# Fatigue Mediates the Relationship Between Pain Interference and Distress in Patients with Persistent Orofacial Pain

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**Aims:** To test the role of fatigue and its subtypes (general, physical, emotional, mental, and vigor) in mediating the relationship between psychological distress and pain interference. **Methods:** Retrospective, de-identified records were examined for 431 patients seeking treatment for persistent orofacial pain. Primary diagnoses of participants were muscle pain (29.8%), joint pain (26.0%), neuropathic pain (19.5%), and other (ie, fibromyalgia, centrally mediated myalgia, tendonitis, dental pain, cervical spine displacement, and no diagnosis; 24.7%). Mediation models were tested with distress as the independent variable, interference as the dependent variable, and fatigue or its subtypes as the mediators. **Results:** After controlling for pain duration and average levels of pain, total fatigue mediated the relationship between distress and interference. Fatigue subtypes partially mediated the relationship between distress and interference, but mediation was strongest with the composite fatigue variable. The results, however, should be interpreted cautiously, as data were collected at a single time point and do not imply causality. **Conclusion:** These results suggest that interventions targeted specifically at fatigue symptoms may be helpful for reducing interference and improving quality of life in patients with persistent orofacial pain.
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**Key words:** *fatigue, orofacial pain, pain interference, psychological distress*

Orofacial pain refers to pain associated with the hard and soft tissues of the head, face, and neck.[1] The International Association for the Study of Pain (IASP) defines persistent pain as "an unpleasant sensory and emotional experience without apparent biological value that has persisted beyond the normal tissue healing time (usually taken to be 3 months)."[2] It is estimated that each year, over 7% of the general population, or 13 million people in the United States, experience a persistent orofacial pain condition that requires treatment.[3] Patients with persistent orofacial pain experience pain as threatening and report high levels of pain-related interference, defined as the perceived effects of pain on various areas of a patient's life including family and marital functioning, work-related activities, and social activities.[4] Interference may be particularly high in those with persistent orofacial pain conditions because such disorders disrupt basic human functions, such as eating, drinking, and communicating.

The high levels of psychological distress reported by patients with orofacial pain may exacerbate their levels of interference. Psychological distress is defined as symptoms of one or more psychological disorders, such as anxiety and depression, which are present in an individual with or without a primary medical diagnosis; this construct is measured in terms of both number and severity of symptoms.[5] Research in patients experiencing cancer pain shows that higher levels of distress are associated with greater reported interference on daily life activities[6]; further, distress mediates the relationship between pain level and functional status.[7] Similarly, anxiety at baseline is associated with greater pain-related interference in patients with widespread pain.[8] These results indicate that

treatments addressing distress may be important in patients' recoveries, as they may influence perceptions of pain interference. Those with orofacial pain have a high prevalence of anxiety, depression, fatigue, posttraumatic stress disorder, personality disorders, and other psychopathology, which may tax mental resources and induce avoidance behaviors related to interruptions in everyday functioning.[9–16] As such, learning about the mediators of the distress/interference relationship in orofacial pain populations may be important for developing successful interventions to improve the quality of life of orofacial pain patients.

Fatigue may represent one potential mechanism by which distress influences interference. Fatigue is defined as a behavioral or physiological symptom that is independent of physical exertion and manifests as somatic, emotional, and/or cognitive symptoms.[17] Mental fatigue is associated with deleterious pain-relevant outcomes including poorer adherence to appointments and medication regimens, reductions in physical activities, and poorer coping with pain-related thoughts.[18] Other types of fatigue are likely relevant as well. A commonly used fatigue questionnaire categorizes five different types of fatigue: general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor.[19] The role of these different types of fatigue in mediating the relationship between psychological distress and interference in orofacial pain patients has not been previously explored.

Distress, impairment, and fatigue are all influenced by pain severity, with higher severity associated with higher levels of physical and psychosocial disability.[20] However, previous research has not examined the relationships among distress, impairment, and fatigue while controlling for pain duration or average levels of pain. Exploring these relationships in patients with persistent pain conditions would be especially important, because such knowledge could elucidate the importance of targeted interventions for symptoms above and beyond pain severity.

