AMERICAN JOURNAL OF RESEARCH IN MEDICAL SCIENCES, 2019
VOL 5, NO. 1, PAGE 1–6
10.5455/ajrms.20181102081059

ORIGINAL ARTICLE

Open Access

Prevalence of depression after treatment with conventional interferon's and ribavirin therapy in patients with hepatitis C using PHQ-9

Attiya Sabeen Rahman[1], Muhammad Amir[2], Shaista Ahmed[1], Qaiser Jamal[1], Mehwish Riaz[1], Muhammad A. Siddiqui[3]

[1]Department of Medicine, Karachi Medical and Dental College and Abbasi Shaheed Hospital, Karachi, Pakistan

[2]Department of Medicine, Lyari General Hospital, Karachi, Pakistan

[3]Research and Performance Support, Saskatchewan Health Authority, Regina, SK, Canada

ABSTRACT

Objective: Patients with Hepatitis C infections suffer commonly from interferon-alpha-induced depression and severe psychiatric disorders. The main purpose of this study was to determine the prevalence of depression in patients with hepatitis C infection after treatment with conventional interferon's and ribavirin.

Methods: The cross-sectional study was conducted from June 2015 to May 2017 in a tertiary care hospital in Karachi. Two Residents from Department of Medicine were trained to take patients' history and conduct interview according to the Patient Health Questionnaire-9 (PHQ-9). A favorable ethical opinion was obtained from the Institutional Ethical Review Committee and after taking informed consent, patient's short history was initially taken. Depression and its severity were also seen and compared between genders.

Results: Fifteen hundred and seventy-one (n = 1,571) participants who met the study's inclusion criteria were participated, of which 41.5% (n = 652) participants were male and 58.8% (n = 919) were female. Average treatment duration of the study participants was 5.56 ± 1.04 months ranged from 1 to 9 months. Overall, more than two-thirds of participants were having mild (38.1%) and moderate (48.9%) depression. Participants were asked multiple questions regarding self-reporting depression component. Most of the participants reported that they experience little interest or pleasure in doing things (70.8%) and having trouble falling or staying asleep or sleeping too much (39.2%) for more than half a day. Similarly, more than half of the participants having difficulty on concentrating things such as reading the newspaper or watching television (58.6%). However, the majority of participant do not think that it would be better off dead or of hurting their self (73%). Out of 1,571 patients, 38.1% had mild depression and 48.9% of patients had moderate depression. Among male participants, 40.5% had mild and 48.2% had moderate depression. In contrast, among female participants, 36.3% had mild and 49.5% had moderate depression. Prevalence of depression among patients with hepatitis C was not found to be associated with gender [$\chi^2(4) = 7.5$, $p < 0.11$].

Conclusion: The prevalence of depression in patients with hepatitis C appears to be very high compared to that in Western patients. Interferon (IFN) α- and ribavirin-induced depression were seen after 24 weeks of treatment; however, different study reports that depressive events with IFN α and ribavirin occurred more frequently during the first 24 weeks of therapy than during the later period of 48 weeks. Active screening and multidisciplinary management of depression is warranted.

ARTICLE HISTORY

Received November 02, 2018
Accepted December 17, 2018
Published January 09, 2019

KEYWORDS

Hepatitis C; depression; prevalence; gender; quality of life; PHQ-9

Contact Muhammad A. Siddiqui ✉ muhammad.siddiqui@saskhealthauthority.ca Research and Performance Support, Saskatchewan Health Authority, Regina, SK, Canada.

Introduction

An estimated 71 million people are afflicted with chronic hepatitis C infection globally and risk of cirrhosis in the liver is about 15%–20% within 20 years in those individuals who develop chronic hepatitis C infection [1]. About 130–150 million people are annually suffering from chronic hepatitis C infection. Every year 50,000–500,000 people depart due to hepatitis C related hepatic diseases [2]. World Health Organisation Eastern Mediterranean & European regions are the most effective regions; they have a prevalence of 2.3% and 1.5%, respectively [1]. About 10 million people were infected by the hepatitis C virus in Pakistan in a total population of 190 million [3]. The drug combination of conventional/pegylated interferon and ribavirin has been the standard care for chronic hepatitis C for the past couple of decades [4].

