Lifetime post-traumatic stress symptoms are related to the health-related quality of life and severity of pain/fatigue in patients with fibromyalgia

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ABSTRACT

Objective. *The aim of the present study was to investigate the impact of lifetime potentially traumatic events, including losses, and of post-traumatic stress symptoms on the severity of illness and health-related quality of life (HRQoL) in patients with fibromyalgia (FM).*

Methods. *Seventy patients with FM, diagnosed according to the American College of Rheumatology criteria, were consecutively enrolled at the Unit of Rheumatology, University of Pisa, Italy. Assessments included: the SCID-I/P; the Fibromyalgia Impact Questionnaire (FIQ); the Medical Outcomes Study Short Form-36 Health Survey (MOS SF-36), and the Trauma and Loss Spectrum Self-Report (TALS-SR) lifetime version.*

Results. *The FIQ total score was related to the number of loss events (Domain I) and to symptoms of grief reactions (Domain II) and re-experiencing (Domain V) of the TALS-SR. The "VAS fatigue" scores (FIQ) were significantly related to the TALS-SR symptoms of grief reactions (Domain II) and re-experiencing (Domain V). The Mental Component Summary and Bodily Pain scores of the MOS SF-36 were significantly related to all TALS-SR domains, the latter with the exception of the VIII (Arousal).*

Conclusion. *Our results corroborate the presence of a relationship between the lifetime exposure to potentially traumatic events, in particular loss events, and lifetime post-traumatic stress symptoms and the severity of illness and HRQoL in patients with FM.*

Introduction

Fibromyalgia (FM) is a severe, chronic, non-articular rheumatic condition characterised by widespread non-articular musculoskeletal pain, hyperalgesia and generalised tender points, in the absence of inflammatory or structural musculoskeletal abnormalities (1-3). FM causes functional disability in daily activities in all affected age groups and adversely affects almost all aspects of health-related quality of life (HRQoL) (4-6).

The modern term of FM was coined in the mid-1970s but it was only in the 1990s that the American College of Rheumatology (ACR) established research diagnostic criteria (pain and tender point evaluation), which are now used to make the diagnosis, as specific laboratory tests have not yet been identified (7, 8). Although recognised as legitimated clinical entity, FM is still a disputed medical condition with prominent associated symptoms-comorbidities that include chronic fatigue, sleep disturbances, mood (depression) and anxiety disorders, and irritable bowel syndrome (1, 9-17).

Several factors have been addressed to contribute to the pathophysiology of FM, both genetics (familial predisposition), abnormal neuroendocrine and autonomic nervous system function (disordered central pain processing), and environmental triggers (mechanical/physical trauma and psychosocial stressors) (3, 12, 17). In particular, the contribution of stress to the pathophysiology of FM has been the subject of considerable debate (2, 18). To date, the most acclaimed hypothesis states that trauma and major life stressful events are not likely to cause FM *per se* but, in genetically susceptible people, early life events, besides acute or prolonged traumatic stress in adulthood, may affect the brain modulatory circuitries of both pain and emotions which account for the enhanced pain responses and co-occurring symptoms that are reported by patients with FM (12, 13, 19).

Nevertheless, despite being numerous, the studies on the impact of potentially traumatic events on FM are still inconclusive (2, 18, 20-25).

Post-traumatic stress disorder (PTSD), as defined in the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV-TR) (26) is an often chronic psychiatric condition, the onset of which typically takes place after exposure to a traumatic event, characterised by a specific set of symptoms including re-experiencing, avoidance and numbing, and arousal. Recently, neurobiological alterations have been detected in PTSD patients with significantly lower levels of Brain-Derived Neurotrophic Factor (BDNF), a neurotrophin which promotes the proliferation, survival and differentiation of neurons, as compared with healthy subjects (27). When chronic, PTSD is often associated with an increased risk for a number of specific and non-specific somatic pathologies, such as cardiovascular and autoimmune disorders, physical complaints and chronic pain, including FM (28-31). Increasing efforts in psychiatry have recently been oriented towards exploring the clinical relevance of not only the full-blown disorder but also of its partial or subthreshold forms, that similarly have shown to be associated with severe impairment and need for treatment (32-38). In the light of these data, dimensional approaches to PTSD, similarly to what reported for other mental disorders (39), have shown an increased relevance in the ongoing debate for the forthcoming DSM-V. Dimensional approaches to PTSD have been conceptualised as consisting of three main dimensions (40-42): the nature of the stressor, the possible responses to trauma and the post-traumatic stress symptoms. In the framework of the Spectrum Project (a USA-Italy collaboration), a questionnaire was developed and validated to assess the "post-traumatic spectrum" by clinicians and researchers of the Department of Psychiatry of the University of Pisa: the Trauma and Loss Spectrum-Self Report (TALS-SR) (42). The instrument is based on a multidimensional approach to post-traumatic stress symptomatology that includes a range of threatening or frightening experiences, as well as a variety of potentially significant losses, to which an individual can be exposed. Further, it explores the spectrum of the peritraumatic reaction and post-traumatic symptoms that may ensue from either type of life events, targeting soft signs and subthreshold conditions, as well as temperamental and personality traits that may constitute risk factors for the development of the disorder.

