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Roles of biological and psychosocial factors in experiencing a psychoneurological symptom cluster in cancer patients

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ABSTRACT

Purpose: (a) To identify subgroups with unique psychoneurological symptom-cluster experience (depression, cognitive impairment, fatigue, sleep disturbance, and pain) and (b) to examine whether the selected demographic, clinical, psychological, and biological factors determine a symptom-cluster experience in cancer patients.

Method: The sample included 203 patients with diverse cancer types recruited from a Korean university hospital. Latent profile analyses were conducted to identify subgroups. Influencing factors of subgroup membership (demographic/clinical variables, hemoglobin level, social support, and psychological stress) were included as covariates in latent profile analysis and analyzed by multinomial logistic regression.

Results: Latent profile analyses classified patients into two subgroups with a unique symptom cluster experience: patients experiencing high intensity in all symptoms within the cluster (the all-high-symptom subgroup, 71%) and patients experiencing low intensity in all symptoms within the cluster (all-low-symptom subgroup, 29%). The validity of the two subgroups was confirmed by the group classification accuracy (97% of the all-low-symptom subgroup and 99% of the all-high-symptom subgroup) and by significant Wald's mean equality tests, showing each symptom (depression, cognitive impairment, fatigue, sleep disturbance, and pain) significantly differentiated the two subgroups (*ps* < .001). Psychological stress independently determined the subgroup membership. Patients with high levels of stress were more likely to be in the all-high-symptom group (OR = 4.69, $p < .0001$). Hemoglobin level, cancer diagnosis, social support, and previous chemotherapy experience did not influence group membership.

Conclusions: A large number of patients experience five psychoneurological symptoms simultaneously due to psychological stress. Interventions targeted to stress would be beneficial for those patients.

1. Introduction

Psychoneurological symptoms, such as depression, cognitive impairment, fatigue, sleep disturbance, and pain, tend to co-occur in cancer patients; these symptoms were identified as a symptom cluster by themselves or with some other symptoms (e.g., anxiety or emotional distress) by statistical procedures, often called a psychoneurological symptom cluster (Kim et al., 2012a; Sullivan et al., 2018). With varying prevalence rates, previous studies confirmed that the subgroup experiencing multiple psychoneurological symptoms as a cluster exists at any stage of cancer treatment (before, during, or after) and regardless of treatment type (chemotherapy, radiation treatment, or biotherapy) or cancer type (Dodd et al., 2011; Doong et al., 2015; Kim et al., 2012b; Illi et al., 2012; Tometich et al., 2019). Moreover, those with psychoneurological symptoms as a cluster experience more functional limitations and lower quality of life than those with only a few or no symptoms (Dirksen et al., 2016; Dodd et al., 2011; Kim et al., 2012b; Sanford et al., 2013).

Yet, it is unclear why certain cancer patients experience a psychoneurological symptom cluster. Most previous studies focused on the demographic and clinical characteristics of patients (e.g., age, gender, education, income, marital status, employment status, comorbid conditions, and treatments by surgery, chemotherapy, and hormonal treatment) but did not find consistent evidence of their roles in experiencing a psychoneurological symptom cluster (Dodd et al., 2010, 2011; Kim et al., 2012b; Miaskowski et al., 2015; Pud et al., 2008). The roles of various biological and psychosocial factors in experiencing a psychoneurological symptom cluster have not been extensively

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evaluated, with only a few studies examining the role of proinflmmatory cytokines (Doong et al., 2015; Illi et al., 2012). For instance, anemia can be a possible mechanism in experiencing a psychoneurological symptom cluster as it is a known biological mechanism of fatigue and cognitive impairment (Stauder et al., 2018) and longitudinal studies showed its association with fatigue and cognitive impairment in cancer patients (Lange et al., 2016). Further, the treatment of anemia improved a cluster of symptoms, including fatigue, sleep disturbance, and function (Gabrilove et al., 2007). Thus, the role of anemic conditions needs to be examined. The role of psychosocial factors (e.g., stress level or social support) should also be investigated, as a psychoneurological cluster may occur as a stress reaction to an uncertain prognosis of disease and unpredictable treatment effects (Kim et al., 2012a).

