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ANXIETY AND DEPRESSION AS KEY DETERMINANTS OF CANCER RELATED FATIGUE AMONG PATIENTS RECEIVING CHEMOTHERAPY

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Abstract

Among non-communicable diseases, cancer is the second leading cause of death worldwide. In Jordan, it is the second leading cause of death. Fatigue is the most reported symptom among cancer patients. The purpose of this study was threefold: (1) to explore the prevalence of fatigue as a side effect of cancer chemotherapy (2) to examine the impact of chemotherapy on fatigue, and (3) to investigate psychological factors (depression and anxiety) that correlate with fatigue. A one group before and after quasi-experimental design was used to conduct this study. The Integrated Fatigue Model (IFM) was used to guide the study. A Convenience sampling technique was used to recriut78 participants diagnosed with cancer and treated with chemotherapy as the primary treatment. The sample was collected from two well-known Jordanian hospitals. Fatigue was measured using the Piper Fatigue Scale (PFS) and the psychological variables (depression and anxiety) were measured using Hospital Anxiety and Depression Scale (HADS). Findings revealed an increase incidence of fatigue after a chemotherapy course. Also revealed was a statistically significant difference between pre and post chemotherapy fatigue mean total scores as well as behavioral, affective, sensory and cognitive dimensions. It was found that depression and anxiety have a positive relationship with fatigue. Depression explained 46% of fatigue score variance. Furthermore, anxiety explains 3.6% of the variance in fatigue scores. It could be concluded that fatigue is a prevalent symptom among cancer patients receiving chemotherapy. Depression and anxiety were identified as possible predictors of fatigue among cancer patients receiving chemotherapy.

Keywords: Cancer Related Fatigue, Depression, Anxiety, Chemotherapy

Introduction

Statistics by the World Health Organization (WHO) indicate that cancer is the second leading cause of death worldwide from non-communicable diseases (WHO, 2015b). Approximately 8.4M have died from cancer and its complications by 2012. The figure is expected to rise by 70% over the next 20 years (WHO, 2015a).

Cancer is the second leading cause of death in Jordan, accounting for 14.6% of the total mortality rate. Between 2000 and 2010, the number of newly discovered cancer cases in Jordan increased by 46% (Tarawneh, Nimri, Arkoob, & Zaghal, 2010).

In the last decade, many studies have emphasized the prevalence of fatigue among cancer patients. There is strong evidence suggesting that fatigue is a prevalent problem among cancer patients receiving chemotherapy and radiation therapy (Abu Obead, Batiha, Al-Jauissy, Alhalaiqa, & AlBashtawy, 2014; Abu Obead et al.,2014a; Erturk, Yildirim, Kilic, Ozer, & Aykar, 2015; Ho et al., 2015; Iwase et al., 2015; Langston, Armes, Levy, Tidey, & Ream, 2013). Cancer Related Fatigue (CRF) is considered the most distressing symptom experienced by cancer patients (Weis, Horneber, & SpringerLink, 2015). The prevalence of fatigue increases substantially when patients receive chemotherapy or radiotherapy (Huijer, Abboud, & Doumit, 2012; Stone et al., 2000). Moreover, cancer patients receiving chemotherapy report more severe fatigue in comparison to patients receiving other treatment modalities (Manir et al., 2012; Schmidt et al., 2012).

There are several factors associated with CRF. According to Stobäus, Müller, Küpferling, Schulzke, and Norman (2015), low protein intake, gender, nausea, vomiting, insomnia and age are considerable risks for CRF. Furthermore, sleep experience, patient age and different types of cancer were significantly associated with CRF (Nunes, Jacob, Adlard, Secola, & Nascimento, 2015).

Fatigue commonly has a negative impact on the patients' Quality of Life (QOL). For example, patients with Parkinson's disease with a higher score of fatigue suffered from more disturbance in their quality of life (Havlikova et al., 2008). CRF has a profound influence on patients QOL. It affects patients functionality and their moods (Yeo, Yeo, & Cannaday, 2015).

