Comorbidity of Fibromyalgia and Psychiatric Disorders

Dan Buskila, MD, and Hagit Cohen, PhD

Corresponding author
Dan Buskila, MD
Department of Medicine H, Soroka Medical Center, POB 151, Beer Sheva 84101, Israel.
E-mail: dbuskila@bgumail.bgu.ac.il

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There are mounting data supporting comorbidity of fibromyalgia syndrome (FMS) and psychiatric conditions. These include depression, panic disorders, anxiety, and post-traumatic stress disorder (PTSD). The nature of the relationship between depression and FMS is not fully understood, and it was hypothesized that chronic pain causes depression, or vice versa, and that chronic pain syndromes are variants of depression. A link between PTSD symptoms and FMS has been reported, and both conditions share similar symptomatology and pathogenetic mechanisms. Assessment of comorbid psychiatric disorders in FMS patients has clinical implications because treatment in these patients should focus both on physical and emotional dimensions of dysfunction.

Introduction

Fibromyalgia syndrome (FMS) is a chronic disorder of diffuse pain or stiffness in the muscles or joints, accompanied by tenderness on examination at specific, predictable anatomic sites known as tender points [1].

Fibromyalgia is a common disorder estimated to affect 2% to 4% of the population [2]. In the past decade, major progress has been made in our understanding of fibromyalgia, which is now recognized as one of many "central" pain syndromes that are common in the general population [3].

Varieties of neuroendocrine disturbances, abnormalities of autonomic function, and specific genes that might confer an increased risk for developing FMS have been implicated in its pathogenesis [4].

Fibromyalgia is one of many related disorders, including chronic fatigue syndrome (CFS), irritable bowel syndrome, Gulf War illness, and more, which may present with similar symptomatology. Numerous studies reported on comorbidity of FMS and psychiatric disorders.

Approximately 30% of patients with FMS have major depression at the time of diagnosis; the lifetime prevalence of depression is 74% and that of an anxiety disorder is 60% [5,6]. In some FMS patients, mood and cognitive problems are much more prominent than tenderness [5].

Hypotheses about the link between depression and chronic pain include the notion that one causes the other or that a common underlying diathesis causes individuals to be more susceptible to both major depressive disorder (MDD) and chronic pain [7].

This review summarizes the evidence for comorbidity of FMS and psychiatric disorders and addresses possible pathogenetic links between depression and post-traumatic stress disorder (PTSD) and FMS.

Psychiatric Comorbidity in Fibromyalgia

Epstein et al. [8] conducted an investigation in four tertiary-care centers to determine if psychiatric comorbidity and psychologic variable were predictive of functional impairment in patients with FMS. In this multicenter study, persons with FMS exhibited marked functional impairment, high levels of some lifetime and current psychiatric disorders, and significant current psychologic distress.

A meta-analytic review of medically unexplained physical symptoms, anxiety, and depression confirmed that irritable bowel syndrome, CFS, non-ulcer dyspepsia, and FMS are related to (but not fully dependent on) depression and anxiety [9].

Approximately 30% of patients with FMS have major depression at the time of diagnosis; the lifetime prevalence of depression is 74%, and that of an anxiety disorder is 60% [5,6].

It was suggested that FMS is one member of a proposed group of psychiatric and medical disorders, collectively termed affective spectrum disorder (ASD) [10•].

The results of a family study of FMS and ASD supported familial aggregation of ASD collectively and familial coaggregation of FMS with other forms of ASD [10•].

Arnold et al. [11] assessed the co-occurrence of fibromyalgia and psychiatric disorders in participants in a fibromyalgia family study. A substantial lifetime psychiatric comorbidity was found in individuals with FMS. It was

suggested that these results have important clinical and theoretical implications, including the possibility that FMS might share underlying pathophysiologic links with some psychiatric disorders [11].

