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## Chronic Pain and Depression

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### Abstract

Today, it is clear that chronic pain and depression are closely related. Depression can cause pain, and chronic pain can cause depression too. According to the American Pain Foundation, about 32 million people in the U.S. report have had pain lasting longer than 1 year. Statistical international data prove that more than half of the patients with pain are depressed or have mood swings, and on average, 65% of depressed people also complain of pain. Patients simultaneously suffering of chronic pain and limited independence are especially vulnerable. Fibromyalgia (FM) is one of the most common chronic pain syndromes, affecting 15 up to 5% of world population, is characterized as diffuse widespread body pain, with definite tender points and clinical features, and also triggers the development of depression. Depression severity in patients with FM worsens severity of pain. Depressive disorders are observed in approximately 90% of patients with FM. Pain triggers development of depressive conditions in patients with chronic character of pain, and time course of disease shows certain pattern of increasing of severity of depression and worsens long term outcomes. Patients with chronic pain must be evaluated for depression, and successful management of pain must include treatment of depressive mood too.

**Keywords:** chronic pain, fibromyalgia, chronic fatigue syndrome, depression and depressive symptoms

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### 1. Introduction

The results of medical investigations conducted in the field of pain unveiled the unbearable burden of living with chronic or long-term pain. Moreover, simultaneous suffering of pain and depression makes that burden heavier and worsens prognosis. Patients with depression emotionally suffer from more severe pain, and in the case of primary pain, they more prone to develop depression.

It is widely accepted that chronic pain is often defined as any pain lasting more than 12 weeks. Whereas acute pain is a normal sensation that alerts about possible injury or inflammation, chronic pain is very different. Chronic pain persists often for several months or even longer.

Chronic pain may arise from an initial injury of the tissue, or there may be an ongoing cause, such as illness. However, there may also be no clear cause. Other health problems, such as fatigue, sleep disturbance, decreased appetite, and mood changes, often accompany chronic pain. Chronic pain may limit patient's motility, which can reduce flexibility, strength, and stamina. This difficulty in carrying out important and enjoyable activities can lead to some level of disability and despair.

Chronic pain can prevent sleep and cause patients to awaken frequently at night. This lack of sleep further results in daytime fatigue and low productivity. The ongoing pain will cause additional irritation and make it difficult to deal with others.

Depression is one of the most common psychological issues people facing who suffer from chronic pain, and it often complicates the patient's conditions and treatment. Current statistical data prove that according to the American Pain Foundation, about 32 million people in the U.S. report have had pain lasting longer than 1 year; from one-quarter to more than half of the population that complain of pain to their doctors are depressed, and on average, 65% of depressed people also complain of pain.

People whose pain limits their independence are especially likely to become depressed.

Because depression in patients with chronic pain frequently goes undiagnosed, it often goes untreated. Pain symptoms and complaints take center stage on most doctor visits; bad mood is usually ignored or explained as the result of long-lasting pain, but not simultaneously growing medical condition. The result is depression along with sleep disturbances, loss of appetite, lack of energy, and decreased physical activity, which may make pain much worse.

Fibromyalgia (FM) is a chronic pain syndrome characterized by generalized pain, the presence of specific tender points (small areas of excessive pain, localized in different areas of the body), sleep disorders, and severe chronic fatigue. In the general population of patients with chronic widespread pain, FM occupies an exclusive position that affects between 2 and 5% of the general population in the United States and is diagnosed more often in women (7:1) [1–4].

A significant increase in the number of patients with a variety of persistent pain syndromes and certain advances in the diagnosis and management of FM expressed interest in the problem of pain by the medical community; the nature of the priority of this syndrome raises the FM up to the level of medical and social problems. Latter is confirmed by a number of international and national associations of fibromyalgia and pain research.

Considering that the known clinical symptoms become apparent, the FM complex problem is more complex than just muscle pain. Persistence of sets of clinical symptoms, not based on morphological, biochemical, and other changes, allows considering FM as somatoform disorder. In addition, there is strong evidence of lowering the threshold of pain sensitivity in

patients with FM. At the same time, clinical application of different methods, such as neuro-sensory potential testing, revealed that the mechanical allodynia in patients with FM is not restricted to tender points and is prevalent [5].

Currently, an increase in the number of FM investigators is considered as functional and somatic pathology [6, 7].

It becomes obvious that the FM is a more complex problem than just widespread muscle pain. This is evidenced by several attempts to create a unified theory of the origin of the FM and equally the development of reliable precise criteria for classification of FM, because of the existing classification based on the integration of different combinations of psycho-somatic disorders, based on a purely phenomenological approach, without taking into account the relationship and common pathogenic mechanisms of development and progression [8–10].