Although several studies have reported correlations between PTSD and FM (2, 9, 17), to the best of our knowledge, no study has investigated the relationship between lifetime post-traumatic stress symptoms and FM. Thus, the aim of the present study is to explore the correlations between the severity of pain and the HRQoL in FM patients with potentially traumatic lifetime events (including "low magnitude" ones and losses) and lifetime post-traumatic stress symptoms assessed by the TALS-SR.

Material and methods

Subjects

A cohort of patients with a diagnosis of FM was consecutively recruited at the Department of Internal Medicine, Rheumatology Division, University of Pisa. Eligible subjects included new and continuing patients, of at least 18 years of age, who met the 1990 American College of Rheumatology criteria for diagnosis of FM (7). Exclusion criteria were: the presence of any inflammatory cause of the pain, concomitant rheumatic diseases, neurologic complications or pregnancy.

The ethics committee of the Azienda Ospedaliero-Universitaria Pisana, Pisa, approved all recruitment and assessment procedures in accordance with the Declaration of Helsinki (1996) and with the guidelines for Good Clinical Practice (1995). Eligible subjects provided written informed consent after receiving a complete description of the study and having the opportunity to ask questions.

The diagnosis of FM was made according to the ACR criteria by a rheumatologist. For each patient, the count and the tenderness at tender points (TPs) were evaluated by means of the Fisher dolorimeter. The rheumatologist advanced the instrument at a rate of 1 kg/s, and the patient was instructed to say when this procedure became painful. The pressure was then stopped, and the threshold measurement was recorded in kg/cm^2. The myalgic score was the sum of the dolorimetry results for all 18 TPs. The TP count was determined by the number of TPs that had a threshold of 4 kg/cm^2. Each positive TP had a pain score between 0 and 3.

All the patients enrolled in the study underwent a psychiatric assessment, performed by clinicians at the Department of Psychiatry, Neurobiology, Pharmacology and Biotechnology, University of Pisa, after a routinely scheduled appointment.

Assessments

Assessments included: the Structured Clinical Interview for the DSM-IV Axis I disorders (SCIDI-I/P) (43); the Trauma and Loss Spectrum-Self Report (TALS-SR) (41); the Fibromyalgia Impact Questionnaire (FIQ) (44); and the Medical Outcomes Study Short Form-36 Health Survey (MOS SF-36) (45). Socio-demographic data were collected using interviewer administered questionnaires. A structured interview format was used to record sex, age, educational level, marital status, employment and duration of illness.

The SCID-I/P was administered by psychiatrists who are trained and certified in the use of the study instruments at the Department of Psychiatry, Neurobiology, Pharmacology and Biotechnology, University of Pisa.

The TALS-SR is a questionnaire that explores the lifetime experience of a range of losses and/or potentially traumatic events, as well as a range of symptoms occurring in the aftermath of the worst event. The TALS-SR provides a dimensional approach to the patient's psychopathology by incorporating information related to subthreshold symptoms and atypical manifestations that might cause serious distress, as well as a broad array of clinical features associated with trauma and loss events. The TALS-SR is composed of 116 items grouped into nine Domains. Items responses

