Pakistan Journal of Social and Clinical Psychology
2019, Vol. 17, No.2, 40-49

Development and Validation of Scale for Neuro-Psychological and Physiological Side Effects of Interferon Therapy (NPPSI) in HCV Patients

Naima Hassan, Amina Muazzam
Lahore College for Women University, Lahore

Ambreen Anjum
The Islamic University of Bahawalpur

Pakistan has the second highest rate of hepatitis C in the world, and it is estimated that 11.85 percent of its population suffers from this medical problem. A valid and comprehensive scale was constructed to help for quantification of neuro-psychological and physical side effects of different treatment regimens available for eradication of hepatitis C infection. The present study was conducted in 3 stages. In stage I, item generation was done empirically through detailed review of literature, detailed interviews with practicing physicians and focus groups with patients. In stage II, factor structure of the scale was explored through exploratory factor analysis on a sample of 250 HCV patients (M = 39.6, SD = 9.4, age = 18-60 years) and confirmed through confirmatory factor analysis on a sample of 230 selected patients of HCV (M = 38.9, SD = 9.2, age = 18-60 years) which resulted in 3 factors with 36 items. Physical factor contained 19 items related to physical complaints such as body aches and anorexia. Psychological factor included 12 items, which were psychological complaints such as crying spells and depression. Neuro factor had 5 items of neurological complaints in nature such as hallucination. In stage III, psychometric properties of the scale were established and it revealed that it is a highly reliable scale with r =.97. Physical, psychological and neurological factors of NPPSI-Scale also revealed high value of alpha coefficient respectively .98, .95 and .92. Convergent and discriminant validity of NPPSI- Scale was also established.

Keywords: hepatitis C, interferon, psychological side effects.

When Hepatitis C virus was isolated in 1989 (Kuo et al., 1989), it was considered less important infection (Alter et al., 1990). Now almost 40 years later, HCV is among the leading global health issues that require widespread actions for its prevention and control (Gerszten, Allison, & Maguire, 2012). In 2017, the international prevalence of hepatitis C was estimated at 1.6 percent, which translates into 170 million people infected with the virus across the world (Blach et al., 2017). Egypt has the highest prevalence rate of hepatitis C infection with more than 14.7 percent of its population suffering from this disease (Mohamoud, 2013). Pakistan is second in the list with approximately 5 percent of the total population carrying this disease as more than 10 million Pakistanis are infected with hepatitis C (Umar, 2010). In fact, no region of the world is safe from this lethal virus.

Treatment of Chronic Hepatitis C Infection

In 1998-99, Alpha Interferon combined with ribavirin was introduced in Pakistan as the leading treatment approach for the Hepatitis C infection. In the past decade, it was used as the first line treatment for chronic hepatitis C infection. Different studies carried out in Pakistan report the cure rate of this treatment to be ranging from 50-80 percent (Nadeem et al., 2007). In 2000, discovery of a more advanced type of interferon (i.e., pegylated interferon) was assumed to be able to revolutionize the treatment of hepatitis C. American Association for the Study of Liver Disease guidelines in 2004, gave the fixed dose of interferon Alpha or pegylated Interferon for the use in patients of HCV (Strader, Wright, Thomas, & Seeff, 2004). Nevertheless, in Pakistan, the cure rate of pegylated interferon was noted to be equal to or slightly more than that of the alpha interferon ranging from 60 to 85 percent (Umar, 2012). Sofosbuvir was the first drug approved and marketed for the treatment of hepatitis C infection. Use of sofosbuvir was included in the treatment guidelines in 2015 (Chung et al., 2015). Initially, the combination of Sofsbuvir and ribavirin in an interferon free regime showed cure rate of 71-84 percent. Foster et al. (2015) found cure rate of 93 percent, when they used pegylated interferon with both of these drugs. After the success of first oral direct acting antiviral treatment, further more effective oral antiviral drugs such as daclatasvir, ledipasvir, and velpatasvir were developed (Pawlotsky et al., 2015). The current treatment guide lines to treat the hepatitis C infection favor the use of interferon free regimes with different oral direct acting anti-viral drugs (Chung et al., 2015).

Side effects of Interferons

Both conventional and pegylated interferons have numerous neuro-psychiatric and physical side effects. These side effects are common among patients receiving treatment of Hepatitis C. A long list of these side effects is reported and the rate of occurrence of these side effects is comparable among both regimes (Manns, 2001; Hunyady, 2011). Constitutional side effects include fatigue, headache and fever (Dusheiko, 1997). Gastrointestinal side effects include nausea, vomiting and anorexia (Sleijfer & Bannink, 2005). Psychiatric Side Effects include insomnia, irritability, and depression (Trask & Esper, 2000). Moreover, dyspnea (Shortness of Breath), chest pain, visual changes, thyroid dysfunction and focal neurological symptoms are also in observation (Hunyady, 2011). About 10-15 percent of patients cannot bear these complaints and tend to discontinue treatment (Manns, 2001).

Neuropsychiatric side effects are the most problematic in these

Correspondence regarding this article should be addressed to Dr. Amina Muazzam, Tenured Associate Professor, Department of Applied Psychology, Lahore College for Women University, Lahore.
E-mail: amina_muazzam@hotmail.com

patients. Since 1987, the psychiatric side effects of alpha interferon are very well documented by Renault and Hoofnagle. These side effects include irritability, anxiety, loss of interest, social withdrawal, depression, delirium, disorientation, clouding of consciousness, suicidal ideation, paranoid ideation, return of craving for alcohol or drugs in addicts, and accentuation of previous symptoms, such as phobias, obsessional thoughts and rituals.

Later on when hepatitis C virus was discovered in late 1980s and by mid-90s, the role of alpha interferon was well established for treatment of this virus, and many trials were done to see the side effects of interferon. Especially noticeable side effects were neuropsychiatric in nature. These side effects contain asthenia, irritability, apathy, increased somnolence, confusion and indecisiveness (Dieperink & Willenbring, 2000). Severe depression and suicidal tendencies are well reported side effects of interferons among other cognitive and behavioral disorders associated with interferon treatment (Kraus, 2005). Sometimes depressive symptoms are so severe in these patients that patients stop treatment before completing the course.

The direct acting antiviral drugs also show certain side effects in the patients. Almost 90 percent patients report some side effects associated with direct acting antiviral treatment (Asselah & Marcellin, 2011). The most commonly reported side effects are fatigue, headache, nausea and neuropsychiatric symptoms such as insomnia and depression (Medeiros et al., 2017). The severity of side effects of direct acting anti-viral drugs is correlated with pretreatment status of liver and stage of liver failure. Patients with compromised liver and renal function tend to face more treatment related side effects of these drugs when compared with patients with preserved liver functions' patients (Mann et al., 2016).