Kitamura et al. (2015) argued that patients receiving chemotherapy had biochemical changes in their brain that affect their cognitive and psychological status and increase their anxiety levels. Moreover, several studies indicate that patients receiving chemotherapy had significant levels of depression and anxiety (Akechi et al., 2012; Iconomou et al., 2008;

Pandey et al., 2006)

Jordanian cancer patients have a higher level of distress as compared to the findings in other cultures (Omran, Saeed, & Simpson, 2012).There is little known about the impact of depression and anxiety on CRF in patients receiving chemotherapy in the Jordanian community. This study aims to fill a gap in the existing body of knowledge by exploring the prevalence of fatigue as a side effect of cancer chemotherapy. This study also aims to make known the impact of depression and anxiety on fatigue among Jordanian patients receiving chemotherapy. The study will answer the following questions:

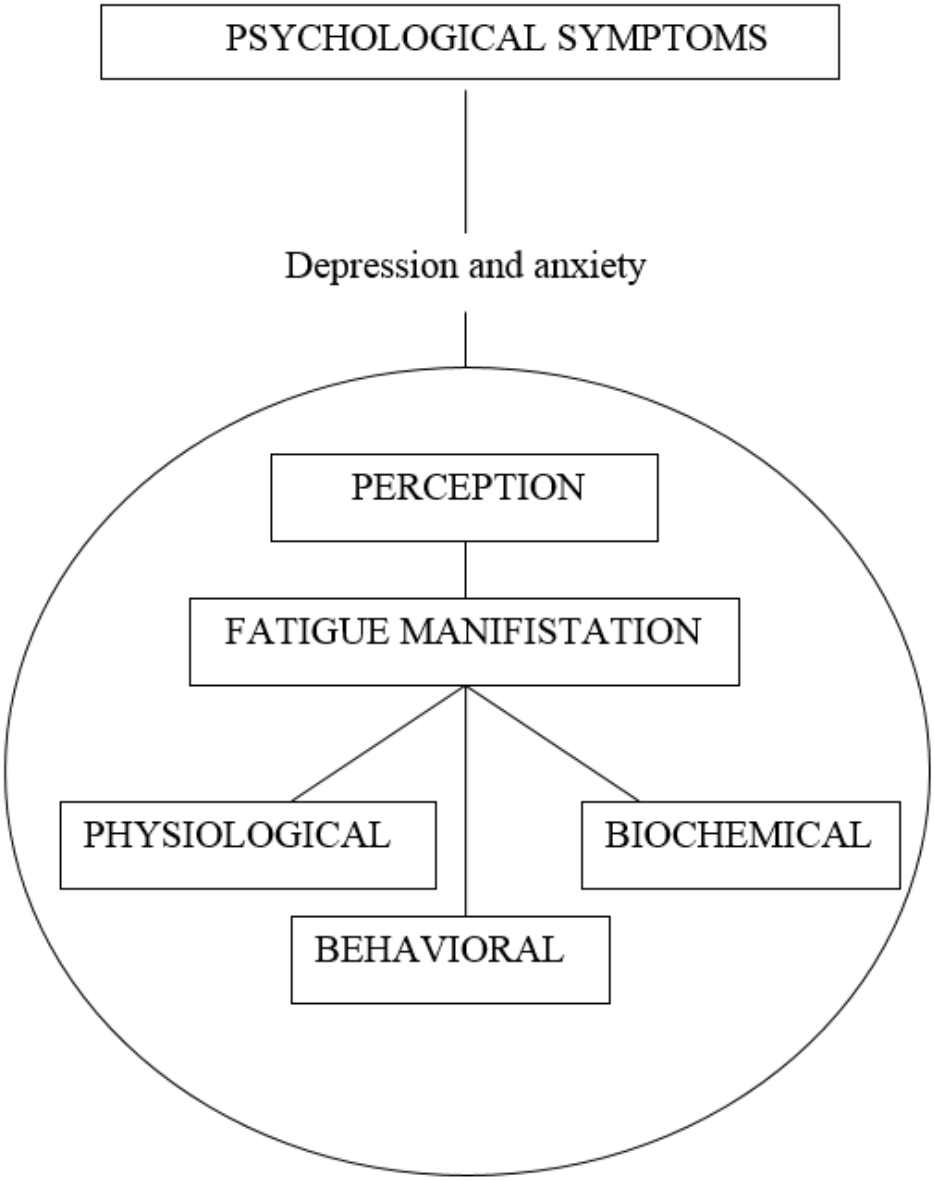
What is the prevalence of fatigue among Jordanian cancer patients who receive chemotherapy as their primary treatment?

