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BASELINE SOCIAL SUPPORT AND INTERFERON INDUCED DEPRESSION INHEPATITIS C PATIENTS

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Abstract
Main objective of the current research was to examine the effect of baseline social support as a risk factor on the subsequent development of interferon induced depression in hepatitis C patients. The sample consisted of N=59 female patients ranging in 31 to 64 years of age (M, 55.62, SD, 06.25) being diagnosed and scheduled for interferon treatment were selected from different hospitals of Peshawar. As an analytic approach the Interrupted Time Series Design was used. The Multidimensional Scale of Perceived Social Support (Zimet, D.G, Dahlem, Zimet, S.G & Farley, 1988) was used to classify participants into low and high scorers. To measure depression in patients before, during, and after end of the therapy, the Siddiqui Shah Depression Scale (Siddiqui, & Shah, 1997) was administered. Findings demonstrated that social support before the therapy had significant effect on reducing the levels of depression in hepatitis C patients before, during and after end of the treatment. The data support hypotheses and conclude that at baseline low level of social support is one of the major risk factor for subsequent development of depression during the course of interferon treatment. The findings have important implications in clinical settings by suggesting an utmost of systematic screening at baseline of the risk factors fundamental for effective interferon treatment and for welfare of patients and neuropsychiatric safety of the treatment.

Keywords: Baseline Social Support, Hepatitis C, Interferon alpha therapy, Depression

One of the major health problems on the global scale is Hepatitis C Virus (Strader, Wright, Thomas, Seeff, 2004). Worldwide rate of prevalence of the disease is 2.2 to 3 percent, about 170 million are infected with the disease and rate of mortality due to hepatitis C estimated is around 350,000 per year (Global Hepatitis Report, 2017). In United States epidemiology of hepatitis C has changed with more increase in young people of 15-to 29 years (Taherkhani, & Farshadpour, 2017). Globally Pakistan is the second largest having burden of hepatitis C with prevalence of 4.8 nationwide (Qureshi, Bile, Jooma, Alam, & Afridi, 2010). Despite generic direct acting antiviral with reduced cost available, still its prevalence remains persistence and there is no evidence of decline (Mahmood, Al Kanaani, Abu Raddal, 2019). According to a recent modeling analysis by Lim, Walker and Mafirakureva et al., (2020) in Pakistan the epidemic of hepatitis C virus is on rise and each year around 70,0000 new infection are reported which is adding currently about 7.7 million people i-e, 04% population of the world. In United States epidemiology of hepatitis C has changed with more increase in young people

of 15 to 29 years (Taherkhani, & Farshadpour, 2017). The disease since the initial stage, within 20 to 30 years can progress to cirrhosis and cancer (Alawazi, Cunningham, Dearden, & Foster, 2010). Due to its clinical complication about 20% of the infected people develop cirrhosis, one to four percent having the disorder develop diseases of liver and Western countries in fact it is one of the leading causes of liver transplant (Patel, Muir, & McHutchison, 2006). North Africa and Middle East are the most affected by hepatitis C having chronically infected 15 million people (Global Hepatitis Report, 2017). Geographically there are wide variations in the prevalence rate of disease, for example, low rates in Western Europe such as 1.8 % in United States 0.6 % in Germany and North America, while higher rates in developing countries. In some countries higher rates have been reported, for instance, in China (3.2%) and in Egypt (22 %), and in Pakistan (4.8 %), cases have been reported which is higher than the North America, and Western Europe (World Hepatitis C Day, 2014 July, 28).The standard treatment for the disease include the pro-inflammatory cytokine interferon alpha (INF) approved by the Federal Drug Authority, a multifunctional protein effective in 40 to 80 % in hepatitis C patients having certain common genotype (Bacon, 2004). The advanced treatment of HCV currently in use with the hepatitis C patients includes the pegylated recombinant interferon (PEG-IFN-α) which once per week is recommended along with an oral anti-viral drug ribavirin (RBV) is also given on daily basis (Fried, et al., 2002, Nesic, *et al*., 2004). In Pakistan the same therapies are given for treatment of hepatitis C (Zuberi, *et al.*, 2008). The duration of treatment ranges from 24 to 48 weeks depending on the HCV genotype (Wilkins, Malcolm, Rania, & Schade, 2010). The Sustained Viological Response (SVR) among patients receiving the treatment is 40 to 80 percent (Fried, *et al.*, 2002). But despite this increase in the SVR its side effects present a major health problem (Fried, *et al.*, 2002; Kraus, Schafer, Csef, & Scheurlen, 2005b; Loftis, & Hauser, 2004).