are coded dichotomously (yes/no) and domain scores are obtained by counting the number of positive answers in a given domain. The first two domains focus on experiences of loss. Domain I (*Loss events)* includes a range of loss events ranging from mild to extreme, including the death of a loved one, the loss of an important relationship, of property, of physical functioning, or of social and economical status. Domain II (*Grief reactions)* comprises a range of symptoms related to the possible occurrence of persistent grief in response to a death. These items include difficulty accepting the death, recurrent pangs of grief, preoccupation with thoughts and memories of the deceased, avoidance of reminders of the loss and guilt or remorse. This domain also includes a section targeting trait-like interpersonal functioning that might comprise a risk factor for persistent grief. Domain III (*Potentially traumatic event*s) lists both DSM-IV qualifying traumas (*e.g*. combat, natural disasters, sexual abuse, severe accidents) and "low-magnitude" events (*e.g*. failure at school or at work, sexual harassment, abortion), that the patient might have experienced in his/her lifetime. Domain IV (R*eactions to losses or upsetting events)* evaluates acute reactions to the trauma or loss. Domains V *(Re-experiencing),* VI *(Avoidance)* and VIII *(Hyperarousal)* include a range of isolated criterion and non-criterion symptoms related to re-experiencing, avoidance and hyperarousal, respectively. Domain VII (*Maladaptive coping*) addresses maladaptive coping responses, for both loss and trauma. Domain IX *(Personal characteristics-risk factors)* explores some personality characteristics that may be related to the loss and/or trauma and that may, based on the literature, represent risk factors for the development of the symptoms. Domain scores are obtained as the count of positive answers. The instrument can be downloaded from the web site: www.spectrum-project.net.

The FIQ is a brief self-administered instrument, designed to evaluate the overall impact of FM over many dimensions of the HRQoL (physical functioning, work status, depression, anxiety, sleep, pain, stiffness, fatigue, and well-being). It consists of 10 items and is scored from 0 to 100, with the latter number being the worst case. The pain and fatigue dimensions are measured by a visual analogue scale (VAS), in which patients reported the severity of pain or of fatigue as a score ranging from 0 (corresponding to "absence") to 10 (corresponding to "very severe"). We considered the FIQ total score to explore the global impact on the HRQoL, and the "VAS pain" and the "VAS fatigue" to explore the severity of pain and fatigue respectively.

The MOS SF-36 is a self-administered questionnaire used to assess general health status and the HRQoL. It consists of 36 items, 35 of which are aggregated into 8 multi-item scales that measure: *Physical Functioning* (PF; extent to which health limits physical activities); *Role Physical* (RP; extent to which physical health interferes with work or other daily activities); *Bodily Pain* (BP; intensity of pain and effect on normal work); *General Health* (GH; personal evaluation of health, current and outlook); *Vitality* (V; feeling energetic); *Social Functioning* (SF; extent to which physical health or emotional problems interfere with normal social activities); *Role Emotional* (RE; extent to which emotional problems interfere with work or other daily activities), and *Mental Health* (MH; general mental health, including depression, anxiety, behavioural and emotional control, general positive affect). The sum of the former four scales represents the *physical component summary* (PCS) score of the MOS SF-36, while the sum of the latter four represents the *mental component summary* (MCS) score. Subscale raw scores are standardised and range from 0 to 100, where 0 is the worst and 100 the best possible health status. We considered the MCS and PCS scores to explore the global impact on the HRQoL, and the BP scale to explore the intensity of pain and its specific impact on work activity.

Statistical analyses

Pearson's correlations were used to investigate the presence of relationships between the TALS-SR and the variables describing the severity of pain and the HRQoL (VAS pain, VAS fatigue, and FIQ total scores; MCS, PCS and BP scores of the MOS SF-36) of FM patients. The data were analysed using the Statistical Package for the Social Sciences (46).

Results

An overall sample of 70 patients with FM was recruited. All patients were women, with a mean age of 49.78±12.7 years. The majority (n=40; 57.14%) of patients were married and employed (n=39; 55.72%). Demographic and clinical characteristics of the study sample are reported in Table I.

Patients reported the following lifetime psychiatric diagnoses, as assessed by the SCID-I/P, according to the DSM-IV-TR (26) criteria:

37 (52.8%) Major Depression;
5 (7%) Bipolar Disorder;
47 (67.1%) Panic Disorder;
1 (1.4%) Generalised Anxiety Disorder;
2 (2.8%) Obsessive-Compulsive Disorder;
2 (2.8%) Eating Disorders;
3 (4.2%) PTSD.

Table I. Demographic characteristics of the study sample (n=70).

	n. (%)
Marital status	
Single	17 (24.3)
Married	40 (57.1)
Separated/Divorced	13 (18.6)
Educational level achieved	
Primary school	17 (24.3)
High school diploma	33 (47.1)
University degree	20 (28.6)
Occupation	
Employed	39 (55.7)
Unemployed/retired	31 (44.3)

Table II. TALS-SR Domains scores (mean±SD) in the study sample (n=70).