Raphael et al. [12••] provided a study estimating FMS prevalence rates in an ethnically and medically diverse sample of women in the metropolitan New York/New Jersey area, and the comorbidity of specific psychiatric disorders with FMS in this sample of women. The estimated overall prevalence of FMS among women in the New York/New Jersey area was 3.7% (95% CI = 3.2, 4.4), with higher rates among racial minorities. Although risk of current MDD was nearly threefold higher in community women with versus without FMS, the groups had similar risk of lifetime MDD. Risk of lifetime anxiety disorders, particularly obsessive compulsive disorder and PTSD, was approximately fivefold higher among women with FMS. It was concluded that the results of this study indicate that the relationship between MDD and FMS may be more complicated than previously thought [12••].

An Italian study reported that patients with FMS showed a higher comorbidity with generalized anxiety disorder, panic disorder, and MDD than did controls [13].

The study showed a high frequency of manic symptoms in the sample of fibromyalgia patients (59%), approximately double that found in the control sample [13].

Considerable co-occurrences were found in chronic widespread pain (CWP) cases for chronic fatigue, joint pain, irritable bowel syndrome, and depressive symptoms [14]. In co-twin control analyses, odds ratios were no longer significant for psychiatric disorders, whereas they decreased but remained significant for most other comorbidities [14].

Thus, there are mounting data supporting the comorbidity of FMS and psychiatric conditions, including depression and anxiety.

Depression and Chronic Pain: What Is the Nature of the Relationship?

Individuals with chronic pain, including FMS, display comorbid depression. A variety of speculations about the nature of the relationship has been proposed, including that chronic pain cause depression, or vice versa, that chronic pain syndromes are variants of depression, and that their co-occurrence in patients is an artifact of selective factors in treatment [15].

Fishbain et al. [7] determined the status for the association of chronic pain and depression and reviewed the evidence for whether depression is an antecedent or consequence of chronic pain. They reviewed 191 studies that related to the pain-depression association. The reviewed studies were consistent in indicating that there is a statistical relationship between chronic pain and depression.

For the relationship between pain and depression, there was greater support for the consequence and predisposition to depression hypothesis than for the antecedent hypothesis. It was concluded that depression is more common in chronic pain patients than in healthy controls as a consequence of the presence of chronic pain. At pain onset, predisposition to depression may increase the likelihood for the development of depression in some chronic pain patients [7].

Dohrenwend et al. [15] conducted a family study assessing the question of why is depression comorbid with chronic myofascial pain. The results of this family study showed that familial MDD and depressive spectrum disorders were increased in control probands with MDD but not in myofascial face pain probands with or without MDD.

It was concluded that this pattern is consistent with the hypothesis that the experience of chronic pain contributes to increased rates of depression in myofascial face pain probands [15].

Raphael et al. [16•] provided a study on familial aggregation of depression in FMS. The results of this study indicated that rates of MDD in the relatives of probands with FMS but without personal histories of MDD were virtually identical to rates of MDD in relatives of probands with MDD. It was concluded that this outcome is consistent with the hypothesis that FMS is a depression spectrum disorder, in which FMS and MDD are characterized by shared, familial-mediated risk factors [16•].

In another study assessing psychiatric comorbidities in a community sample of women with FMS, the same authors reported results suggesting a complex relationship between MDD and FMS, in which current but not lifetime risk of MDD is increased, and highlighted the importance of method variance in this analysis [12••].

The effect of symptoms of depression and/or clinically diagnosed MDD on pain processing was evaluated in patients with FMS [17••]. In patients with FMS, neither the extent of depression nor the presence of comorbid MDD modulated the sensory discriminative aspects of pain processing, as measured by sensory testing or functional MRI. However, depression was associated with the magnitude of neural activation in brain regions that process the affective motivational dimensions of pain. It was suggested that there are parallel, somewhat independent neural pain processing networks for sensory and affective pain elements [17••].

Zautra et al. [18] tested the question of whether patients with FMS showed affective profiles that were unique from profiles of women with chronic pain from osteoarthritis. They found little evidence that FMS patients had greater difficulty in the management of negative emotion than did their osteoarthritis counterparts.