## 2. Aims of study

Given the extreme heterogeneity of clinical manifestations and the heterogeneity of quantitative measurements of different blood parameters, as well as a significant reduction in the quality of life in patients with FM, we set the main goal—the study of pathogenic features and diagnostic criteria as a basis for effective management of fibromyalgia. In accordance with the purpose, the following tasks were formulated:

- to examine the severity of the main clinical symptoms of FM, especially their relationships depending on the duration of the disease;
- to assess the level of physical and mental components of quality of life and the nature of their relationship with the symptoms of FM;
- to identify the role of pain, sleep disorders, duration of the disease as risk factors for developing depression in patients with FM.

## 3. Study design

The material of the study is based on 151 patients with verified diagnosis of FM; average age of the patients is  $49.8 \pm 13.3$  years ( $M \pm SD$ ): among 129 women, average age is  $49.7 \pm 13.7$  years, and 22 men, average age is  $50.1 \pm 5$  years; the ratio of women to men is about 6:1. The average duration of the disease in patients with FM, regardless of age and sex, was  $4.5 \pm 2.4$  years ( $M \pm SD$ ). FM patients with typical complains to persistent pain, poor sleep, chronic fatigue, general weakness, forgetfulness, and emotional instability were screened.

Inclusion criteria: The presence of pain at 11 tender points or more, negative rheumatology, age over 10 up to 79 years.

Exclusion criteria: Positive rheumatology, the presence of comorbidity with verified diagnosis of multiple sclerosis, diabetes, cancer, alcoholic neuropathy—diseases that are character-

ized by a poly-neuropathic pain; the age of patients—younger than 10 and older than 80 years due to allodynia, common in children and the elderly.

Type of study: From the perspective of evidence-based medicine, the study is observational, prospective, and noninvasive in nature. Due to study design no case-matching control group was selected and/or compared.

Research methods: The intensity of pain was assessed by visual analog scale (VAS) and the quality of sleep on a 10-point scale (“Questionnaire scoring subjective characteristics of sleep”). To identify the level of depressive symptoms all included in the study, patients with FM were evaluated by validated and standardized questionnaire Beck Depression Inventory (BDI) [11], which allows differentiating both the low level of depression and major depression. Total score in points is as follows: (0–9) the absence of depression, (10–25) low level of depression, and (26–39) major depression.

To examine the risk factors in patients with FM were used conventional relative risks: odds ratio (OR) and relative risk (RR)—the ratio of the probability (chance) events in the same group to the probability of an event in another group. OR and RR values between 0 and 1.0 correspond to the reduction in risk, >1.0 an increase in the relative risk [12–14].

The quality of life of patients was assessed by a questionnaire SF-36 HRQOL (v.2) [12, 15]. The latter consists of 11 questions, including 36 points, each of which has own set of positive symptoms and denies the allegations. The SF-36 application is mostly justified by the opportunity to assess the overall quality of life and its physical and mental components.

Ethic regulations: Inclusion of patients to the study was done with their informed consent. The ethical aspect of the study was reviewed by the Committee on Bioethics of Yerevan State Medical University; decision was made to comply with the requirements of relevant studies required for ethical standards.

The evaluation of the statistical significance of differences in the studied parameters was carried out by student's t-criterion. Statistical analysis was performed using software packages STATISTICA 6, GraphPad Prism 4, and GraphPad Prism 5. When carrying out the statistical analysis, follow the guidelines by Rosner [16] and De Muth [17].

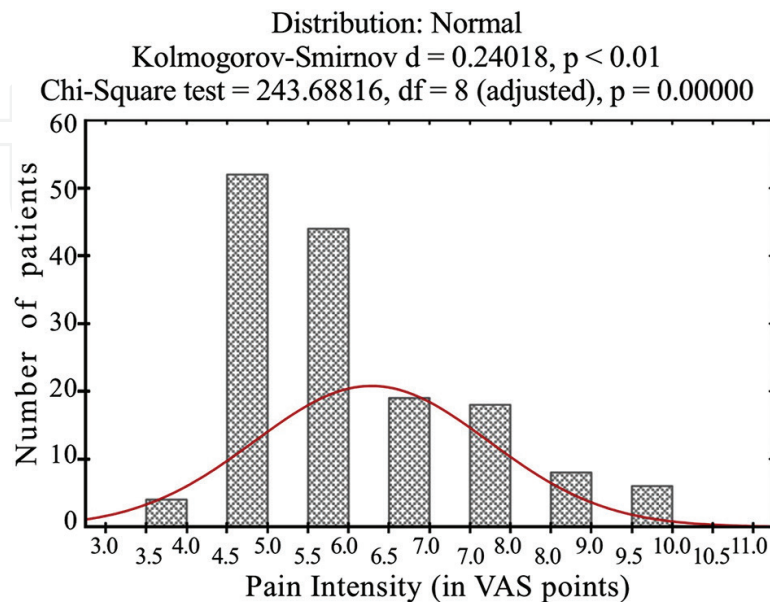
## **4. Quantification of the major clinical symptoms of fibromyalgia and their relationship**

