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Fatigue in female patients with major depression: The effect of comorbid anxiety disorders

P. Ferentinos,¹ V.P. Kontaxakis,¹ B.J. Havaki-Kontaxaki,² D. Dikeos,²
G.N. Papadimitriou,² L. Lykouras¹

¹2nd Department of Psychiatry, Attikon General Hospital, University of Athens, Medical School, Athens,

²1st Department of Psychiatry, Eginition Hospital, University of Athens, Medical School, Athens, Greece

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Several studies have investigated fatigue in the general population, in primary care facilities as well as in patients with fatigue-related physical diseases, but only marginally in patients with Major Depressive Disorder (MDD). Therefore, the investigation of correlates of depression-related fatigue is highly warranted and expected to facilitate the implementation of effective fatigue-specific treatment strategies. Depressed patients often suffer from comorbid anxiety disorders (CADs) or subthreshold anxiety symptoms. This study aimed to investigate the independent correlation of the severity of fatigue in female patients with MDD with the presence, number and type of CADs. We studied 70 consecutive female MDD patients (48.6% inpatients), aged 23–65 years (mean 48.2±10.6 years), currently in a Major Depressive Episode [17-item Hamilton Depression Rating Scale (HDRS) score≥17] and free of other fatigue-associated conditions. Diagnostic assessments were made with the short structured DSM-IV-based MINI version 5.0.0. Reported fatigue was assessed with the 14-item Chalder Fatigue Questionnaire (FQ). Correlations between the FQ score and age, inpatient status, HDRS score, presence and number of CADs were calculated. Then, stepwise multiple regression analyses were performed, with the FQ score as the dependent variable, so as to isolate independent predictors of the severity of fatigue. 92.9% of patients had clinically significant fatigue. 62.9% were suffering from at least one CAD (38.6% met criteria for one CAD, 21.4% for two and 2.9% for three). 51.4% were diagnosed with generalized anxiety disorder (GAD), 25.7% with panic disorder and/or agoraphobia (PD/AP), 17.1% with social anxiety disorder and 7.1% with obsessive-compulsive disorder. The FQ score was significantly correlated with the HDRS score ($r=0.406$, $p<0.001$), the presence of any CAD(s) ($\rho=0.4$, $p=0.001$), the number of CADs ($\rho=0.393$, $p=0.001$), the presence of GAD ($\rho=0.421$, $p<0.001$) and the presence of PD/AP ($\rho=0.252$, $p=0.035$). In multiple regression analyses, the presence and number of CADs and the presence of comorbid GAD turned out as significant independent predictors of the FQ score along with the HDRS score. The severity of fatigue in female MDD patients is independently correlated with the presence and number of CADs and, in specific, comorbid GAD. Our findings imply that: (1) this effect might in part account for greater impairment/disability and adverse prognosis for MDD with CADs; (2) high levels

of fatigue, putatively clustering with anxiety symptoms, may be a marker of severity and anxiety disorders comorbidity for MDD and may define an "anxious-fatigued" subtype/phenotype in this population; (3) medications and psychotherapies for the management of severe depression-related fatigue should also target CADs.

Key words: Fatigue, anxiety disorders, comorbidity, generalized anxiety disorder, major depression

Introduction

Fatigue is considered a core symptom of major depressive disorder (MDD); its prevalence in depressed patients ranges in various studies from 73 to 94%.^{1,2} Fatigue is also a common residual symptom of depressive disorders with a slow and poor response to antidepressant treatment³ and a major risk factor of chronicity of MDD.⁴ Moreover, the severity of reported fatigue is a key predictor of quality of life and social and occupational functioning in MDD patients.⁵ However, fatigue in these patients has been studied far less than in other fatigue-related conditions. Several studies have investigated fatigue in the general population, in primary care facilities as well as in patients with fatigue-related physical diseases, but only marginally in MDD patients;⁶ the severity of fatigue in these patients has been found to correlate with the severity of depression,^{7,8} sleep disturbances⁹ and female gender.¹⁰ Therefore, the investigation of correlates of depression-related fatigue is highly warranted and expected to facilitate the implementation of effective fatigue-specific treatment strategies.

