

# Drug induced anxiety and depression in patients treated for chronic hepatitis C

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## ABSTRACT

**Background:** Depression is common in patients treated for Hepatitis C who receive interferon and ribavirin. This has been a major challenge in past for treatment compliance. Depression is believed to be less common with newer direct acting antivirals. This study aims to compare different regimens for drug induced anxiety and depression using Hospital Anxiety and Depression Scale (HADS) questionnaire.

**Subjects and Methods:** This observational study was done at Lahore General Hospital, Lahore from 1<sup>st</sup> January 2016 till 15<sup>th</sup> February 2017. A total of 126 patients of chronic Hepatitis C requiring treatment with no baseline depression or anxiety as assessed by HADS questionnaire were enrolled. Patients were divided in 3 groups depending upon their treatment regimen. Two regimens were pegylated interferon based while one was interferon free using sofosbuvir. All patients completed their treatment. Frequency of anxiety and depression were evaluated using HADS questionnaire at the end of treatment.

**Results:** A total of 126 patients, 44 males and 82 females, were enrolled; of these 62 (49.2%) received Pegylated interferon (PEG-IFN) + ribavirin, 27 (21.4%) received PEG-IFN + ribavirin+ sofosbuvir and 37 (29.4%) received sofosbuvir + ribavirin. Out of 126 patients, 40 (31.7 %) had definite anxiety at end of treatment while 46 (36.5%) had definite depression at end of treatment. Definite anxiety and depression were significantly low in sofosbuvir+ ribavirin group.

**Conclusion:** Anxiety and depression are much less common with direct acting antivirals than interferon-based regimens for chronic hepatitis C treatment.

## Keywords:

Anxiety, depression, chronic hepatitis C, HADS

## INTRODUCTION

Hepatitis C virus infection is now considered a global world problem affecting all the nations worldwide. Global prevalence of hepatitis C is estimated around 2.8% representing 180 million people.<sup>1</sup> A recent meta-analyses reported an estimated pooled mean HCV prevalence in Pakistan at 6.2% among general population, 34.5% among high-risk clinical populations, 16.9% among special clinical populations, 55.9% among populations with liver-related conditions and 53.6% among intravenous drug abusers.<sup>2</sup> HCV percentage prevalence in the adult population has been 11.55% for Pakistan and HCV genotype 3a prevalence is reported as 63.45%, the highest of all genotypes.<sup>3</sup> Treatment of choice for chronic hepatitis C (CHC) infection till late 2015 was combination of pegylated

interferon alpha (Peg-IFN) and ribavirin (RBV); which was used for 24 to 48 weeks depending on genotype of virus.<sup>4</sup> The most common psychiatric side effect of interferon based treatment is depression.<sup>5</sup> An incidence of 42.4% for depression and/or anxiety disorders during Peg-IFN treatment has been reported.<sup>6</sup> Interferon-ribavirin therapy can induce a range of depressive symptoms including suicidal ideation and behavior.<sup>4</sup> Depressive symptoms arise during initial few weeks of treatment and are more marked between 4 to 16 weeks.<sup>7</sup> In a meta-analysis of 22 prospective observational studies for patients treated with interferon-ribavirin; the cumulative incidence of depression was found to be 6% at week 4, 20% at week 12, 25% at week 24 and 28% at week 48.<sup>8</sup> Anxiety is a risk factor for suicide in depressive patients highlighting need of screening for anxiety in depressive patients.<sup>9</sup> This had been a major challenge for treatment compliance and a cause of treatment failure in the interferon era. Depression can be diagnosed with various clinical questionnaires. The

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Table 1: Distribution of patients by treatment group

| Treatment Regimen              | Patients |        |            |
|--------------------------------|----------|--------|------------|
|                                | Male     | Female | Total      |
| Peg IFN + Ribavirin            | 19       | 43     | 62 (49.2%) |
| PegIFN + Ribavirin+ Sofosbuvir | 8        | 19     | 27 (21.4%) |
| Sofosbuvir + Ribavirin         | 17       | 20     | 37 (29.4%) |
| Total                          | 44       | 82     | 126        |

Hospital Anxiety and Depression Scale (HADS) is a widely used, simple and well validated tool for monitoring and assessment of symptoms of anxiety and depression.<sup>10-12</sup> It is used for the diagnosis of anxiety and depression and has separate subscales for both.<sup>10</sup> Although direct acting antivirals (DAA) are recommended to treat CHC patients, Interferon based therapy is still used in many Asian countries and resource limited regions.<sup>13</sup> It is believed that depression is less common with newer direct acting agents like sofosbuvir resulting in better compliance and treatment outcome. According to one study DAA are associated with improvement in depression scores.<sup>12</sup> The objective of this study was to compare the incidence of depression and anxiety in patients treated with various regimens for CHC after approval of newer direct acting antivirals.