Contrary to the literature on FMS, differences between groups in neuroticism, depression, and anxiety were not substantial. Furthermore, FMS patients did not report greater negative affect than did patients with osteoarthritis. The results of this study identified dysfunctional positive affect regulation as a key feature of FMS [18].

A recent study examined the association between comorbidity of FMS and depression and occupational status [19].

It was found that FMS and MDD independently and negatively are associated with labor force participation.

Karst et al. [20] identified abnormality in the self-monitoring mechanism in patients with FMS and somatoform pain disorder. They concluded that central pain disorders such as FMS and somatoform pain disorders interfere with the correct functioning of the self-monitoring mechanism that normally allows us to distinguish self-produced from externally produced tactile stimuli [20]. In addition, Palomino et al. [21] evaluated the contribution of condition-specific helplessness and loss to depression in FMS. The findings of this study confirmed the importance of helplessness and demonstrated that the cognitive meaning of having FMS plays a more central role in predicting depressive symptomatology than do illness-related stressors, such as pain or disability.

PTSD, Tenderness, and FMS

Behavioral and psychologic factors have an important role in symptom expression in FMS. Population-based studies have demonstrated that distress can lead to pain and pain can lead to distress. Much interest has been focused on the role that stress plays in the development of physical or mental disability.

Anderberg et al. [22] observed that stressful life events may trigger the succeeding development of FMS. Amir et al. [23] reported that the prevalence of FMS in PTSD patients was 21%, versus 0% in control subjects. The PTSD group was more tender than the control group. It was suggested that previous reports on diffuse pain in PTSD in fact described undiagnosed FMS.

Cohen et al. [24] assessed the frequency of PTSD in 77 patients with FMS. Fifty-seven of the FMS sample had clinically significant levels of PTSD symptoms. This study showed a significant overlap between FMS and PTSD, according to the currently accepted diagnostic criteria for each.

Sherman et al. [25] reported similar results: approximately 56% of FMS patients reported clinically significant levels of PTSD-like symptoms. It was suggested that PTSD-like symptoms are prevalent in FMS patients and may influence adaptation to this chronic illness. Patients seen in a referral clinic (n = 571) were evaluated for FMS and CFS criteria [26].

Critical components of the diagnostic criteria of FMS and CFS were examined for their relationship with PTSD. Patients who had both tender points and diffuse pain had a higher prevalence of PTSD compared with those who had neither of these FMS criteria. Stratification by MDD and adjustment for sociodemographic factors and chronic fatigue revealed that the association of PTSD with FMS criteria was confined to those with MDD [26].

Like other unexplained pain syndromes, frequent mastalgia was strongly associated with PTSD and other psychiatric conditions [27]. Patterns of physical comorbidity among women with PTSD were explored using Michigan Medicaid claims data [28]. PTSD-diagnosed women were compared with randomly selected women in three health outcome areas: International Classification of Diseases-9 categories of disease, chronic conditions associated with sexual assault history in previous research, and reproductive health conditions.

PTSD was associated with increased risk of all categories of diseases, endometriosis, and dyspareunia. When PTSD was not complicated by other mental health conditions, odds ratios for chronic conditions ranged from 1.9 for FMS to 4.3 for irritable bowel syndrome. Comorbidity with depression or a dissociative or borderline personality disorder raised risks in a dose-response pattern [28].

Arguelles et al. [29] found that symptoms of PTSD, as measured by the Impact of Events Scale (IES), in a twin study, were strongly related to the presence of CWP. Furthermore, the increased prevalence of CWP across terciles of increasing IES scores was strong and significant even after adjusting for sociodemographic factors, body mass index, and depression. This study found a strong association between PTSD symptoms and CWP that was not explained by a shared familial or genetic vulnerability to both conditions. It was suggested that future studies need to examine the viability of mutual maintenance and shared vulnerability models as well as the central nervous system mechanisms that may play a role in the link between PTSD and pain [29].