What is the impact of chemotherapy on fatigue levels among cancer patients who receive chemotherapy?

What is the effect of depression and anxiety levels on patient fatigue levels among Jordanian cancer patients receiving chemotherapy?

The Integrated Fatigue Model (IFM) was used to guide this study. This framework permits multiple disciplinary perspectives, definitions, and theories about fatigue to be analyzed. This framework is described as a core of the subjective (perceptual) and objective (physiological, biochemical and metabolic, and behavioral) indicators of fatigue reported in the literature. At the center of the framework are the metabolic, neuro-physiological, situational, and developmental stressor patterns that may cause or modulate the signs and symptoms of fatigue (Piper, Lindsey, & Dodd, 1987). Psychological factors, including usual response to stressors, depression, anxiety, motivation, distraction, boredom, beliefs, and attitudes, may influence fatigue. This study will focus on the psychological symptoms related to depression and anxiety (See Figure 1).

Figure I: Integrated Fatigue Model



Method

Research design

The design of this study was a one group before and after quasi-experimental design. This design is appropriate to explore the impact of chemotherapy on fatigue. Moreover, it also helped to identify other psychological variables that affect fatigue in cancer patient receiving chemotherapy.

Sample

The participants of the study were recruited using a convenience sampling technique. Each participant was required to be: (a) above 18 years of age, (b) free from severe mental or cognitive impairment (c) receiving chemotherapy as a primary treatment, (d) able to read, write and understand Arabic, (e) free of cardiac, respiratory and medical illnesses and (f) able to give consent to participate in this study. All participants agreed to participate and were able to complete the study tool.

Instruments

Piper fatigue scale (PFS) is a subjective multidimensional instrument that measures fatigue in patients and assesses the amount and level of fatigue, degree of stress or interference experienced in daily activities, and feelings or sensations that indicate fatigue.

PFS is composed of 22 items with numerical scales. Each one is rated from 0 to 10 were higher score represent more fatigue severity. These items are used to measure subjective fatigue from four dimensions perspective: behavioral; affective; sensory and cognitive. The aggregates are used to calculate the total fatigue score and the four sub-scale/dimensional scores. Five additional questions are recommended to be kept in the scale because these questions provided qualitative data. One item in particular gives a categorical way in which to assess fatigue duration among respondents, other items asked about causes of fatigue, best thing to alleviate it, and the experience of any other symptoms. The scores of PFS are categorized into four levels: 0 none, 1-3 mild, 4-6 moderate and 7-10 severe. The Arabic version of PFS was tested and found reliable. The internal consistency of the Arabic version of PFS was established in other studies (Abu Obead et al.,2014). Moreover, a pilot study was performed before conducting this study, which revealed that the Cronbach alpha for the total score was (alpha =0.965). It also revealed that for the four dimensions, behavioral, affective, sensory, and cognitive dimension were (alpha =0.896, 0.96, 0.96, and 0.91 respectively).