TALS-SR Domains	mean±SD
I Loss events	4.01 ± 2.07
II Grief reactions	9.67 ± 5.96
III Potentially traumatic events	4.69 ± 2.88
IV Reaction to losses or upsetting events	6.91 ± 3.97
V Re-experiencing	3.01 ± 2.19
VI Avoidance and numbing	3.44 ± 3.23
VIII Arousal	2.99 ± 1.93

Table III. Pearson's correlations between the TALS-SR Domains scores and the FIQ (Total, VAS pain, VAS fatigue) and MOS SF-36 (BP MCS, PCS) scores.

TALS-SR Domains	FIQ	VAS pain	VAS fatigue	BP	MCS	PCS
I – Loss events	r=0.263 *p*=0.033	r=0.119 *p*=0.347	r=0.122 *p*=0.328	r=-0.236 *p*=0.049	r=-0.307 *p*=0.010	r=-0.149 *p*=0.218
II – Grief reactions	r=0.389 *p*=0.001*	r=0.126 *p*=0.317	r=0.316 *p*=0.010	r=-0.349 *p*=0.003	r=-0.651 *p*=0.000*	r=-0.155 *p*=0.201
III – Potentially traumatic events	r=0.202 *p*=0.105	r=0.188 *p*=0.134	r=0.145 *p*=0.246	r=-0.253 *p*=0.034	r=-0.383 *p*=0.001*	r=-0.088 *p*=0.470
IV – Reaction to losses or upsetting events	r=0.183 *p*=0.142	r=-0.066 *p*=0.600	r=0.163 *p*=0.192	r=-0.244 *p*=0.041	r=-0.551 *p*=0.000*	r=-0.100 *p*=0.410
V – Re-experiencing	r=0.276 *p*=0.025	r=0.053 *p*=0.673	r=0.268 *p*=0.029	r=-0.366 *p*=0.002	r=-0.514 *p*=0.000*	r=-0.164 *p*=0.176
VI – Avoidance and numbing	r=0.174 *p*=0.163	r=0.072 *p*=0.569	r=0.159 *p*=0.203	r=-0.298 *p*=0.012	r=-0.443 *p*=0.000*	r=-0.052 *p*=0.669
VIII – Arousal	r=-0.002 *p*=0.989	r=-0.057 *p*=0.652	r=0.032 *p*=0.801	r=-0.215 *p*=0.074	r=-0.415 *p*=0.000*	r=-0.137 *p*=0.258

*$p<.05$ after Bonferroni's correction.

The TALS-SR domains scores (mean ± SD) are reported in Table II.

Table III shows Pearson's correlations: the FIQ total scores were significantly related to the TALS-SR Domain I (*Loss events*), II (*Grief reactions*) and V (*Potentially traumatic events*) domains scores. The "VAS fatigue" scores of the FIQ were significantly related both to the TALS-SR Domains II (*Grief reactions*) and V (*Re-experiencing*) scores. A significant association was also found between the BP scores of the MOS SF-36 and all the TALS-SR domain scores except the VIII (*Arousal*). Furthermore, the MCS scores of the MOS SF-36 were significantly related to all the domains of the TALS-SR.

Discussion

The results of the present study corroborate the impact of lifetime trauma exposure, including losses, and of post-traumatic spectrum symptoms on the severity of pain and fatigue, as well as on the HRQoL, in patients with FM.

The results of our study in fact show a significant correlation between the global impact of FM on the HRQoL, as measured by means of the FIQ total score, and the number of losses and of symptoms of unresolved grief, which the patients may have experienced during their lifespan, encoded in the TALS-SR. Bereavement is one of the most distressing life-events and the loss of a loved one has been associated with significant morbidity and mortality (47-49) and with mood and anxiety disorders (50-52). Increasingly literature highlights the relevance of symptoms of unresolved or complicated grief (CG) that may develop in percentages between 10 and 20% of bereaved subjects and are related to significant distress and impairment (53-56). For these reasons, CG is currently under consideration for inclusion in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DMS-V) and Internal Statistical Classification of Diseases and Related Health Problems, Eleventh Revision (ICD-11). Our results corroborate the impact of losses and of CG symptoms on the HRQoL of patients with FM. While discussing these results a major limitation of the study should be taken into account as our sample included only women. This finding is in agreement with the literature on FM, showing significantly higher rates of the disorder amongst women with percentages as high as 90% (57). Similarly, CG affects more bereaved women than men (58), thus this may impact on the high rates of CG symptoms reported.