Given that pain interference is associated with negative psychological and physiological outcomes, and is likely exacerbated by distress in patients with persistent orofacial pain, the aim of the current study was to test the role of fatigue and its subtypes (general, physical, emotional, mental, and vigor) in mediating the relationship between psychological distress and pain interference. Extant research supports the presence of a relationship between psychological distress, interference, and fatigue in patients with persistent pain, but no study to date has incorporated these variables into a comprehensive model. Further, no study to date has tested the role of different types of fatigue in mediating the relationships between distress and impairment, despite the fact that such knowledge could lead to more specifically targeted interventions. In the current study, it was predicted that there would be a positive relationship between psychological distress and interference in patients with orofacial pain. It was also predicted that such a relationship would be mediated by fatigue after controlling for average pain severity. Based on extant literature, it was predicted that mental fatigue would be the strongest mediator of all the fatigue subtypes.

## Materials and Methods

### Participants

Data were obtained from 523 patients receiving an initial examination at an orofacial pain clinic in the United States between 2008 and 2012. To be included in the study, participants had to report experiencing pain for longer than 3 months to eliminate those with acute pain conditions. All participants had orofacial pain as determined by a licensed dentist trained in the diagnosis of orofacial pain conditions.

### Procedures

Patients completed a standardized battery of questionnaires as part of the routine intake protocol at the orofacial pain clinic at the University of Kentucky, where the study was conducted. Prior to filling out the questionnaires, participants consented to their de-identified data being used for retrospective research purposes. The current study used this clinical record of de-identified data. As such, the Institutional Review Board waived the requirement for informed consent and gave approval for the study to be conducted.

### Measures

***Distress.*** The Symptom Checklist 90-Revised (SCL) is a 90-item self-report measure that asks patients to rate 90 symptoms by using a scale of 0 ("Not at all"), 1 ("A little bit"), 2 ("Moderately"), 3 ("Quite a bit"), and 4 ("Extremely").[21] The measure produces 9 subscales and 3 composite scales designed to assess symptom severity, frequency, and a composite of severity and frequency. Raw scores are converted to *t* scores based on standardized norms. In the current study, only the Global Symptom Index (GSI) composite index was analyzed. Several studies have shown that the GSI validly assesses psychological distress in persistent pain populations.[22–25] Previous studies have found the GSI to have good internal consistency (Cronbach's $\alpha = 0.97$).[22,24]

***Pain Interference.*** The West Haven-Yale Multidimensional Pain Inventory (WHYMPI) is a widely used self-report measure that examines how pain impacts daily life across a variety of domains.[4] It was specifically designed for use in persistent pain

populations and has been validated for use in patients with orofacial pain conditions.[26–28] The WHYMPI contains 52 items and assesses functioning across 12 domains, with higher scores representing a higher level of the corresponding construct. In the current study, only the interference subscale of the WHYMPI was analyzed. The interference subscale has 9 items and is designed to measure the extent to which pain disrupts vocational, social/recreational, and family/marital functioning. Previous studies have shown the inference subscale to have high internal consistency (Cronbach's $\alpha = 0.90$).[4]

***Fatigue and Fatigue Subtypes.*** The Multidimensional Fatigue Inventory–Short Form is a 30-item questionnaire assessing fatigue symptoms over the past week.[17] The scale consists of five subscales (general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor) as well as an aggregated total score in which the vigor score is subtracted from the sum of the other four scales. Participants rate each of the items on a 5-point scale ranging from 0 ("Not at all") to 4 ("Extremely"), with higher scores representing more of the corresponding construct. Sample items include "I feel upset," "I am worn out," and "I feel run down." Previous research has established the validity of the subscale and total scores in clinical populations, and subsequent work has replicated these findings by using confirmatory factor analytic techniques.[19] The internal consistency of each of the five subtypes described above have been adequate in patients with orofacial pain (Cronbach's $\alpha$'s = 0.96, 0.89, 0.89, 0.90, and 0.88, respectively).[13–17]

***Average Pain Severity.*** Participants were asked to use a visual analog scale to rate their average levels of pain in the last month. Participants marked their level of pain on a 100-mm line with anchors of "No pain at all" and "The most intense pain you can imagine." A ruler was then used to quantify the mark, resulting in a possible range from 0 to 100. Visual analog scales are widely used for measuring pain symptoms, despite some arguments that they are not always valid as between-person measures.[29]