Amital et al. [30•] investigated the comorbidity of FMS and PTSD in a cohort of men after an intensive, initial, defined traumatic event. One hundred and twenty-four men (55 patients with PTSD, 20 patients with major depression, and 49 controls) were evaluated for the presence of FMS. Forty-nine percent of PTSD patients, compared with 5% of major depression patients and no normal controls, fulfilled criteria for diagnosing FMS. Significant correlations were detected between tender points and measured parameters in the PTSD group. It was concluded that in male patients, PTSD is highly associated with FMS [30•].

The comorbidity of FMS and PTSD has clinical implications. The degree and impact of these disorders are highly interrelated [30•]. PTSD-like symptoms may influence adaptation to the chronic state of FMS. Clinicians should be aware of the presence of this comorbidity, because the failure to attend to PTSD symptoms in treatment may impede successful outcomes [25].

PTSD and FMS: Do They Share Common Pathophysiologic Mechanisms?

As mentioned previously, several studies have reported an association between PTSD and FMS. Traumatic experiences clearly influence mental as well as physical health. The experience of trauma has been associated with increased somatic and physical complaints. The coincidence of physical pain and traumatic events

raises the question of an association between FMS and PTSD, and hence the need to establish whether this is a causal or consequent relationship. There is notable degree of symptom and pathogenetic overlap between FMS and PTSD. Depressive and anxiety symptoms are common in both FMS and PTSD. As mentioned earlier, symptoms of depression and anxiety are often found in patients with FMS [8,9,10•,11,12••]. But it is well-known that PTSD is highly comorbid with major anxiety disorders [31].

Fibromyalgia and PTSD affect women more frequently than men. FMS and PTSD are disorders associated with increased stress and stressor perception [32,33]. This characteristic is supported by studies showing a blunted physiologic stress response in FMS and in PTSD [34,35]. The literature to date suggests that relatively low baseline cortisol is associated with the development of PTSD [34]. As with FMS, most studies are consistent with hypoactivity of the hypothalamic-pituitary-adrenal (HPA) axis, although whether this occurs as a result of a central or peripheral abnormality is not known [36].

Both PTSD and FMS are disorders, characterized by abnormal illness behavior, reduced physical activity, and exaggerated pain sensitivity [24]. It seems possible that some of these features may be related to reduced HPA axis activity.

Autonomic nervous system dysregulation has been reported in both FMS and PTSD. Using power spectrum analysis of heart rate variability (HRV), we demonstrated a significant reduction in HRV, vagal tone, and augmented sympathetic activity in FMS patients at rest, compared with normal age-matched controls [37–39].

This reflects a basal autonomic state of hyperactivation characterized by increased sympathetic and decreased parasympathetic tone. Similarly, a basal autonomic state of hyperactivation, with increased sympathetic and decreased parasympathetic tone, in the form of higher HRV values, has been reported in trauma victims with PTSD, compared with non-exposed healthy control subjects [40,41].

Adult growth hormone deficiency has been found in a subset of patients with FMS [42], and Morris et al. [43] reported that the growth hormone response to clonidine was significantly blunted in the nondepressed PTSD group compared with both the depressed PTSD group and the control group. This suggests that post-synaptic $\alpha 2$ receptors are subsensitive. This finding is consistent with other studies showing increased noradrenergic activity in PTSD.

Both FMS and PTSD are associated with sleep disturbances, although of different sleep architecture [44,45]. Genetic factors may play a role in the etiopathology of both FMS [4,46,47] and PTSD [48]. This includes familial aggregation of these syndromes as well as similar polymorphisms of genes in the serotoninergic and dopaminergic systems [4,46–50].

FMS and PTSD patients show a high degree of overlap in both psychologic and physiologic symptoms. Thus, it may be speculated that they share at least in part common or similar pathophysiologic mechanisms. A core feature in the *Diagnostic and Statistical Manual of Mental Disorders* IV diagnosis of PTSD is the linking of a distinct configuration of symptoms with an identifiable traumatic event, as a mandatory precondition for making the diagnosis.

