment with Pegylated IFN alpha-2b (PEG IFN) plus ribavirin found that 38.9% of patients exhibited moderate to severe depressive symptoms. A local study by Shakoor A, et al.,[2] used major depressive episode of diagnostic and statistical manual (DSM-IV) reported that 39% patients had depression which was more common in female (44.4%) as compared to male (28.7%). Qureshi MO, et al.,[14] reported that frequency of depression was 72.6% in patients of CHC which is concordance with our results. The study used Hospital Anxiety and Depression Scale (HADS). The difference of frequency in literature is mainly due to study population and the depression assessment scale used in the study. It is also important to discuss that many of contemporary studies document that the rate of depression among untreated patients with CHC range from 24% to 62% [22-24] and nearly two-thirds of depressed patients with CHC required antidepressant treatment[22-24].

In our study the mean age of patients was 32.59 ± 8.56 years. Their ages ranged from 16-56 years, and majority of them were in the 4th& 5th decades of life. Other studies have reported an elderly age (45-55 years)[6,7], which may be due to reason that in our country the CHC has taken form of an epidemic and patients get HCV infection from mothers and till they become adult they develop CHC.

Fried MW, et al.,[13]reported patients treated with Pegasus had a lower incidence of depression than those treated with interferon (22% vs. 30%). Our study also found similar results but the frequencies were higher. In our study interferon treated patients had higher rates of depression than those treated with Pegasus (79.6% vs 62.5%; p value= 0.131).

Other studies found that rate of suicidal ideation in CHC pateints treated with IFNa was upto 26% of patients endorsed suicidal ideation & as much as 6.9% discontinued HCV treatment (pegylated IFN α) early, because of suicidal ideation[25-28].

The current study also evaluated and found that psychiatric symptoms were more in those patients who had received treatment before 3-6 months period (78-100%) than those who received it with three months period (76%; p value= 0.092).

There is a debate that HCV patients having psychiatric problems or prone to develop depression, should be treated with interferon or not[29]. Use of prophylactic anti-depressant is an answer to this problem. In a study Schaefer M, et al., [30] noted prophylactic use of antidepressants (like citalopram) as well as intensive psychiatric care can spread most of patients (14% treated vs. 64% among untreated with antidepressant; P value = 0.032) from developing major depression during antiviral treatment. We also noted that about 27% patients had psychiatric illness before treatment with interferon and only half of these had been treated for that psychiatric illness. In those who took treatment depression rate were much lesser than those who did not. (64% vs 79.4%; p value= 0.152) These results are backed by findings of review study which concluded that better treatment outcomes can be achieved by early identification of depression during HCV treatment and pre-emptive treatment approach[31]. Thus treatment for depression should be started early and psychosis managed with antipsychotics.

Although depression has been the focus of neuropsychiatric complications from interferon-alpha (IFNa), emerging evidence has contributed to our understanding of IFNa-induced suicidal ideation and attempts. In fact, suicidal ideation has also commonly been identified among these patients and completed suicides have also been reported[25]. In our study the rate of suicidal thought was 16.8%. These findings highlight the need to examine potential therapeutic options for managing depression and anxiety during interferon therapy.

It is utmost important that CHC patients which need antiviral therapy should be screened for psychiatric symptoms before the start of interferon/Pegasus treatment. They should be educated prior to treatment about a clear description of likely side effects and their time course. Besides at risk patients must be identified and pre-treated with antidepressant treatment. Mood and suicidal ideation should be monitored closely during interferon therapy.

Our strength included diagnostic criteria based on the ICD guidelines. Data was collected by investigators themselves, Hospital cards were used as proof of treatment, limited number of studies has been conducted on this issue in Hyderabad.

Our main limitation was the Temporality issue as it is cross sectional study, next time larger sample size can be taken into account by including more hospitals as only one hospital was taken.

CONCLUSION

Current standard treatment of CHC consists of interferon alpha (IFN-α) &pegylated recombinant interferon alpha (PEG- IFN-α) combined with oral ribavirin (RBV). This antiviral treatment is associated with significant psychiatric side effects like, depressive mood, GI disturbances, fatigue, anxiety, irritability, concentration difficulties, insomnia and suicidal ideation etc. Depression and anxiety were found to be common in CHC patients who had been or are being treated with antiviral treatment. This leads to increased risk of morbidity and mortality. Screening for risk of depression, proper education regarding side effects and timely treatment through anti-depressant followed by close monitoring is mandatory to achieve success in antiviral treatment.

ACKNOWLEDGMENT

I personally want to acknowledge Dr Farah Ahmad for her out of way support & continuous guidance in completion of this Research Paper. Without her help & support, I would not have been able to complete this task. I also acknowledge my wife; a Senior Psychiatrist & Dr. Karam Ali Shah in collection of DATA. At last but not the least, I acknowledge academic help from my friends Dr. Kirpal Das Makheja, Dr Bharat Kumar Maheshwari, & Dr. Wara Iftikhar. Thanks to all with my Love.