### SUBJECTS AND METHODS

This descriptive observational study was done in the outpatient department of Medicine and Gastroenterology, Lahore General Hospital, Lahore from 1<sup>st</sup> January 2016 to 15<sup>th</sup> February 2017. All patients of Hepatitis C, genotype 3, requiring treatment with no baseline depression or anxiety as assessed by HADS questionnaire were enrolled. Patients having chronic medical illnesses like diabetes, coronary artery disease, hypothyroidism or malignancy were excluded. Patients, of both genders, were divided in 3 groups depending upon their treatment regimen. Patients in group A received pegylated interferon with ribavirin for 24 weeks; group B received pegylated interferon, ribavirin and sofosbuvir for 12 weeks, while group C received sofosbuvir and ribavirin for 24 weeks. All patients successfully completed their treatment. Incidence of anxiety and depression was evaluated using HADS questionnaire at the end of treatment. Patients were classified as non-case, borderline case and definitive case for both anxiety and depression. The results were compared for significance by applying conventional chi-square test. p-value less than 0.05 was considered significant. **Cramer's V statistics was used to measure association between anxiety and depression with treatment.**

### RESULTS

A total of 126 patients were enrolled. Out of these 44 (34.9%) were males and 82 (65.1%) were females. Mean age of patients was 39.17±10.23 years. Patients were divided in 3 groups depending upon their treatment regimen. Out of total 126 patients, 62 (49.2%) received Pegylated interferon (PEG IFN) + ribavirin, 27 (21.4%) received PEG IFN + ribavirin+ sofosbuvir and 37 (29.4%) received sofosbuvir + ribavirin (Table 1). Patients were classified as non-case, border line case and definitive case for both anxiety and depression. Out of 126 patients, 69 (54.8%) patients had no anxiety, 17 (13.5%) had border line anxiety while 40 (31.7 %) patients had definite anxiety at end of treatment. Out of 126 patients, 59 (46.8%) patients had no depression, 21 (16.7%) had border line depression while 46 (36.5%) had definite depression at end of treatment. Incidence of definite anxiety and depression was significantly low in sofosbuvir+ ribavirin group (Table 2). These results showed weak association between anxiety and treatment (**Cramer's V =0.229**), similarly there was weak association between depression and treatment (**Cramer's V =0.278**).

### DISCUSSION

Treatment induced anxiety and depression is common in patients treated with pegylated interferon and ribavirin-based treatment for hepatitis C and remains a major cause of treatment failure and non-compliance with treatment. Newer direct acting antivirals are believed to improve treatment associated anxiety and depression. This study compared incidence of anxiety and depression in different treatment groups. Incidence of definite anxiety and depression was found much less in sofosbuvir+ribavirin group as compared to PEG-IFN+ ribavirin group alone. Similarly, incidence of definite anxiety and depression decreased in PEG-IFN+ ribavirin+ sofosbuvir group as compared to PEG-IFN+ ribavirin group which suggests that direct acting antivirals may help in reducing anxiety and depression. These findings are comparable with the study of Tang and coworkers which showed that treatment with DAA

Table 2: Distribution of anxiety and depression

| Variable   | Treatment          |                                |                       | Total      | p-value* |
|------------|--------------------|--------------------------------|-----------------------|------------|----------|
|            | PEG IFN+ Ribavirin | PEG IFN+ Ribavirin+ Sofosbuvir | Sofosbuvir+ Ribavirin |            |          |
| Anxiety    | Non-case           | 26 (20.6%)                     | 15 (11.9%)            | 28 (22.2%) | 0.010    |
|            | Borderline case    | 10 (7.9%)                      | 2 (1.6%)              | 5 (4.0%)   |          |
|            | Definitive case    | 26 (20.6%)                     | 10 (7.9%)             | 4 (3.2%)   |          |
| Depression | Non-case           | 22 (17.5%)                     | 10 (7.9%)             | 27 (21.4%) | 0.001    |
|            | Borderline case    | 10 (7.9%)                      | 4 (3.2%)              | 7 (5.6%)   |          |
|            | Definitive case    | 30 (23.8%)                     | 13 (10.3%)            | 3 (2.4%)   |          |