The major question is why after traumatic events/experiences some (FMS patients) develop somatic problems and others (PTSD patients) develop psychiatric complaints. From a clinical existential point of view, it can be said that the "pain" of PTSD patients is related to experiencing. Living with the trauma and pain, day in and day out, without any significant surcease over time, is integral to the disability and suffering of these patients. It is not unconceivable that the "emotional pain" may be transmuted or converted into physical pain, especially because physical symptoms are socioculturally more acceptable than mental and emotional symptoms. The somatic complaints of FMS patients may be in part secondary adaptive mechanisms of avoidance, shaped by post-traumatic factors.

It may also be that these somatic complaints and the persistence of multiple unexplained physical symptoms in both FMS and PTSD patients may be a phenomenon of somatoform disorders. Associations between trauma/PTSD and somatoform disorders, and between somatization and onset of CWP, have been reported [51–53].

Psychologic Factors: A Tool for Subgrouping FMS

Although the American College of Rheumatology criteria for fibromyalgia are used to identify individuals with both widespread pain and tenderness, individuals who meet these criteria are not a homogeneous group [5]. Fibromyalgia patients differ in their accompanying clinical symptoms, as well as in the relative contributions of biologic, psychologic, and cognitive factors to their symptom expression [5].

Thieme et al. [54] evaluated the prevalence as well as predictors of psychiatric disorders in patients with FMS. The 115 FMS patients were grouped into one of three psychosocial subgroups based on responses to the Multidimensional Pain Inventory (MPI)—Dysfunctional, Interpersonally Distressed, and Adaptive Copers. The results of this study suggested that FMS is not a homogeneous diagnosis but shows varying proportions of comorbid anxiety and depression dependent on psychosocial characteristics of the patients. It was concluded that it is important not to treat patients with FMS as a homogeneous group. Rather, assessment of FMS patients should not only examine the presence of widespread pain and the number of tender points, but also the presence of affective distress, and treatment should focus both on physical and emotional dysfunction [54].

Giesecke et al. [5] attempted to identify FMS patient subsets by incorporating psychologic features as well as the degree of hyperalgesia/tenderness. Three subgroups of FMS emerged. One subgroup of patients (n = 50) was characterized by moderate mood ratings, moderate levels of catastrophizing and perceived control over pain, and low levels of tenderness.

A second subgroup (n = 31) displayed significantly increased values on the mood assessments, the highest values on the catastrophizing subscale, the lowest values for perceived control over pain, and high levels of tenderness. The third group (n = 16) had normal mood ratings, very low levels of catastrophizing, and the highest level of perceived control over pain, but these patients showed extreme tenderness on evoked pain testing. It was concluded that these data help support the clinical impression that there are distinct subgroups of patients with fibromyalgia.

The clinical profiles of FMS patients at a community mental health center were studied; 75 FMS patients and 55 healthy controls were included [55]. Two different patterns were obtained: group A (32%), with a typical chronic pain profile, and group B (68%), with a psychologic maladjustment profile. The authors obtained an index of psychopathological profile in FMS, which would form a new scale from MMPI-2 for discriminating psychopathologic severity in FMS [55].

Conclusions

Numerous studies report on comorbidity of FMS and psychiatric disorders. Hypotheses about the link between depression and chronic pain include the notion that one causes the other or that shared pathogenetic mechanisms cause susceptible individuals to develop both conditions.

PTSD was found to be highly associated with FMS. There is notable degree of symptom and pathogenetic overlap between FMS and PTSD. Recognizing comorbidity of FMS and psychiatric disorders has important clinical implications because treatment of these patients should address both physical and emotional factors. Assessment of psychologic features in FMS patients may help to obtain a more rational subgrouping of these patients and in designing better management.

