

FIBROMYALGIA: DEPRESSION DEGREE, PAIN INTENSITY AND SLEEP DISTURBANCES AS QUANTITATIVE INDICATORS OF SYNDROME SEVERITY

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ABSTRACT

The problem of fibromyalgia as the chronic pain syndrome becomes an actual problem of modern medicine, because of the high prevalence (up to 7-10% of the population), a significant reduction of life quality, sleep and a sharp limitation of patients' activity. Fibromyalgia syndrome characterized by generalized pain, the presence of tender areas, sleep disturbances and severe fatigue has no quantitative characteristics despite the availability of reliable clinical diagnostic criteria. Therefore, a paradoxical situation is formed, when both clinical syndrome and even the scheme of disease management are well described, but reliable conventional criteria of disease severity do not exist yet. As a result of a long-term study of 151 patients with fibromyalgia, quantitative indicators of depression, pain intensity and sleep disturbances were recorded, which revealed the presence of a convincing connection between these indicators and the severity of fibromyalgia.

As a result of the conducted study it was revealed that with disease duration of 1-3 years the percentage of patients with pain intensity of more or less than 5 points by visual analogue scale was approximately the same and accounted for 51.9% and 48.1%, respectively. A progressive increase of patients (up to 64.1% and 73.5%) with pain intensity syndrome of more than 5 points was noticed among patients whose disease duration was up to 3-5 years.

It was established that unlike the dynamics observed in case of pain, the indicator of sleep disturbance intensity is gradually reduced with the increase of fibromyalgia duration.

During the observation of depression indicators, it was noticed that the longer fibromyalgia duration, the lower the percentage of patients without depression signs. It is notable that among the group of patients with disease duration of more than 5 years a sharp increase is noticed in the number of patients with major depression and this happens by the reduction of specific proportion of patients with moderate depression. These findings are consistent with the results of a number of authors, according to which depressive disturbances are observed in approximately 90% of patients with fibromyalgia and major depression – in 62-86% of cases.

Thus, it should be established that the parallelism is observed in the escalation of depression and the severity of pain syndrome with the increase of disease duration in patients with fibromyalgia, which is accompanied by the reduction of sleep disturbances' severity indicator.

KEYWORDS: fibromyalgia, depression, pain, sleep disturbance.

INTRODUCTION

Fibromyalgia is a chronic pain syndrome characterized by generalized pain, the presence of specific tender points (small areas of painfulness, localized in different regions of body), sleep disturbances and severe chronic fatigue. Fibromyalgia occupies an exclusive position in general population of patients with chronic widespread pain, that affects between 2% to 5% of general population in

the United States, and is more often diagnosed in women (7:1) [Baldry P, 2001; Wolfe F, Häuser W, 2011; Arnold L et al., 2012; Kingsley J, 2012].

A significant increase in the number of patients with a variety of persistent pain syndromes, certain advances in diagnostics and management of fibromyalgia, and expressed interest to the problem of pain by medical community, gives a character of preferred medical and social problem to fibromyalgia. It can be confirmed by a number of international and national associations of fibromyalgia and pain. For example, the following associations are established in the United States at present:

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“National Fibromyalgia Research Association”, “American Fibromyalgia Syndrome Association”, “National Fibromyalgia & Chronic Pain Association”. “European Network of Fibromyalgia Associations” operate within EU, as well as a number of national associations of fibromyalgia, including “Fibromyalgia Association UK” and many others.

While considering the well-known clinical symptoms, it becomes evident, that fibromyalgia is a systemic problem, more complicated than just a muscle pain. The persistence of sets of clinical symptoms, not based on morphological, biochemical and other changes, allows to consider fibromyalgia as somatoform disturbance [Winfield J, 2001]. The symptoms involved in somatoform disorders are not intentional, i.e. a man doesn't feel and control their appearance. In addition, there is an abundant evidence of reducing the threshold of pain sensitivity in patients with fibromyalgia. At the same time the use of different methods of sensorinerval testing revealed that the mechanical allodynia in patients with fibromyalgia is not restricted by tender points and has a prevalent character [Blankfield A, 2012]. Currently, the number of fibromyalgia investigators considering fibromyalgia as a functional and somatic pathology is increasing [Goldenberg D et al., 2011; Joustra M et al., 2015].