Therefore, the present study aimed to (a) identify subgroups with unique psychoneurological symptom-cluster experiences during cancer treatment, and (b) examine whether selected demographic and clinical characteristics and psychosocial and biological factors (perceived stress, social support, and hemoglobin) determine a symptom-cluster experience. The current analyses focused on the five symptoms identified as a psychoneurological cluster (depression, cognitive impairment, fatigue, sleep disturbance, and pain; Kim et al., 2008).

2. Methods

2.1. Sample and setting

This study was part of a larger project that evaluated the psychometric properties of symptom measures (Kim and Barsevick, 2019). We recruited adult cancer patients from a conveniently selected university hospital (infusion and inpatient rooms) in Seoul, South Korea. Selected patients were diagnosed with cancer and either undergoing or expecting systemic treatments (chemotherapy or biotherapy), were mentally alert, and could speak and read Korean. We excluded patients with current psychiatric or neurological disorders. We recruited a total of 249 patients and collected data at two time points.

For the present analyses, we used only baseline data and selected only those patients whose hemoglobin levels in the past 2 weeks from baseline were available from medical records. We set the time window (the past 2 weeks) to best coincide with the recall time frame of symptom measures (i.e., the past week) and to best examine the influence of anemic conditions. The final sample size was 203 for the present analyses. Baseline data accrued on the same day or one day prior to the scheduled chemotherapy (first chemotherapy for those initiating treatments; another cycle for those undergoing treatment).

3. Measures

3.1. Indicators determining subgroups

3.1.1. Cognitive impairment: functional assessment of Cancer Therapy–Cognitive Function—the cognitive impairment subscale (FACT-Cog)

The Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog, version 3; Wagner et al., 2009) is a widely used reliable and valid measure with four subscales (perceived cognitive impairments, comments from others, perceived cognitive ability, and impact on quality of life). For this study, we used only the perceived cognitive impairments subscale (18-item). Respondents indicated on a 5-point Likert-type scale ranging from 0, “never,” to 4, “several times a day,” the frequency of each occurrence for the past 7 days. Its Korean version was validated: for the subscale, Cronbach's alpha = .95 (Park et al., 2015).

3.1.2. Fatigue: The Functional Assessment of Cancer Therapy–Fatigue (FACIT-F)

The FACIT-F (version 4; Cella et al., 2002) is a widely used fatigue measure with 13 items. It asks respondents to rate their fatigue intensity and its impact on their daily life over the past week on a 5-point Likert-type scale (0 = not at all, 4 = very much). Validity (e.g., factorial validation and criterion validity) and reliability (.90 < Cronbach's alphas < .95) were confirmed (Smith et al., 2010).

3.1.3. Pain: the intensity subscale of the brief pain inventory (BPI)

The intensity subscale of the BPI was used to measure pain intensity; the BPI consists of two subscales of intensity and interference in daily function. The intensity subscale comprises four items: the worst and least pain for the past week, the average pain, and the pain at the present moment. The scale for each item ranges such that 0 = no pain and 10 = pain as bad as the patient can imagine. Its Korean version was validated in patients with advanced cancer: the two subscales confirmed by factor analysis; expected correlations with the pain-management index, depression, and quality of life; and a high Cronbach's alpha of .85 for the intensity subscale (Yun et al., 2004).

3.1.4. Depression: single-item numeric rating scale

The single-item numeric-rating scale was evaluated in our previous study with college students (ICC = 0.62; correlation with the depression measure = .56; Kim and Ivo, 2016). The rating scale is a simple graphic measure designed to visualize the dull distress image of depression and asks respondents to indicate their level of depression over the past week on an 11-point scale (0 = none, 10 = unbearably severe).

3.1.5. Sleep disturbance: single-item numeric rating scale

We applied the same graphic numeric-rating scale as the depression scale to assess sleep disturbance. Respondents indicated the level of sleep disturbance they experienced for the past week on 0–10 scale (0 = none, 10 = unbearably severe). This item has clear face validity, using the words “sleep disturbance.”

3.2. Covariates associated with subgroup membership

3.2.1. Stress: the Perceived Stress Scale

The 4-item short version of the Perceived Stress Scale (Cohen et al., 1983) was used to measure perceived stress. Each item asked respondents to indicate how unpredictable, uncontrollable, and overwhelming their life has been for the past week on a 5-point-Likert-type scale (0 = never to 4 = very often). Higher scale scores indicate higher stress level. With the college student sample, Kim (2016) validated the 4-item Korean version with an acceptable level of reliability (e.g., split-half coefficient = 0.81. test–retest correlation = 0.67) and factorial and criterion validity.