More research is necessary with larger samples of FMS patients in different clinical settings (tertiary care and community) to better determine the nature of the comorbidity of psychiatric disorders in FMS.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Dadabhoy D, Clauw DJ: **Fibromyalgia progress in diagnosis and treatment.** *Curr Pain Headache Rep* 2005, **9:**399–404.
2. Neumann L, Buskila D: **Epidemiology of fibromyalgia.** *Curr Pain Headeche Rep* 2003, **7:**362–368.
3. Harris RE, Clauw DJ: **How do we know that the pain in fibromyalgia is "real"?** *Curr pain Headache Rep* 2006, **10:**403–407.
4. Buskila D, Sarzi-Puttini P, Ablin JN: **The genetics of fibromyalgia syndrome.** *Pharmacogenomics* 2007, **8:**67–74.
5. Giesecke T, Williams DA, Harris RT, et al.: **Subgrouping of fibromyalgia patients on the basis of pressure pain thresholds and psychological factors.** *Arthritis Rheum* 2003, **48:**2916–2922.
6. Arnold LM, Hudson JI, Hess EV, et al.: **Family study of fibromyalgia.** *Arthritis Rheum* 2004, **50:**944–952.
7. Fishbain DA, Cutler R, Rosomoff HL, Rosomoff RS: **Chronic pain-associated depression: antecedent or consequence of chronic pain? A review.** *Clin J Pain* 1997, **13:**116–137.
8. Epstein SA, Kay G, Clauw D, et al.: **Psychiatric disorders in patients with fibromyalgia.** *Psychosomatics* 1999, **40:**57–63.
9. Henningsem P, Zimmermann T, Sattel H: **Medically unexplained physical symptoms, anxiety, and depression: a meta-analytic review.** *Psychosom Med* 2003, **65:**528–533.
10. • Hudson JI, Hrnold LM, Keck PE Jr, et al.: **Family study of fibromyalgia and affective spectrum disorder.** *Biol Psychiatry* 2004, **56:**884–891.

A study supporting familial aggregation of affective spectrum disorder collectively and familial aggregation of fibromyalgia with other forms of ASD.

11. Arnold LM, Hudson JI, Keck PE, et al.: **Comorbidity of fibromyalgia and psychiatric disorders.** *J Clin Psychiatry* 2006, **67:**1219–1225.
12. •• Raphael KG, Janal MN, Nayak S, et al.: **Psychiatric comorbidities in a community sample of women with fibromyalgia.** *Pain* 2006, **124:**117–125.

A community-based study indicating that the relationship between MDD and FMS may be more complicated than previously thought.

13. Carta MG, Cardia C, Mannu F, et al.: **The high frequency of manic symptoms in fibromyalgia does influence the choice of treatment?** *Clin Pract Epidemol Ment Health* 2006, **2:**36–41.
14. Kato K, Sullivan PF, Evengard B, Pedersen NL: **Chronic widespread pain and its comorbidities: a population-based study.** *Arch Intern Med* 2006, **166:**1649–1654.
15. Dohrenwend BP, Raphael KG, Marback JJ, Gallagher RM: **Why is depression comorbid with chronic myofascial face pain? A family study test of alternative hypotheses.** *Pain* 1999, **83:**183–192.
16. • Raphael KG, Janal MN, Nayak S, et al.: **Familial aggregation of depression in fibromyalgia: a community-based test of alternate hypotheses.** *Pain* 2004, **110:**449–460.

A family study suggesting that FMS is a depression spectrum disorder, in which FMS and MDD are characterized by shared familial-mediated risk factors.

17. •• Giesecke T, Gracely RH, Williams DA, et al.: **The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort.** *Arthritis Rheum* 2005, **52:**1577–1584.

In FMS patients neither the extent of depression nor the presence of comorbid major depression modulates the sensory-discriminative aspects of pain processing.