Consistent with these data, significant correlations between 'moderate' and 'good' were also found between the symptoms of grief reactions (TALS-SR Domain II) and the VAS fatigue scores of the FIQ and the BP and MCS scores of the MOS SF-36. As the BP but not the VAS pain scores correlated with TALS-SR Domains I and II, it seems that the traumatic events and the post-traumatic stress symptomatology affect not the pain reported per se but the functional impairment related to the symptoms of FM and, consequently, to the global HRQoL.

Significant correlations were reported between the number of potentially traumatic events (TALS-SR Domain III) and the BP and MCS scores. This domain includes not only major trauma but also the so-called "low magnitude events" (41, 42, 59) that have been recently highlighted to have a potential role in the onset of post-traumatic stress symptoms. Patients with FM reported a significant correlation with the experience of these events and the impact on the HRQoL.

It is worth noticing the significant correlations between almost all the TALS-SR domains and the MCS of the MOS-SF-36 corroborate these results and the negative role of even subthreshold post-traumatic stress symptoms. In fact, only three patients out of seventy, reported a full-blown PTSD. In particular, post-traumatic stress symptoms are related to lower MCS scores that include impairment in vitality, social and role functioning due to mental and emotional problems. The significant,

despite weaker correlation of almost all the TALS-SR domain scores and the BP component of the MOS SF-36 further confirms the role of these symptoms on the global impact that the patients reported to have had on the effect on normal work related to the pain. Thus, the interaction between the severity of illness and a worse HRQoL mostly affects the component related to the mental health status. In this regard, it is important to notice that the scores reported on the TALS-SR domains are intermediate as compared to those reported by patients with PTSD or healthy control subjects (42). This may be interpreted considering that FM patients are either more sensitive to stress or present lifetime subthreshold post-traumatic stress symptomatology that may have a role in the manifestation of the disorder.

There is increasing evidence in the literature of a correlation between PTSD or post-traumatic stress reactions and mood spectrum (60-62). Higher PTSD rates and more severe post-traumatic stress symptoms have in fact been reported in patients with mood disorders, particularly bipolar disorder (53-64). In this regard, Pollack *et al*. (65) reported the presence of mania/hypomania to be the most critical risk factor for the onset of PTSD sequelae following indirect traumatic exposure to the September 11 terroristic attacks. Conversely, mood disorders and mood spectrum symptoms appear to be related to higher PTSD rates, more severe post-traumatic stress symptoms and an increased risk for suicide (66, 67). In a previous report (6) we found significant correlations between mood spectrum symptoms, particularly manic, and disease severity and quality of life in patients with FM, as previously investigated in patients with rheumatoid arthritis (68). In line with these studies, our results could be interpreted as suggesting a relationship between lifetime manic stress symptoms and an increased risk for post-traumatic spectrum symptoms and a more severe disease severity and quality of life in patients with FM. In a more speculative vein, it is possible to hypothesise that mood spectrum symptoms might favour the development of PTSD under appropriate circumstances and this may be related to a more severe FM. Further studies are needed in order to address these issues.

Some limitations of the present study should be taken into account. First, as already mentioned, our sample included only women. Second, the sample size is small and larger samples may be needed in order to confirm our findings. Furthermore, we performed multiple correlation analyses (n=42) without a Bonferroni's correction which, when applied, decreased the number of significant correlations. In fact, only the correlations of the MCS with all the TALS-SR domains, except those regarding the loss events domains, along with the correlations of the FIQ with the TALS-SR domain Grief reactions, were confirmed. Third, the TALS-SR is a lifetime assessment that does not provide information about the severity and the temporal sequence of the post-traumatic spectrum symptoms, as well as the relationship with the onset of FM.

In conclusion, the results of the present study seem to corroborate a relationship between stress and FM, and in particular they suggest the role of even minor trauma including loss events and of subthreshold post-traumatic stress symptomatology. Thus, further studies are needed to investigate this relationship in larger samples together with genetic and biomarker studies.