3.2.2. Social support: single-item scale

Social support was measured by a single item. The item asked respondents their perceived level of support (psychological or economic) from others on a 5-point Likert-type scale (0 = not at all; 4 = very satisfactory).

3.2.3. Demographic and clinical characteristics

Demographic characteristics included age, gender, marital status, education level, and current working status; all data were self-reported. Clinical characteristics were classification of cancer diagnosis, comorbid conditions, chemotherapy experience, and hemoglobin level (tested within 2 weeks), all retrieved from medical records. For classification of cancer diagnosis, we tested breast cancer and hematologic malignancy as they were the majority.

3.3. Recall time-frame and scoring for analysis

For all measures, recall time-frame was the past week. For the multi-item scales, we used the item mean score to make a similar score distribution across measures. For all symptom measures, higher scores indicated more severe symptoms.

4. Statistical analysis

To identify subgroups, we conducted a latent profile analysis with covariates using M*plus* v.7.12. M*plus* classifies participants with unique profiles on the indicators, using latent-variable modeling. The best model was selected based on the following criteria: (a) the model's convergence with a stable solution; (b) the Akaike's information criterion (AIC), where a smaller AIC was preferable (Akaike, 1974); (c) the Bayesian information criterion (BIC), where a smaller BIC was preferable (Schwarz, 1978); (d) the Lo-Mendell Rubin Test and the Bootstrap Likelihood Ratio Test (bLRT; for both $p < .05$ indicates the present number of subgroups is present rather than one lower number of subgroups; Asparouhov and Muthén, 2012) (e) an entropy (i.e., the summary of the latent-class probability for most likely latent-class membership based on the estimated model); value higher than 0.8; and (f) the interpretability of classes (e.g., distinguishability of each class in indicator variables, the size of nontrivial classes, and the meaningfulness of classes). Where these criteria suggested different results, we selected a solution using subjective assessment of the preponderance of evidence. We examined model convergence through replication of maximum log-likelihood values across iterations using random starting values of 1,000 sets. We examined influencing factors of subgroup membership by including covariates. This process is analogous to multinomial logistic regression predicting the latent nominal variable. Sample sizes were not predetermined; however, we considered the sample sizes in selecting the number of covariates in the final model. With the large effect size ($w = .5$), a sample size of 142 was recommended for 10 variables including indicators and covariates; 162 for 11 variables; 218 for 13 variables (Dziak et al., 2014). Thus, we considered up to 11 variables in the model; this led to 6 covariates in addition to 5 indicators.

5. Ethical considerations

Institutional Review Boards approved the protocol for the study (MC12QISI0102). We obtained written informed consent from all participants.

6. Results

6.1. Sample characteristics

As shown on Table 1, the mean age of the sample was about 51 years with a range of 19–80 years. The sample included slightly more female participants than male (57.6%). The majority were married (81%), highly educated (47.8% with college or more), and currently not working (69.5%). Types of cancer varied, with higher proportions of hematologic (36.9%) and breast (23.6%) cancer; 35% had comorbid conditions, most frequently diabetes and hypertension. As for chemotherapy experience, 75% had been previously treated with chemotherapy (another cycle of the same regimen or a different regimen); 25% were awaiting their first treatment. Previous treatments other than chemotherapy were quite rare: surgery occurred in only 22 and radiation in only 4 cases. The mean hemoglobin level was 11.7 mg/dL; 19.7% had lower than 10 mg/dL. On average, patients experienced moderate levels of stress (mean = 1.99, 38.8% had 2 points or higher on a 0–4 scale); 35% reported no or a little bit of social support (mean = 1.5 on a 0–4 scale).

Table 1
Sample characteristics (N = 203).