18. Zautra AJ, Fasman R, Reich JW, et al.: **Fibromyalgia: evidence for deficits in positive affect regulation.** *Psychosom Med* 2005, **67:**147–155.
19. Kassman A, Patten SB: **Major depression, fibromyalgia and labour force participation: a population-based cross-sectional study.** *BMC Musculoskelet Disord* 2006, **7:**4.
20. Karst M, Rahe-Meyer N, Gueduex A, et al.: **Abnormality in the self monitoring mechanism in patients with fibromyalgia and somatoform pain disorder.** *Psychosom Med* 2005, **67:**111–115.
21. Palomino RA, Nicassio PM, Greenberg MA, Medina EP Jr: **Helplessness and loss as mediators between pain and depressive symptoms in fibromyalgia.** *Pain* 2007, **129:**185–194.

22. Anderberg UM, Marteins Dottir I, Theorell T, Von Knorring L: **The impact of life events in female patients with fibromyalgia and in female healthy controls.** *Eur Psychiatry* 2000, **15:**295–301.
23. Amir M, Kaplan Z, Neumann L, et al.: **Posttraumatic stress disorder, tenderness and fibromyalgia.** *J Psychosom Res* 1997, **42:**607–613.
24. Cohen H, Neumann L, Haiman Y, et al.: **Prevalence of post-traumatic stress disorder in fibromyalgia patients: overlapping syndromes or posttraumatic fibromyalgia syndrome?** *Semin Arthirtis Rheum* 2002, **32:**38–50.
25. Sherman JJ, Turk DC, Okifuji A: **Prevalence and impact of posttraumatic stress disorder-like symptoms on patients with fibromyalgia syndrome.** *Clin J Pain* 2000, **16:**127–134.
26. Roy-Byrne P, Smith WR, Goldberg J, et al.: **Post-traumatic stress disorder among patients with chronic pain and chronic fatigue.** *Psychol Med* 2004, **34:**363–368.
27. Johnson KM, Bradley KA, Bush K, et al.: **Frequency of mastalgia among women veterans. Association with psychiatric conditions and unexplained pain syndromes.** *J Gen Intern Med* 2006, **21(Suppl 3):**S70–S75.
28. Seng JS, Clark MK, McCarthy AM, Ronis DL: **PTSD and physical comorbidity among women receiving Medicaid: results from service-use data.** *J Trauma Stress* 2006, **19:**45–56.
29. Arguelles LM, Afari N, Buchwald DS, et al.: **A twin study of posttraumatic stress disorder symptoms and chronic widespread pain.** *Pain* 2006, **124:**150–157.
30.• Amital D, Fostick L, Polliack ML, et al.: **Posttraumatic stress disorder, tenderness, and fibromyalgia syndrome: are they different entities?** *J Psychosom Res* 2006, **61:**663–669.
In male patients, PTSD is highly associated with FMS. The degree and impact of these disorders are also highly related.
31. Kessler RC, Sonnega A, Bromet E, et al.: **Posttraumatic stress disorder in the National Comorbidity Survey.** *Arch Gen Psychiatry* 1995, **52:**1048–1060.
32. Ravindren AV, Griffiths J, Waddell C, Anisman H: **Stressful life events and coping styles in relation to dysthymia and major depressive disorder: variations associated with alleviation of symptoms following pharmacotherapy.** *Prog Neuropsychopharmacol Biol Psychiatry* 1995, **19:**637–653.
33. Wilke WS: **Fibromyalgia. Recognizing and addressing the multiple interrelated factors.** *Postgrad Med* 1996, **100:**153–156.
34. Yehuda R: **Current status of cortisol findings in post-traumatic stress disorder.** *Psychiatr Clin North Am* 2002, **25:**341–368.
35. McCain GA, Tilbe KS: **Diurnal hormone variation in fibromyalgia syndrome: a comparison with rheumatoid arthritis.** *J Rheumatol* 1989, **19(Suppl):**154–157.