References

1. THEADOM A, CROPLEY M, HUMPHREY K: Exploring the role of sleep and coping in quality of life in fibromyalgia. *J Psychosom Res* 2007; 62: 145-51.
2. HAVILAND MG, MORTON KR, ODA K, FRASER GE: Traumatic experiences, major life stressors, and self-reporting a physician-given fibromyalgia diagnosis. *Psychiatry Res* 2010; 177: 335-41.
3. BRANCO JC: State-of-the-art on fibromyalgia mechanism. *Acta Reumatol Port* 2010; 35: 10-5.
4. JACOBSEN S, PETERSEN IS, DANNESKIOLD-SAMSOE B: Clinical features in patients with chronic muscle pain–with special reference to fibromyalgia. *Scand J Rheumatol* 1993; 22: 69-76.
5. HAWLEY DJ, WOLFE F, CATHEY MA: Pain, functional disability,and psychological status: a 12-month study of severity in fibromyalgia. *J Rheumatol* 1988; 15: 1551-6.
6. DELL'OSSO L, BAZZICHI L, CONSOLI G *et al*.: Manic spectrum symptoms are correlated to the severity of pain and the health-related quality of life in patients with fibromyalgia. *Clin Exp Rheumatol* 2009; 27: 57-61.
7. WOLFE F, SMYTHE HA, YUNES MB *et al*.: The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990; 33: 160-72.
8. GOLDENBERG DL: Diagnosis and differential diagnosis of fibromyalgia. *Am J Med* 2009; 122: S14-21.
9. WOLFE F, CATHEY MA, KLEINHEKSEL SM *et al*.: Psychological status in primari fibrositis and fibrositis associated with rheumatoid arthritis. *J Rheumatol* 1984; 11: 500-6.
10. KIRMAYER LJ, ROBBINS JM, KAPUSTA MA: Somatization and depression in fibromyalgia syndrome. *Am J Psychiatry* 1988; 145: 950-4.
11. EPSTEIN SA, KAY G, CLAUW D *et al*.: Psychiatric disorders in patients with fibromyalgia. A multicenter investigation. *Psychosomatics* 1999; 40: 57-63.
12. BRADLEY LA: Pathophysiologic mechanism of fibromyalgia and its related disorders. *J Clin Psychiatry* 2008; 69: 6-13.
13. SCHWEINHARDT P, SAURO KM, BUSHNELL MC: Fibromyalgia: a disorder of the brain?. *Neuroscientist* 2008; 14: 415-21.
14. WOLFE F, RASKER JJ: Fibromyalgia *In*: FIRESTEIN, GS, BUDD RC, HARRIS JR, EE, MCINNES IB, RUDDY S, SERGENT JS (Eds.). *Kelley's Textbook of Rheumatology*, 8th ed. Elsevier, Amsterdam 2008.
15. WOLFE F: Fibromyalgia wars. *J Rheumatol* 2009; 36: 671-8.
16. CULPEPPER L: Recognizing and diagnosing fibromyalgia. *J Clin Psychiatry* 2010; 71: e30
17. VAN HOUDENHOVE B, KEMPKE S, LUYTEN P: State Psychiatric aspects of chronic fatigue syndrome and fibromyalgia. *Curr Psychiatry Rep* 2010; 12: 208-14.
18. ABLIN JN, COHEN H, CLAUW DJ *et al*.: A tale of two cities – the effect of low intensity conflict on prevalence and characteristics of musculoskeletal pain and somatic symptoms associated with chronic stress. *Clin Exp Rheumatol* 2010; 28 (Suppl. 63) S15-S21.
19. CROFFORD LJ: Violence, stress, and somatic syndromes. *Trauma Violence Abuse* 2007; 8: 299-313.
20. BOISSET-PIORO MH, ESDAILE JM, FITZ-CHARLES MA: Sexual and physical abuse in women with fibromyalgia syndrome. *Arthritis Rheum* 1995; 38: 235-41.
21. WALKER EA, KEEGAN D, GARDNER G, SULLIVAN M, BERNSTEIN D, KATON WJ: Psychosocial factors in fibromyalgia compared with rheumatoid arthritis: II. Sexual, physical, and emotional abuse and neglect. *Psychosom Med* 1997; 59: 572-7.
22. VAN HOUDENHOVE B, NEERINCKX E, LYSENS R *et al*.: Victimization in chronic fatigue syndrome and fibromyalgia in tertiary care: a controlled study on prevalence and characteristics. *Psychosomatics* 2001; 42: 21-8.
23. RAPHAEL KG, CHANDLER HK, CICCONE DS: Is childhood abuse a risk factor for chronic pain in adulthood? *Curr Pain Headache Rep* 2004; 8: 99-110.
24. CICCONE DS, ELLIOT DK, CHANDLER HK, NAYAK S, RAPHAEL KG: Sexual and physical abuse in women with fibromyalgia syn-