The Hospital Anxiety and Depression Scale (HADS) is a widly used instrument to evaluate depression and anxiety (psychological distress) among hospitalized subjects. This questionnaire is composed of 14 items, seven of which measure anxiety and seven measure of depression. Each item is rated on a scale of 0 (best status) to 3 (worst status). The possible scores for depression and anxiety range from 0 to 21 with normal scores ranging from 0-7 and scores of 8-10 indicating borderline depression or anxiety. A score of 11 or more indicate significant psychological morbidity. The reliability of this questionnaire was established in a pilot study before conducting this research. Both anxiety and depression have good internal consistency (alpha

= .785 and .841 respectively).

Results

A total of 78 participants completed all phases of the study. Among these participants, 56 participants (83%) were from Al-Bashir hospital and 22 (28%) participants were from King Abdullah University Hospital (n=78). All participant met the inclusion criteria, agreed to participate, and were able to complete the study measurements. (See table 1).

Table 1: Socio-demographic characteristics of the sample (n=78)

Character	Category	Frequency	%	Mean	SD	Range
Sex	Male	51	65.4			
	Female	27	34.6			
Age in years				44.76	14.11	19-67
Marital Status	Married	51	65.4			
	Single	17	21.8			
	Widow	8	10.3			
	Divorced	2	2.6			
Level of Education	1-10 years	31	39.7			
	11-12 years	18	23.0			
	>12 years	29	37.1			
Occupation	Unemployed	33	42.3			
	Skilled work	31	39.7			
	Unskilled work	14	17.9			
Monthly Income (JD)				246.15	119.22	100-900

Prevalence of Fatigue

The PFS was administrated twice, the first time before chemotherapy and a second time after one week of chemotherapy. All subscales scores were increased as follows: the mean total PFS scores increased from 3.76 (SD= 1.98) to 5.71 (SD= 2.19) after one week of taking chemotherapy. The increase in subscales was as follow: the mean scores for behavioral subscale increased from 3.98 (SD=2.25) to 5.95 (SD=2.43), sensory subscale increased from 4.21 (SD=2.28) to 6.46 (SD=2.56), affective subscale increased from 3.83 (SD=2.29) to 5.93 (SD=2.68), and cognitive subscale increased from 3.09 (SD=2.03) to 4.66 (SD=2.21). This increase in fatigue scores is reflected by the increase in the severity of fatigue. About 60.3% of the participants complained of mild fatigue before treatment according to PFS cut off points; this percentage decreased to 25.6% after treatments. However, 28.2% of the participants complained of moderate fatigue before treatments; this ratio rose to 42.3% after treatments. About 10.3% of participants complained of severe fatigue before treatment, and this percentage also increased to 30.8% of participants after one week of treatment. The increase in fatigue scores was seen in all PFS subscales (See table 2).

Table 2: Pre-Treatment and Post-Treatment Changes in PFS

		Behavioral	Sensory	Affective	Cognitive	Total PFS
Pre treatment	Mean	3.98	4.21	3.83	3.09	3.76
	SD	2.25	2.28	2.29	2.03	1.98
Post treatment	Mean	5.95	6.46	5.93	4.66	5.71
	SD	2.43	2.56	2.68	2.21	2.19
	Highest Score	10	10	10	10	10

The following responses were obtained from the qualitative data. When participants were asked about what they believe is most directly contributing to or causing their fatigue, most participants indicated that chemotherapy was the cause of their fatigue. When participants were asked the best thing they have found to relieve their fatigue, the answer was praying, reading Holly Koran, rest, and some of them said that fatigue was relieved by light activities. All participants believed that stopping chemotherapy is the best thing to relieve fatigue. When participants were asked to describe their fatigue, most of them answered that fatigue is the most distressing symptom affecting their lives.

Impact of Chemotherapy on Fatigue

Fatigue was measured before and after taking chemotherapy. A paired-sample t-test was used for total scores and each subscale of PFS. The result showed a significant difference between respondents' mean total scores of fatigue pre and post chemotherapy as measured by the total PFS questionnaire ($t = -5.37$ $df = 77$, $P < 0.05$). In addition, significant differences were found between pre and post chemotherapy scores for all subscales, namely behavioral, affective, sensory, and cognitive dimensions ($t = -5.22, -5.04, -5.19, -4.67$ $df = 77$ respectively, $P < 0.05$). (See table 3).