Interferon is a drug, which acts both as an antiviral and an immune-modulatory agent. The interferon alpha protein presents antiviral, antiproliferative, and immune-modulatory activity. Ribavirin, in addition to direct inhibition to hepatitis C virus (HCV) replication, also has immune-modulatory activity [5]. The variation of actual success rate in the treatment of naive patients (i.e., sustained viral eradication) is partly depends on the viral genotype and the viral load and also on the drug adherence [6–9]. Due to the number and severity of side effects of antiviral therapy, drug adherence remains a problem [8]. The patients who were given interferon therapy due to hepatitis C infections suffer commonly from interferon-alpha-induced depression and severe psychiatric disorders [10] and occurrence of flu-like symptoms, hematological toxicity, elevated transaminases, nausea, fatigue, and psychiatric sequelae are also reported [11]. About 15%–60% of the patients suffer from psychiatric side effects due to interferon-alpha therapy. There have been different studies and consensus statements that claim patients suffering from psychiatric conditions and depression. The treatment of antiviral therapy should be withheld in such patients suffering from HCV infection [8].

With chronic hepatitis C infection, neuropsychiatric symptoms are commonly associated with it, as well as its sequelae and its treatment. During interferon treatment, the major depressive disorder occurs within a few months of the therapy [12]. In about 20%–50% of patients, induction of significant symptoms of depression occurs due to interferon alpha therapy [13]. The induction of depression due to interferon alpha is unknown. It is suggested that interferon suppresses hippocampal neurogenesis and induces depression via its receptor on the brain [14].

A risk between 30% and 70% of treatment-emergent depression is associated with interferon [15]. The risk can be due to interferon or to an interaction between interferon and the indication for which it was prescribed. There are various mechanisms that have been found to explain interferon-related depression, which includes neuro-hormonal, neurochemical, and neurohistological mechanisms. There is a reduction in the risk of interferon-related depression with prophylactic treatment with anti-depressants. Antidepressants are effective in treating this condition [15].

The risk of depression-recurrence remains unknown due to interferon therapy. In previous prospective studies, the incidence of interferon-alpha-induced depression in patients who achieved remission of depressive episodes by the end of interferon-alpha therapy was 59.1%, whereas the other 40.9% achieved remission after 12 weeks [10,16]. However, there have been reports of recurrence of depression and suicidal thoughts even after the antiviral therapy that ended 6 months earlier [10]. Although most interferon-alpha-induced depression achieve remission after therapy [16]. The main purpose of the study was to measure the prevalence of depression in patients with hepatitis C infection after treatment with conventional interferon and ribavirin in our population.

Methods

A cross-sectional study was conducted from June 2015 to May 2017 in a tertiary care hospital in Karachi. All patients attending the liver clinic and diagnosed as hepatitis C infection at Lyari general hospital and Abbasi Shaheed hospital were included in the study. All patients received treatment with conventional interferon therapy (3 million units thrice weekly with ribavirin 800–1,200 mg daily for 24 weeks). Patients who were already suffering from depression or were recently diagnosed with depression were excluded from the study. After completion of the therapy, patient health questionnaire-9 (PHQ-9) [17] was filled by study participants. Two residents from the department were trained to take patients' history and conduct interview according to the PHQ-9 questionnaire. A favorable ethical opinion was obtained from the Institutional Ethical Review Committee and after