Significance of the study

The study proposes to develop a measure to assess the side effects of the drugs used for treatment of hepatitis C. As already discussed above, the Interferon therapy used for the treatment of hepatitis C is linked with a vast number of neuro-psychiatric and physical side effects, whereas the newer treatment regimens which are interferon free regimes also have some psychiatric and neurological side effects. Although many studies have established the well-known neuro-psychiatric side effects of these drugs, there is no way to quantify and statistically elaborate the side effects of interferon and direct acting antiviral drugs. Treating physicians commonly come across a very disturbing question: When the suffering of a patient becomes sever enough during the course of treatment that treatment needs to be stopped or altered. The rationale of this study lies in finding answer to this very question. This study would help the researchers and practicing physicians to design better treatment regimens for the elimination of HCV while minimally effecting the quality of life of these patients and can give an estimation that when to discontinue or revise the treatment if the side effects are worsening.

Objectives of the study

The objectives of the study are as follows:

1. To develop a scale to reliably quantify the severity of side effects faced by patients receiving treatment for eradication of hepatitis C infection.
2. To establish psychometric properties of the newly developed scale.

Method

This study was performed in two stages. The first stage includes development of an indigenous scale to assess neuro-psychological and physical side effects of interferon therapy in HCV patients. The second stage revolves around establishing psychometric properties of newly developed scale.

Stage I: Development of a List of Neuro-Psychological and Physical side effects of Interferon Scale (NPPSI-S)

This stage was aimed to acquire a list of items that can cater the side effects of interferon therapy in HCV patients and the constituent factor structure of those items.

Step I: Item generation

A collection of items was gathered through the following sources: literature review, unstructured interviews with physicians and focus groups with patients.

Detailed Literature Review: Detailed literature review was performed using google scholar and pub med search engine. More than 50 articles were reviewed with key words of hepatitis C, interferon and side effects. studies dating as back as 1989 to 2018 were reviewed.

Initially conventional interferon injections and ribavirin were the treatment of choice for HCV infection. Use of conventional interferon was associated with several side effects. Such as, Fatigue, Fever, Myalgias, Backache, Anorexia, Nausea, Reduced attention span and Difficulty sleeping (Renault, 1989). Depression has long been strongly associated with use of interferon, as are other cognitive and mood disorders (Valentine, 1998). Moreover, cases of delirium and acute personality changes in patients having interferon therapy were reported (Goeb, 2003. Schafer, 1999. Schafer, 2000). Mania, hypomania, cognitive dysfunctions are further side effects experienced by the use of interferon injections (Crone, 2004). With the development of Pegylated interferon, it was speculated that patients may face less side effects but research showed similar profile of side effects in the pegylated group (Fried, 2002). About 10-14 percent patients using interferon therapy have to withdraw from the treatment due to side effects of these drugs (Fried 2002). Although the development of oral antiviral drugs has initiated a new era in the field of HCV eradication therapy and now various combinations of oral, interferon free regimes are preferred for HCV treatment. But these oral drugs are also not entirely side effect free (Jakobsen, 2017). Side effects associated with oral antivirals are headache, nausea, GI disturbances and mood changes (Aghemo, 2018).

Unstructured Interviews with Physicians: In the second phase, unstructured interviews were conducted with practicing physicians (n=3), with 10 years of practice in assessment and treatment of HCV with interferon and oral anti-viral therapy. Expert sampling technique which is a type of purposive sampling was used to select the sample for these interviews, because expert sampling technique helps where knowledge about the phenomena being study rooted in a certain form of expertise (Etikan & Bala, 2017). Each expert was a competent practicing physician who had a great command over their field of treating HCV with interferon treatment.

Procedure

Interviews were conducted by the first author. These interviews lasted for a maximum of thirty minutes and consisted of 2 steps. In first step, after taking verbal consent from the experts, they were briefed about the purpose and concept of the study. In second step, a prepared questionnaire was offered to the experts with open ended questions (e.g., What are the most common hazardous side effects that can appear during the treatment of hepatitis C? What is the

intensity of these symptoms? Which symptoms appear more: psychological or physical? Did you have to stop the treatment for hepatitis C due to these side effects? etc.) Experts were also requested to make any additions and share their thoughts regarding side effects experienced by the patients during the course of treatment for HCV. At the end of interview, experts were duly thanked for their valuable time and help. Through these interviews, items collected were: fever, body aches, anorexia, abdominal discomfort, low self-esteem, dementia, cardiac problems, altered BP, suicidal tendencies, confusion, paranoia, tremors, hypomania, hallucinations, paresthesia, fatigue, stomach aches, anxiety, depression, shivering, freckles, vomiting, dizziness, difficulty in breathing, fits, body imbalance and mood swings.

Focus Groups: To identify the items, two focus groups were conducted with patients of HCV receiving treatment of interferon therapy and oral antiviral therapy.

Sample

Homogenous purposive sampling strategy was opted to conduct focus groups. In first focus group 4 female and 4 male HCV patients receiving treatment were selected with age range of 18-60 years (*M*=37.0, *SD*=8.24). In the second focus group, 5 female and 3 male HCV patients receiving treatment for HCV with age range of 18-60 years (*M*=41.5, *SD*=8.5) were selected. Sample for both focus groups was taken from hepatitis clinic of semi-private hospital of Lahore. Only those patients were selected for focus group, who were visiting clinic for last visit before the end of their treatment course. The reason for selecting these patients was that they have experienced the course of treatment and were about to finish their treatment. Logically, they were a better source of information for reporting the side effects of treatment of HCV.

Procedure

During the focus group, initially the patients were explained about the purpose of study in a brief 2-minute verbal presentation by the author. Patients were encouraged to share their experience of having treatment for hepatitis C infection. Moreover, they were asked to report complications faced during treatment. A brief open ended questionnaire was used to facilitate the patients for reporting side effects (e.g., Have you experienced any adverse effects of these medicines/injections? During your treatment, which worrisome symptoms compelled you to consult a doctor? etc.) Through detail questioning sessions, different side effects and complains were probed. Items identified through focus groups were fever, body pains, loss of appetite, difficulty in sleeping, tremors, leg numbness, altered blood pressure, cold intolerance, forgetfulness, hair loss, headache, hopelessness, fatigue, depression, aggression, constipation, irritability, skin dryness, suicidal thoughts, dizziness, crying spells, palpitations, hair fall, difficulty in breathing, nose bleeding and leg aches. Patients were thanked at the end of study and a list of reported side effects was generated based on the findings of these focus groups.

Step II: Item Content Validity through Expert Rating

After obtaining a pool of items through detailed literature review, focus groups and unstructured interview with physicians, item content validity index for NPPSI scale was established. For this purpose, overlapping and repetitive items were excluded and a list of 45 items was prepared for NPPSI scale.

