

## Research article Ερευνητική εργασία

# Fatigue and somatic anxiety in patients with major depression

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The objective this study aimed to investigate the independent contribution of somatic anxiety to the severity of depression-related fatigue. Seventy-six patients (85.5% female), aged 23–65 years (mean  $48.7 \pm 10.6$ ), diagnosed with major depressive disorder and currently in a major depressive episode (MINI 5.0.0.) with a 17-item Hamilton Depression Rating Scale (HDRS) score  $\geq 17$ , were studied. Forty-nine patients (64.5%) were concurrently suffering from anxiety disorder(s). Patients with physical diseases or other fatigue-related conditions were excluded. Reported fatigue was measured with the 14-item Fatigue Questionnaire (FQ). Based on HDRS item 11 (somatic anxiety) scores, patients were divided into those with somatic anxiety (HDRS-11 $\geq 2$ ) and those without (HDRS-11 $\leq 1$ ). Pearson's ( $r$ ) and Spearman's ( $\rho$ ) correlations between FQ score, age, gender, inpatient status, HDRS score and somatic anxiety status were calculated. A multiple regression analysis was then performed, with FQ as the dependent variable. Fifty-seven patients (75%) were rated as suffering from somatic anxiety (HDRS-11 $\geq 2$ ). Patients with somatic anxiety had significantly higher HDRS and FQ scores. The FQ score significantly correlated with the HDRS score ( $r=0.36$ ,  $p=0.001$ ) and somatic anxiety status ( $\rho=0.35$ ,  $p=0.002$ ). The FQ score was independently predicted by HDRS score and somatic anxiety status, with standardised beta coefficients of 0.259 ( $p=0.028$ ) and 0.255 ( $p=0.031$ ), respectively.  $R^2$  was 0.185. Both the severity of depression and the presence of somatic anxiety independently correlate with the severity of reported fatigue in patients with major depression. This finding has potential implications for the management of depression-related fatigue.

**Key words:** Major depression, somatic anxiety, fatigue.

## Introduction

Fatigue is a frequent symptom in the general population and one of the principal presenting symptoms in primary care facilities.<sup>1,2</sup> Fatigue is also associated with a wide variety of conditions (physical diseases, neurological or psychiatric disorders, chronic fatigue syndrome), in which it is a major determinant of prognosis and functional capacity.<sup>3</sup> Various self-report measures have been introduced to assess the severity and prevalence of fatigue in various settings.<sup>4,5</sup> The Fatigue Questionnaire<sup>6</sup> is the most widely used multidimensional measure assessing the intensity of reported fatigue-related symptoms.

Depressive and anxiety symptoms are prevalent in many fatigue-related conditions and have been found to correlate with the severity of reported fatigue. Studies in the community and in primary care settings have found that the severity of reported fatigue correlates with the severity of both depression and anxiety.<sup>7-10</sup> Furthermore, several studies have isolated strong independent correlations between the severity of reported fatigue and the intensity of depressive and anxiety symptoms in patients with fatigue-related diseases or conditions, such as multiple sclerosis,<sup>11-13</sup> Parkinson's disease,<sup>14</sup> cancer,<sup>15,16</sup> HIV infection,<sup>17,18</sup> fibromyalgia,<sup>19,20</sup> systemic lupus erythematosus,<sup>21-23</sup> sleep apnea,<sup>24</sup> and chronic fatigue syndrome.<sup>25-27</sup>

Fatigue is a core symptom of major depression as well as a prodromal and a residual symptom of depressive disorders.<sup>28,29</sup> It is prevalent in 73–97% of depressed patients and has a detrimental impact on their level of functioning and quality of life.<sup>30,31</sup> However, fatigue in major depression is understudied compared to other fatigue-related conditions. A few studies have recently attempted to isolate predictors of depression-related fatigue; female gender, sleep disturbances and the severity of depression are the main ones that have been located.<sup>32-35</sup> Depressed patients often suffer from comorbid anxiety disorders or subthreshold anxiety symptoms.<sup>36,37</sup> However, the independent contribution of somatic anxiety symptoms (i.e. effects of autonomic overactivity) to the severity of depression-related fatigue has not been investigated and this was the objective of this study. The isolation of potential additional predictors of depression-related fatigue might allow

clinicians to manage this debilitating symptom in a more specific and efficient way.