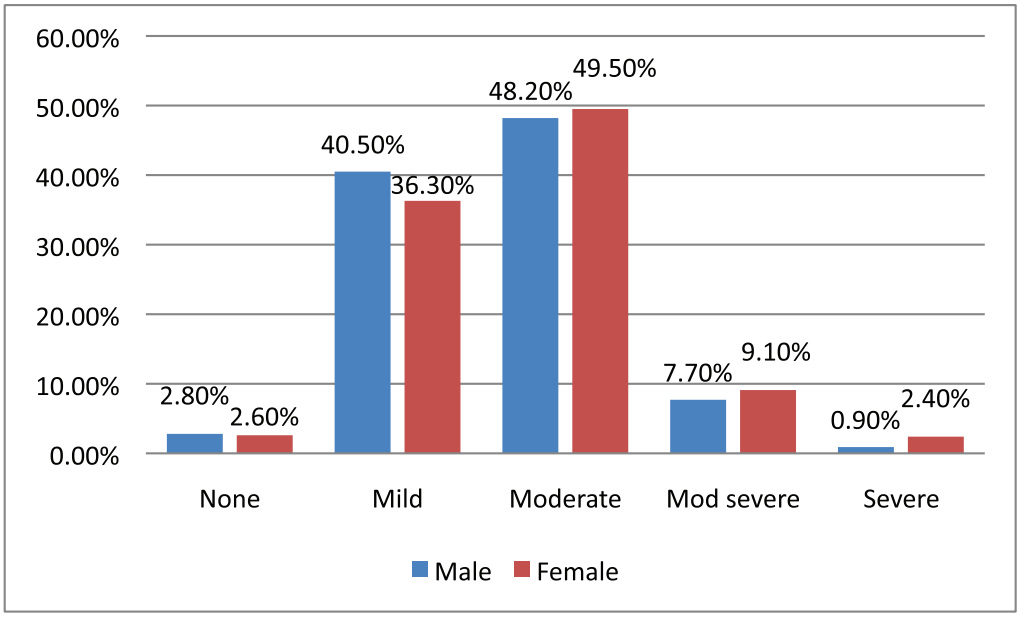

Figure 1. Gender and prevalence of depression.

taking informed written consent, the patient's short history was initially taken. Depression and its severity were also observed and compared between genders.

PHQ-9 is a self-reporting depression component of the Primary Care Evaluation of Mental Disorder Procedure 11, which has been validated for use in primary care for the diagnosis of depression [18]. It scores each of the nine Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria from 0 (not at all) to 3 (nearly every day). PHQ-9 can also be used to evaluate the severity of symptoms (score 1–4 minimal or none; 5–9 mild; 10–14 moderate; 15–19 moderately severe; and 20–27 severe) and has been used for monitoring symptom progression or remission over time. A study conducted in rural Pakistan had used Urdu translations of PHQ as screening tests for depressive disorders in Pakistani population [19].

Data analysis was performed using SPSS (IBM SPSS Statistics 22.0). Descriptive statistics analyses (mean, SD for interval variables, and the frequency with percentages for categorical variables) were performed for the study variables. χ^2 tests were applied to test for associations between dependent and independent variables.

Results

Fifteen hundred and seventy-one (n = 1,571) participants who met the study's inclusion criteria were participated, of which 41.5% (n = 652) participants were male and 58.8% (n = 919) were female. Average treatment duration of the study participants was 5.56 ± 1.04 months ranged from 1 to 9 months. Overall, more than two-thirds of participants were having depression; mild (38.1%) and moderate (48.9%) depression (Table 1).

Participants were asked multiple questions regarding self-reporting depression component (Table 2). Most of the participants reported that they experience little interest or pleasure in doing things (70.8%) and having trouble falling or staying asleep or sleeping too much (39.2%) for more than half a day. Similarly, more than half of the participants having difficulty on concentrating things such as reading the newspaper or watching television (58.6%). However, the majority of participants do not think that it would be better off dead or of hurting their self (73%).