### **4.1. Pain symptom evaluation**

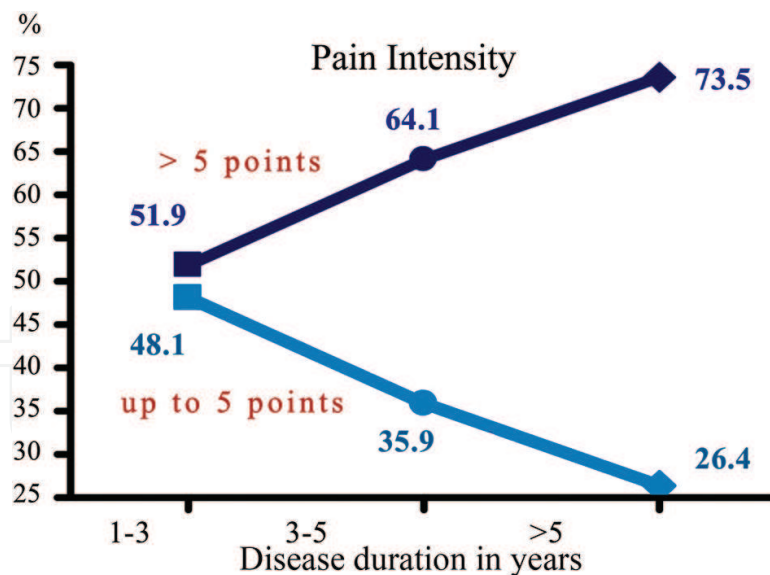
Test results on VAS show that in the total sample of patients with FM, pain intensity in the range of 1–5 points ( $4.9 \pm 0.25$ ,  $M \pm SE$ ) was detected in 37.1% of patients and 10.6 points ( $7.1 \pm 1.25$ ) in 62.9% of patients. These values were 59.0 and 41.0% for men and among women, 33.3 and 66.7% (**Figure 1**).

The study on the severity of pain in patients with FM, depending on the duration of the disease, revealed approximately the same the percentage of cases with the intensity of pain more or <5

points on the VAS scale, 51.9 and 48.1%, respectively. The group of patients with disease duration of FM for 3–5 years, especially more than 5 years, have seen a progressive increase in the percentage of patients with pain intensity >5 points, respectively, to 64.1 and 73.5% (**Figure 2**).



**Figure 1.** Results of the frequency distribution analysis indicator of the intensity of pain in the total sample of patients with FM.