REFERENCES

1. Ford C, Halliday K, Foster G, Jack K, Rowan N, Hess CS, et al., Guidance for the prevention, testing, treatment and management of hepatitis C in primary care.
2. Shakoor A, Shafqat F, Mehmud TH, Akram M, Riaz S, Iqbal Z, Khan AA. Frequency of depression and somatic symptoms in patients on interferon alpha/ribavirin for chronic hepatitis C. J Ayub Med Coll Abbottabad 2010; 22(4):06-9.
3. Gadit A A M. Mood disorder associated with gastrointestinal and liver diseases: Are there many challenges? J Pak Med Assoc 2010; 60(12):1064-5
4. Asnis, Gregory M, Garza DL, Richard. Interferon-Induced Depression in Chronic Hepatitis C: A Review of Its Prevalence, Risk Factors, Biology, and Treatment Approaches. J Clin Gastroent 2006; 40(4):322-35
5. Hauser P, Khosla J, Aurora H, et al. A prospective study of the incidence and open-label treatment of interferon-induced major depressive disorder in patients with hepatitis C. Mol Psych 2002; 7: 942–7.
6. Raison CL, Borisov AS, Broadwell SD, et al., Depression during pegylated interferon-alpha plus ribavirin therapy: prevalence and prediction. J Clin Psychiatry 2005; 66: 41–8.
7. Dan AA, Martin LM, Crone C, et al., Depression, anemia and health-related quality of life in chronic hepatitis C. J Hepatol 2006; 44: 491–8.
8. Cacoub P, Ratziu V, Myers RP, Ghillani P, Piette JC, Mousalli J et al. Impact of treatment on extra hepatic manifestations in patients with chronic hepatitis C. J Hepatol 2002; 36: 812–8.
9. Schaefer M, Engelbrecht MA, Gut O, et al., Interferon alpha (IFNa) and psychiatric syndromes: a review. Pro Neuro- Psychopharml BiolPsychi 2002; 26: 731–46.
10. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al., Peginterferon alfa-2b plus Ribavirin compared with Interferon alfa- 2b plus Ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet.2001 ;(358):958-65.
11. Maddock C, Landau S, Barry K, et al., Psychopathological symptoms during interferon-alpha and ribavirin treatment: effects on virologic response. MolPsychi 2005; 10: 332–3.
12. Interferon and Ribavirin Treatment Side Effects National Hepatitis C Program Office. http://www.hepatitis.va.gov-/provider/reviews/treatment-side-effects.asp 2013.
13. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL Jr, et al., Peginterferon alpha-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975–82.
14. Qureshi MO ,Khokhar N, Shafqat F. Severity of depression in hepatitis B and hepatitis C patients. J Col PhysSurg Pak 2012; 22 (10): 632-4.
15. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis. 2005; 9: 558 – 67.
16. Hauser P, Soler R, Reed S, et al. Prophylactic treatment of depression induced by interferon-alpha. Psychosomatics 2000; 41: 439–41.
17. Strader DB, Wright T, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management,and treatment of hepatitis C. Hepatology. 2004; 39(4):1147–71
18. World Health Organization. Hepatitis C. Fact sheet N°164. 2000.
19. Lamagni TL, Davison KL, Hope VD, Luutu JW, Newham JA, Parry JV, Gill ON. Poor hepatitis B vaccine coverage in injecting drug users: England, 1995 and 1996. Commun Dis Public Health. 1999; 2(3):174-7.
20. Bonaccorso S, Marino V, Puzella A, Pasquini M, Biondi M, Artini M, et al. Increased depressive ratings in patients with hepatitis C receiving interferon alpha based immunotherapy are related to interferon-alpha-induced changes in the serotonergic system. J ClinPsychopharmacol 2002; 22:86–90.
21. Fábregas BC, de Ávila RE, Faria MN, Moura AS, Carmo RA, Teixeira AL. Health related quality of life among patients with chronic hepatitis C: a cross-sectional study of sociodemographic, psychopathological and psychiatric determinants. Braz J Infect Dis. 2013; 17(6):633-9.
22. Lee DH, Jamal H, Regenstein FG, Perrilo RP. Morbidity of chronic hepatitis C as seen in a tertiary care medical center. Dig Dis Sci. 1997;42 :186-91.
23. Yovtcheva SP, Rifai MA, Moles JK, Van der Linden BJ. Psychiatric comorbidity among hepatitis C-positive patients.Psychosomatics. 2001; 42 :411-5.
24. El-Sarag HB, Kunik M, Richardson P, Rabaneck L. Psychiatric disorders among veterans with hepatitis C infection. Gastroenterol. 2002;123 :476-82.
25. Yu ML, Dai CY, Lee LP et al., Outcome of chronic hepatitis C patient who required early termination of pegylated interferon-alpha plus ribavirin combination therapy. AntivirTher. 2006; 11(8):1015-9.
26. Evon DM, Ramcharren D, Belle SH, Terrault NA, Fontana RJ, Fried MW. 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):2949-58.
27. Dieperink E, Ho SB, Tetrick L, Thuras P, Dua K, Willnebring ML. Suicidal ideation during Interferon-alpha2b and

Ribavirin treatment of patients with chronic hepatitis C. Gen Hosp Psychiatry. 2004; 26:237-40.
28. Cheng YC, Chen CC, Ho AS,Chiu NY. Prolonged psychosis associated with Interferon therapy in a patient with hepatitis C: case study and literature review. Psychosomatics. 2009; 50(5):538-42.
29. Horsmans Y. Interferon-induced depression in chronic hepatitis C. J Antimicrobial Chemotherapy. 2006 ; 58:711-3.
30. Schaefer M, Schwaiger M, Garkisch AS. Prevention of interferon-alpha associated depression in psychiatric risk patients with chronic hepatitis C. J Hepatol. 2005;42:793–8.
31. Sockalingam S, Abbey SE.Managing depression during hepatitisC treatment.Can J Psychiatry. 2009; 54(9):614-25.