It becomes obvious that fibromyalgia is a more complex problem than just a widespread muscle pain. This is testified by several attempts to create a unified theory of the origin of fibromyalgia and equally the development of reliable precise criteria for classification of fibromyalgia, because the existing classification based on the integration of different combinations of psycho-somatic disturbances are established on a purely phenomenological approach, without taking into account the interrelation and common pathogenetic mechanisms of their development and progression [Giesecke T et al., 2003; Thieme K et al., 2004; Müller W et al., 2007; Wolfe F, Häuser W, 2011].

Considering the extreme heterogeneity of clinical manifestations and the heterogeneity of quantitative measurements of different blood parameters, as well as a significant reduction in life quality of patients with fibromyalgia, the main goal was set – 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 main clinical symptoms of fibromyalgia, and especially the characteristics of their interrelation depending on the disease duration;
- to assess the level of physical and mental components of life quality and the character of their interrelation with the symptoms of fibromyalgia;
- to identify the role of pain, sleep disturbances, duration of the disease as a risk factor for the development of major depression in patients with fibromyalgia;
- to develop the evidential base for effective management of fibromyalgia based on main features of the study of pathogenic and diagnostic criteria.

MATERIALS AND METHODS

The material of the study is based on 151 patients with verified diagnosis of fibromyalgia, average age of patients: 49.8 ± 13.3 years ($M \pm SD$), among them 129 women - average age of 49.7 ± 13.7 years and 22 men - average age of 50.1 ± 5 years; the ratio of women to men is about 6:1. The average duration of the disease in patients with fibromyalgia of total sample, regardless of age and sex was 4.5 ± 2.4 years ($M \pm SD$).

Study design: A screening for fibromyalgia was conducted in patients complaining of persistent pain, poor sleep, chronic fatigue, general weakness, forgetfulness, emotional lability.

Inclusion criteria:

- presence of pain at 11 tender points or more during pressing;
- negative rheumatology.

Exclusion criteria:

- positive rheumatology;
- the presence of comorbidity with verified diagnosis of multiple sclerosis, diabetes, oncologic diseases, alcoholic neuropathy - diseases that are characterized by polyneuropathy with pain syndrome;
- the age of patients - younger than 10 and older than 80 years inasmuch allodynia is often common in children and the elderlies.

Type of study: From the perspective of evidential medicine present study has observational, prospective, non-invasive character. In the absence of need for comparative characteristics or examination of treatment effectiveness the sample is supposed to be one-group, without case-matching control group.

The intensity of pain was assessed by visual analogue scale, the quality of sleep - on a 10-point scale ("Questionnaire scoring subjective characteristics of sleep"). For the identification of depression in examined patients with fibromyalgia A psychotherapy was conducted using a validated and standardized questionnaire of depression in Armenia – Beck Depression Inventory (BDI) [Beck A et al., 1996], which allows to differentiate the low level of depression and major depression. Depression index is assessed in points and is classified in the following way: 0-9 the absence of depression, 10-25 low level of depression, 26-39 major depression.

Conventional indicators of relative risk were used to examine risk factors in patients with fibromyalgia: 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 of risk, greater than 1.0 – to the increase of relative risk [Robbins A et al., 2002; Viera A, 2008].

The assessment of life quality of patients was carried out using a questionnaire of Health-Related Quality of Life (HRQOL SF-36) [Ware J, Kosinski M, 2001]. The latter consists of 11 questions including 36 points, each of which has its own set of positive and negative statements. Mostly SF-36 provides an opportunity to assess the overall life quality and its physical and mental components.