Procedure

The list of 45 items was presented to 6 practicing physicians having at least 10 years' experience in the treatment of hepatitis patients with interferon and oral antiviral therapy. Experts were instructed to carefully go through each item on the list and give their response in accordance of item's relevance and readability on a 4-point rating scale that is 1=not relevant, 2= to some extent relevant, 3= relevant and 4= highly relevant.

Item Content Validity Index (I-CVI) was computed for every item through dividing the no. of agreements on that item with total number of experts. According to Lynn (1986), if the number of raters or experts is equal or more than 6 then Item content validity index should be .78 to 1.

Table 1
Ratings of Experts and No. of Agreements and I-CVI for NPPSI-Scale.

Item	Expert 1	Expert 2	Expert 3	Expert 4	Expert 5	Expert 6	No. of agreement	ICVI
1	3	4	3	3	4	3	6	**1**
2	4	4	3	4	3	1	5	**.83**
3	4	4	4	3	4	3	6	**1**
4	4	3	4	3	4	4	6	**1**
5	3	3	4	4	3	4	6	**1**
6	3	3	4	4	4	4	6	**1**
7	3	4	4	3	4	4	6	**1**
8	4	4	3	1	3	3	5	**.83**
9	4	3	3	3	4	3	6	**1**
10	4	2	3	4	3	3	5	**.83**
11	3	4	3	4	2	3	6	**1**
12	4	4	4	3	3	4	6	**1**
13	4	2	2	3	4	3	4	.67
14	3	4	4	1	3	3	5	**.83**
15	4	4	3	3	3	3	6	**1**
16	3	3	4	3	4	3	6	**1**
17	4	2	3	4	3	3	5	**.83**
18	4	3	4	3	4	4	6	**1**
19	4	4	4	3	3	4	6	**1**
20	3	4	3	4	3	4	6	**1**
21	4	1	4	2	2	3	3	.5
22	4	4	3	3	3	4	6	**1**
23	3	4	3	2	3	4	5	**.83**
24	4	3	3	3	4	3	6	**1**
25	3	3	4	3	3	4	6	**1**
27	3	4	3	3	4	3	6	**1**
28	3	4	4	3	4	1	5	**.83**
29	4	3	4	3	4	4	6	**1**
30	3	4	4	4	3	4	6	**1**
31	3	4	2	4	4	4	5	**.83**
32	3	1	3	2	3	3	4	.67
33	3	3	3	4	3	4	6	**1**
34	3	3	1	4	4	4	5	**.83**
35	3	3	4	4	4	4	6	**1**
36	3	4	4	2	3	3	5	**.83**
37	4	4	4	3	3	3	6	**1**
38	3	4	3	3	4	3	6	**1**
39	3	1	4	3	4	4	5	**.83**
40	1	2	3	2	4	1	2	.33
41	3	4	4	3	4	3	6	**1**
42	4	3	4	4	3	3	6	**1**
43	3	4	4	3	3	3	6	**1**
44	4	4	4	4	3	4	6	**1**
45	1	3	2	4	1	3	3	.5

Note. Factor loadings >.78 in bold.

Table 1 shows the ratings of items by the experts. Keeping in view this criterion by Lynn (1986), 40 items out of 45 items were retained after calculating I-CVI for items of NPPSI scale. The Scale Content Validity Index (S-CVI) was computed using this formula:
S-CVI= Total item CVIs/ Total no. of items
S-CVI= 37.13/45
S-CVI= .83

Step III: Pilot Study

A pilot study was conducted to establish the face validity of the scale and to rule out any other ambiguity. For this purpose, following steps were taken:

Sample

Non probability purposive sample technique was used to select participants. 30 patients with age range of 18-60 year (*M* = 37.8, *SD* = 8.4), who were receiving final dose of interferon and antiviral treatment for HCV were selected for pilot study.

Procedure

The objective of the pilot study was to test the viability of the sca le and to finalize the elements for the exploratory factor analysis. Items gathered through S-CVI were arranged in form of 4-point rating scale (1= *never*, 1= *to some extent*, 2= *more*, 3= *much more*). Scale items were given to the patients of HCV, who going through treatment. Participants were asked to rate the items according to their experience during treatment on a 4-point rating scales. Criteria for item retention was endorsement received >20% and < 80 %. No item was excluded from the list by following the above mentioned criteria and all 40 items were retained in the final version of NPPSI scale.

Step IV: Establishing Construct Validity through Factor Analysis

Factor analysis is a traditional statistical method to determine the construct validity of an instrument (Cronbach &Meehl, 1955). To determine the construct validity and factor structure of NPPSI scale, factor analysis was applied.

Sample

A sample of 250 HCV patients (N= 250) with the age range 18-60 years (*M* = 39.7, *SD*= 9.40), who were visiting to receive final dose of treatment, was selected from private hospital of Lahore. It has been recommended to take at least of 200 sample for factor analysis (Gorsuch, 1983). Information regarding demographic variables were also collected. Table 2 represents the demographic information of the patients.

Table 2
Demographic Characteristics of the Participants of the Study (N = 250)

Variables	*f(%)*	*M(SD)*
Gender		
Male	119(47.6)	
Female	131(52.4)	
Age		39.7(9.4)
18-30	39(15.6)	
31-45	122(48.8)	
46-60	89(35.6)	
Education		
<8 years	81(32.4)	
Matriculation	104(41.6)	
Graduation	47(18.8)	
Post-Graduation	18(7.2)	
Marital Status		
Single	41(16.4)	
Married	187(74.8)	
Divorced	10(4)	
Widowed	12(4.8)	
Type of Treatment		
Conventional interferon	70(28)	
Pegylated Interferon	60(24)	
Pegylated Interferon + Oral antiviral	60(24)	
Oral antiviral	60(24)	

Procedure

Informed consent was taken from the participants and confidentiality was ensured. A list of 40 items for NPPSI scale was presented to the participants. They were asked to report and rate the symptoms they have faced during the treatment according to their experience. After collecting data, participants were thanked for their cooperation and showing interest in completing the questionnaire. Factor analysis was run through SPSS.

Results

Factor analysis was applied using a principle component analysis through varimax rotation for the extraction of factors. Varimax rotation enhances the comprehensibility of factors by increasing the variance of factors (Kim & Mueller, 1978). Items with eigen value less than 1 were excluded. Kaiser Myer Olkin (KMO) test value was also calculated to test the adequacy of the data which was .94 and it indicates the adequacy of sample. Bartlett Test of Sphericity (BTS) value 12007.388 was significant at $p < .001$, which represents variables are correlated and can be represented by underlying factors which provides justification for running a principal component analysis.