## Data Analyses Plan

All analyses were conducted using IBM SPSS Version 20, unless otherwise noted. Missing data were handled using list-wise deletion. Missing data analyses revealed that 74 participants were missing data for pain duration, 3 were missing data for WHYMPI interference, 8 were missing data for GSI, and 15 were missing data for average pain levels. As such, the final models with all variables included were based on a sample of 431 participants, as some were missing data on more than one of the aforementioned variables. To test whether pain severity, pain duration, distress, interference, or fatigue were different between those who had missing data and those who did not, *t* tests were conducted.

Prior to analyses, data were checked for violations of the assumptions of regression. Analyses revealed that data were linear, independent of other observations, and normally distributed, and as such, no corrections were made. Outliers were tested using the difference in fit standardized (DFFITS) criteria of influence, which measures how the regression equation would change if a case were omitted.[30] Analyses using the widely used DFFITS > ± 1 criteria did not identify any outliers, thus no cases were removed from analyses.

To test the relationship between all study variables, zero-order correlations were first computed. To test the relationship between distress and interference, a linear regression model was run with distress as the independent variable and interference as the dependent variable.

To test the prediction that fatigue and its subtypes would mediate the relationship between distress and interference, mediation models were tested with GSI as the independent variable, WHYMPI interference as the dependent variable, and fatigue as the mediator. Mediation refers to a statistical technique used to test whether the relationship between an independent variable (ie, distress) and a dependent variable (ie, interference) is caused by a mediating variable (ie, total fatigue).[31] For true mediation, the independent variable has to significantly predict both the mediator (a path) and the dependent variable (c path). The mediator also has to significantly predict the dependent variable (b path). A relationship is said to be fully mediated when the relationship between the independent variable and the dependent variable becomes null after controlling for the mediator (c′ path); if the c′ path is less significant than the c path but still significantly different from zero (that is, the *P* value is still below $P = .05$), the relationship is said to be partially mediated (not fully).[32,33] For a graphic representation of mediation, see Fig 1. In the current study, mediation models were conducted using the Preacher and Hayes macros with 5,000 bootstrap samples and a 0.95 bias corrected and accelerated (BCa) confidence interval.[33] To achieve significant mediation, 0 must fall outside the range of this confidence interval; see cited reviews for a detailed mathematical explanation of bootstrapping, BCa estimates, and mediation.[33–35]

Separate models were run for each of the fatigue mediations: general fatigue, physical fatigue, emotional fatigue, mental fatigue, vigor, and total fatigue. In all analyses, pain duration and average pain severity were entered in as covariates so the results would provide insight regarding the relationship between the variables of interest above and beyond the effects of pain duration and average pain severity.

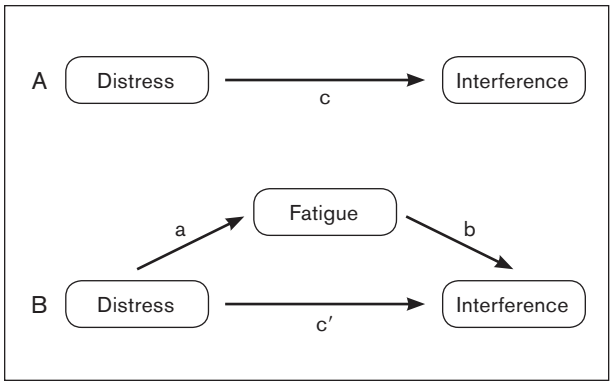


**Fig 1** Graphic representation of fatigue mediating the relationship between distress and interference. Note A shows the theoretical relationship between distress and interference (c path). B shows the theoretical model where fatigue mediates the relationship between distress and interference. In this model, the c′ path represents the relationship between distress and interference after the variance of fatigue is removed.