## Material and method

### Subjects

Subjects included in the study were consecutive patients of both sexes, aged 18–65 years, who were either hospitalized in one of the wards of the Psychiatric Clinic, or treated at the outpatient service of Eginition Hospital from March 2005 to March 2007. All patients had a diagnosis of Major Depressive Disorder (MDD) and were currently in a Major Depressive Episode (MDE), as assessed by the short structured DSM-IV-based interview MINI version 5.0.0.<sup>38</sup> Moreover, all patients had a 17-item Hamilton Depression Rating Scale (HDRS)<sup>39</sup> score  $\geq 17$ .<sup>40</sup>

Exclusion criteria were: (1) other diagnoses interfering with patients' cooperation in the study (catatonic or psychotic features in the present episode, organic mental disorders, mental retardation), (2) other DSM-IV axis I mental disorders except anxiety disorders (alcohol or other substance abuse during the last 6 months, eating disorder during the last 6 months, sleep disorders) potentially associated with clinically significant fatigue, (3) severe physical diseases or other fatigue-related conditions (severe obesity with BMI >45, pregnancy, fatigue-associated medications except psychotropics), (4) a recent (i.e. less than 3 weeks ago) change in the drug treatment regimen.

All patients had their medical history recorded. A thorough physical examination was carried out and blood was drawn for a biochemical profile, total blood count and basic endocrinological tests within  $\pm 2$  days from the clinical/psychometric evaluations. Patients were further tested once clinical evaluations and routine laboratory tests provided evidence for physical diseases potentially associated with prominent fatigue. When patients met one or more of the exclusion criteria, they did not enter the analyses. All patients were asked to provide written informed consent before participating in the study. The study protocol was approved by the Research Ethics Committee of Eginition Hospital. Subjects finally included were 76 patients, aged between 23 and 65 years (mean  $48.7 \pm 10.6$  years); 65 were females (85.5%) and 38 (50%) were inpatients. Forty-nine

patients (64.5%) were concurrently suffering from anxiety disorder(s), as assessed with the MINI. The majority of patients (N=63, 82.9%) were under anti-depressant medication (47.4% on SSRIs and 35.5% on SNRIs).

### **Measures**

The following instruments were used for cross-sectional assessment of the severity of fatigue and depression.

#### **Fatigue**

The severity of fatigue during the last two weeks prior to assessment was recorded by means of the Fatigue Questionnaire (FQ), a frequently used, established, self-report fatigue questionnaire, comprising 14 items measuring the intensity of fatigue-related symptoms. Each item is rated on a 4-point Likert scale (0 "better than usual", 1 "no more than usual", 2 "worse than usual", 3 "much worse than usual"). The FQ score is the sum of all items' scores. Greek translation and back translation of the FQ was made according to the guidelines of the World Health Organization.<sup>41</sup> The FQ consists of two subscales: a mental and a physical fatigue subscale.<sup>6</sup>

#### **Depression**

The severity of depression was assessed with the 17-item HDRS, which is one of the most widely used observer-rated instruments to assess the severity of depressive symptoms in MDD patients. Ratings are completed by the examiner on the basis of patient interview (depressive symptoms experienced over the past week), information provided by relatives or nurses and observations. Eight items are scored from 0 to 2 and nine items are scored from 0 to 4. A cut-off point of 17 is often used to ensure a degree of depression severity.<sup>40</sup>

#### **Somatic anxiety**

HDRS item 11 measures somatic anxiety and includes physiological concomitants of anxiety, i.e. "butterflies", indigestion, stomach cramps, belching, diarrhoea, palpitations, hyperventilation, paraesthesias, sweating, flushing, tremor, headache, urinary frequency.<sup>39</sup> It is rated on a 5-point Likert scale (0=absent, 1=mild, 2=moderate, 3=severe, 4=incapacitating). Using the median HDRS item 11 score (i.e.

2) as a cut-off point, patients were divided into those with somatic anxiety (HDRS-11 score  $\geq 2$ ) and those without (HDRS-11 score  $\leq 1$ ).