Determining the criteria of eigen value > 1 and factor loading >.35, principle component factor analysis was applied. It generated in over extraction in form of four factors with one item "aggression" in fourth factor containing high cross loading of that item in second factor as well. Item no. 26 was loaded on second and third factor but had higher factor loading in third factor. Item no. 20, 28, 31, and 32 were excluded due to lower factor loadings. Keeping in view the initial result, principle component factor analysis was again performed using 3 factor solution. The criterion of scree plot was also followed (Cattell, 1966). Table 3 represents the eigen values, percentages of variance and cumulative percentage of three factors.

Table 3
Eigen Value, Percentage of Variance and Cumulative Percentage of 36 items of three factors using Principle Component Analysis (N= 250).

Factors	Eigen Value	Percentages of Variance	Cumulative Percentage
1	17.2	47.9	47.9
2	8.4	23.5	71.4
3	3.7	10.4	81.9

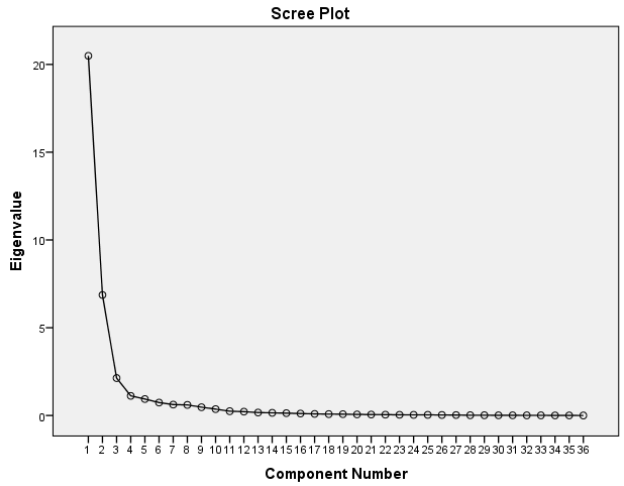

Figure 1: Scree Plot displaying the extraction of Factors for NPPSI-S

Table 4
Factor Loadings of 36 Items of NPSI for Three Factors using Varimax Rotation (N=250)

	Factor Loadings			
Items	Physical	Factor	Psychological Factor	Neurological Factor
1	**.91**		.14	.14
2	**.88**		.13	.16
3	**.88**		.13	.18
4	**.85**		-.58	.07
5	**.94**		.20	.17
6	**.94**		.21	.17
7	**.80**		.09	.20
8	**.89**		.18	.11
9	**.88**		.19	.19
10	**.92**		.19	.17
11	**.92**		.18	.16
12	**.84**		.10	.24
13	**.90**		.17	.13
14	**.85**		.16	.13
15	**.87**		.14	.17
16	**.85**		-.05	.07
17	**.92**		.23	.16
18	**.94**		.19	.17
19	**.82**		.15	.18
20	.57		.01	**.73**
21	.59		.04	**.74**
22	.58		.03	**.75**
23	.58		.02	**.70**
24	.40		**.63**	.53
25	.04		.59	**.61**
26	03		**.61**	.59
27	.08		**.77**	.50
28	.33		**.78**	.11
29	.27		**.96**	.16
30	.34		**.87**	.07
31	.42		**.94**	.15
32	.33		**.87**	.05
33	.07		**.89**	.07
34	.02		**.91**	.00
35	.02		**.90**	.10
36	.04		**.78**	.11

Table 4 shows the factor loadings of three factors. In first Factor, 19 items contained high factor loadings, these items were theoretically related to physical side effects of interferon and oral antiviral therapy for HCV patients. It was named as "physical side effects" factor. In rest of the items, 12 items secured high factor loadings on factor 2 and all these items were described as psychological side effects. Item number 26 showed high factor loading on both factor 2 and factor 3 but it showed higher factor loading on factor 3, so it remained in it. This factor was named as "psychological side effects" factor. Remaining 5 items executed high factor loadings on factor 3 and these items were mainly neurological in nature. This factor was named as "neurological side effects" factor. Resulted factor structure is as given below:

Physical Factor

19 items were loaded on this factor with factor loadings above .30. Items included in this factor were fever, body aches, leg ache, stomach ache, headache, constipation, vomiting, anorexia, cold intolerance, dryness of skin, freckles, shivering, weakness, increased heart rate, dizziness, difficulty in breathing, altered blood pressure, hair fall and tiredness. Items included in this category were physical in nature thus this factor was named as physical side effects factor.

Psychological Factor

12 items were included in this factor. All items were psychological complaints. Mood swings, irritability, anxiety, low confidence, crying spells, hopelessness, depression, insomnia, poor concentration, confusion, suicidal ideation and aggression. So it was named as psychological factor.

Neuro Factor

Item loaded on this factor were neurological complains in nature, therefore it was tagged as neuro factor. This factor has 5 items namely leg numbness, paresthesia, tremors, muscle weakness, hallucinations. It was named as neurological factor.

Stage II: Confirmatory Factor Analysis (CFA)

Exploratory factor analysis (EFA) revealed three factor solution of the 36 items of NPPSI scale. To confirm the three factors of NPPSI scale, confirmatory factor analysis was run using IBM SPSS Amos version 23 on another sample of 230 participants (M = 38.9, SD = 9.2, age = 18-60 years) which was taken using a purposive sampling technique. Participants were the HCV patients receiving final dose of treatment for HCV. Male patients were 61.3 percent and 38.7 percent were female patients.

Procedure

Three factors of NPPSI-Scale were analyzed in CFA. In the present study, various indices were used to explain the good model fit for example, Comparative fit Index (CFI), Goodness of fit index (GFI), Tucker-Lewis Index (TLI), and the root mean square error of approximation (RMSEA) Bentler, 1990; Bollen, 1990; Bentler & Bentler, 1980).