Out of 1,571 patients, 2.8% male and 2.6% female patients had minimal or no depression. Moderate depression was found in 48.2% male and 49.5% female patients. Similarly, moderately severe depression was found in 7.7% male and 9.1% in female patients (Fig. 1). Prevalence of depression among patients with hepatitis C was not found to be associated with gender [$\chi^2(4) = 7.5$, $p < 0.11$].

Table 1. Frequency of depression.

	Frequency	Percentages
None	42	2.7
Mild	598	38.1
Moderate	769	48.9
Mod-severe	134	8.5
Severe	28	1.8

Table 2. Participants' response regarding self-reporting depression component (*n* = 1,571).

	Not at all *n* (%)	More than half a day *n* (%)	Nearly every day *n* (%)	Several days *n* (%)
Little interest or pleasure in doing things	81 (5.2)	1,112 (70.8)	256 (16.3)	122 (7.8)
Feeling down depressed or hopeless	483 (53.7)	341 (21.7)	234 (14.9)	153 (9.7)
Trouble falling or staying asleep or sleeping too much	45 (2.9)	616 (39.2)	666 (42.4)	244 (15.5)
Feeling tired or having little energy	50 (3.2)	517 (32.9)	629 (40)	375 (23.9)
Poor appetite or over eating	60 (3.8)	557 (35.5)	584 (37.2)	370 (23.6)
Feeling bad about yourself or that you have a failure or have let yourself or your family down	886 (56.4)	387 (24.6)	231 (14.7)	67 (4.3)
Trouble concentrating on things such as reading the newspaper or watching television	349 (22.2)	921 (58.6)	243 (15.5)	58 (3.7)
Moving or speaking so slowly that other people could have noticed. Or the opposite-being so fidgety or restless that you have been moving around a lot more than usual	644 (41)	594 (37.8)	275 (17.5)	58 (3.7)
Thoughts that you would be better off dead or of hurting yourself	1,147 (73)	293 (18.7)	58 (3.7)	73 (4.6)

Discussion

Our study results showed that 42.9% male and 57.1% female patients had minimal or no depression. Moderate depression was found in 44.1% male and 55.9% female patients. Moderately severe depression was found in 40.8% male and 59.2% in female patients. Prevalence of depression among patients with hepatitis C was not found to be associated with gender.

Neuropsychiatric symptoms are commonly associated with chronic hepatitis C virus infection, its sequelae, and its treatment [12]. Depression is one of the most common and serious side effects of IFN [14]. IFN-associated depression can lead to deterioration in the quality of life and has become a major contribution to treatment withdrawal, non-compliance, a dose reduction of IFN/Ribavirin (RBV), and even attempted suicide [20–22]. Therefore, there is an urgency in preventing the occurrence of depression in IFN-α-based therapy [22].

In this study, the predominant study population are female (59%), these results are consistent with a study by Shakoor et al. [23] in Lahore in which 63% population comprised of females, this might be due to same population structure of Karachi and Lahore city in contrast to the study done in Toronto, Canada, their sample mainly comprised of males (66%) probably due to a high-risk behavior [24]. In this study, IFN α- and ribavirin-induced depression were seen after 24 weeks of treatment, different study reports that depressive events with IFN α and ribavirin occurred more frequently during the first 24 weeks of therapy than during the later period of 48 weeks [25–27].

In this study, in a sample of 1,517 patients, approximately 97.3% patients were suffering from mild to severe depression. In other studies, the prevalence of depression was reported to be between 20% and 50% [13]. In a local study, 37% [27] and 39% [12] patients fulfilled the diagnostic criteria of DSMIV for a major depressive episode, respectively, limited studies are present in past which use PHQ 9 to assess depression. In our study, the percentage of the depressive patient is more because PHQ 9 cut off chosen was low. PHQ 9 is less likely to miss cases because of its low cut off score; this is the advantage over other depressive tools. However, it is very important to rule out cases of minimal depression too in interferon treatment because it can lead to severe consequences if left unassessed and untreated. The PHQ-9 has the advantage of being much shorter than most other available depression scales and, unlike most of these scales, and can establish a diagnosis of major depressive disorder because it draws from DSM-IV criteria [28].