The neuropsychiatric disorders associated with the IFN-α therapy have been found by numerous researchers (Dieperink, Willenbring, & Ho, 2000; Malaguranera, *et al.*, 1998; Yates & Gleason, 1998). In a study the researchers examined a 25 years old inpatient with hepatitis C infection and found that patient during the IFN developed symptoms of depression, withdrawal, distress and resulted lack in response to medication and to quitted therapy (Wolfelschneider, Schreiber, Markou, Gieler, & Brosig, 2006). The patient after getting psychotherapy was re-administered with IFN-α and discharged after successful completion. Findings conclude psychotherapy an adequate treatment for overcoming psychological effects of IFN-α induced depression.

Some researchers in 74 patients that were under treatment with PEG IFN along with oral RBV examined risk of depression by administering the depression scale. Results showed that on three follow up visits significant enhance was found in their depression scores compared to their pre-treatment depression scores (Pavlovic, Delic, Maric, Vukovic, & Gasic, 2011).

In a meta analysis the researchers searched electronic data bases up to 2005 to examine the psychiatric side effects of the IFN among patients of multiple sclerosis. Out of 150 articles reviewed, 16 demonstrated both symptoms of depression and suicide in the patients (Goeb, *et al*., 2005). The findings of numerous research revealed discontinuation of the therapy at the initial stage in 0.2 to 12.5 % of the patients due to its side effects (European Study Group on Interferon beta-1b, 1998; Raison,Demetrasshvili, Capuron, & Miller,2005a; Zephir, *et al*., 2003).

Numerous researches have reported higher level of depression in those hepatitis C patients who were not available social support during the treatment (Evon, Ramcharran, Belle, Fontana, & Fried, 2009; McCabe, McKern, McDonald, 2004, William,Turner, & Hatzakis, 2004). Porcelli, Cozzolongo, Lanzilotta, Giannuzzi, and Leandro (2014) in their study examined the effects of social support on association between autoaggressive immune function and depression among multiple sclerosis patients diagnosed with major depression. Social support was measured pre-test and T-cell production of interferon-gama (a-pathogenesis) and depressive symptoms were assessed both pre-treatment and post-treatment. The findings showed that both T-cell production of interferon-gamma and levels of depression were significantly reduced in patients who perceived higher social support at baseline as compared to those perceived low social support.

Frick, Motzke, Fischer, Busch and Bumeder (2005) studied the effect of social support on survival in 99 patients of different malignancies undergoing blood stem cell transplantation. At baseline two subscales of the Social Support Scale, the positive support and problematic support were administered. Results showed that mean survival was high (3.2) in patients who perceived positive social support at baseline than those perceived problematic social support (0.94).

In another research the researchers in 81 patients infected with hepatitis C but not receiving the interferon therapy examined depression, anxiety, social support and resilience as a protective factors of mental health. Findings revealed that high social support and resilience predicted low level of depression in the patients. Female gender, patients having no spouse and those recently diagnosed, scored higher on the depression scale (Erim, *et al*., 2010).

Casey, *et al*., 2006) in their study examined factors with suicidal ideation and found that compared to those perceived high social support, individuals with low social support reported more suicidal ideations. Some research examined the impact of social support on drug and alcohol use in children and found that children who were more prone to different drug and alcohol use perceived low social support than those perceived high social support (Chu, Saucie & Hafner, 2010).

An estimate reports that in Pakistan 18 million population have acquired the hepatitis C disease and day by day the disorder is increasing due to non or/and lack of availability of vaccine against the disease (World Hepatitis C Day, 2014 July, 28). The standard treatment include pro-inflammatory cytokine interferon-alpha (INF-α) combined with oral ribavirin a multifunctional protein which is a successful antiviral drug but numerous psychiatric side effect have been associated with it the most common among them is depression reported by numerous researches (Capuron, Ravaud, Miller & Dantzer, 2004, Dieperink, *et al.,* 2000; Schaefer, Capuron, & Friebe, 2012). Because of these side effects majority of the patients either reduce dose or discontinue treatment. In view of aforementioned researches it seemed essential to examine the effect of pre-treatment factors on development of depression in hepatitis C patients during and after end of treatment, among them social support is one of the most important. The current study was thus, designed to examine its effect so that to identify preventive measures to reduce depressive symptoms and provide maximum benefits of the therapy to the patients.

Hypotheses

Following hypotheses were formulated.

1. Hepatitis C patients having low baseline social support score will obtain high score on SSDS during the therapy than those with high baseline social support score.
2. Post-therapy score of hepatitis C patients with low baseline social support score will be high than those with high baseline social support scores on SSDS.