Results

Table 5
The Factor Loading for 36 Items of NPPSI-Scale with CFA (N=230)

	Factor Loadings		
Items	Physical Factor	Psychological Factor	Neurological Factor
1.	.95		
2.	.93		
3.	.94		
4.	.87		

5.	.99				
6.	.99				
7.	.93				
8.	.94				
9.	.95				
10.	.99				
11.	.98				
12.	.93				
13.	.93				
14.	.90				
15.	.92				
16.	.87				
17.	.92				
18.	.97				
19.	.90				
20		.61			
21		.62			
22		.87			
23		.86			
24		.98			
25		.97			
26		.80			
27		.91			
28		.71			
29		.75			
30		.76			
31		.69			
32				.99	
33				.99	
34				.93	
35				.96	
36				.21	

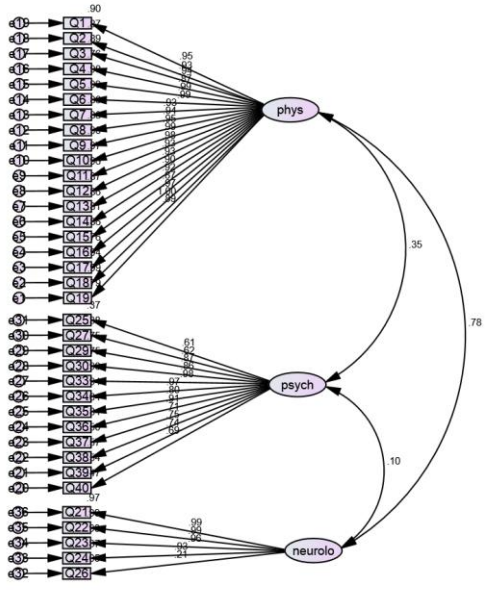

Figure 2. *The Final Factor Model of the NPPSI-Scale*

Table 5 and figure 2 describe the results of factor loading model fit and indices of NPPSI-Scale retained through CFA. Findings of EFA of NPPSI-Scale (with item loading greater than .30) were examined in CFA. The final structure model of NPPS-ScaleI conform 36 items having 19 items in physical symptoms factor, 12 items in psychological factor and 5 items in neurological symptoms factor. According to Hair, Black, Babin and Anderson (2010), standardized loading estimates should be greater than .30. Factor loadings retained through confirmatory analysis of NPPSI ranged from .61to .99.

Measurement Model of NPPSI-Scale

Table 6
Model Fit Indices for of CFA for NPPSI-Scale (N = 230)

Model	df	$\chi 2/df$	TLI	CFI	GFI	RMSEA
3 factor solution	75	2.10	.91	.92	.93	.05

df= degree of freedom, TLI= Tucker-Lewis index, CFI= comparative fix index, GFI= Goodness of fit index, RMSEA= root mean square error of approximation, ***p<0.001

After application of CFA, a final version of NPPSI-Scale was obtained with three subscales and 36 items.

Table 7
Item total correlation for 36 items of NPPSI-S (N=230)

Item no.	*r*	Item no.	*r*
1	.71**	21	.56**
2	.67**	22	.55*
3	.68**	23	.49**
4	.71**	24	.37**
5	.73**	25	.65**
6	.64**	26	.72**
7	.64**	27	.53**
8	.74**	28	.67**
9	.69**	29	.78**
10	.73**	30	.76**
11	.63**	31	.56**
12	.71**	32	.46**
13	.72**	33	.46**
14	.76**	34	.54**
15	.70**	35	.64**
16	.71**	36	.62**
17	.66**		
18	.64**		
19	.61**		
20	.48**		

**p<0.01

Stage III: Determining Psychometric Properties

Reliability

The alpha reliability coefficient for NPPSI-Scale of 36 items was .97. The high value of alpha coefficient reflects that NPPSI-Scale is internally consistent and highly reliable scale. Physical, psychological and neurological factors of NPPSI-Scale also revealed high value of alpha coefficient respectively .98, .95 & .92.

Table 8
Inter-Correlation Matrix, alpha coefficient and Means and Standard Deviation for three Subscales and Total Score of NPPSI-Scale (N= 230)

	Variables	1	2	3	4	α
1.	NPPSI-S	-	.66**	.92**	.78**	.97
2.	Physical	-	-	.36**	.38**	.98
3.	Psychological	-	-	-	.70**	.95
4.	Neurological	-	-	-	-	.92

**p< 0.01

Table 8 shows that all the subscales of the NPPSI-Scale are highly reliable. All subscales of NPPSI-Scale are also positively correlated with total scale as well.

Convergent Validity

Convergent validity of the scale was established using Neuropsychiatric Inventory Questionnaire (NPI-Q) (*r = .79)* developed by Cummings et al. (1994) assessing 50 patients of HCV with age range of 18-25 years (*M*=42.2, *SD*=10.0). NPI-Q is a brief version of a larger NPI (Neuropsychiatric inventory) that was initially developed to assess the neuropsychiatric symptoms in patients of Alzheimer's disease and other memory related disorders. But later on NPI-Q has been used to assess other conditions that may cause behavior changes.

It was hypothesized that 12 items of NPI-Q will positively correlate with 36 items of NPPSI-Scale. The correlation coefficient between total scores of both instruments was $r = .70$, $p < .001$. It revealed that HCV patients receiving treatment with interferon and oral antiviral therapy experienced physical neurological and psychological side effects score high on NPPSI-Scale, will score high on NPI as well. Thus establishing the convergent validity of NPPSI-Scale.

Discriminant Validity

Discriminant validity of the scale was established by using WHO-health related quality of life-brief (2004) and NPPSI-S. Discriminant validity was computed by taking 100 participants (*M*=41.2, *SD*=10.1) who were visiting the hospital for final dose of treatment for HCV. Participants were selected from private hospital of Lahore. WHOQOL-BREF and NPPSI-S was administered on the participants and results were analyzed. Findings revealed significant negative correlation coefficient $r = -.72$, $p< .001$ which suggests that HCV patient receiving treatment score high on NPPSI-S will have poor quality of life hence discriminant validity is supported.

Discussion

This study resulted in the development and validation of a 36-item scale for measuring side effects associated with interferon therapy in HCV patients. Exploratory and subsequent confirmatory factor analysis revealed three factors or subscales: Physical side effects, Psychological side effects, and Neurological side effects.

Suffering of a patient is always prioritized and should be accounted for when designing the treatment regime for a disease. This study is based on the idea of objectively measuring subjective complaints of the patients during course of treatment for HCV. Many tools have been constructed earlier for the quantification of subjective feelings of the patients such as depression or pain for example, pain scale by Borg (Borg, 1998), and Anxiety and depression symptom scales (Watson, 1995). Current study is the first of its kind in Pakistan to consider the side effects of a drug while treating a patient. Currently the physicians in developed world are emphasizing in treating the patients rather than treating the numbers written on the lab reports. Current study gives voice to the sufferings of patients. Just like pain scales that are now in use all over the world, this scale is also based on verbal complaints of patients and consider the symptoms of the patients rather than just lab reports.

The primary step of this study was to construct an indigenous tool to measure the side effects of HCV treatment experienced by the patients. To accomplish this task, a comprehensive procedure was executed for scale development. At first items were generated through detailed literature review, unstructured interviews with physicians and focus groups with patients of HCV receiving treatment which resulted in a pool of 45 items. Further, content validity index was established through expert rating. CVI was found satisfactory with the value of .83 in accordance of criterion by Lynn (1986) with elimination of 5 items. Exploratory factor analysis was run on 40 items which resulted in clearly defined three factor structure with 81.9 percent of the variance. Total 36 items were retained with factor loading >.3 through exploratory factor analysis. Factors were named as physical factor, psychological factor and neurological factor. Resulted factor structure of the scale was reliable.