Depressed patients often suffer from comorbid anxiety disorders or subthreshold anxiety symptoms.^{11,12} In fact, the term "anxious depression" has been coined to describe the highly prevalent co-occurrence of depression and anxiety spectrum disorders.¹³ Assessment of co-morbid anxiety in patients with depression is of great importance since patients with both anxious and depressive symptoms have been shown to have poorer clinical outcomes, a worse prognosis, a more protracted course of illness, worse psychosocial functioning, and decreased response and compliance to treatment.¹⁴⁻¹⁷ The objective of this study was to investigate the independent correlation of the severity of fatigue in female MDD patients with the presence, type and number of comorbid anxiety disorders (CADs).

Material and method

Subjects

Subjects participating in the study were consecutive female patients, aged 18–65 years, who were either hospitalized in one of the wards of the Psychiatric Clinic, or treated at the outpatient service of the Eginition Hospital, University of Athens; all of them had a main diagnosis of MDD and were currently in a Major Depressive Episode (MDE), as assessed by the same examiner-psychiatrist (PF) with the short structured DSM-IV-based Mini International Neuropsychiatric Interview (MINI) version 5.0.0.¹⁸ Moreover, all patients had a 17-item Hamilton Depression Rating Scale (HDRS)¹⁹ score ≥ 17 .²⁰ Patients' clinical diagnosis (of MDD and specific CADs) was verified by an independent chief psychiatrist (VK) according to DSM-IV criteria. Demographic (age, employment status, education, family status) and clinical characteristics (MDD duration, age at onset, number of MDEs, duration of current MDE, chronicity, lifetime number of suicide attempts and lifetime number of psychiatric hospitalizations) of patients were also recorded.

Patients were excluded if: (1) additional diagnoses or specifiers interfered with cooperation in the study (catatonic or psychotic features in the present episode, organic mental disorders, mental retardation), (2) they met criteria for other DSM-IV axis I mental disorders potentially associated with clinically significant fatigue (except anxiety disorders), (3) they suffered from severe fatigue-associated physical diseases (e.g., infections, neoplasms, rheumatic, haematological, endocrine diseases, etc.), (4) other fatigue-related conditions were met (severe obesity with BMI > 45, pregnancy, fatigue-associated medications except psychotropics), (5) a recent (i.e. less than 3 weeks ago) change in the drug treatment regimen had been effected.

All patients had their medical history recorded. A thorough physical examination was carried out and

blood was drawn for a biochemical profile, basic endocrinological tests and complete blood count within ± 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 analysis. Selected 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.

A total of 77 patients (41 outpatients and 36 inpatients) were screened. Out of them, 2 inpatients and 2 outpatients were excluded since they suffered from a physical disease (multiple sclerosis, anemia, chronic obstructive pulmonary disease) or condition (severe obesity with BMI > 45) potentially associated with clinically significant fatigue; moreover, another outpatient was excluded as diagnosed with "Bipolar II disorder, currently in a MDE", while another 2 outpatients refused to participate in the study. Subjects finally included were 70 female patients, aged between 23 and 65 years (mean 48.2 ± 10.6 years); 34 were inpatients (48.6%). All patients were under antidepressant medication (57.1% on SSRIs and 42.9% on SNRIs).

Measures

Fatigue

The severity of fatigue reported by patients during the last two weeks prior to assessment was recorded by means of the 14-item Fatigue Questionnaire (FQ).²¹ The FQ is an established, self-report fatigue questionnaire assessing the intensity of fatigue-related symptoms.^{22,23} 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 (range 0–42). An alternative scoring method uses a bimodal response system which dichotomizes Likert scores (0, 0, 1, 1), giving a score range of 0–14. Receiver Operating Characteristics analysis has demonstrated that a cut-off of 4 or higher (3/4) best defines cases of clinically significant fatigue when the bimodal response format is used.²¹ The FQ was recently standardised in MDD patients by our group.²⁴ Previous validity studies have confirmed a two dimension structure: a

physical (FQphys: items 1–8) and a mental (FQment: items 9–14) fatigue subscale.²¹

Depression

The severity of patients' depression was assessed by 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. 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.²⁰ All ratings were completed by the same examiner-psychiatrist (PF) on the basis of patient interview (depressive symptoms experienced over the past week), information provided by relatives or nurses and observations.