In the current study, females were found to be more depressed as compared to males, these findings consisted with the study [27] in which 36 chronic hepatitis C patients were followed during their treatment and at the end, depression was seen more in females; this might be due to the reason that females are more prone to develop depression due to other social and stress factors.

In this study, approximately 57% patients reported that they experience sleep disturbances,

i.e., trouble falling or staying asleep or sleeping too much nearly every day or several days, while, in another study, 40% patients reported sleep disturbances [23]. In the current study, approximately 95% patient showed little interest or pleasure in doing things but in the previous study [19], only 45% patients reported a loss of interest or enjoyment. In our study, 27% patients reported thoughts that you would be better off dead or of hurting yourself, whereas Shakoor et al. [23] has reported it to be 30%, these percentages are very high as reported in other studies, i.e., 1.8% [27] and 4% [29], respectively.

Conclusion

The prevalence of depression in patients with hepatitis C appears to be very high compared to that in Western patients. IFN α- and ribavirin-induced depression were seen after 24 weeks of treatment; however, different study reports that depressive events with IFN α and ribavirin occurred more frequently during the first 24 weeks of therapy than during the later period of 48 weeks. Active screening and multidisciplinary management of depression is warranted.

References

[1] World Health Organization. Hepatitis C. Fact Sheet. [Online]. Available via http://www.who.int/mediacentre/factsheets/fs164/en/ (Accessed January 2018).

[2] World Health Organization. Hepatitis C. Media Centre. Fact Sheet. [Online]. Available via http://www.who.int/mediacentre/factsheets/fs164_apr2014/en/ (Accessed June 2018).

[3] Umar M, Khaar HT, Akhter TS, Aslam F, Ahmad SI, Asghar RM, et al. Diagnosis, management and prevention of hepatitis C in Pakistan 2017. J Ayub Med Coll Abbottabad 2016; 28(4 Suppl 1):S839–82.

[4] Huang M, Jiang J-D, Peng Z. Recent advances in the anti-HCV mechanisms of interferon. Acta Pharm Sinica B 2014; 4(4):241–7; doi:10.1016/j.apsb.2014.06.010

[5] Melo CE, de Araújo ESA, Barone AA. Basic aspects of the treatment for hepatitis C: mechanisms of action of interferon alpha and ribavirin and the bases of individualization. Braz J Infect Dis 2007; 11(Supplement1):43–44.

[6] Zeuzem S, Diago M, Gane E, Reddy KR, Pockros P, Prati D, et al. Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. Gastroenterology 2004; 127(6):1724–32.

[7] 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(9286):958–65.

[8] Horsmans Y. Interferon-induced depression in chronic hepatitis C. J Antimicrob Chemother. 2006;58(4):711-3. doi: 10.1093/jac/dkl331.

[9] Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004; 140(5):346–55.

[10] Chiu WC, Su YP, Su KP, Chen PC. Recurrence of depressive disorders after interferon-induced depression. Transl Psych 2017; 7(2):e1026; doi:10.1038/tp.2016.274

[11] Sleijfer S, Bannink M, Van Gool AR, Kruit WH, Stoter G. Side effects of interferon-alpha therapy. Pharm World Sci 2005; 27(6):423–31; doi:10.1007/s11096-005-1319-7

[12] Cvitanovic MZ, Lasic D, Karelovic D, Milic L. Interferon-alpha induced depression in a patient with hepatitis C. Psychiatr Danubina 2014; 26(1):84–5.