### **Statistical analysis**

Descriptive statistics were used to check the distributions of all variables. Student's independent samples t-test or Mann-Whitney U test (as appropriate) and Pearson Chi-square test were used for the comparison of continuous and categorical variables, respectively, between patients with somatic anxiety and those without. Pearson's (r) and Spearman's (rho) coefficients were employed in bivariate correlations between the FQ score as the dependent variable and the independent variables (age, gender, inpatient status, HDRS score and somatic anxiety status), as well as in intercorrelations between the independent variables to test for collinearity.

Then, a stepwise multiple regression analysis was performed, with the FQ score as the dependent variable, so as to isolate independent predictors of the severity of fatigue. Any variable found to correlate with the FQ score at a  $p < 0.1$  entered the regression analysis. Whenever two independent variables had a Pearson's or Spearman's correlation coefficient  $\geq 0.7$  between them, one of them was excluded from the multivariate analysis for collinearity.<sup>42</sup>

### **Results**

Age, HDRS and FQ scores had approximately normal distributions. HDRS scores ranged from 17 to 33 (mean  $21.7 \pm 5.1$ ). FQ scores ranged from 8 to 42 (mean  $30.3 \pm 7.6$ ); 65.8% of patients had a mean item score of  $> 2$ . Fifty-seven patients (75%) were rated as suffering from somatic anxiety (HDRS-11 score  $\geq 2$ ).

Patients with somatic anxiety did not significantly differ from those without in age ( $t = 0.19$ ,  $df = 74$ ,  $P = 0.85$ ), gender ( $\chi^2 = 0.89$ ,  $p = 0.35$ ) and inpatient status ( $\chi^2 = 0.63$ ,  $p = 0.43$ ). However, patients with somatic anxiety had significantly higher scores both on the HDRS ( $t = 3.83$ ,  $df = 74$ ,  $p < 0.001$ ) and the FQ ( $t = 3.32$ ,  $df = 74$ ,  $p < 0.001$ ). Inpatients scored higher on the HDRS ( $t = 2.71$ ,  $df = 74$ ,  $p = 0.008$ ) than outpatients, but these two groups did not significantly differ in the FQ score ( $t = 0.36$ ,  $df = 74$ ,  $p = 0.72$ ). There were not significant differences between males and females both

in the HDRS (U test,  $z=1.58$ ,  $p=0.11$ ) and FQ scores (U test,  $z=1.69$ ,  $p=0.09$ ). Medicated and non-medicated patients had not significant differences in HDRS ( $t=0.87$ ,  $df=74$ ,  $P=0.39$ ) and FQ scores ( $t=0.34$ ,  $df=74$ ,  $p=0.74$ ). Patients on SNRIs did not significantly differ from those on SSRIs in HDRS ( $t=0.80$ ,  $df=61$ ,  $p=0.42$ ) and FQ scores ( $t=0.82$ ,  $df=61$ ,  $p=0.41$ ).

Bivariate (Pearson's or Spearman's, as appropriate) correlations between FQ scores and the independent variables are shown in table 1. FQ scores significantly correlated with HDRS scores ( $r=0.36$ ,  $p=0.001$ ) and somatic anxiety status ( $\rho=0.35$ ,  $p=0.002$ ). Age, gender, HDRS score and somatic anxiety status entered the multiple regression model with the FQ score as the dependent variable. The HDRS score and somatic anxiety status turned out to be the only significant predictors of the FQ score, with standardized beta coefficients of 0.259 ( $p=0.028$ ) and 0.255 ( $p=0.031$ ), respectively.  $R^2$  was 0.185.

**Discussion**

The present study aimed to investigate whether somatic anxiety independently correlates with the severity of fatigue reported by patients with unipolar non-psychotic major depression. Depressed patients

with other axis I mental disorders (except anxiety disorders) or severe physical diseases potentially associated with prominent fatigue were excluded, so that the confounding effect of other fatigue-related conditions is avoided. Moreover, included patients were either drug-free (17.1%) or, when medicated (82.9%), on a stabilized antidepressant treatment regimen, so as to avoid the confounding effect of side-effects associated with treatment initiation or modification. The correlation of the severity of reported fatigue with anxiety symptoms has been investigated in the general population,<sup>9,10</sup> in patients with chronic fatigue syndrome,<sup>27</sup> neurological or physical diseases,<sup>11-24</sup> but not in patients with major depression. Fatigue is highly prevalent in these patients and has a debilitating effect on them; therefore, the isolation of independent predictors of fatigue reported by depressed patients and the implementation of effective treatment strategies are highly warranted.<sup>43</sup>