Statistical analysis

Descriptive statistics were used to explore the sample's demographic and clinical characteristics. 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 patient subgroups. Pearson's (r) or Spearman's (rho) coefficients were then employed to calculate bivariate correlations between the FQ score as the dependent variable and the independent variables (age, inpatient status, HDRS score, presence and number of CADs), as well as in intercorrelations between the independent variables to test for collinearity. Then, stepwise multiple regression analyses were performed, with the FQ score as the dependent variable, so as to isolate independent predictors of the severity of fatigue. Whenever two independent variables had a Pearson's or Spearman's correlation coefficient ≥ 0.7 between them, one of them was excluded from the multivariate analysis for collinearity.²⁵ All statistical analyses were carried out using SPSS version 14.0 for Windows.

Results

Patient demographic and clinical characteristics

Demographic and clinical characteristics of the total sample are presented in table 1. There were no missing data regarding all measures administered. HDRS and FQ scores were approximately normally

Table 1. Demographic and clinical characteristics of the total sample (N=70) and comparison of patients with (N=44) and without (N=26) comorbid anxiety disorders

	<i>Total sample</i>	<i>MDD with CAD</i>	<i>MDD without CAD</i>	<i>Statistics</i>
Age (y)	48.2±10.6	47.8±10.4	48.9±11.2	ns ^a
Inpatient	48.6%	52.3%	42.3%	ns ^b
Employed	31.4%	27.3%	38.5%	ns ^b
Education (y)	10.6±4.5	10.7±4.0	10.2±5.3	ns ^a
Living alone	40.0%	36.4%	46.2%	ns ^b
MDD duration (y)	13.1±10.8	13.8±10.7	11.8±11.0	ns ^a
Age at onset (y)	35.1±12.6	34.0±12.5	37.1±12.7	ns ^a
Number of episodes	3.8±2.7	3.9±2.5	3.6±3.0	ns ^c
Duration of current episode (m)	8.9±12.8	9.5±15.5	7.7±5.9	ns ^c
Chronicity	7.1%	9.1%	3.8%	ns ^b
Lifetime number of suicide attempts	0.8±1.7	0.9±1.5	0.7±2.0	ns ^c
Lifetime number of psychiatric hospitalizations	1.5±2.4	1.6±2.4	1.4±2.4	ns ^c
HDRS	21.4±5.1	23.6±4.6	17.8±3.8	p<0.001 ^a
FQ	30.4±8.0	32.9±6.5	26.1±8.6	p<0.001 ^a

^aIndependent samples t-test, ^bPearson's chi-square, ^cMann-Whitney U test

MDD=Major Depressive Disorder, CAD=comorbid anxiety disorder(s), HDRS=Hamilton Depression Rating Scale score, FQ=Fatigue Questionnaire score, ns=non-significant, y=years; m=months

distributed. HDRS scores ranged from 17 to 33 (mean 21.4±5.1), while FQ scores ranged from 8 to 42 (mean 30.4±8.0). The mean FQphys score was 18.3±4.8 (range 7–24), while the mean FQment score was 12.0±3.8 (range 1–18). Sixty-five patients (92.9%) had fatigue of clinically significant severity, on the basis of the cut-off of ≥4 when the dichotomized item scores (bimodal response format) were used.

Forty-four patients (62.9%) were concurrently suffering from at least one anxiety disorder, as assessed with the MINI; 38.6% of patients met criteria for one CAD, 21.4% for two and 2.9% for three. The prevalence of CADs diagnosed was 51.4% for generalized anxiety disorder (GAD), 25.7% for panic disorder (PD) and/or agoraphobia (AP), 17.1% for social anxiety disorder (SAD) and 7.1% for obsessive-compulsive disorder (OCD).

Comparisons between groups and correlations

Inpatients and outpatients did not significantly differ in age ($t=1.72$, $df=68$, $p=0.09$), HDRS score (22.6±5.3 vs 20.4±4.8, respectively; $t=1.83$, $df=68$, $p=0.07$) and FQ score (30.0±8.3 vs 30.8±7.7, respectively; $t=0.42$, $df=68$, $p=0.67$). Patients on SNRIs did not significantly differ from those on SSRIs in HDRS scores ($t=1.15$, $df=68$, $p=0.26$), FQ scores ($t=1.93$, $df=68$, $p=0.06$) and frequency of CADs ($\chi^2=1.75$, $p=0.19$).