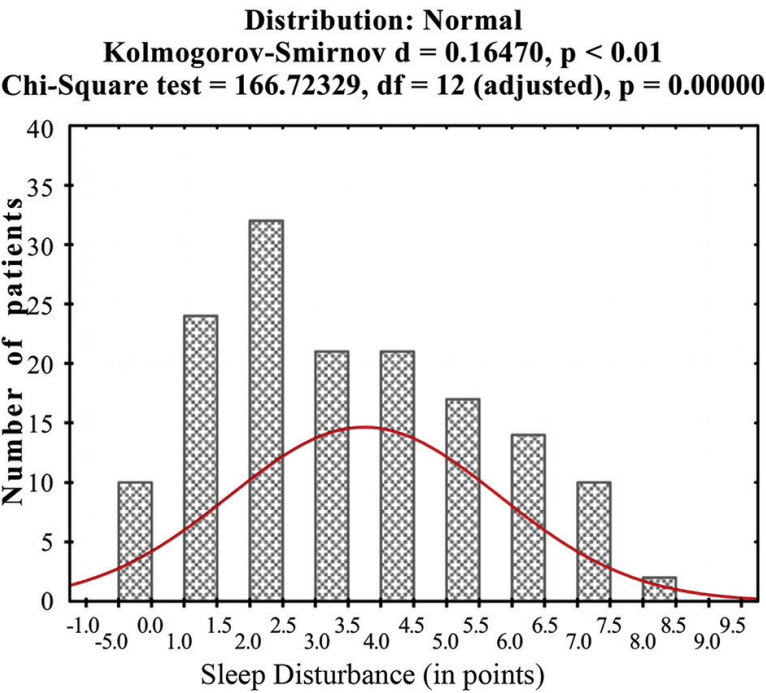


**Figure 2.** Intensity of pain in patients with FM, depending on the duration of the disease.

#### 4.2. Sleep disorders

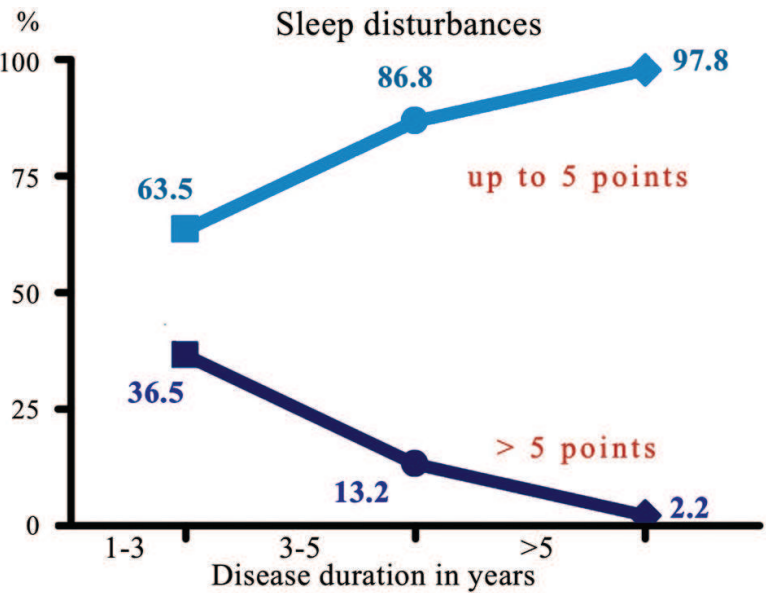
In the total sample of patients with FM, sleep disorders within 1–5 points ( $2.7 \pm 0.13$ ,  $M \pm SE$ ) were detected in 76.2% of patients and 6–10 points ( $6.5 \pm 0.12$ ) in 23.8% of patients, respectively, in men: 72.7 and 27.3% and in women: 33.3 and 66.7% (**Figure 3**).





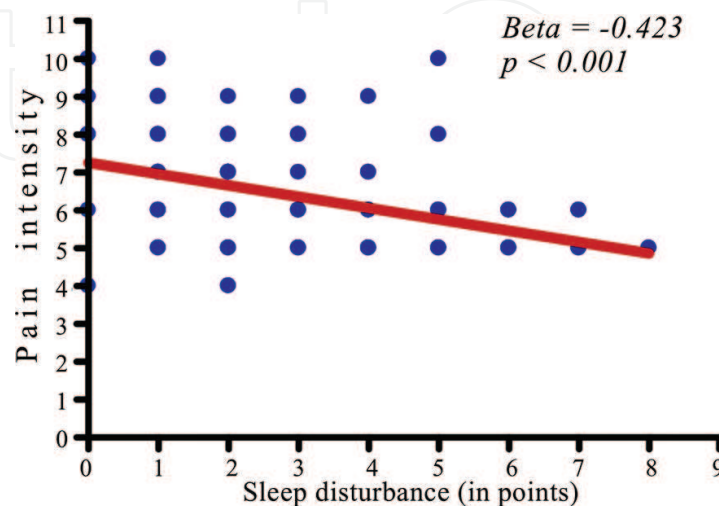
**Figure 3.** The results of frequency analysis of the distribution of index sleep disorders in the total sample of patients with FM.

It is well established that severity of sleep disorders is gradually reduced within the time-course of FM. For example, if a group of patients with disease duration of 1–3 years and the severity of sleep disorders <5 points found in 63.5% of cases, the duration of the disease for 3–5 years of the specified figure is 86.8% and more than 5 years is 97.8%. Against this background, notable decrease in the percentage of patients with severity of sleep disorders >5 points from 36.5 to 13.2% and 2.2% (**Figure 4**).