36. Grofford LJ, Young EA, Engleberg NC, et al.: **Basal circadian and pulsatile ACTH, and cortisol secretion in patients with fibromyalgia and/or chronic fatigue syndrome.** *Brain Behav Immun* 2004, **18:**314–325.
37. Cohen H, Neumann L, Kotler M, Buskila D: **Autonomic nervous system derangement in fibromyalgia syndrome and related disorders.** *Isr Med Assoc J* 2001, **3:**755–760.
38. Cohen H, Neumann L, Shore M, et al.: **Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability.** *Semin Arthritis Rheum* 2000, **29:**217–227.
39. Cohen H, Neumann L, Alhosshle A, et al.: **Abnormal sympathovagal balance in men with fibromyalgia.** *J Rheumatol* 2001, **28:**581–589.
40. Cohen H, Kotler M, Matar M, Kaplan Z: **Normalization of heart rate variability in post-traumatic stress disorder patients following treatment: preliminary results.** *Isr Med Assoc J* 2000, **2:**296–301.
41. Cohen H, Benjamin J, Geva AB, et al.: **Autonomic dysregulation in panic disorder: application of heart rate variability at rest and in response to recollection of trauma or panic attacks.** *Psychiatry Res* 2000, **96:**1–13.
42. Bennett RM: **Adult growth hormone deficiency in patients with fibromyalgia.** *Curr Rheumatol Rep* 2002, **4:**306–312.
43. Morris P, Hopwood M, Maguire K, et al.: **Blunted growth hormone response to clonidine in post-traumatic stress disorder.** *Psychoneuroendocrinology* 2004, **29:**269–278.
44. Moldofsky H: **Management of sleep disorders in fibromyalgia.** *Rheum Dis Clin North Am* 2002, **28:**353–365.
45. Lavie P: **Sleep disturbances in the wake of traumatic events.** *N Engl J Med* 2001, **345:**1825–1832.
46. Ablin JN, Cohen H, Buskila D: **Mechanisms of disease: genetics of fibromyalgia.** *Nat Clin Pract Rheumatol* 2006, **2:**671–678.
47. Buskila D, Sarzi-Puttini P: **Biology and therapy of fibromyalgia. Genetic aspects of fibromyalgia syndrome.** *Arthritis Res Ther* 2006, **8:**218–222.
48. Koenen KC, Lyons MJ, Goldenberg J, et al.: **A high risk twin study of combat-related PTSD comorbidity.** *Twin Res* 2003, **6:**218–226.
49. Lee HJ, Lee MS, Kang RH, et al.: **Influence of the serotonin transporter promoter gene polymorphism on susceptibility to posttraumatic stress disorder.** *Depress Anxiety* 2005, **21:**135–139.
50. Lawford BR, McD Young R, Noble EP, et al.: **D2 dopamine receptor gene polymorphism: paroxetine and social functioning in posttraumatic stress disorder.** *Eur Neuropsychopharmacol* 2003, **13:**313–320.
51. Beckham JC, Moore SD, Feldman ME, et al.: **Health status, somatization and severity of posttraumatic stress disorder in Vietnam combat veterans with posttraumatic stress disorder.** *Am J Psychiatry* 1998, **155:**1565–1569.
52. Andreski P, Chilcoat H, Breslau N: **Post traumatic stress disorder and somatization symptoms: a prospective study.** *Psychiatry Res* 1998, **79:**131–138.
53. McBeth J, Macfarlane GI, Benjamin S, Silman AJ: **Features of somatization predict the onset of chronic widespread pain: results of a large population-based study.** *Arthritis Rheum* 2001, **44:**940–946.
54. Thieme K, Turk DC, Flor H: **Comorbid depression and anxiety in fibromyalgia syndrome: relationship to somatic and psychosocial variables.** *Psychosom Med* 2004, **66:**837–844.
55. Blasco CL, Mallo CM, Mencia PA, et al.: **Clinical profiles in fibromyalgia patients of the community mental health center: a predictive index of psychopathological severity.** *Actas Esp Psiquiatr* 2006, **34:**112–122.