Patients with CADs (N=44) did not significantly differ from those without (N=26) in age, inpatient status,

education years, employment status, family status, MDD duration, age at onset, number of MDEs, chronicity, lifetime number of suicide attempts and lifetime number of psychiatric hospitalizations; however, the former had significantly higher HDRS ($t=5.5$, $df=68$, $p<0.001$) and FQ scores ($t=3.76$, $df=68$, $p<0.001$) (table 1). When patients with (N=36) and without (N=34) comorbid GAD were compared on the same set of parameters, the former had a greater number of MDEs (U test, $z=2.25$, $p=0.025$), a trend for more lifetime suicide attempts (U test, $z=1.80$, $p=0.072$) as well as higher HDRS ($t=5.0$, $df=68$, $p<0.001$) and FQ scores ($t=3.7$, $df=68$, $p<0.001$).

Bivariate (Pearson's or Spearman's, as appropriate) correlations between FQ score, age, inpatient status, HDRS score and the presence or number of CADs are shown in table 2. The FQ score was significantly correlated with the HDRS score ($r=0.406$, $p<0.001$), the presence of any CAD(s) ($\rho=0.4$, $p=0.001$), the number of CADs ($\rho=0.393$, $p=0.001$), the presence of GAD ($\rho=0.421$, $p<0.001$) and the presence of PD/AP ($\rho=0.252$, $p=0.035$).

Multiple regression analysis

Given that the presence of any CAD(s), the number of CADs and the presence of GAD were found collinear, with intercorrelation coefficients >0.7 between them (table 2), three distinct multiple regression

Table 2. Correlations between FQ score, age, inpatient status, HDRS score, presence and number of comorbid anxiety disorders in female MDD patients.

	<i>FQ</i>	<i>Age</i>	<i>Inpatient status</i>	<i>HDRS</i>	<i>CAD</i>	<i>Number of CADs</i>	<i>GAD</i>	<i>PD/AP</i>	<i>SAD</i>	<i>OCD</i>
FQ	1									
Age	<i>-0.084</i> 0.491	1								
Inpatient status	-0.038 0.758	0.208 0.084	1							
HDRS	0.406(**) <0.001	0.181 0.133	0.211 0.080	1						
CAD	0.400(**) 0.001	-0.075 0.539	0.096 0.428	0.563(**) <0.001	1					
Number of CADs	0.393(**) 0.001	-0.087 0.474	0.057 0.638	0.566(**) <0.001	0.891(**) <0.001	1				
GAD	0.421(**) <0.001	-0.005 0.968	0.087 0.476	0.524(**) <0.001	0.791(**) <0.001	0.744(**) <0.001	1			
PD/AP	0.252(*) 0.035	-0.059 0.627	0.082 0.499	0.478(**) <0.001	0.452(**) <0.001	0.675(**) <0.001	0.179 0.137	1		
SAD	0.012 0.920	-0.142 0.242	0.007 0.954	-0.072 0.555	0.189 0.117	0.358(**) 0.002	0.116 0.338	0.137 0.259	1	
OCD	0.000 1.000	-0.118 0.330	-0.159 0.190	0.025 0.839	0.213 0.076	0.275(*) 0.021	-0.063 0.602	0.091 0.455	-0.068 0.574	1

Spearman's rho or Pearson's r (in bold italics) correlation co-efficients (upper line of each cell) with corresponding p-values (lower line)

*P<0.05, **P<0.01 (2-tailed)

MDD=Major Depressive Disorder; FQ=Fatigue Questionnaire score; inpatient status (0: outpatient, 1: inpatient); gender (0: female, 1: male); HDRS=Hamilton Depression Rating Scale score; CAD=comorbid anxiety disorder(s); GAD=generalized anxiety disorder, PD/AP=panic disorder and/or agoraphobia; SAD=social anxiety disorder; OCD=obsessive-compulsive disorder (for CAD, GAD, PD/AP, SAD, OCD, 0: absence, 1: presence)

models with the FQ score as the dependent variable were built. In all three, age, inpatient status and the HDRS score were included among the independent variables. In the first model, the presence of any CAD(s) was also included among the independent variables and turned out as the only significant predictor of the FQ score, with a standardised beta coefficient of 0.415 ($p<0.001$, $R^2=0.172$). In the second model, the number of CADs was also included and turned out as the only significant predictor of the FQ score, with a standardised beta coefficient of 0.411 ($p<0.001$, $R^2=0.169$). In the third model, the presence of specific anxiety disorders (GAD, PD/AP, SAD, OCD) was also included; the HDRS score and the presence of GAD turned out as the only significant predictors of the FQ score, with standardised beta coefficients of 0.264 ($p=0.041$) and 0.271 ($p=0.036$), respectively, and an R^2 of 0.218. Of notice, the statistical signifi-

cance and standardized beta coefficients in the three aforementioned models remained unchanged when SSRIs/SNRIs status was also included among the independent variables.