Variables	Category	*Mean(range) or n*	SD or %
Age		51.34(19–80)	12.89
Gender	Female	117	57.6
	Male	86	42.4
	Missing	0	
Marital Status	Married	165	81.3
	Single	38	18.7
	Missing	0	
Education	Primary	12	5.9
	Middle school	15	7.4
	High school	79	38.9
	College or more	97	47.8
	Missing	0	
Current Working status Health Problems	Working	59	29.1
	Not working	141	69.5
	Missing	3	1.5
Comorbid condition	None	132	65.0
	At least one	71	35.0
	Missing	0	
Type of cancer	Hematologic	75	36.9
	Breast	48	23.6
	Colorectal	33	16.3
	Lung	21	10.3
	Others	26	12.8
Chemotherapy experience	Waiting for the first treatment	51	25.1
	Waiting for another treatment	152	74.9
Blood hemoglobin level		11.7(7.5–16.1)	1.9
Blood hematocrit percentage		34.9(22–47.5)	5.5
Perceived stress level		1.5(0.0–3.5)	0.7
Social support		1.9(0–4)	1.1

6.2. Subgroup with unique symptom-cluster experience

We chose the model with 2-subgroups based on the model-selection criteria (see Table 2). Although AIC and BIC were slightly smaller in the 3-subgroup solution than the 2-subgroup solution, all other criteria indicated the 2-subgroup solution better fit the data (entropy of .94 and significant Lo-Mendel Rubin Test $p < .001$). Table 3 summarizes the mean scores of individual symptom severity in each group. The severity of symptoms characterizes each group and accordingly, groups were named the all-high-symptom group (71%) and all-low-symptom group (29%). Clinically, fatigue, cognitive impairment, and pain were at a mild level; depression and sleep disturbance were, on average, moderate in the all-high group. In contrast, all symptoms were quite low in the all-low-symptom group. Fig. 1 presents the symptom profile of two subgroups on the same metric for a better comparison of subgroups. All symptoms in the all-high subgroup were higher than in the all-low subgroup.

A posteriori classification based on the selected model correctly classified 97% of the all-low-symptom subgroup and 99% of the all-high-symptom subgroup, summarized to an entropy value of .94. Statistical differences between the two groups in the severity of each symptom were tested using a Wald test of mean equality for latent class indicators. The severity of each symptom was statistically higher in the all-high group than the all-low group ($ps < .001$). The high classification accuracy and the statistical differences between two groups for each symptom confirmed the validity of the findings.

6.3. Determinants of subgroup memberships

Covariates, influencing factors, are to be *a priori* determined in latent profile modeling. Initially, we selected a relatively large number of variables from demographic and clinical characteristics (a total of five: age, gender, type of cancer, comorbid conditions, and chemotherapy

Table 2
Comparisons of models with different number of classes (i.e., subgroups).

No. of classes	Log likelihood	AIC	BIC (sample size adjusted)	Entropy	Lo–Mendell Rubin test	Bootstrapped likelihood ratio test
2	−1587.87	3227.75	3231.14	.94	0.001	< 0.001
3	−1526.43	3236.86	3142.33	.82	0.11	< 0.001

Note. AIC = Akaike's information criterion, BIC = Bayesian information criterion.

experience), in addition to three psychosocial and biological factors. However, we had to decrease the number of covariates for the final model selection because the considered variables were relatively large in number in relation to the sample size; more importantly, most demographic and clinical variables were categorical, causing insufficient binomial distributions. Thus, we tested each demographic and clinical variable in the initial modeling, similar to stepwise multiple regression procedures: selection criterion was improving the model or not failing the parameter estimation. We, finally, selected only two variables (cancer diagnosis and chemotherapy experience). This approach allowed us to estimate parameters with the given sample.

For the final model, we included five covariates: empirically, two clinical variables (cancer diagnosis and chemotherapy experience); theoretically, two psychosocial variables (perceived stress and social support); and one biological variable (hemoglobin level). In logistic regression (see Table 4), only perceived stress significantly influenced subgroup membership. Patients with high levels of stress were more likely to be in the all-high-symptom group (OR = 4.69, $p < .001$). Hemoglobin level, cancer diagnosis, social supports, and chemotherapy experience did not influence group membership. For classification of cancer diagnosis, we tested breast cancer and hematologic malignancy in a separate model and results did not differ. Our final selection was, however, breast cancer, as the selected cluster was identified with the breast cancer sample.