## Results

### Participants

In this study, participants' primary diagnoses were as follows: muscle pain (29.8%), joint pain (26.0%), neuropathic pain (19.5%), and other (ie, fibromyalgia, centrally mediated myalgia, tendonitis, dental pain, cervical spine displacement, and no diagnosis; 24.7%). Seventy-eight percent of patients also had a secondary orofacial pain diagnosis. The diagnoses were established based on the guidelines from the American Academy of Orofacial Pain.[36] Mean age of the current sample was 46.1 years (SD = 14.79), with a sex breakdown of 82.4% female. Average pain duration at the time of initial appointment was 65.3 months (SD = 92.8).

### Missing Data Analyses

Ninety-two of the 523 participants were excluded from the final models because they were missing data on one or more variable. To test whether these participants differed from those included in the analyses, *t* tests were conducted. Results revealed that the groups did not differ from each other in pain severity, pain severity, distress, pain interference, general fatigue, physical fatigue, emotional fatigue, vigor, or total fatigue (all *P* values > .05). However, those who were excluded had slightly higher mental fatigue (mean = 1.11, SD 1.08) than those who were included (mean = 0.88, SD 0.88), ($t[521] = -2.19$, $P = .03$).

### Correlations Among Study Variables

Table 1 shows correlations and descriptive statistics for all variables.

### Relationship Between Distress and Interference

Linear regression was used to test the relationship between distress and interference, with the covariates of pain duration and average pain severity entered simultaneously with GSI in the model. Results revealed that GSI significantly predicted WHYMPI interference above and beyond pain duration and average pain severity (Total $R^2 = 0.412$, $\beta = 0.303$, $t[428] = 7.691$, $P < .001$).

### Mediation of Fatigue and Its Subtypes

Results revealed that each of the fatigue subtypes except vigor partially mediated the relationship between distress and interference, although the effects were relatively small. The composite total fatigue score most strongly mediated this relationship. Details of all mediation analyses can be found in Table 2.

## Discussion

It was hypothesized that there would be a positive relationship between distress and interference in patients with persistent orofacial pain. The results support this hypothesis, as distress predicted interference above and beyond pain duration and pain severity. Further, it was hypothesized that all five subtypes of fatigue would mediate the relationship between distress and interference, and that mental fatigue would have the greatest effect on this relationship. Each fatigue subtype except vigor partially mediated the relationship between distress and interference. However, mental fatigue was not the strongest mediator of this relationship. Instead, general, physical, emotional, and mental fatigue each added unique variance, which together led to the composite total fatigue score acting as the strongest mediator between distress and interference in these patients with persistent pain. The relationships between psychological distress and pain interference were mediated by overall levels of fatigue after removing the variance associated with pain duration and average level of pain; however, because all data were collected at a single time point, causality cannot be definitively established.

**Table 1 Bivariate Correlations Among Study Variables and Descriptive Statistics**

| Variable | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| 1. Sex – Female | – | −0.16** | 0.04 | 0.02 | 0.02 | −0.01 | −0.06 | −0.05 | 0.00 |
| 2. SCL GSI | | – | 0.45** | 0.66** | 0.65** | 0.73** | 0.67** | −0.50** | 0.81** |
| 3. WHYMPI Interference | | | – | 0.47** | 0.45** | 0.41** | 0.41** | −0.31** | 0.52** |
| 4. Fatigue – General | | | | – | 0.65** | 0.61** | 0.58** | −0.49** | 0.86** |
| 5. Fatigue – Physical | | | | | – | 0.60** | 0.62** | −0.35** | 0.81** |
| 6. Fatigue – Emotional | | | | | | – | 0.60** | −0.50** | 0.83** |
| 7. Fatigue – Mental | | | | | | | – | −0.33** | 0.79** |
| 8. Fatigue – Vigor | | | | | | | | – | −0.67** |
| 9. Total fatigue score | | | | | | | | | – |
| | | | | | | | | | |
| Mean | 82.4% | 57.37 | 46.27 | 1.68 | 0.95 | 1.04 | 0.92 | 1.65 | 2.94 |
| (SD) | | (10.55) | (17.47) | (1.17) | (0.91) | (0.96) | (0.92) | (0.88) | (3.84) |

**Correlation is significant at the .01 level (2-tailed); GSI = Global Symptom Index; SCL = Symptom Check List-90 Revised; WHYMPI = West Haven-Yale Multidimensional Pain Inventory.