Discussion

The present study aimed to investigate the effect of CADs on the severity of fatigue in female patients with unipolar non-psychotic MDD. Patients with physical diseases or other conditions potentially associated with prominent fatigue were excluded, so that the confounding effect of other fatigue-related conditions is avoided. In general, levels of fatigue reported by patients in our sample (92.9%) are in line with data from previous studies.^{1,2,7} One of the advantages of this study compared to many previous ones is that the severity of fatigue in MDD patients was

measured with a specific fatigue measure (FQ) that is the only one to have been standardized specifically for depressed patients.²⁴ FQ scores in our sample showed moderate correlations with the severity of depression, corroborating previous findings.^{7,8} FQ scores had non-significant correlations with age, in accordance with data from previous studies.^{8,10}

In general, the high comorbidity rates of MDD and anxiety disorders detected in our sample are in line with previous reports. Landmark epidemiological community surveys have reported high prevalence rates of a lifetime anxiety disorder in MDD patients: 47% in the Epidemiologic Catchment Area study;²⁶ 58% in the National Comorbidity Survey (NCS).¹¹ The ORs for comorbidity of MDD with the specific anxiety disorders were: 6.0 for GAD, 4.0 for PD and Post-Traumatic Stress Disorder (PTSD), and 2.9 for SAD (mean OR=4.2).¹¹ In primary care samples, comorbidity of depressive and anxiety disorders seems to be more common than either disorder alone.²⁷ The largest study to date to investigate clinical correlates of anxious features in MDD outpatients with a dimensional approach reported a prevalence estimate of anxious depression of 46%; patients with anxious MDD were significantly more likely to be older, unemployed, less educated and more severely depressed.²⁸ Studies in psychiatric, community and primary care samples have shown that MDD patients with CADs have poorer clinical outcomes, more severe symptoms, a worse prognosis, worse overall functioning, greater suicide potential, increased treatment seeking, higher frequency and intensity of side-effects, greater refractoriness and reduced compliance to treatment.^{11,15,17,28-30} Recently published data from the multi-center Coordinated Anxiety Learning and Management (CALM) study in primary care outpatients showed that when the number of CADs increases, mental and physical functioning and well-being deteriorates and disability increases.³¹

Comorbidity between GAD and MDD is particularly strong. The NCS follow-up study recorded a high rate of lifetime comorbidity between the two disorders (OR=6.6).³² Moreover, a number of primary care studies have shown that 35–50% of patients with current major depression have comorbid GAD; this is often higher than rates of other comorbid disorders.¹⁴ Compared to depressed patients without GAD, depressed patients with comorbid GAD have an earlier

age at onset, higher levels of suicidal ideation and pathological worry, poorer social functioning, and a greater frequency of other anxiety disorders, eating disorders, and somatoform disorders.³³ Community and primary care studies show that MDD comorbid with GAD is associated with more impairment and disability, compromised quality of life, greater health-care utilization and a poorer or slower response to both pharmacotherapy and psychotherapy than MDD without GAD.^{11,30,34,35}

Fatigue tends to be highly correlated with psychological distress (depression and anxiety) both in community and primary care settings.³⁶⁻³⁸ In a factor-analytic study of depressive symptoms in MDD outpatients, lack of energy/fatigability was significantly correlated with depressive anhedonia and anxiety/irritability.³⁹ Several studies have assessed the impact of CADs (and/or specifically comorbid GAD) on global measures of functioning, disability or health-related quality of life (e.g. the 36-item Short-Form Health Survey) in MDD patients.^{15,28,30,33} In most of these studies, a significant effect of CADs on fatigue severity can indirectly be deduced from specific items or subscales of the generic measures used. Our study is the first to investigate the effect of CADs on the severity of fatigue in MDD patients, as directly recorded with a specific fatigue measure (FQ); a main outcome was that the presence of CADs was an independent predictor of the severity of reported fatigue (FQ score) in MDD patients. This finding implies that the negative impact of CADs on the course and prognosis of MDD documented in community, psychiatric and primary care samples is in part accounted for by higher levels of fatigue reported by anxious MDD patients, as fatigue is known to predict a chronic course and early relapse of MDD.⁴ Furthermore, our study recorded a "dose-response" relationship between the number of CADs and levels of fatigue in MDD patients, in line with the results of the CALM study.³¹ A third finding of our study was that the presence of GAD, in specific, correlated independently with the severity of fatigue in female MDD patients, in accordance with greater impairment/disability and reduced functioning associated with MDD/GAD comorbidity in community and primary care studies.