**Figure 4.** The severity of sleep disorders in patients with FM, depending on the duration of the disease.

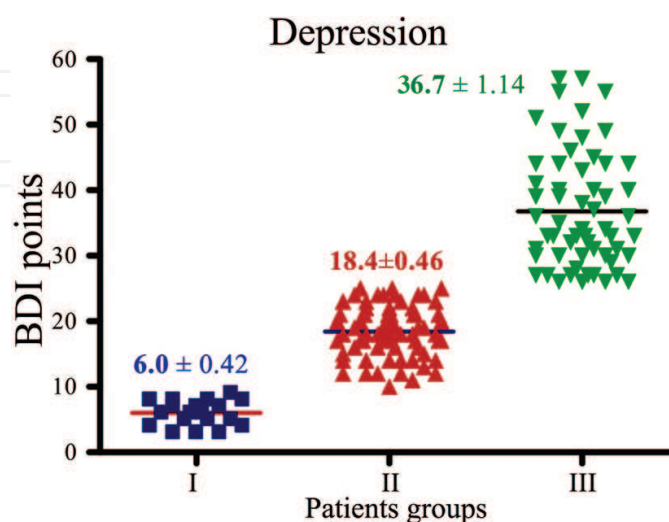
These data coincidence with the recent results of Paul-Savoie [18] who believes that the role of deficiency of endogenous inhibitors of pain mechanisms and sleep disorder in the FM is quite polemical, and requires further analysis. Indeed, as evidenced by these data, indicators of the level of pain and sleep disorders in patients with common ferromagnetic sample are statistically significant negative correlation (Figure 5).



**Figure 5.** The relationship level of pain and sleep disorders in patients with FM.

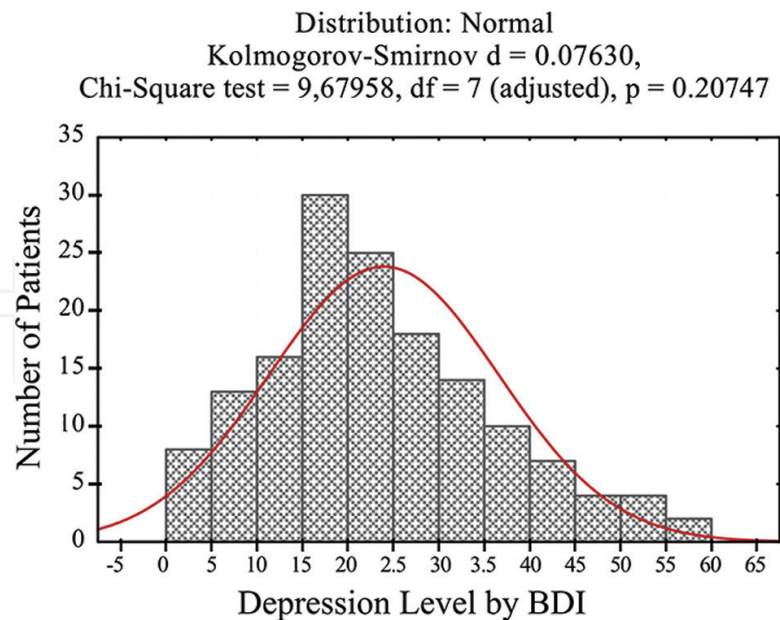
### 4.3. Depressive symptoms

The Beck Depression Inventory questionnaire in patients, included in this study, found that the number of examinees with FM in 86.8% of cases has positive depressive symptoms and the absence of depression at 13.2% of patients. The severity of depressive symptoms in the group of positive patients was distributed as mild level of depression in 54.9% of detected cases and 45.1% of major depression (Figures 6 and 7).



**Figure 6.** The test results of patients with FM on the depression scale BDI. Legend: *I* no signs of depression, *II* light level of depression, and *III* major depression.

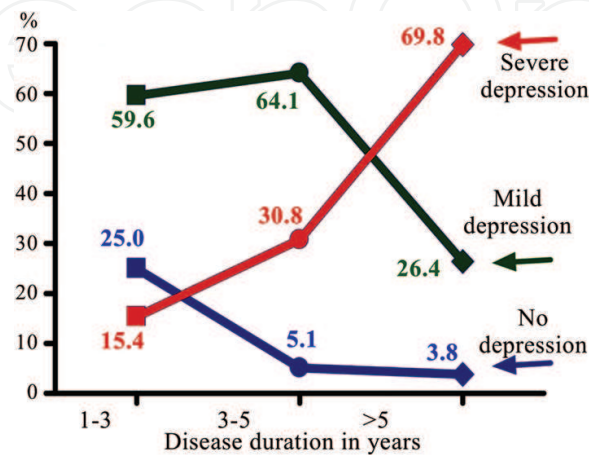




**Figure 7.** Frequency distribution of the index level of depression in the total sample of patients with FM.

These findings are consistent with the results of a number of authors, according to which the depressive disorders were observed in approximately 90% of patients with FM and major depression was established in 62–86% of cases [12, 19–22].