Confirmatory factor analysis was performed to confirm the factor structure acquired through exploratory factor analysis. It confirmed the model fit indices of three factor scale. This study resulted in construction of a scale with subdividing the 36 item NPPSI scale in three sub scales. These sub scales are Physical side effects, psychological side effects and neurological side effects. These sub scales showed very strong factor loadings values.

Discriminant and convergent validity were also established as convergent validity is the most approved strategy to establish validity for newly develop scale (Brun, Rajaobelina, & Ricard, 2014).

The most common side effects experienced by patients receiving interferon therapy were physical in nature. The current study identified 19 physical symptoms that were validated after CFA. The physical side effects of interferon therapy are known since 1989. It was reported in 1989 that patients experience "Flu like syndrome" 4 to 8 hours after being injected with interferon injection. This syndrome consists of fever with chills and rigors, nausea and fatigue. (Renault, 1989). These side effects are more prominent at the start of the therapy and tend to decrease in severity with subsequent doses (Dusheiko, 1997)

Along with physical side effects, interferon therapy further leads to psychological side effects. This study found up to 12 psychological side effects that are most commonly experienced by patients undergoing treatment for hepatitis C with interferon injections. In a hallmark study, the prevalence of psychiatric symptoms was studied in detail among patients receiving long term interferon therapy. In this study, 17 percent of patients were noted to have psychiatric symptoms. These symptoms were categorized in three groups namely; organic personality syndrome which included symptoms such as irritability and aggression; an organic affective syndrome characterized by severe emotional lability, depression, and easy crying; and a delirium like syndrome depicting altered consciousness, agitation, paranoia, and suicidal ideation (Renault, 1987)

The appearance of psychiatric symptoms in patients being treated by interferon has been widely studied. Some authors have claimed that almost 70 percent of these patients may experience psychiatric symptoms to some degree. A few of these patients may suffer with these symptoms to such a degree that it may warrant dose adjustments or treatment cessation, while some patients needed concurrent use of psychiatric drugs to continue use of interferon for viral eradication. (Trask, 2000)

Depression is one of the most common side effects of interferon therapy. A study found that up to 33 percent patients who developed major depressive disorder while being treated with interferon and 85 percent of the sufferers from depression respond to antidepressive drugs (Hauser, 2002). Another study found moderate to severe depression among 39 percent users of pegylated interferon at some stage during the course of treatment (Raison, 2005) Furthermore, a

local study found 32 percent of Pakistanis developed depression after starting treatment with interferon (Majeed, 2009). The current study also found a strong association between interferon therapy and depressive symptoms. All other psychiatric side effects were also reported and validated through this study.

Third domain of the NPPSI scale deals with neurological side effects that were experienced by patients receiving interferon therapy. This study found that up to five neurological symptoms were experienced by patients during therapy. These side effects are although very rare. But they make an important part of NPPSI-Scale, as these side effects are more devastating and may cause an irreversible damage to neurological structure of nervous system.

Leg numbness, paresthesia, tremors, muscle weakness, and hallucinations are the neurological side effects that are validated through NPPSI-S. These symptoms have been reported as early as 1983 among users of interferon for treatment of certain cancers. Paresthesia and loss of power in legs has been reported in patients with breast cancers after use of interferon injections (Smedley, 1983)

This study showed that physical side effects such as fever, body aches, headache, loss of appetite were more common in all four treatment regimes. Patients receiving any kind of treatment regime be it injectable regimes with conventional or pegylated interferon or injection free regime with only oral antiviral treatment faced more physical side effects. The psychological side effects were second most common type of side effects after physical side effects.

Depression, mood swings, anxiety, crying spells were among the most common psychological side effects faced by patients receiving treatment for hepatitis C. Neurological side effects such as leg numbness, tremors, muscle weakness were among the rarest side effects face by HCV patients during the course of treatment.

However, the neurological side effects appeared although less frequently among other side effects, these side effects were mostly seen with the use of conventional interferon. The oral antiviral drugs showed almost negligible number of neurological side effects among all regimes.

Comparatively, the psychological side effects were most commonly noted in the group of patients that were using pegylated interferon along with oral antiviral drugs. The reporting of psychological side effects was more common with simultaneous use of both injectable pegylated interferon and oral antiviral drugs. Those regimes which contained either pegylated interferon only or oral antiviral drugs with no injections whatsoever showed relatively less psychological side effects among these patients.

Conclusion

This study resulted in construction of a valid, internally consistent and reliable scale for the quantification of Neurological, psychological and physiological side effects of hepatitis C treatment. This scale will help in establishing the drug regimens for better treatment of hepatitis C and lesser side effects faced by the patients. This will ensure better treatment adherence and lesser treatment related fears and stress. This scale is constructed keeping in mind the neuropsychiatric side effects of interferon therapy, so this scale can also be used in studying the treatment related side effects in other disease where interferon therapy is used such as multiple sclerosis and various cancers. Moreover, the era of interferon is not over at all for hepatitis C infection as the oral antiviral drugs are already showing resistance against hepatitis C virus (Sarrazin & Zeuzem, 2010). Now many physicians are using combinations of pegylated interferon with two or more direct acting antiviral drugs for more resistant cases (Pawlotsky, 2016). So this scale will have important implications in future to guide the physicians in constructing a safe and better treatment regime for hepatitis patients.

Implications

This scale is a valuable tool for measurement of side effects during treatment of hepatitis C infection. Validity of this scale is established on Pakistani population but it can also be administered on other ethnic groups to further elaborate its efficacy. Although this scale was developed with treatment related side effects of interferon injections in view. This scale can also be used on injection free oral regimes for treatment of hepatitis C infection.

Use of interferon has declined after the discovery of oral antiviral drugs but interferons are still being used for treatment of many other diseases such as cancers and multiple sclerosis. This scale can be administered on the patients receiving interferon treatment for other diseases. New oral antiviral regimes are widely being used now for the treatment of hepatitis C infection, but cases of resistance to these drugs is also been reported. It can be assumed that these patients with resistance to oral antiviral drugs may resume the use of interferon in combination with oral antiviral drugs. In such cases, this scale will be of utmost importance to measure the side effects during treatment.

This scale can be used to measure physical and neuro-psychiatric side effects related to other drugs used for treating diseases other than hepatitis C infection. But mainly this scale is a helpful tool for physicians to manage the patients during course of treatment with regards to the side effects of the drugs. This scale can guide the physicians about when to alter the course of treatment due to side effects or stop the treatment altogether. A reasonable criteria can be established to design the treatment protocols using this scale.