7. Discussion

With 203 cancer patients, we discovered that patients either experienced all symptoms in the selected psychoneurological cluster at a higher level or all of them at a lower level. Experiencing psychoneurological symptoms was independent of selected demographic, clinical, and biological variables; however, it did align with higher stress levels, independent of other variables. Several other studies examined subgroups with unique psychoneurological symptom experience using either latent-variable modeling (i.e., latent profile analysis or latent class analysis; Dodd et al., 2011; Doong et al., 2015; Illi et al., 2012; Tometich et al., 2019) or conventional cluster analysis (Dodd et al., 2010; Kim et al., 2012b; Pud et al., 2008). Those studies selected a similar symptom combination as a cluster (e.g., pain, fatigue, sleep disturbance, and depression) to our study, though the authors did not specifically name it a psychoneurological cluster. All previous studies reported a group experiencing all symptoms in a selected cluster. Yet, what makes our findings unique is the discovery of the role of stress in experiencing a psychoneurological symptom cluster. No other studies examined the role of stress to determine a psychoneurological symptom-cluster experience.

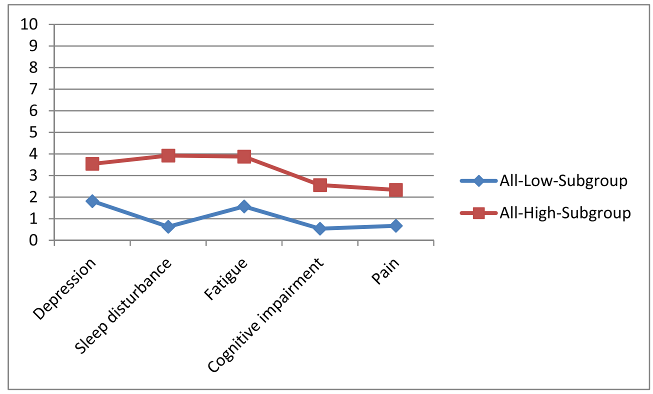

Fig. 1. Symptom profile of each subgroups presented on the same scale. Note. Mean scores for fatigue and cognitive impairment (0–4) were converted to 0 to 10 scale, so that all measures the same scale (0–10).

Table 4
Influencing Factors of Subgroup Membership (reference = all-high-symptom group) (N = 200[a]).

Variables	*B*	*SE B*	Odds ratio	95% CI
Diagnosis (breast cancer vs. others)	−0.20	0.51	0.81	(0.29, 2.24)
Previous chemotherapy experience	−0.90	0.79	0.40	(0.08, 1.92)
Hemoglobin level	0.04	0.13	1.04	(0.80, 1.35)
Perceived stress	1.54	0.32	4.69	(2.49, 8.83)***
Social support	0.21	0.17	1.23	(0.87, 1.74)

Note. ***$p < .001$. [a]Three cases were excluded due to missing information for covariates.

Our findings indicate that reducing stress is critical in managing a psychoneurological cluster, particularly in patients waiting for treatment in first or subsequent cycles. An ultimate outcome of symptom-cluster research is to develop interventions targeting a symptom cluster, beyond the traditional approach targeting individual symptoms. For instance, a recent study examined the effects of back massage on a psychoneurological symptom cluster of fatigue, pain, and sleep disturbance (Miladinia et al., 2017). Another study evaluated the feasibility of psychoeducational interventions targeting a symptom cluster of fatigue, pain, and sleep disturbance (Nguyen et al., 2018). The key intervention component for a symptom cluster is unclear in the current

Table 3
Subgroups of psych-neurological symptom cluster experience.

	Total (N = 200[a])		All- low- symptom group (n = 58, 29%)		All-high- symptom group (n = 142, 71%)		Wald tests for mean equality	
	M	*SD*	*M*	*SD*	*M*	*SD*	Est/SE	*p*
Depression	2.85	2.41	1.18	1.07	3.54	2.48	8.67	< .001
Sleep disturbance	2.95	2.71	0.62	0.89	3.92	2.64	11.07	< .001
Fatigue	1.28	0.76	0.62	0.37	1.55	0.72	11.29	< .001
Cognitive impairment	0.78	0.71	0.21	0.18	1.02	0.71	11.92	< .001
Pain	1.84	1.72	0.67	0.74	2.33	1.83	6.05	< .001

Note. Scale score range for depression, sleep disturbance, and pain was 0–s10; for fatigue and cognitive impairment 0–4. [a]Three cases were excluded for missing information for covariates. Est/SE = Estimate divided by Standard Error.

literature. Our data highlight that specific strategies to reduce stress could improve the outcomes of interventions targeting a psychoneurological cluster.