Method

Sample

The sample included N=59 patients scheduled for interferon treatment with the age range between 31 to 64 years (*M*, 55.62, *SD*, 06.25). Duration of symptoms of the disease before diagnosis in the participants was five to six months. The educational level of the sample was six years of schooling to metric. All the participants belonged to middle and lowers socioeconomic status. Using a software Sample Size Determination in health studies the size of sample was calculated (Lawanga, & Lemeshow, 1991). The participants were selected from different hospitals of Peshawar using the Convenience Sampling Technique. The criteria of their inclusion was having being diagnosed with hepatitis C, undergoing the IFN-α for the first time and not having other diseases such as neurological diseases, serious cardiovascular and those who had addiction to any psychoactive drugs.

Study Design

To measure level of depression in patients at baseline, during the treatment and two months post-therapy the Interrupted Time Series Design was used.

Instruments

Demographic Information Sheet

The demographic sheet was used to collect relevant information such as education, age, previous medical conditions and previous or current use of any antidepressant drugs.

Multidimensional Scale of Perceived Social Support (MSPSS)

The Multidimensional Scale of Perceived Social Support (MSPSS) was developed by Zimet, *et al.*, in 1988 to measures perception of social support available. A 7 points Likert type rating scale the MSPSS includes three subscales, namely Friends (items, 6, 7, 9, 12) Family (item, 3, 4, 8 & 11), and Significant Other (items, 1, 2, 5, 10). The reliability determined of the whole scale using coefficient alpha range from 0.85 to 0.91 and using test-retest method ranges from 0.72 to 0.55 with 275 undergraduates. In Pakistan the test was translated in Urdu by Jibeen and Khalid in 2010 using the method of forward and backward translation (Brislin, 1973). The current study used Urdu version of the MSPSS prepared by Jibeen and Khalid (2010). The reliability of the scale computed for the present sample is 0.81. **Siddiqui-Shah Depression Scale (SSDS)**

The SSDS was developed by Siddiqui and Shah in 1997 to measures depression in clinical and non-clinical populations. It includes 36 items which are scored on 4 response categories: Never (0), Sometime, (1), Usually (2), and Always, (3). By summing all items total score is obtained. Possible score range from 0-36, (Low), 37-72, (Moderate), and 73-108 (High). High score shows higher level of depression. Reliability of the scale determined by the author by split half method for non-clinical group is r =.80 and for clinical group is r =.79, while correlations of scale with Zung Depression Self Rating Scale (Zung, 1965) is 0.55 and with psychiatric rating of depression is 0.40. For the current study sample the reliability computed is 0.79.

Procedure

Patients diagnosed with the disease and planned for interferon treatment were approached and requested to cooperate with the researcher. Each participant was informed about the requirements and protocols of the study and their written consents were obtained. After a brief introduction the MSPSS (Zimet, *et al.*,1988) was administered with the entire sample and those scored higher at pre-treatment on the MSPSS were separated than low scorers on the said scale. To measure their depression the SSDS (Siddiqui & Shah, 1997) was administered pre-treatment, during therapy and after completion of two months of the therapy. The findings of three data points, i-e, pre-treatment, during, and two months post treatment were compared.

Results

Table 1 *Demographic Characteristics of the Sample*

	Low BSSS (*n*=32)		High BSSS (*n*=27)	
Age in Years	Frequency	Percentage	Frequency	Percentage
31-40	08	25.00%	07	25.92%
41-50	12	37.5%	09	33.33%
51-64	11	34.37%	11	40.74%
Total	32			
Education				
Primary	11	34.37%	06	22.22%
Middle	16	50.00%	10	37.03%
Metric	04	12.5%	11	40.74%
Illiterate	01	3.12%		
Total	32		27	
Socioeconomic Status				
Middle(40,000	11	34.37%	07	21.32%
Lower (Rs.20,000)	21	65.62%	20	62.5%

Total	32			27	
Duration of Symptoms of Illness before Diagnosis					
0-5 months	11	4.37%		08	29.2%
5-6 months		65.62%		19	70.37%
Total	21 32			27	

Note: BSSS= Baseline Social Support Scorers

Table 2 *Mean Difference at Baseline between Hepatitis C Patients Having Low and High Social Support on Siddique Shah Depression Scale*

	Depression Scores at Baseline					95%CI		
Groups of Hepatitis C Patients	*N*	*M*	*SD*	*t-(55)*	*P*	*LL*	*UL*	*Cohen's d*
Patients with Low BSSS	32	41.65	7.20	8.02	.004	14.10	23.50	2.17
Patients with High BSSS	27	22.85	10.42					

Note=IFN=Interferon, BSS=Baseline Social Support Scorers; LL=Lower limit, UL=Upper limit

Data in the table no 2 reveal significance difference in hepatitis C patients at baseline in terms of depression.