In general, the percentages of fatigue and somatic anxiety of clinically significant severity reported by patients in our sample are in accordance with data from previous studies.<sup>30,31,33,35-37,44</sup> The severity of fatigue did not have significant correlations with age, in accordance with data from previous studies.<sup>32,34,35</sup>

**Table 1.** Correlations between FQ score, age, gender, inpatient status, depression severity (HDRS score) and somatic anxiety status in patients with major depression.

	<i>FQ</i>	<i>Age</i>	<i>Inpatient status</i>	<i>Gender</i>	<i>HDRS</i>	<i>Somatic anxiety status</i>
FQ	1.000					
Age	-0.054	1.000				
	0.641					
Inpatient status	0.000	0.183	1.000			
	1.000	0.113				
Gender	-0.195	0.108	0.037	1.000		
	0.092	0.352	0.748			
HDRS	0.362(**)	0.156	0.293(*)	0.183	1.000	
	0.001	0.179	0.010	0.114		
Somatic anxiety status	0.352(**)	-0.037	0.091	-0.108	0.394(**)	1.000
	0.002	0.753	0.434	0.353	<0.001	

Pearson's r or Spearman's rho correlation coefficients with corresponding p-values, \* $P<0.05$ , \*\* $P<0.01$  (two-tailed)

Gender (0: female, 1: male); inpatient status (0: outpatient, 1: inpatient); somatic anxiety status (0: without somatic anxiety, 1: with somatic anxiety)

Fatigue scores did not significantly differ between males and females, in contrast to findings from previous reports which have recorded higher levels of fatigue in female subjects.<sup>32,34</sup> This may be due to the low percentage of males (14.5%) in our sample, which may have concealed gender differences in fatigue scores, as well as to males having slightly higher, albeit not to a statistically significant degree, HDRS scores than females (mean 24.3 vs 21.3). Inpatients were more depressed than outpatients, as expected, but their difference in HDRS scores (means 23.3 vs 20.2) was not great enough to yield a statistically significant difference in FQ scores, as well.

The severity of fatigue was significantly correlated with the severity of depression (HDRS score) in our sample, corroborating previous findings.<sup>33-35,44</sup> Fatigue scores were significantly higher in patients with somatic anxiety compared to those without, independent of the severity of depression. This finding has potential implications for the rationale of therapeutic interventions needed to alleviate depression-related fatigue. Somatic anxiety lowering medications, such as anxiolytics or beta-blockers, might prove to be helpful, when properly selected and dosaged, in the management of fatigue-related complaints in depressed patients.

Certain limitations of this study should be noted. First, the vast majority of patients studied were under antidepressant medication (SSRIs or SNRIs). Fatigue and somatic anxiety in depressed subjects

under treatment can be associated both with depression per se and with its treatment. Nevertheless, recorded fatigue severity was not correlated with being or not medicated nor with the kind of antidepressant received (SSRIs or SNRIs), suggesting that antidepressant-related fatigue might, at least in part, be compensated for by the alleviating effects of antidepressants on depression-associated fatigue. Moreover, newer antidepressants are far less associated with fatigue and other physical complaints than older tricyclic drugs.<sup>45</sup> Second, the low percentage of males in our sample may have concealed gender differences in fatigue scores. A final limitation was that estimates of somatic anxiety relied exclusively on HDRS item 11, which concerns physiological concomitants of anxiety, and no specific somatic anxiety scale was used. Therefore, our results should be replicated in studies using specific anxiety scales also measuring a somatic anxiety component.

In conclusion, our results suggest that the severity of depression as well as the presence of somatic anxiety independently correlate with the severity of reported fatigue in patients with major depression; this finding has potential implications for the management of depression-related fatigue. However, further studies are warranted to investigate questions about the causality of recorded associations between fatigue and somatic anxiety in major depression as well as the underlying pathophysiological mechanisms.