drome: a test of the trauma hypothesis. *Clin J Pain* 2005; 21: 378-86.
25. RUSSELL IJ, RAPHAEL KG: Fibromyalgia syndrome: presentation, diagnosis, differential diagnosis, and vulnerability. *CNS Spectrums* 2008; 13: 6-11.
26. AMERICAN PSYCHIATRIC ASSOCIATION: Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision. APA 2000.
27. DELL'OSSO L, CARMASSI C, DEL DEBBIO A *et al*.: Brain-derived neurotrophic factor plasma levels in patients suffering from post-traumatic stress disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2009; 33: 899-902.
28. BOSCARINO JA: Posttraumatic stress disorder and physical illness: results from clinical and epidemiologic studies. *Ann N Y Acad Sci* 2004; 1032: 141-53.
29. ROHLEDER N, KARL A: Role of endocrine and inflammatory alterations in comorbid somatic diseases of post-traumatic stress disorder. *Minerva Endocrinol* 2006; 31: 273-88.
30. BUSKILA D, ABLIN JN, BEN-ZION I *et al*.: A painfull train of events: increased prevalence of fibromyalgia in survivors of a major train crash. *Clin Exp Reumatol* 2009; 27 (Suppl. 56): S79-85.
31. BOSCARINO JA, FORSBERG CW, GOLDBERG J: A twin study of the association between PTSD symptoms and rheumatoid arthritis. *Psychosom Med* 2010: 72: 481-6.
32. WEISS DS, MARMAR CR, SCHLENGER WE *et al*.: The prevalence of lifetime and partial post-traumatic stress disorder in Vietnam theater veterans. *J Trauma Stress* 1992; 3: 365-76.
33. STEIN MB, WALKER JR, HAZEN AL, FORDE DR: Full and partial posttraumatic stress disorder: findings from a community survey. *Am J Psychiatry* 1997; 154: 1114-9.
34. MARSHALL RD, OLFSON M, HELLMAN F, BLANCO C, GUARDINO M, STRUENING EL: Partial Comorbidity, impairment, and suicidality in subthreshold PTSD. *Am J Psychiatry* 2001; 158: 1467-73.
35. BRESLAU N, LUCIA VC, DAVIS GC: Partial PTSD versus full PTSD: an empirical examination of associated impairment. *Psychol Med* 2004; 34: 1205-14.
36. MYLLE J, MAES M: Partial posttraumatic stress disorder revisited. *J Affect Disord* 2004; 78: 37-48.
37. HEPP U, GAMMA A, MILOS G *et al*.: Prevalence of exposure to potentially traumatic events and PTSD. The Zurich Cohort Study. *Eur Arch Psychiatry Clin Neurosc* 2006; 256: 151-8.
38. FRIEDMAN MJ, RESICK PA, BRYANT RA, BREWIN CR: Considering PTSD for DSM-5. *Depress Anxiety* 2010; 28: 750-69.
39. FRANK E, CASSANO GB, SHEAR MK *et al*.: The spectrum model: a more coherent approach to the complexity of psychiatric symptomatology. *CNS Spectr* 1998; 3: 23-34.
40. MOREAU C, ZISOOK S: Rationale for a post-traumatic stress spectrum disorder. *Psychiatr Clin North Am* 2002; 25: 775-90.
41. DELL'OSSO L, SHEAR MK, CARMASSI C, RUCCI P, MASER JD, FRANK E: Validity and reliability of the Structured Clinical Interview for the Trauma and Loss Spectrum (SCI-TALS). *Clin Pract Epidemiol Ment Health* 2008; 4: 2-9.
42. DELL'OSSO L, CARMASSI C, RUCCI P *et al*.: A multidimensional spectrum approach to post-traumatic stress disorder: comparison between the Structured Clinical Interview for Trauma and Loss Spectrum (SCI-TALS) and the Self-Report instrument (TALS-SR). *Compr Psychiatry* 2009; 50: 485-90.
43. FIRST MB, SPITZER RL, WILLIAMS JBW, GIBBON M: Structured Clinical Interview for DSM-IV-Patient Edition (SCID-P). American Psychiatric Press, Washington, DC 1995. A multicenter investigation. *Psychosomatics* 1999; 40: 57-63.
44. SARZI-PUTTINI P, ATZENI F, FIORINI T: Validation of an Italian version of the Fibromyalgia Impact Questionnaire (FIQ-I). *Clin Exp Rheumatol* 2003; 21: 459-64.
45. MCHORNEY CA, WARE JE JR, LU JF, SHERBOURNE CD: The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care* 1994; 32: 40-66.
46. SPSS Inc. SPSS for Windows, Rel. 16.0., 2007 Chicago: SPSS