Several lines of evidence might provide an explanation for our findings. Fatigue is a major symptom

of both MDD and GAD; therefore, when both conditions are present clinically significant fatigue is more probable to be reported. Both depression and anxiety might, as well, be considered as pathoplastic factors for fatigue through psychoneuro-endocrinological or immunological mechanisms. Activation of the hypothalamic-pituitary-adrenal (HPA) axis and high concentrations of pro-inflammatory cytokines (such as IL-1 β , IL-6 and TNF- α) associated with both chronic stress/anxiety and major depression contribute to a pro-inflammatory response in the brain.^{40,41} This condition mediates most stress- and depression-related symptoms, such as sleep compromise, fatigue, anorexia and decreased libido, and forms the basis of the "sickness" hypothesis of chronic stress and depression.⁴⁰ Moreover, brain inflammation is associated with neurotoxicity and neurodegeneration of critical brain structures, putatively accounting for symptoms such as fatigue and cognitive dysfunction in affective disorders.⁴² MDD patients with comorbid anxiety were shown to have a higher cortisol awakening response⁴³ and attenuated cortisol or adrenocorticotrophic hormone (ACTH) responses to HPA axis challenge tests compared to patients with "pure" depression.⁴⁴ However, no study has yet compared cytokine profiles of MDD patients with comorbid anxiety and those without.

Studies in primary care and community twin samples have stressed the independence of prolonged fatigue from psychological distress (anxiety/depression), with only partial genetic covariation between them.^{36,45-47} In a large multi-center study exploring the familiarity of symptom dimensions in MDD, anxiety symptoms and fatigability/exhaustion loaded on two separate factors which showed the highest degrees of correlation between depressed siblings (i.e. familiarity).⁴⁸ Therefore, the co-occurrence of high levels of fatigue and anxiety symptoms in a subgroup of MDD patients may define an "anxious-fatigued" subtype with possibly distinct genetic and clinical characteristics. Family and twin studies have shown that depression and anxiety disorders co-aggregate in families and share, to a considerable extent, common genetic liabilities; more specifically, MDD and GAD in females have been reported to have a genetic correlation of unity, i.e. vulnerability to both disorders is influenced by the same genetic factors.⁴⁹ Genetic pleiotropy has been proposed as an explanation for the high comorbidity rates of MDD and

GAD.⁵⁰ Furthermore, first-degree relatives of patients with anxious depression have been reported to have a higher risk of depression²⁹ and GAD³³ compared to first-degree relatives of patients with "pure" depression (without comorbid anxiety), suggesting a higher familial prevalence and a heavier genetic loading for both depression and GAD in anxious depressed patients. Comorbid anxiety symptoms (or comorbid GAD) could, therefore, be conceptualized as familiarity/heritability and severity markers for MDD.²⁹ According to the findings of our study, it might be hypothesized that high levels of fatigue, putatively clustering with anxious phenotypes, are a marker of severity and anxiety disorders comorbidity for MDD.

A potential implication of our findings regards the rationale of therapeutic interventions needed to alleviate depression-related fatigue. Unfortunately, little solid empirical evidence is available to guide what modifications might optimize treatment of anxious depression; the first study to systematically investigate how the presence of comorbid anxiety may impact treatment planning for MDD outpatients indicated that practitioners solely tend to prescribe a greater number of psychotropics to depressed patients with comorbid anxiety.⁵¹ Yet, there is strong evidence that while all antidepressant medications are approximately equally effective for the treatment of depression, serotonin-acting antidepressants are superior over norepinephrine-acting antidepressants in the treatment of anxiety disorders; moreover, various psychotherapies have proved effective in treating anxiety disorders.¹⁶ Our findings imply that treatment regimes designed to manage severe fatigue-related complaints in MDD patients might be expected to include properly selected, dosaged and titrated medications as well as psychotherapeutic options which should also target CADs.