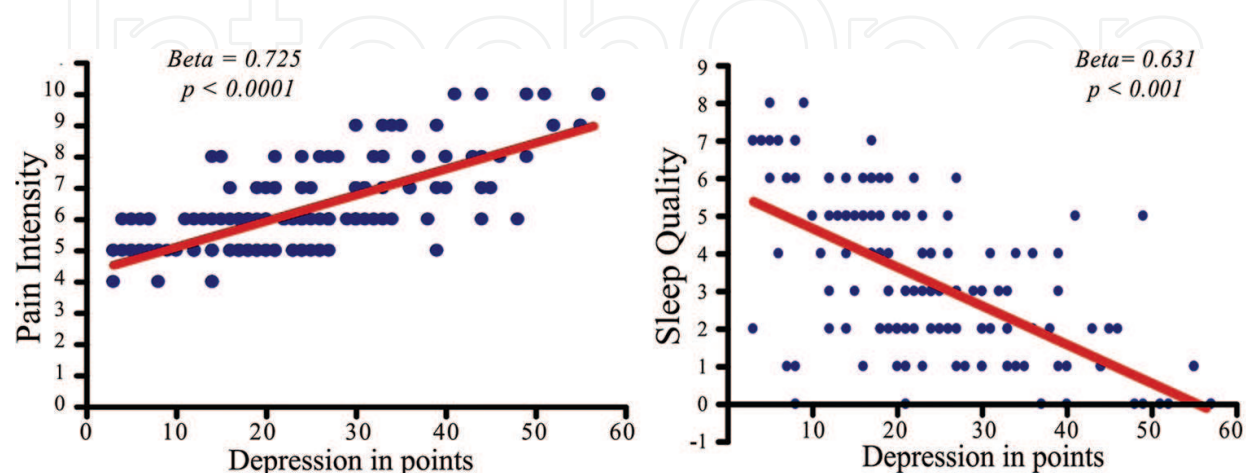
It is well established that increasing the FM duration develops a sharp decrease in the percentage of patients with no signs of depression, while drawn to that of patients with a disease duration of more than 5 years there has been a sharp increase in the percentage of patients with major depression symptoms that occur due to reduction in the specific proportion of patients with moderate depression (**Figure 8**).



**Figure 8.** Dynamics of changes in the structure of depressive symptoms depending on the duration of the disease.

Thus, it should be regarded as established that increasing the duration of the disease in patients with FM observed parallelism in an escalation of depression and the severity of pain syndrome, which is accompanied by a reduction in the index of severity of sleep disorders.

At the same time, the data revealed that the rate of depressive mood in FM was significantly positively correlated with the indicator of the level of pain ( $r = 0.725$ ,  $P < 0.0001$ ) and negatively with the exponent of sleep disorders ( $r = -0.631$ ,  $P < 0.001$ ) (Figure 9).



**Figure 9.** The relationship of depression with indicators of the level of pain and the degree of sleep disorders.

It should be emphasized that correlation between depression and pain in FM must be regarded as certain fact, while numerous data suggest that underlying pain symptoms and depression in FM share common pathogenic mechanisms [22–25]. Taking into account that according to the test results, using Beck Depression Inventory questionnaire in the studied sample of patients identified in 45.1% of major depression (according to DSM-IVTM ICD-9-CM Codes), with the aim of studying the role of pain symptoms, sleep disorders, and disease duration in the development of major depression in the FM calculated indicators such as the relative risk odds ratio (OR) and relative risk (RR). OR and RR values between 0 and 1.0 correspond to the reduction and  $>1.0$  increase in the relative risk [13, 14].

The results of these studies suggest that the relative risk of major depression in patients with FM in the pain intensity in the range of 1–5 points is significantly lower (OR = 0.119, RR = 0.182) than at the level of pain  $>5$  points (OR = 0.830, RR = 0.889), although in both cases they are lower than in the total sample. It is noteworthy that increasing the duration of the disease in patients with FM marked increase in the risk of developing major depression. So, if patients with a disease duration of FM for 1–3 years had OR = 0.283, RR = 0.393, and for 3–5 years had OR = 0.693, RR = 0.787, the relative risk of major depression in patients with “experience” of more than 5 years increases dramatically: OR = 3.577, RR = 1.782.

Enough interesting pattern is revealed in the study of the role of sleep disorders as a relative risk factor for major depression. As evidenced by the data presented, the relative risk of major depression revealed the severity of sleep disorders in the 1–3 score (OR = 1.871, RR = 1.396), whereas, in sleep disorders exceeding 3 points, relative risk is lower than for the total sample, accounting at 3–5 points: OR = 0.415, RR = 0.538 and  $>5$  points: OR = 0.129, RR = 0.196 (Table 1).