[13] Pierucci-Lagha A, Covault J, Bonkovsky HL, Feinn R, Abreu C, Sterling RK, et al. A functional serotonin transporter gene polymorphism and depressive effects associated with interferon-alpha treatment. Psychosomatics 2010; 51(2):137–48; doi:10.1176/appi.psy.51.2.137

[14] Zheng L-S, Hitoshi S, Kaneko N, Takao K, Miyakawa T, Tanaka Y, et al. Mechanisms for interferon-α-induced depression and neural stem cell dysfunction. Stem Cell Rep 2014; 3(1):73–84; doi: 10.1016/j.stemcr.2014.05.015

[15] Pinto EF, Andrade C. Interferon-related depression: a primer on mechanisms, treatment, and prevention of a common clinical problem. Curr Neuropharmacol 2016; 14(7):743–8.

[16] Horikawa N, Yamazaki T, Izumi N, Uchihara M. Incidence and clinical course of major depression in patients with chronic hepatitis type C undergoing interferon-alpha therapy: a prospective study. Gen Hosp Psychiatry 2003; 25(1):34–8.

[17] Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001; 16(9):606–13.

[18] Spitzer RL, Kroenke K, Williams JW; Patient Health Questionnaire Primary Care Study G. Validation and utility of a self-report version of prime-md: the phq primary care study. JAMA 1999; 282(18):1737–44; doi:10.1001/jama.282.18.1737

[19] Husain N, Gater R, Tomenson B, Creed F. Comparison of the personal health questionnaire and the self reporting questionnaire in rural Pakistan. J Pak Med Assoc 2006; 56(8):366–70.

[20] Zdilar D, Franco-Bronson K, Buchler N, Locala JA, Younossi ZM. Hepatitis C, interferon alfa, and

depression. Hepatology 2000; 31(6):1207–11; doi:10.1053/jhep.2000.7880

[21] Kraus MR, Schafer A, Csef H, Faller H, Mork H, Scheurlen M. Compliance with therapy in patients with chronic hepatitis C: associations with psychiatric symptoms, interpersonal problems, and mode of acquisition. Dig Dis Sci 2001; 46(10):2060–5.

[22] Hou XJ, Xu JH, Wang J, Yu YY. Can antidepressants prevent pegylated interferon-alpha/ribavirin-associated depression in patients with chronic hepatitis C: meta-analysis of randomized, double-blind, placebo-controlled trials? PLoS One 2013; 8(10):e76799; doi:10.1371/journal.pone.0076799

[23] Shakoor A, Shafqat F, Mehmud T, Akram M, Riaz S, Iqbal Z, et al. Frequency of depression and somatic symptoms in patients on interferon alpha/ribavirin for chronic hepatitis C. J Ayub Med Coll Abbottabad 2010; 22(4):6–9.

[24] Sockalingam S, Blank D, Al Jarad A, Alosaimi F, Hirschfield G, Abbey SE. A comparison of depression screening instruments in hepatitis C and the impact of depression on somatic symptoms. Psychosomatics 2011; 52(5):433–40; doi:10.1016/j.psym.2011.02.006

[25] Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347(13):975–82; doi:10.1056/NEJMoa020047

[26] Fried MW. Side effects of therapy of hepatitis C and their management. Hepatology 2002; 36(5 Suppl 1):S237–44; doi:10.1053/jhep.2002.36810

[27] Akhtar S, Azhar M, Yasmeen A. Rate of depression among hepatitis C patients treated with interferon alpha and ribavirin. Pakistan J Med Health Sci 2013; 7(4): 989.

[28] Dbouk N, Arguedas MR, Sheikh A. Assessment of the PHQ-9 as a screening tool for depression in patients with chronic hepatitis C. Dig Dis Sci 2008; 53(4):1100–6; doi:10.1007/s10620-007-9985-z

[29] Koskinas J, Merkouraki P, Manesis E, Hadziyannis S. Assessment of depression in patients with chronic viral hepatitis: effect of interferon treatment. Dig Dis 2002; 20(3–4):284–8; doi:10.1159/000067682