The following limitations of this study should be noted: All enrolled patients were on a stabilized antidepressant regimen (SSRIs or SNRIs) for at least 3 weeks, so that side-effects emerging during medication titration or withdrawal were avoided. Yet, fatigue and comorbid anxiety in depressed subjects under treatment may be associated both with depression per se and with its treatment. Nevertheless, recorded fatigue severity was not correlated with the kind of antidepressant received (SSRIs or SNRIs). Another limitation in this study was that only female

patients were included. Therefore, our results are not generalizable to all MDD patients. Further studies including both female and male subjects are needed in order to investigate potential sex differences or similarities of the effect of comorbid anxiety on depression-related fatigue.

In conclusion, the severity of fatigue in female MDD patients, as recorded with the FQ, is independently correlated with the presence and number of CADs and in specific comorbid GAD. This effect might in part account for greater impairment/disability, reduced functioning and adverse prognosis

associated with MDD comorbid with anxiety disorders (and, in specific, GAD) documented in community, psychiatric and primary care samples. Our results lend support to the hypothesis that high levels of fatigue, putatively clustering with anxiety symptoms, are a marker of severity and anxiety disorders comorbidity for MDD and may define an "anxious-fatigued" subtype/phenotype in this population. Finally, our findings imply that medications and psychotherapies selected for the management of severe depression-related fatigue should also target CADs.

Η κόπωση σε γυναίκες ασθενείς με μείζονα κατάθλιψη: Η επίδραση των συννοσηρών αγχώδων διαταραχών

**Π. Φερεντίνος,¹ Β.Π. Κονταξάκης,¹ Μ.Ι. Χαβάκη-Κονταξάκη,² Δ. Δικαίος,²
Γ.Ν. Παπαδημητρίου,² Λ. Λύκουρας¹**

¹Β΄ Ψυχιατρική Κλινική, ΓΝΑ Αττικό, Πανεπιστήμιο Αθηνών, Ιατρική Σχολή, Αθήνα,

²Α΄ Ψυχιατρική Κλινική, Αιγινήτειο Νοσοκομείο, Πανεπιστήμιο Αθηνών, Ιατρική Σχολή, Αθήνα

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Αρκετές μελέτες έχουν διερευνήσει την κόπωση στον γενικό πληθυσμό, στις υπηρεσίες πρωτοβάθμιας φροντίδας και σε ασθενείς με σωματικές νόσους που σχετίζονται με κόπωση αλλά μόνο περιστασιακά σε ασθενείς με Μείζονα Καταθλιπτική Διαταραχή (ΜΚΔ). Ως εκ τούτου, η διερεύνηση παραμέτρων που σχετίζονται με την κόπωση στη μείζονα κατάθλιψη είναι ζητούμενο και αναμένεται να διευκολύνει την ανάπτυξη αποτελεσματικών, ειδικών για την κόπωση θεραπευτικών στρατηγικών. Οι ασθενείς με κατάθλιψη πάσχουν συχνά από συννοσηρές αγχώδεις διαταραχές (ΣΑΔ) ή από υπο-ουδικά αγχώδη συμπτώματα. Η μελέτη αυτή είχε ως σκοπό της να διερευνήσει ανεξάρτητες συσχετίσεις της βαρύτητας της κόπωσης σε ασθενείς με ΜΚΔ με την παρουσία, τον αριθμό και τον τύπο των ΣΑΔ. Μελετήθηκαν διαδοχικά 70 γυναίκες με ΜΚΔ (48,6% νοσηλευόμενες), ηλικίας 23–65 ετών (μ.ό. 48,2±10,6), που βρίσκονταν σε Μείζον Καταθλιπτικό Επεισόδιο [βαθμολογία στην κλίμακα κατάθλιψης του Hamilton (HDRS)≥17] και δεν έπασχαν από άλλες σχετιζόμενες με κόπωση καταστάσεις. Οι διαγνωστικές εκτιμήσεις πραγματοποιήθηκαν με τη βραχεία δομημένη συνέντευξη MINI 5.0.0. βάσει των κριτηρίων του DSM-IV. Η αναφερόμενη κόπωση καταγράφηκε με το ερωτηματολόγιο 14 λημμάτων Fatigue Questionnaire (FQ) της Chalder. Υπολογίσθηκαν οι συσχετίσεις ανάμεσα στη βαθμολογία στο FQ και την ηλικία, το καθεστώς νοσηλείας ή μη, τη βαθμολογία στην HDRS, την παρουσία και τον αριθμό των ΣΑΔ. Στη συνέχεια, διενεργήθηκαν αναλύσεις πολλαπλής γραμμικής παλινδρόμησης με τη βαθμολογία στο FQ ως εξαρτημένη μεταβλητή, ώστε να απομονωθούν ανεξάρτητοι προβλεπτικοί παράγοντες της βαρύτητας της κόπωσης: 92,9% των ασθενών είχαν κλινικά σημαντική κόπωση, 62,9% έπασχαν από τουλάχιστον μία ΣΑΔ (38,6% πληρούσαν κριτήρια για μία ΣΑΔ, 21,4% για δύο και 2,9% για τρεις), 51,4% είχαν διάγνωση Διαταραχής Γενικευμένου Άγχους