The coming era is the era of tailor-made treatment for specific patients. Where drugs and treatment regime will be designed according to particular parameters of the patients, such as age, gender and ethnic back ground of the patients. The current study also demonstrates the gender difference and prevalence of different groups of side effects. Although the studied sample is small and very reliable deductions cannot be made by these finding. It is possible to use this scale to design better treatment protocols for different genders and ethnic backgrounds. This study also defines the role of psychologist in designing treatment protocols and administration of treatment to patients.

Limitations and Suggestions

This study was aimed to construct a reliable scale for the measurement of side effects of treatment for hepatitis C. The sample size in this study was small and belonged to same geographical and ethnic (Punjabi) background. This fact may limit the generalizability of the results. Therefore, larger multicenter studies are needed to further elaborate the side effects of antiviral drugs. This study is done on the patients receiving treatment of hepatitis C, but there was no pretreatment evaluation of the patients. It is needed that this study is further conducted including pretreatment assessments to further establish the practicality of the scale. Furthermore this scale should be used in centers for treatment of hepatitis C with participation of psychologists. Counseling sessions should be provided to the patients suffering from side effects of treatment and the effects of counseling can be recorded using this scale. Interferon are used for many different diseases other than hepatitis C. We studied the effects of interferons in patients with hepatitis C infection, however this scale

can be used to study the side effects of interferon in patient receiving them for other diseases.

References

Alter, M. J., Hadler, S. C., Judson, F. N., Mares, A., Alexander, W. J., Hu, P. Y., ... & Margolis, H. S. (1990). Risk factors for acute non-A, non-B hepatitis in the United States and association with hepatitis C virus infection. *Jama*, *264*(17), 2231-2235.

Asselah, T., & Marcellin, P. (2011). New direct- acting antivirals' combination for the treatment of chronic hepatitis C. *Liver International*, *31*, 68-77.

Bentler, P. M., & Bonett, D. G. (1980). Significance tests and goodness of fit in the analysis of covariance structures. *Psychological Bulletin*, *88*(3), 588-606.

Bentler, P. M. (1990). Comparative fit indexes in structural models. *Psychological Bulletin, 107*, 238-246.

Bollen (1990). Overall fit in covariance structure models: Two types of sample size effects. *Psychological Bulletin, 107*, 256-259.

Borg, G. (1998). *Borg's perceived exertion and pain scales*. The UK: Human kinetics.

Blach, S., Zeuzem, S., Manns, M., Altraif, I., Duberg, A. S., Muljono, D. H.,... & Abaalkhail, F. (2017). Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *The Lancet Gastroenterology & Hepatology*, *2*(3), 161-176.

Cattell, R. B. (1966). The screen test for the number of factors. *Multivariate Behavioral Research, 1*, 245-276

Chung, R. T., Davis, G. L., Jensen, D. M., Masur, H., Saag, M. S., ... & Fontana, R. J. (2015). Hepatitis C guidance: AASLD- IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology*, *62*(3), 932-954.

Cronbach, L. J., & Meehl, P. E. (1955). Construct validity in psychological tests. *Psychological Bulletin*, 52, 281-302.

Crone, C. C., Gabriel, G. M., & Wise, T. N. (2004). Managing the neuropsychiatric side effects of interferon-based therapy for hepatitis C. *Cleveland Clinic Journal of Medicine*, *71*(3), 27-32. doi:10.3949/ccjm.71.suppl_3.s27

Cummings, J., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A., &Gorbein, J. (1994). The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. *Neurology. 44*, 2308-2314.

Dieperink, E., Willenbring, M., & Ho, S. B. (2000). Neuropsychiatric symptoms associated with hepatitis C and interferon alpha: a review. *American Journal of Psychiatry*, *157*(6), 867-876.

Dusheiko, G. (1997). Side effects of α interferon in chronic hepatitis C. *Hepatology*, *26*(S3), 112S-121S.

Feld, J. J. (2014). The beginning of the end: what is the future of interferon therapy for chronic hepatitis C. *Antiviral Research*, *105*, 32-38.

Foster, G. R., Pianko, S., Brown, A., Forton, D., Nahass, R. G., George, J., ... & Han, B. (2015). Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infections. *Gastroenterology*, *149*(6), 1462-1470.

Gerszten, E., Allison, M. J., & Maguire, B. (2012). Paleopathology in South American mummies: a review and new findings. *Pathobiology*, *79*(5), 247-256.

Goeb, J. L., Cailleau, A., Laine, P., Etcharry-Bouyx, F., Maugin, D., Duverger, P., ... & Garre, J. B. (2003). Acute delirium, delusion, and depression during IFN-β-1a therapy for multiple sclerosis: a case report. *Clinical Neuropharmacology*, *26*(1), 5-7.

Gorsuch, R. L. (1983). *Factor analysis*. (2nd ed.) Hillsdale: Lawrence Erlbaum Associates.

Hair, J. F., Black, W. C., Babin, B. T., Anderson, R. E., & Tatham, R. L. (2010). *Multivariate Data Analysis*. (6th ed.). New Jersey: Pearson Prentice Hall.

Hauser, P., Khosla, J., Aurora, H., Laurin, J., Kling, M. A., Hill, J., ... & Meyers, C. A. (2002). A prospective study of the incidence and open-label treatment of interferon-induced major depressive disorder in patients with hepatitis C. *Molecular Psychiatry*, *7*(9), 942- 947.

Hunyady, B., Kovács, B., &Battyáni, Z. (2011). Side-effects of pegylated interferon plus ribavirin therapy with or without protease inhibitor direct acting antiviral agents during treatment of chronic hepatitis C virus infection. *Orvosihetilap*, *152*(50), 1997-2009.

Kanwal, F., Hoang, T., Spiegel, B. M., Eisen, S., Dominitz, J. A., Gifford, A., ... & Asch, S. M. (2007). Predictors of treatment in patients with chronic hepatitis C infection— role of patient versus nonpatient factors. *Hepatology*, *46*(6), 1741-1749.

Kraus, M. R., Schäfer, A., Csef, H., &Scheurlen, M. (2005). Psychiatric side effects of pegylated interferon alfa-2b as compared to conventional interferon alfa-2b in patients with chronic hepatitis C. *World Journal of Gastroenterology: WJG*, *11*(12), 1769-1774.

Kuo, G., Choo, Q. L., Alter, H. J., Gitnick, G. L., Redeker, A. G., Purcell, R. H., …Stevens, C. E. (1989). An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. *Science*, *244*(4902), 362-364.

Lynn, M.R. (1986). Determination and quantification of content validity. *Nursing Research, 35*, 382– 385.

Majeed, S. (2009). Prevalence of depression among hepatitis c patients. *Khyber Medical University Journal*, *1*(2), 42-45.