Table 3 *Mean Difference between Low and High Social Support Scorers at Baseline and at Week 24th on SSDS*

		Baseline Scores	At week 24th			95%CI		
Groups of Hepatits C Patients	*N*	*M(SD)*	*M(SD)*	*t-value*	*P*	*LL*	*UL*	*Cohen's d*
Patients with Low BSSS	32	41.65(7.20)	49.13(18.57)	2.00(30)	.05	0.14	15.11	0.54
Patients with High BSSS	27	22.85(10.42)	23.08(8.33)	.22(25)	.82	1.88	2.35	0.02

Note=IFN=Interferon, BSSS=Baseline Social Support Scorers, LL=Lower limit, UL=Upper limit

Findings in table 3 demonstrate significant difference between patients. Compared to high baseline social support scorers patients with low baseline social support obtained high mean score on the depression scale during the IFN therapy (at week 24th time, 1) and support first hypothesis of the study.

Table 4 *Comparison of Mean between Low and High Social Support Scorers at Pre and Two Months after Completion on SSDS*

Groups of Hepatitis C patients		Baseline-IFN	Two month after completion-IFN			95%CI		*Cohen's d*
	N	*M(SD)*	*M(SD)*	*t(df)*	*P*	*LL*	*UL*	
Low BLSSS	32	41.65(07.20)	49.94(19.76)	2.12(30)	.04	0.33	16.25	0.65
High BLSSS	27	22.85(10.42)	23.70(07.83)	0.51(25)	.77	1.77	3.47	0.03

Note=IFN=Interferon, BLSS=Baseline Social Support Scorers, LL=Lower limit, UL=Upper limit

Data in table 4 reveal that hepatitis C patients with low baseline social support scored high on the SSDS than with high baseline social support. It can safely be assumed that patients having low baseline social support are more vulnerable to develop depression after two months of post therapy than having high baseline social support and thus support second hypothesis of the study.

Table 4 *Repeated Measure ANOVA and Post Hoc Analyses for Comparing Difference in Mean Among Low and High Social Support Scorers on SSDS*

Groups of Hepatitis C Patients	BL-IFN *M(SD)*	24th Week *M(SD)*	Post- IFN *M(SD)*	*F*	*P*	i-j	Mean Difference(i-j)	SE	P	LB UB
Low BSSS (n=32)	41.65(7.20)	49.13(18.57)	49.94(19.78)	4.52	.04	*BL-24th Week*	*7.48**	*2.7*	0.5	15.11 0.14
						BL-Post	8.29*	3.89	0.4	16.25 0.33
						24th Week –Post	0.80	1.04	.44	2.93 1.31
HighBSSS (n=27)	22.85(10.42)	23.08(08.33)	23.69(07.83)	0.44	.44	*BL-24th Week*	0.23	1.03	.82	2.35 1.89
						BL-Post	.84	1.27	.51	3.47 1.78
						24th Week –Post	.61	0.61	.32	.65 1.88

Note=IFN=Interferon, BLSS=Baseline Social Support Scorers, LL=Lower limit, UL=Upper limit

Table no 4 show significant difference in low and high social support scorers on the SSDS. Patients with low social support experienced high levels of depression in three time points on the SSDS than high baseline social support scorers which support our both hypotheses. The Post Hot test calculated by using the Least Significant Difference reveals significant difference in terms of depression experienced by low and high baseline social support scorers at baseline, during treatment and two months post therapy. There is no significant difference in three time points on the depression scale among low social support scorers.

Discussion

Findings of the study strongly support the research hypotheses. Hepatitis C patients with low baseline social support scores obtained high score on the SSDS during, at 24th week and two months after completion of the therapy than low social support scorers. The results show significant difference in terms of depression between low and high baseline social support scorers on the SSDS in three time points (table,1,2,3). These results are in accordance with previous research reporting that hepatitis C patients with pre-treatment low perceived social support experience high level of depression during the treatment than those having pre-therapy high social support scorers (Evon, Ramcharran, Belle, Fontana, & Fried, *et al.*, 2009; McCabe, *et al*., 2004; William, *et al.*, 2004).