**Table 2 Effect of Fatigue on the Relationship Between SCL GSI Scores and WHYMPI Interference Scores**

| Mediator | | Coefficient | Standard error | *t* | *P* | 95% Confidence interval |
|---|---|---|---|---|---|---|
| 1. Fatigue – General | c | 0.50 | 0.06 | 7.69 | < .001 | |
| | c′ | 0.28 | 0.08 | 3.45 | < .001 | 0.13–0.33* |
| 2. Fatigue – Physical | c | 0.50 | 0.06 | 7.69 | < .001 | |
| | c′ | 0.37 | 0.08 | 4.57 | < .001 | 0.02–0.24* |
| 3. Fatigue – Emotional | c | 0.50 | 0.06 | 7.69 | < .001 | |
| | c′ | 0.47 | 0.08 | 6.00 | < .001 | 0.26–0.48* |
| 4. Fatigue – Mental | c | 0.50 | 0.06 | 7.69 | < .001 | |
| | c′ | 0.34 | 0.08 | 4.13 | < .001 | 0.04–0.27* |
| 5. Fatigue – Vigor | c | 0.50 | 0.06 | 7.69 | < .001 | |
| | c′ | 0.43 | 0.07 | 5.92 | < .001 | -0.03–0.15 |
| 6. Total fatigue score | c | 0.50 | 0.06 | 7.69 | < .001 | |
| | c′ | 0.10 | 0.10 | 1.02 | .31 | 0.21–0.57* |

*Significant partial mediation; c = Regression coefficient of the c path (see Fig 1); c′ = c-prime path (regression coefficient of the c path after accounting for the variance of the mediating variable); SCL = Symptom Check List-90 Revised; GSI = Global Symptom Index; WHYMPI = West Haven-Yale Multidimensional Pain Inventory; 95% confidence interval refers to the BCa confidence interval, not the interval around the c′ coefficient.

Previous research has established that pain interference is an important predictor of future disability in those experiencing persistent pain; in samples of multiple sclerosis patients, for example, greater interference was significantly associated with disease severity and level of perceived gait disability.[37] In a study of patients with persistent pain conditions, average pain severity was significantly associated with higher levels of interference and lower levels of life control, and both were predictive of depression.[38] The results of the present study extend these findings by suggesting that the relationships between psychological distress and interference are not due solely to average pain severity, as strong relationships were found even after controlling for pain severity assessed via a visual analog scale. The results further elucidate the contributions of overall levels of fatigue on the relationships between psychological distress and interference.

The contributions of fatigue to the pain experience are multifarious. Fatigue compromises one's ability to regulate cognitive aspects of pain effectively, and patients with persistent pain (including those with orofacial pain) are under significant levels of mental fatigue.[18,39] A number of factors that independently predict fatigue, including dyspnea, lack of appetite, and feeling sad and irritable, may lead to interference with life activities and worsening psychological and physical outcomes.[40] Greater levels of fatigue may prevent people from engaging in moderate levels of exercise and other behaviors that have been shown to be associated with improved outcomes in patients with persistent pain.[41] Fatigue may also cause people to avoid doing everyday household activities; such avoidance may cause relief in the short term but ultimately be counterproductive in the long term. Through engaging in avoidant behavior, people may begin to grow increasingly fearful of and debilitated

by their pain, leading to a downward spiral of avoidance and interference.[42] The contributions of fatigue to the cycle of fear and avoidance should be more thoroughly explored in future research.

Interestingly, the effects of total fatigue were not primarily driven by a specific type of fatigue. Instead, general, physical, emotional, and mental fatigue each partially mediated the relationship between distress and interference, although the effect sizes for the influence of these fatigue subtypes were relatively small. It appears that they each contributed independently to the overall fatigue experience. The relationships between subtypes of fatigue and how they interact with psychological and physiological factors to predict interference and other pain-related outcomes should be explored in future research. For instance, functional magnetic resonance imaging could be used to examine the impact of experimentally induced fatigue and its subtypes on pain matrix activation.[43]

Alternate explanations exist for the obtained results. Although mediation analyses were used, all measures were collected at a single time point, making it impossible to determine causality. As such, it could be the case that interference leads to psychological distress. In this light, patients who experience pain-related interference may become frustrated by the reductions in everyday activity caused by the pain. This frustration may manifest as psychological distress, which could then lead to further interference, resulting in a self-perpetuating cycle. Future studies should explore the directionality of the distress/interference cycle by using longitudinal data and how this cycle contributes to pain and psychological well-being in patients with persistent orofacial pain.