(ΔΓΑ), 25,7% Διαταραχής Πανικού ή/και Αγοραφοβίας (ΔΠ/ΑΦ), 17,1% Κοινωνικής Φοβίας και 7,1% Ιδιοψυχαναγκαστικής Διαταραχής. Η βαθμολογία στο FQ συσχετίστηκε σε βαθμό στατιστικά σημαντικό με τη βαθμολογία στην HDRS ($r=0,406$, $p<0,001$), την παρουσία οποιασδήποτε ΣΑΔ ($\rho=0,4$, $p=0,001$), τον αριθμό των ΣΑΔ ($\rho=0,393$, $p=0,001$), την παρουσία ΔΓΑ ($\rho=0,421$, $p<0,001$) και την παρουσία ΔΠ/ΑΦ ($\rho=0,252$, $p=0,035$). Στις αναλύσεις πολλαπλής γραμμικής παλινδρόμησης, η παρουσία οποιασδήποτε ΣΑΔ, ο αριθμός των ΣΑΔ και η παρουσία συννοσηρής ΔΓΑ αναδείχθηκαν ως στατιστικά σημαντικοί ανεξάρτητοι προβλεπτικοί παράγοντες της βαθμολογίας στο FQ μαζί με τη βαθμολογία στην HDRS. Η βαρύτητα της κόπωσης στις γυναίκες ασθενείς με ΜΚΔ συσχετίζεται ανεξάρτητα με την παρουσία και τον αριθμό ΣΑΔ και, ειδικότερα, με την παρουσία συννοσηρής ΔΓΑ. Τα ευρήματά μας καταδεικνύουν ότι: (1) η συσχέτιση αυτή εξηγεί πιθανώς εν μέρει τη μεγαλύτερη επιβάρυνση/αναπηρία και τη χειρότερη πρόγνωση της ΜΚΔ με ΣΑΔ, (2) τα υψηλά επίπεδα κόπωσης, που συνοδεύονται συχνά από αγχώδη συμπτώματα, αποτελούν πιθανώς δείκτη βαρύτητας και συννόησης με αγχώδεις διαταραχές στην ΜΚΔ και ορίζουν ίσως έναν υπότυπο/φαινότυπο με άγχος και κόπωση στον πληθυσμό αυτών των ασθενών, (3) τα φάρμακα και οι ψυχοθεραπείες για την αντιμετώπιση της σχετιζόμενης με την κατάθλιψη κόπωσης θα πρέπει να στοχεύουν παράλληλα και στην αντιμετώπιση των συννοσηρών αγχωδών διαταραχών.

Λέξεις ευρητηρίου: Αγχώδεις διαταραχές, διαταραχή γενικευμένου άγχους, κόπωση, μείζων κατάθλιψη, συννόηση

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Corresponding author: P. Ferentinos, Lecturer in Psychiatry, 2nd Department of Psychiatry, Attikon General Hospital, University of Athens, Medical School, 1 Rimini street, GR-124 62 Athens, Greece
 Tel: +30 210-58 32 446, Fax: +30 210-53 26 453
 e-mail: pferentinos@med.uoa.gr