\*p<0.05 was considered significant

based therapies in patients with mental health disorders is safe and that sofosbuvir based therapy is associated with improvement in depression score.<sup>14</sup> However this was a retrospective cohort study while our study is prospective cohort study, they used 3 different sofosbuvir based regimens while we used 2 sofosbuvir based regimens; one regimen containing both sofosbuvir and interferon, they used Beck's Depression inventory (BDI) while we used HADS questionnaire for assessing depression and anxiety, they studied patients with genotype 1 while we had all patients with genotype 3. Younossi and coauthors reported that patients treated with sofosbuvir and ribavirin had significant improvement in patient reported outcomes, including depression and anxiety.<sup>15</sup> Similar observations have been reported by Youssef and colleagues who concluded that interferon-based treatment required more nursing and physician attention due to increased anxiety levels.<sup>16</sup> Limitations of this study are small sample size, lack of controls, failure to assess simultaneous presence of HIV and its impact on final HADS score, failure to correlate outcome measures like SVR with anxiety and depression scores. However, the main aim of our study was to assess onset of new depression and anxiety and its relevance to adherence with DAA containing treatment regimen.

## CONCLUSIONS

Anxiety and depression are much less common with direct acting antivirals than interferon-based regimens for hepatitis C treatment.

## REFERENCES

1. Agyeman AA, Asenso RO, Mprah A, Ashiagbor G. Epidemiology of Hepatitis C in Ghana: a systematic review and meta-analysis. *BMC Infect Dis* 2016;16: 391.
2. Al Kanaani Z, Mahmud S, Kouyoumjian SP, Abu-Raddad LJ. The epidemiology of hepatitis C virus in Pakistan: systematic review and meta-analyses. *R Soc Open Sci*. 2018; 5(4):180257.
3. Arshad A, Ashfaq UA. Epidemiology of hepatitis C infection in Pakistan: Current Estimate and Major Risk Factors. *Crit Rev Eukaryot Gene Expr*. 2017; 27(1): 63-77.
4. Lucaci LA, Dumitrascu DL. Depression and suicide ideation in chronic hepatitis C patients untreated and treated with interferon: prevalence, prevention, and treatment. *Ann Gastroenterol*. 2015; 28(4): 440-7.
5. Baranyi A, Meinitzer A, Stepan A, Matejka J, Stauber R, Kapfhammer HP, et al. Interferon  $\alpha$  therapy in patients with chronic hepatitis C infection: biopsychosocial consequences. *Nervenarzt*. 2012; 83(9):1169-77.
6. Sertoz OO, Tuncel OK, Tasbakan MI, Pullukcu H, Onmus IR, Yamazhan T, et al. Depression and anxiety disorders during pegylated interferon treatment in chronic hepatitis B. *Psychiatry and Clinical Psychopharmacology*, 2017; 27(1): 47-53.
7. Dieperink E, Ho SB, Tetrack L, Thuras P, Dua K, Willenbring ML. Suicidal ideation during interferon-alpha2b and ribavirin treatment of patients with chronic hepatitis C. *Gen Hosp Psychiatry*. 2004; 26(3): 237- 40.
8. Udina M, Castellví P, Moreno-España J, Navinés R, Valdés M, Forns X, et al. Interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. *J Clin Psychiatry*. 2012; 73(8):1128-38.
9. Janssen HL, Brouwer JT, van der Mast RC, Schalm SW. Suicide associated with alfa-interferon therapy for chronic viral hepatitis. *J Hepatol*. 1994; 21(2): 241-3.
10. Michopoulos I, Douzenis A, Kalkavoura C, Christodoulou C, Michalopoulou P, Kalemí G, et al. Hospital Anxiety and Depression Scale (HADS): validation in a Greek general hospital sample. *Ann Gen Psychiatry*. 2008; 6:7-4.
11. Stern A F. The Hospital Anxiety and Depression Scale. *Occupational Medicine*. 2014; 64(5): 393-4.
12. Snaith RP. The Hospital Anxiety And Depression Scale. *Health Qual Life Outcomes*. 2003; 1: 29.
13. Lemoine M, Nayagam S, Thursz M. Viral hepatitis in resource-limited countries and access to antiviral therapies: current and future challenges. *Future Virol*. 2013; 8(4): 371-80.
14. Tang LS, Masur J, Sims Z, Nelson A, Osinusi A, Kohli A, et al. Safe and effective sofosbuvir-based therapy in patients with mental health disease on hepatitis C virus treatment. *World J Hepatol*. 2016; 8(31):1318-26.
15. Younossi ZM, Stepanova M, Henry L, Gane E, Jacobson IM, Lawitz E, et al. Effects of sofosbuvir-based treatment, with and without interferon, on outcome and productivity of patients with chronic hepatitis C. *Clin Gastroenterol Hepatol* 2014; 12: 1349-59.
16. Youssef NFA, El Kassas M, Farag A, Shepherd A. Health-related quality of Life in patients with chronic hepatitis C receiving Sofosbuvir-based treatment, with and without Interferon: a prospective observational study in Egypt. *BMC Gastroenterol*. 2017; 17: 18.