Indicators	OR	RR	SS	SP
Pain intensity				
1–5 points	0.119*** 0.041 ÷ 0.349	0.182*** 0.069 ÷ 0.480	0.063 0.017 ÷ 0.154	0.638 0.554 ÷ 0.717
>5 points	0.830* 0.486 ÷ 1.416	0.889* 0.632 ÷ 1.249	0.358 0.261 ÷ 0.465	0.597 0.515 ÷ 0.675
Disease duration				
1–3 years	0.283** 0.124 ÷ 0.644	0.393** 0.201 ÷ 0.767	0.119 0.052 ÷ 0.221	0.676 0.591 ÷ 0.754
3–5 years	0.693* 0.325 ÷ 1.474	0.787* 0.472 ÷ 1.313	0.169 0.090 ÷ 0.276	0.773 0.687 ÷ 0.844
>5 years	3.577*** 1.855 ÷ 6.900	1.782*** 1.369 ÷ 2.320	0.398 0.300 ÷ 0.501	0.844 0.762 ÷ 0.906
Sleep disturbances				
1–3 points	1.871* 1.074 ÷ 3.260	1.396* 1.050 ÷ 1.857	0.415 0.318 ÷ 0.518	0.724 0.638 ÷ 0.799
3–5 points	0.415* 0.178 ÷ 0.968	0.538* 0.282 ÷ 1.029	0.119 0.052 ÷ 0.228	0.754 0.667 ÷ 0.827
>5 points	0.129** 0.029–0.570	0.196** 0.051–0.756	0.032 0.051–0.756	0.793 0.708–0.862
*P < 0.05, **P < 0.01, ***P < 0.001.				

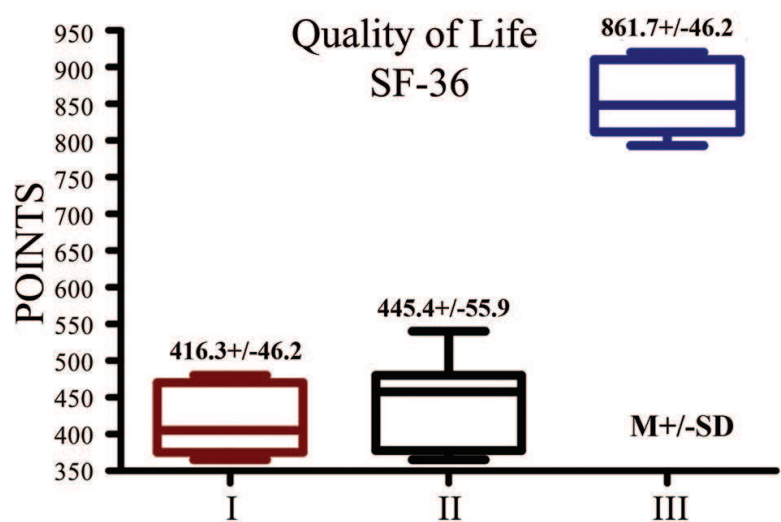
**Table 1.** Characteristics of relative risk factors in patients with major depression FM. Designations: OR, odds ratio; RR, relative risk; SS, sensitivity; SP, specificity.

Over the past decade has been widely used the term “quality of life” (QoL), which was acquired as interdisciplinary concept, an area of interest of researchers representing different industries and medical societies. It has turned scientific mind in the 1960s as a reaction to the dominance of objective indicators for assessing the usefulness of life factors such as income level, disease, and others. In contrast to objective criteria, the development and use of indicators of subjective well-being were needed. The term “quality of life,” which, in the medical literature, is actually first used by Elkinton [26], is currently in the focus of researchers and is widely used in all the areas of clinical medicine.