47. SCHAEFER C, QUESENBERRY CP, WI S: Mortality following conjugal bereavement and the effects of a shared environment. *Am J Epidemiol* 1995; 141: 1142-52.
48. LI J, PRECHT DH, MORTENSEN PB, OLSEN J: Mortality in parents after death of a child in Denmark: a nationwide follow-up study. *Lancet* 2003; 361: 363-7.
49. CHRISTAKIS N, ALLISON P: Mortality after the hospitalization of a spouse. *N Engl J Med* 2006; 354: 719-30.
50. ONRUST SA, CUIJPERS P: Mood and anxiety disorders in widowhood: a systematic review. *Aging Ment Health* 2006;10: 327-34.
51. KERSTING A, KROKER K, HORSTMANN J *et al*.: Complicated grief in patients with unipolar depression. *J Affect Dis* 2009; 118: 201-4.
52. PRIGERSON HG, FRANK E, KASL SV *et al*.: Complicated grief and bereavement-related depression as distinct disorders: preliminary empirical validation in elderly bereaved spouses. *Am J Psychiatry* 1995; 152: 22-30.
53. PRIGERSON HG, BIERHALS AJ, KASL SV *et al*.: Traumatic grief as a risk factor for mental and physical morbidity. *Am J Psichiatry* 1997; 154, 616-23.
54. PRIGERSON HG, HOROWITZ MJ, JACOBS SC, PARKES CM, ASLAN M, GOODKIN K: Prolonged grief disorder: psychometric validation of criteria proposed for DSM-V and ICD-11. *Plos Med* 2009; 6: e1000122.
55. ZISOOK S, SHEAR MK: Grief and bereavement: what psychiatrists need to know. *World Psychiatry* 2009; 8: 67-74
56. DELL'OSSO L, CARMASSI C, RUCCI P, CIAPPARELLI A, CONVERSANO C, MARAZZITI D: Complicated grief and Suicidality: The impact of Subthreshold Mood Symptoms. *CNS Spectr* 2011 Jan 15; pii: Stahl. [Epub ahead of print].
57. YUNUS MB: Gender differences in fibromyalgia and other related syndromes. *J Gend Specific Med* 2002. 5: 42-7.
58. CHEN JH, BIERHALS AJ, PRIGERSON HG, KASL SV, MAZURE CM, JACOBS S: Gender differences in the effects of bereavement-related psychological distress in health outcomes. *Psychol Med* 1999; 29: 367-80.
59. STEIN AL, TRAN GQ, LUND LM, HAJI U, DASHEVSKY BA, BAKER DG: Correlates for posttraumatic stress disorder in Gulf War veterans: a retrospective study of main and moderating effects. *Anxiety Disord* 2005; 19: 861-76.
60. DELL'OSSO L, ARMANI A, RUCCI P *et al*.: Measuring mood spectrum: comparison of interview (SCI-MOODS) and self-report (MOODS-SR) instruments. *Compr Psychiatry* 2002; 43: 69-73.
61. CASSANO GB, RUCCI P, FRANK E *et al*.: The mood spectrum in unipolar and bipolar disorder: arguments for a unitary approach. *American J Psychiatry* 2004; 161: 1264-9.
62. CASSANO GB, DELL'OSSO L, FRANK E *et al*.: The bipolar spectrum: a clinical reality in search of diagnostic criteria and an assessment methodology. *J Affect Disord* 1999; 54: 319-28.
63. OQUENDO M, BRENT DA, BIRMAHER B *et al*.: Posttraumatic stress disorder comorbid with major depression: factors mediating the association with suicidal behavior. *Am J Psychiatry* 2005; 162: 560-6.
64. SIMON NM, OTTO MW, WISNIEWSKI SR *et al*.: Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry* 2004; 161: 2222-9.
65. POLLACK MH, SIMON NM, FAGIOLINI *et al*.: Persistent posttraumatic stress disorder following September 11 in patients with bipolar disorder. *J Clin Psychiatry* 2006; 67: 394-9.
66. OQUENDO MA, FRIEND JM, HALBERSTAM B *et al*.: Association of comorbid posttraumatic stress disorder and major depression with greater risk for suicidal behavior. *Am J Psychiatry* 2003; 160: 580-2.
67. DELL'OSSO L, CARMASSI C, RUCCI P *et al*.: Lifetime subthreshold mania is related to suicidality in posttraumatic stress disorder. C*NS Spectr* 2009; 14: 262-6.
68. BAZZICHI L, MASER J, PICCINNI A *et al*.: Quality of life in rheumatoid arthritis: impact of disability and lifetime depressive spectrum symptomatology. *Clin Exp Rheumatol* 2005; 23: 783-8.