Clinicians need to be aware that a large number of patients who are waiting for treatment experience multiple psychoneurological symptoms as a cluster and should consider stress-management strategies for those patients. The co-occurring tendency of depression, cognitive impairment, fatigue, sleep disturbance, and pain has clinical implications for symptom assessments. Clinicians should assess all symptoms in a cluster together. The use of a scale or electronic record system assessing the psychoneurological cluster can assist clinicians to identify those patients at risk early in their treatment.

Another notable finding is the identification of only two subgroups of patients with much higher prevalence of patients experiencing all symptoms in a cluster (i.e., 71% in the present study vs. less than 20% in most other studies). Most other studies discovered more than two groups. That is, additional groups emerged, experiencing one or two symptoms more intensely than other symptoms in a cluster (Dodd et al., 2010; Kim et al., 2012b; Pud et al., 2008; Tometich et al., 2019). The various design factors may have contributed to such differences in findings. In particular, assessment timing might have contributed. In the present study, all patients were surveyed on the same day or one day prior to the scheduled systemic treatment (first or another cycle). Such homogeneity of the measurement time points would have resulted in relatively similar psychoneurological symptom experiences. Also, the inclusion of covariates in the model could have made our solution different. Although most other studies evaluated differences of subgroups in selected variables, separately from the main analysis of subgroup classification, the present study examined the potential influencing factors as covariates in the model, allowing them to directly influence group classification. Furthermore, the inclusion of stress level in the model was the first trial in the present study, as all other studies exclusively focused on clinical and demographic factors.

We expected the subgroup with predominantly high levels of fatigue and cognitive impairment, if this subgroup exists, to have had lower hemoglobin levels. However, this possibility was not confirmed, possibly due to the limited number of anemia cases examined (mean Hb = 11.73 mg/dL). Future studies need to reevaluate the role of anemia in samples with a very diverse hematologic status. As for other biological factors, several recent studies examined the role of proinflammatory cytokines. Despite preliminary data on the association between proinflammatory cytokines and psychoneurological symptom-cluster experiences (Doong et al., 2015; Illi et al., 2012), the evidence of their roles is inconclusive, due to inconsistent findings (i.e., association with a certain cytokine). More conclusive evidence is needed on the roles of biological factors in determining a psychoneurological-symptom-cluster experience.

Cancer type and chemotherapy experience did not influence subgroup membership. Some studies (Astrup et al., 2017; Miaskowski et al., 2014) reported a lack of association with previous chemotherapy experiences and cancer type; but others reported cancer diagnosis and treatment were associated with subgroups (Miaskowski et al., 2015). Direct comparisons with the present study, however, require caution because those studies used a large number of symptoms to classify subgroups, including psychoneurological and physical symptoms. Also, those studies evaluated differences in subgroups in demographic and clinical variables (i.e., bivariate analysis in nature) whereas our study evaluated direct influences on subgroup membership using multivariate analysis. Based on mixed findings from previous studies and the lack of association from the present study, we conclude no evidence exists of the role of particular demographic and clinical factors in experiencing a psychoneurological cluster.

Limitations include the use of single-item measures for depression, sleep disturbance, and social support. Although those selected measures have clear face validity, we acknowledge that single-item measures have weaker validity and reliability than comprehensive measures (Kim and Ivo, 2016). On average, symptom severity was low or moderate in the study sample, which may also bias the findings. Future studies need to employ strategies to recruit patients with various levels of symptoms.

In this study, we collected data from a relatively heterogeneous sample with different disease phases and diagnoses and such variability could confound the findings due to the relatively small sample size. Last, in considering the data-collection time points, particularly for those chemo-naive patients, anxiety level can be an important predictor of a symptom-cluster experience or a core symptom of another cluster. We leave this possibility for future studies. Note that the present study selected a particular symptom cluster based on previous empirical studies. We selected stress rather than anxiety as a psychological predictor, because anxiety is a stress reaction.

7.1. Clinical implications

The current findings warrant the need for clinicians to be aware that a large number of patients waiting for treatment experience multiple psychoneurological symptoms as a cluster. Clinicians should consider stress-management strategies for those patients. For future studies, we suggest investigating interventions targeted to psychological stress. We also suggest investigating other biological mechanisms that can be used to develop symptom-management strategies.

Conflict of interest

All authors confirm they have no conflict of interest for this work.

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