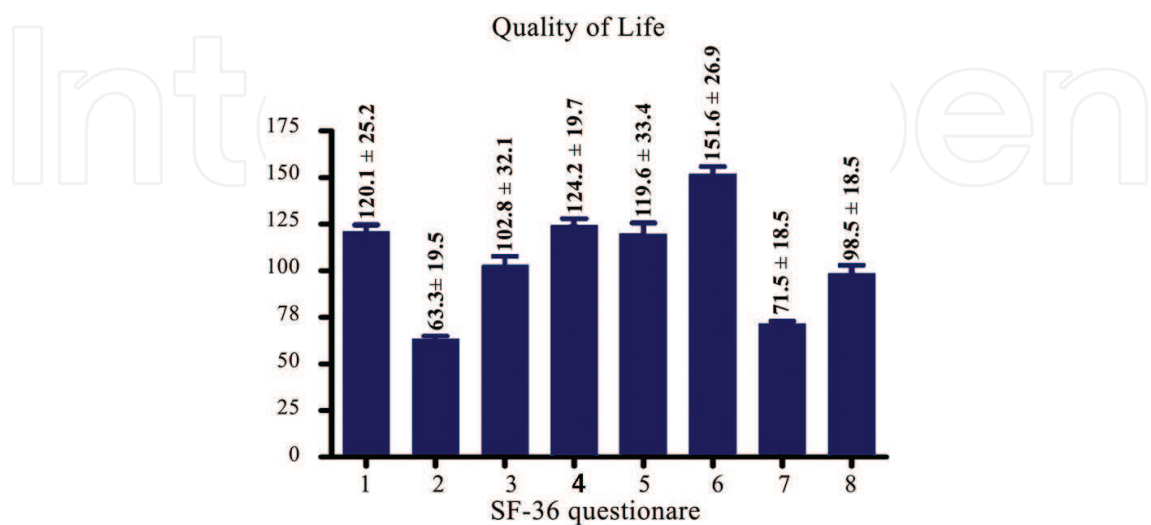
Given that the polymorphism of the pathogenesis of FM, as well as an escalation in patients with signs of psycho-somatization, domestic and psychosocial maladjustment, induced spectrum of stressful factors, along with the monitoring of the main clinical symptoms of the disease and, especially, depression, assessment of physical and mental components of QoL plays an important role. The basis of modern trends of the development of psychometric research on the principle of multimodality, involving a transition from uni-variant representations to the multi-variant approach, provides a wide variation in various individual categories including data plane, data sources, methods of inspection, and other constructs.

The terms “multimodality” and “constructs” meant that rational choice construct is defined by the current level of research, with the distinction of traditional constructs integrated in global constructs and multidimensional constructs; for example, the test is to assess the level of quality of life—health-related quality of life (HRQOL the SF-36)—by which the quality of life of patients with FM was studied.

The test results of patients with FM, regardless of age, gender, and duration of illness, revealed a reduced level of quality of life, and the reduction in its total level is equal to the result of a reduced level of physical and mental component of quality of life that is inherent mainly in psychosomatic pathology. Below are data from a study of various indicators of the quality of life of patients with FM which show that the lowest levels are detected on the scale of physical activity, physical pain, emotional factor, and psychic health (**Figures 10 and 11**).



**Figure 10.** The physical (and) mental (II) components and total level (III) QoL FM (based on the SF-36).



**Figure 11.** The level of various indicators of quality of life of patients with FM. Legend: 1 physical condition, physical activity 2, 3, physical pain, general health, 4, 5, vitality, social activity of 6 and 7 emotional factor, 8 mental health (by the SF-36).

Nonparametric correlation method was studied in patients with FM correlated with indicators of depression and quality of life scales. Studies conducted with the help of SF-36 indicate a negative, statistically significant correlation of depression not only with mental ( $r = -0.663$ ,  $P < 0.001$ ), but also with the physical component ( $r = -0.447$ ) as well as with the total level of QOL ( $r = -0.548$ ,  $P < 0.001$ ). It is essential to identify the highest rates of negative correlation of depression with different indices of SF-36 scale with the “viability” ( $r = -0.613$ ,  $P < 0.001$ ).

## 5. Conclusion

As it is well known, the study of various aspects of FM, almost the same diagnostic criterion and the target of pharmacological intervention, is depression. Considering that depressive symptoms were detected in 86.8% of patients suffering from FM, special attention was paid to the study of major depression (according to DSM-IV “major depression”), which is found in patients in 45.1% of cases and occurs almost twice as likely to have women, which is comparable with those of a number of authors. Presented published data together with the results of this study convincingly show highly informative indicators of physical and mental components of quality of life, especially in the study of various aspects of FM and depression.

This approach was dictated by the fact that in many cases, major depressive signs, acting as dominant clinical manifestations of FM, are characterized by severe symptoms and high risk of suicides in this connection; the group of patients needs more specialized mental healthcare.

Similar humoral and neuronal pathogenically identified mechanisms trigger the development of both FM and depression, and clinical investigations pronounced the correlation of depression with pain, proving the fact that after a diagnosis of FM, quantitative indicators of depression and pain, along with an assessment of indicators of physical and mental components of QoL, become reliable criterion for efficacy of treatment and follow-up monitoring of the disease. It also must be considered that exacerbation of the chronic pain with depressive symptoms could lead to severe incapability and temporary disability, worsening the condition and chances to better outcomes. Those patients need more both medical and social attention, which finally increases the costs of treatment and burden to society.

Current effective treatment of chronic pain must refer to the presence and severity of depression, and depression effective management must include pain control therapies as well.

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