Table 3: Results of Paired–Sample t-test for Fatigue Scores

PFS subscale	Time	Mean	SD	t	df	Sig
Behavioral	Pre chemotherapy	3.98	2.25	-5.224	77	0.000
	Post chemotherapy	5.95	2.43			
Affective	Pre chemotherapy	3.83	2.29	-5.035	77	0.000
	Post chemotherapy	5.93	2.68			
Sensory	Pre chemotherapy	4.22	2.28	-5.192	77	0.000
	Post chemotherapy	6.46	2.56			
Cognitive	Pre chemotherapy	3.09	2.03	-4.665	77	0.000
	Post chemotherapy	4.66	2.21			
Total PFS	Pre chemotherapy	3.76	1.98	-5.367	77	0.000
	Post chemotherapy	5.71	2.19			

Factors Affect Fatigue Score

Spearman rho was used to assess the relationship between fatigue scores after chemotherapy and categorical variables. The results showed no relationship between sex, marital status and fatigue (r= 0.016, 0.005 respectively, p>0.05). Furthermore, the Pearson Product Moment Correlation was used to test the significant relationships between fatigue and continuous variables. The further analysis used multiple stepwise regressions to test the relationship between fatigue score and psychological symptom (depression and anxiety) and demographic variables (age, educational level and income). The Pearson Product Moment Correlation revealed no significant relationship between fatigue scores after chemotherapy as measured by PFS and age, educational level and income. However, there was a significant relationship between fatigue, depression and anxiety (r=0.68, r= 0.67 respectively, p<0.1) (See table 4).

Table 4: Pearson Product Moment Correlation

Variables	PFS scores
Age	-0.111
Educational Level	-0.006
Income	-0.098
Anxiety	0.67*
Depression	0.68*

*P< 0.01

The stepwise multiple regression tests revealed that depression was a significant predictor of variance in fatigue and explained about 46% (Beta= .398, p<0.01) of the variance in the total fatigue score. It also revealed adding anxiety to the model can explain another 3.6% (Beta=.34, p<0.05) of this variance (See table 5).

Table 5: Stepwise Multiple Regression

Model	R	R^2	Adjusted R^2	Std. Error of the Estimate	Change Statistics				
					R^2 Change	F Change	df1	df2	Sig F Change
1	.681[a]	.463	.456	1.61850	.463	65.611	1	76	.000
2	.706[b]	.499	.486	1.57395	.036	5.363	1	75	.023

a. Predictors: (Constant), depression

b. Predictors: (Constant), depression, anxiety

c. Dependent Variable: PIPER FATIGUE SCALE

Discussion and Analysis

There was a significant difference between PFS scores before and after chemotherapy treatments; this difference was reflected in the increase of prevalence of total PFS and the subscales mean scores. There were significant relationships between fatigue scores as measured by PFS and both

depression and anxiety. Furthermore, depression and anxiety were significant predictors of fatigue.

Prevalence of fatigue in patient receiving chemotherapy

The mean total PFS score was 3.76 (SD= 1.98), and after one week of receiving the chemotherapy, it was increased to 5.71 (SD= 2.19). Accordingly, it is clear that the mean fatigue score increased by 52%. All patients report fatigue with 73.1% reporting moderate to high level of fatigue after chemotherapy comparing to 38.5% before chemotherapy. It is clear that the level of fatigue increased after chemotherapy.