## **Κόπωση και σωματικό άγχος σε ασθενείς με μείζονα κατάθλιψη**

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Σκοπός της παρούσας μελέτης ήταν η διερεύνηση της ανεξάρτητης συνεισφοράς του σωματικού άγχους στη βαρύτητα της κόπωσης που σχετίζεται με τη μείζονα κατάθλιψη. Μελετήθηκαν 76 ασθενείς (85,5% γυναίκες, 50% εσωτερικοί ασθενείς), ηλικίας 23-65 ετών (ΜΟ 48,7±10,6), που εί-

χαν διαγνωσθεί με μείζονα καταθλιπτική διαταραχή και βρίσκονταν τη δεδομένη στιγμή σε μείζον καταθλιπτικό επεισόδιο (με βάση τη βραχεία δομημένη συνέντευξη MINI 5.0.0.). Όλοι οι ασθενείς είχαν ελάχιστη βαθμολογία 17 στην κλίμακα κατάθλιψης του Hamilton των 17 λημμάτων (HDRS). Αποκλείστηκαν ασθενείς με σωματικές νόσους ή άλλες καταστάσεις που συνοδεύονται από έντονη κόπωση. Η αναφερόμενη κόπωση μετρήθηκε με το ερωτηματολόγιο κόπωσης (FQ), των Chalder et al (1993), που έχει 14 λήμματα και αποτελείται από δύο υποκλίμακες, σωματικής και διανοητικής κόπωσης. Με βάση τη διάμεσο βαθμολογία (δηλαδή 2) στο λήμμα 11 της HDRS, που μετράει σωματικό άγχος, οι ασθενείς διαιρέθηκαν σε όσους είχαν σωματικό άγχος (HDRS-11 $\geq$ 2) και σε όσους δεν είχαν (HDRS-11 $\leq$ 1). Στη συνέχεια, υπολογίσθηκαν οι συντελεστές συσχέτισης Pearson (r) ή Spearman (rho) ανάμεσα στη βαθμολογία στο FQ, την ηλικία, το φύλο, την ύπαρξη ή μη σε νοσηλεία, τη βαθμολογία στην HDRS και την ύπαρξη ή μη σωματικού άγχους. Τελικά, πραγματοποιήθηκε ανάλυση πολλαπλής παλινδρόμησης με το FQ ως εξηγημένη μεταβλητή για τη διερεύνηση των παραμέτρων που συσχετιζόνταν ανεξάρτητα με τη βαρύτητα της αναφερόμενης κόπωσης. 49 ασθενείς (64.5%) διεγνώσθησαν επιπλέον με τουλάχιστον μία αγχώδη διαταραχή. 57 ασθενείς (75%) βρέθηκαν να έχουν σωματικό άγχος (HDRS-11 $\geq$ 2). Οι ασθενείς με σωματικό άγχος είχαν σε βαθμό στατιστικά σημαντικό υψηλότερη βαθμολογία στις κλίμακες HDRS (t=3,83, df=74, p<0,001) και FQ (t=3.32, df=74, p<0,001) σε σύγκριση με τους ασθενείς χωρίς σωματικό άγχος. Η βαθμολογία στο FQ συσχετίστηκε σε βαθμό στατιστικά σημαντικό με τη βαθμολογία στην HDRS (r=0,36, p=0,001) και με την ύπαρξη σωματικού άγχους (rho=0,35, p=0,002). Η βαθμολογία στην HDRS και η ύπαρξη σωματικού άγχους συσχετιζόνταν ανεξάρτητα με τη βαθμολογία στο FQ στην ανάλυση πολλαπλής παλινδρόμησης, με σταθμισμένους συντελεστές βήτα 0,259 (p=0,028) και 0,255 (P=0,031), αντίστοιχα. Η τιμή του R<sup>2</sup> ήταν 0,185. Τόσο η βαρύτητα της κατάθλιψης όσο και η παρουσία σωματικού άγχους συσχετίζονται ανεξάρτητα με τη βαρύτητα της αναφερόμενης κόπωσης σε ασθενείς με μείζονα κατάθλιψη. Το εύρημα αυτό είναι πιθανώς χρήσιμο στην αντιμετώπιση της κόπωσης που σχετίζεται με τη μείζονα κατάθλιψη.

**Λέξεις ευρητηρίου:** Μείζονα καταθλιπτική διαταραχή, σωματικό άγχος, κόπωση.

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