The present results have important implications for the treatment of persistent pain in patients with orofacial disorders. Specifically, the findings highlight the importance of targeting fatigue to improve psychological well-being. Interventions aimed at reducing perceived fatigue in the masseter, trapezius, and other related muscle groups have been shown to be effective in reducing both pain levels and interference in patients with persistent orofacial pain.[44,45] Intervention programs aimed at targeting all subtypes of fatigue may prove to be even more effective. Cognitive-behavioral therapy to reduce fatigue in patients with cancer pain is effective in both limiting physical symptoms and minimizing psychological distress,[46] and randomized controlled trials have found that cognitive behavioral therapy for patients with chronic fatigue syndrome can lead to significant improvements in approximately 70% of patients.[47] Those improvements were maintained at 6-month follow-up.[47] In these treatment programs, patients were educated about the function and effects of fatigue, taught to monitor their symptoms of fatigue, sleep, and pain, and assigned a detailed schedule of structured physical activity.[47] Similar interventions might be helpful in reducing pain interference and improving quality of life for patients with persistent orofacial pain. Future research should test the efficacy of fatigue intervention across different types of orofacial pain disorders.

Because persistent pain often causes people to modify their thoughts and actions, experiencing pain can in and of itself be fatiguing. Based on this rationale, some pain-management approaches include mindfulness training, where patients are taught to notice their pain and accept it nonjudgmentally. Evidence suggests that mindfulness-based approaches are effective in helping people manage their pain symptoms.[48,49] People's ability to accept their pain has been linked to lower mental fatigue in patients with orofacial pain disorders.[50] Future work could test whether acceptance and mindfulness skills moderate the relationship between pain and the different fatigue subtypes, and if so, what effects this has on psychological well-being in those with persistent orofacial pain.

The current study is not without limitations. As mentioned earlier, all measures were collected at a single time point. As such, causality cannot be established. Future research should use prospective longitudinal data in an attempt to replicate these findings. The statistical analyses used were based on the assumption that the relationships between distress and interference, distress and fatigue, and fatigue and interference all had the same confounding variables. Unmeasured variables that affect one of these relationships but not the other could have biased the models. In this light, it is important that the results be interpreted cautiously. Participants completed these measures at the pain clinic prior to receiving treatment, and may have over-reported the extent to which pain was interfering with their daily activities to ensure that the dentists appreciated their level of suffering. Participants who were missing data also had slightly higher levels of mental fatigue than those whose data were included, possibly resulting in a biased estimation of the role of mental fatigue in mediating the relationships between distress and interference.

Additionally, average pain was assessed using a visual analog scale, which may have limitations for use in patients with persistent pain.[29] However, there are several advantages to using visual analog scales,[51] such as their high correlation with pain measured on verbal and numeric ratings scales, and the fact that they have ratio scale properties.[52–56] Finally, the current study collapsed data across a wide range of orofacial pain types, including intracapsular pain,

muscle pain, and neuropathic pain. Future research should establish whether the reported relationships are consistent across diagnostic categories. Despite these shortcomings, the findings of the current study are important in helping unravel the relationships between distress, interference, and types of fatigue.

In summary, total level of fatigue mediated the relationship between distress and pain interference after controlling for average pain levels in a population of orofacial pain patients. The results should be interpreted cautiously, as data were collected at a single time point and do not imply causality. Nevertheless, these data are the first to examine the relationship between daily functioning, fatigue, and psychological outcomes in persistent orofacial pain populations, above and beyond average levels of pain. Because fatigue is so prominent in persistent pain disorders, future research should be devoted to examining the specific contributions of different types of fatigue influencing the functioning of patients with persistent pain conditions. Such knowledge would be scientifically informative, and has the potential to affect novel treatments to improve quality of life and psychological well-being in patients with orofacial and other persistent pain conditions.

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