Prevalence of CRF varies widely in the studies depending on how fatigue is assessed and the strictness of the used criteria (Minton & Stone, 2008; Prue, Rankin, Allen, Gracey, & Cramp, 2006). According to Karthikeyan, Jumnani, Prabhu, Manoor, and Supe (2012), patients receiving chemotherapy suffered from higher fatigue score as compared to other treatment modalities. The level of fatigue increased significantly with more chemotherapy cycles (Goedendorp et al., 2012; Spichiger et al., 2011). There are several explanations for the prevalence of fatigue among cancer patients who receive chemotherapy. It was found that chemotherapy is associated with biochemical changes in the brain that result in psychosocial and cognitive changes (Kitamura et al., 2015). These changes could result in an increased fatigue level in patients receiving chemotherapy.

The complexity of the phenomenon of fatigue could be used to explain the increase in fatigue score post-treatment with chemotherapy. Fatigue is a multidimensional, multifaceted, and subjective condition. Fatigue can be caused by many factors, both intrinsic to the patients and extrinsic such as therapeutic intervention (Piper et al., 1987). It has been known that fatigue is the utmost reported distressing symptom among patients receiving radiotherapy and chemotherapy (Huijer et al., 2012; Stone et al., 2000). The metabolic, neurophysiological, situational, and developmental stressor patterns which are related to use of chemotherapy can cause and modulate the signs and symptoms of fatigue.

Depression and anxiety as predictor of CRF

The change in level of psychological symptoms (depression and anxiety) to morbid depression and anxiety may account for the increase in the prevalence of fatigue. There was a significant relationship between fatigue and the severity of psychological symptoms (anxiety and depression). Based on regression analysis, depression was a significant predictor of variance in fatigue and explains about 46% of this variance. On the other hand, anxiety explains 3.6% of the variance in fatigue.

Depression was found to be a significant predictor of fatigue in several

research studies (Mota, Pimenta, & Caponera, 2012; Pertl, Hevey, Collier, Lambe, & O'Dwyer, 2014). Depression is associated with sleep disturbance, and it affects the quality and the quantity of sleep (Gupta, Dahiya, & Bhatia, 2009). Sleep disturbance and interruption could result in increased tiredness, and consequently, increased fatigue. Moreover, depression results in a lack of energy and change of appetite which could increase the level of fatigue.

The result of this study is congruent with previous studies. In large systemic review with a combined sample size of 12,103, anxiety and depression were associated with fatigue in most of the studies (Brown & Kroenke, 2009). Anxiety may cause overwhelming fatigue as a result of the maladaptive response. The maladaptive response could exaggerate the fatigue manifestations and increase the fatigue level.

The perspective of more conservative Arabic Jordanian community for cancer is different from other populations. The network of social support system and the strong religious believes may interfere with the feeling of anxiety. The emotional distress that results from feeling the loss can misrepresent and amplify fatigue. The vantage point of the qualitative part of PFS indicates that participant may feel relief when they are praying and reading the Holy Koran.

Implications

There are several implications for this study. For instance, health team members could utilize a symptom-oriented approach in the assessment and management of fatigue with more focus on patients suffering from depression and anxiety. Furthermore, the result could be used as evidence related practice to educate cancer patients about how to manage fatigue. Moreover, the results could help in the development of a protocol for the management and care of cancer patients suffering from fatigue. It will also help in raising the consciousness of all health team members involved in the care of cancer patients with regards to fatigue and helping patients deal with it.

Conclusion

The sample size was a major limitation since only 78 participants were able to complete this study. The results of the inferential statistics must, therefore, be interpreted with extreme caution, as generalizability is not granted due to the use of convenience sample.

Despite the limitation of this study and the facts about cancer and chemotherapy, it can be concluded that fatigue is a prevalent symptom among cancer population receiving chemotherapy. Psychological factors (depression and anxiety) were identified as possible contributors to fatigue among cancer patients who receive chemotherapy.

The Piper Fatigue Scale is a highly reliable instrument for measuring fatigue in cancer patients and can be used for efficient assessment of fatigue in this population. These significant predictors can be used in the assessment of high-risk patients in a symptom-oriented approach for finding an individualized solution to the problem.

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