Manns, M. P., McHutchison, J. G., Gordon, S. C., Rustgi, V. K., Shiffman, M., Reindollar, R., ... & International Hepatitis Interventional Therapy Group. (2001). Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *The Lancet*, *358*(9286), 958-965.

Medeiros, T., de MoraisSalviato, C., do Rosário, N. F., do NascimentoSaraiva, G., Esberard, E. B. C., Almeida, J. R., ... & da Silva, A. A. (2017). Adverse effects of direct acting antiviral-based regimens in chronic hepatitis C patients: a Brazilian experience. *International Journal of Clinical Pharmacy*, *39*(6), 1304-1311.

Mohamoud, Y. A., Mumtaz, G. R., Riome, S., Miller, D., & Abu-Raddad, L. J. (2013). The epidemiology of hepatitis C virus in Egypt: a systematic review and data synthesis. *BMC Infectious Diseases*, *13*(1), 288. https://doi.org/10.1186/1471-2334-13-288

Nadeem, A., Aslam, M., Hussain, T., Hussain, M. M., & Khan, S. A. (2007). Efficacy of combined interferon alpha and ribavirin therapy in patients of chronic hepatitis C. *Pakistan Journal of Physiology*, *3*(2). http://www.pjp.pps.org.pk/index.php /PJP/ article/view/649

Ogden, J. (2003). Some problems with social cognition models: A pragmatic and conceptual analysis. *Health Psychology*, *22*(4), 424.

Okanoue, T., Sakamoto, S., Itoh, Y., Minami, M., Yasui, K., Sakamoto, M., ... & Sawa, Y. (1996). Side effects of high-dose interferon therapy for chronic hepatitis C. *Journal of*

Hepatology, *25*(3), 283-291.

Pawlotsky, J. M., Aghemo, A., Back, D., Dusheiko, G., Forns, X., Puoti, M., &Sarrazin, C. (2015). EASL recommendations on treatment of hepatitis C 2015. *Journal of Hepatology*, *63*(1), 199-236.

Pawlotsky, J. M. (2016). Hepatitis C virus resistance to direct-acting antiviral drugs in interferon-free regimens. *Gastroenterology*, *151*(1), 70-86.

Raison, C. L., Borisov, A. S., Broadwell, S. D., Capuron, L., Woolwine, B. J., Jacobson, I. M., ... & Miller, A. H. (2005). Depression during pegylated interferon-alpha plus ribavirin therapy: prevalence and prediction. *The Journal of Clinical Psychiatry*, *66*(1), 41.

Renault, P. F., Hoofnagle, J. H., Park, Y., Mullen, K. D., Peters, M., Jones, D. B., ... & Jones, E. A. (1987). Psychiatric complications of long-term interferon Alfa therapy. *Archives of Internal Medicine*, *147*(9), 1577-1580.

Renault, P. F., & Hoofnagle, J. H. (1989). Side effects of alpha interferon. *Seminars in Liver Disease*, *9*(4) 273-277).

Sarrazin, C., & Zeuzem, S. (2010). Resistance to direct antiviral agents in patients with hepatitis C virus infection. *Gastroenterology*, *138*(2), 447-462.

Schäfer, M., Boetsch, T., & Laakmann, G. (2000). CASE REPORT Psychosis in a methadone- substituted patient during interferon- alpha treatment of hepatitis C. *Addiction*, *95*(7), 1101-1104.

Schäfer, M., Messer, T., Wegner, U., Schmid-Wendtner, M. H., & Volkenandt, M. (1999). Psychiatric side effects during adjuvant therapy with interferon-alphain patients with malignant melanoma. Clinical evaluation as well as diagnostic and therapeutic possibilities. *Der Hautarzt; Zeitschrift fur Dermatologie, Venerologie, und verwandte Gebiete*, *50*(9), 654-658.

Schaefer, M., Schmidt, F., Folwaczny, C., Lorenz, R., Martin, G., Schindlbeck, N., ... & Loeschke, K. (2003). Adherence and mental side effects during hepatitis C treatment with interferon alfa and ribavirin in psychiatric risk groups. *Hepatology*, *37*(2), 443-451.

Senn, S. S. (2008). *Statistical issues in drug development* (69). New Jersey: John Wiley & Sons.

Sleijfer, S., Bannink, M., Van Gool, A. R., Kruit, W. H., & Stoter, G. (2005). Side effects of interferon-α therapy. *Pharmacy world and science*, *27*(6), 423-431.

Smedley, H., Katrak, M., Sikora, K., & Wheeler, T. (1983). Neurological effects of recombinant human interferon. *British Medical Journal (Clinical Research Edition)*, *286*(6361), 262-264.

Strader, D. B., Wright, T., Thomas, D. L., & Seeff, L. B. (2004). AASLD practice guideline. *Diagnosis, management, and treatment of hepatitis C. Hepatology*, *39*, 1147-71.

Suvarna, V. (2010). Phase IV of drug development. *Perspectives in clinical research*, *1*(2), 57-60.

Tabachnik, B. G., & Fidell, L. S. (1996). *Using multivariate statistics* (3rd Ed.). New York: Harper Collins.

Trask, P. C., Esper, P., Riba, M., & Redman, B. (2000). Psychiatric side effects of interferon therapy: prevalence, proposed mechanisms, and future directions. *Journal of Clinical Oncology*, *18*(11), 2316-2326.

Umar, M., Bushra, H., Ahmad, M., Ahmad, M., Khurram, M., Usman, S., ... & Naeem, A. (2010). Hepatitis C in Pakistan: a review of available data. *Hepatitis Monthly*, *10*(3), 205-214.

Umar, M., & Bilal, M. (2012). Hepatitis C, a mega menace: A Pakistani perspective. *Journal of Pakistan Medical Studies*, *2*(2), 68-72.

Watson, D., Weber, K., Assenheimer, J. S., Clark, L. A., Strauss, M. E., & McCormick, R. A. (1995). Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. *Journal of Abnormal Psychology*, *104*(1), 3-14. doi: 10.1037/0021-843X.104.1.3

World Health Organization Quality of Life (WHOQOL)-BREF. (2004). *World Health Organization*. Retrieved from http://www.who.int/substanceabuse/researchtools/en/english whoqol.pdf

Yates, William R., & Gleason, O. (1998). Hepatitis C and depression. *Depression and Anxiety*, 7(4), 188-193.

Zacks, S., Beavers, K., Theodore, D., Dougherty, K., Batey, B., Shumaker, J., ... & Michael, W. (2006). Social stigmatization and hepatitis C virus infection. *Journal of Clinical Gastroenterology*, *40*(3), 220-224.

Received: October 01st, 2019
Revisions received: January 10th, 2020