Numerous research reports that individuals having lower social support develop high level of depression and anxiety during interferon therapy than those with high level of support (Barrera, 1986; Cohen, & Wills, 1985). For example, in a longitudinal research Kovacs, *et al.,* (2015) during a low dose IFN treatment examined the effect of social support on anxiety and depression in 127 melanoma patients. Social support, depression and anxiety were measured pre-therapy, and after every three months during 12 months follow up. Findings demonstrated enhance in their depressive symptoms, however, those reported satisfaction with available social support at pre-treatment revealed significantly moderate level of depression than those not satisfied with available social support.

Other research examined the biopsychosocial effects of interferon alpha therapy on the chronic hepatitis C patients. For example, Baranyi *et al.,* (2014) in their study assessed the biological and psychiatric impact at baseline, during at 1st, 3rd, 6th and three months after the completion of therapy in hepatitis C patients. The results showed that low social support, female gender, small circle of friends, low financial security, reduced social functioning, poor physical health, impaired sexual satisfaction, and pre-existing psychiatric vulnerability were contributing factors intensified depression among patients.

In another study the researchers investigated relation between neural pathways in brain and social support. Findings revealed that low social support diminished activation of brain area involved in distress. Results further showed that reduced activation lowered cortisol (hormone produces stress) that plays an essential role in reducing stress (Eisenberger, Taylor, Gable, Hilmert & Lieberman, (2007). In some research high social support reduced cardiovascular reactions in patients having cardiovascular diseases (Uchino, 2006).

Numerous research have reported high levels of depression in people who experienced low social support, including major depressive disorders (Lakey, & Cronin, 2008) social phobia, (Torgrud, *et al.*, 2004) panic disorder (Huang, Yen, & Lung, 2010) post traumatic stress disorder (Brewin, Andrew, & Valentine, 2000) eating disorders (Stice, Presnell, & Spangler, 2002) and dysthymic disorder (Kline, Taylor, Dickstein, & Harding, 1988).

Research demonstrates an association between health outcomes and social support. Uchino, for example, (2009) studied the impact of social support on development of life threatening diseases. Findings revealed more cardiovascular diseases and high mortality rate in individuals who reported low social support. Other research demonstrate poor immune functions and higher inflammation in patients with low levels of social support (Glaser, McGuire, Robles, & Glaser, 2002; Uchino, 2006). Some researchers found more severe pain in patients having arthritis at their acute stage and long term functional disability with low social support (Evers, Kraaimaat, Geenen, Jacobes, & Bijlsma, 2003).

In their study Norman, *et al.*, (2005) investigated the effect of social support in patients of schizophrenia. Findings revealed that patients with low level of social support experienced more severity in symptoms of their disorder than with high social support. Research report that emotional support compared to other support is the most important in elevating stress and enhancing well being among people (Kessler, &, McLeod, 1984). For instance, Loucks, Berkman, Gruenewal and Seeman, (2006) between social support and levels of inflammation found a positive correlation.

Similarly Jemmott and Magloir (1988) investigated in students during the final examination the impact of social support on the functions of immune system on stress and found that students having high social support available had higher secretion of immunoglobin-A which plays a key role against several respiratory infections. Other researcher in their investigation on spouses of cancer patients also found a positive association between high social support and increased immune functioning (Baron & Mullen,1990).

These empirical evidences clearly supports findings of the current research and hypotheses regarding the effect of low baseline social support on the development of depression in hepatitis C patients during and after completion of interferon therapy.

Limitations and Suggestions

The present study is not without limitations which should be considered by future researchers. Numerous other variables predict depression in hepatitis C patients including low socioeconomic status, use of substance in patients and low education which should be studied by future researchers. Present research examined the effect of pre-therapy social support on development of depression three time points, i-e, at baseline, during 24th week and two months after end of the therapy. Assessment of disorder more than three points in hepatitis C patients is recommended. In current research a self- rating scale was used to measure depressive symptoms in participants, evaluation of the same factor by the psychiatrists in the sample could provide a cross check with results which might show more valid results.

Implications

The findings of the present research have certain important implications. Screening of the pre-therapy social support need to be included as a part of the therapy to get more clinical benefits from therapy. Effective psychological therapies should be administered in case when patients perceive low social support in start of the therapy which need to be continued till maximum stability in psychological

treatment is achieved. By providing social support to patients will allow the gastroenterologists do not stop treatment, achieve maximum success in therapy and not to exclude patients with high risk, particularly in Pakistan where majority of the patients come from low socioeconomic class having various psychological problems, therefore, timely psychological treatment before the IFN therapy will maximize success in their interferon treatment.

Conclusion

In the light of results it is concluded that pre-treatment low social support is one of the main risk factor responsible for development of depression in patients in response to IFN therapy.

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