Ethic aspects: Inclusion of patients to the study is done with their informed consent. The ethical aspect of the study was reviewed by the Committee on Bioethics of YSMU, which made a decision to comply relevant studies with the requirements of essential ethical standards. The evaluation of the statistical significance of differences in 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. While carrying out the statistical analysis, follow guidelines of Rosner B. (2010) and De Muth JE (2009).

RESULTS

Quantative assessment of major clinical symptoms of fibromyalgia and their interrelation

Pain symptom: Test results on visual analogue

scale show that in total sample of patients with fibromyalgia the pain intensity in the range of 1-5 points (4.9 ± 0.25 , $M \pm SE$) was detected in 37.1%, 10.6 points (7.1 ± 1.25) – 62.9% of patients. These values were 59.0% in men and 41.0% among women – 33.3% and 66.7% (Fig. 1).

The study of pain severity in patients with fibromyalgia depending on the duration of the disease allowed to reveal that with disease duration of 1-3 years the number of patients with pain intensity of more or less than 5 points by visual analogue scale was approximately the same and accounted for 51.9% and 48.1%, respectively. A progressive increase of pain intensity syndrome (up to 64.1% and 73.5%) of more than 5 points was noticed among patients with disease duration up to 3-5 years, especially more than 5 years (Fig. 2).

Sleep disturbances: In total sample of patients with fibromyalgia sleep disturbances within 1-5 points (2.7 ± 0.13 , $M \pm SE$) were detected in 76.2% of patients, 6-10 points (6.5 ± 0.12) – 23.8%; respectively in men: 72.7% and 27.3%, women – 33.3% and 66.7% (Fig. 3).

It is well established that unlike the dynamics observed in case of pain, the indicator of sleep disturbance intensity is gradually reduced with the increase of fibromyalgia duration. For example, if in a group of patients with disease duration of 1-3 years the severity of sleep disturbances <5 points found in 63.5% of cases, the duration of the disease at 3-5 years of the specified figure is 86.8%, and more than 5 years – 97.8%. On this background, the decrease in the percentage of patients with severity of sleep disturbances is notable for more than 5 points from 36.5% to 13.2% and 2.2% (Fig. 4).

These data, to a certain extent, are conformable with the results of Paul-Savoie E. and co-authors (2012), who believe that the role of deficiency of endogenous pain inhibitors in developmental mechanisms of sleep disturbances in fibromyalgia, being quite polemical, requires further analysis.

Indeed, as these data testify the indicators of pain level and sleep disturbances in patients with common ferromagnetic sample are in statistically significant negative correlation (Fig. 5).

Depression: It was established that, the depression severity was detected in 86.8% of cases, the absence of depression – at 13.2%, from the

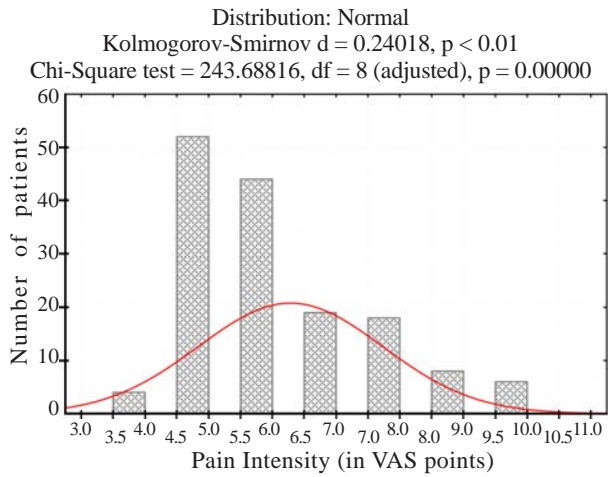


FIGURE 1. Results of the frequency distribution analysis of pain intensity indicator in total sample of patients with fibromyalgia.

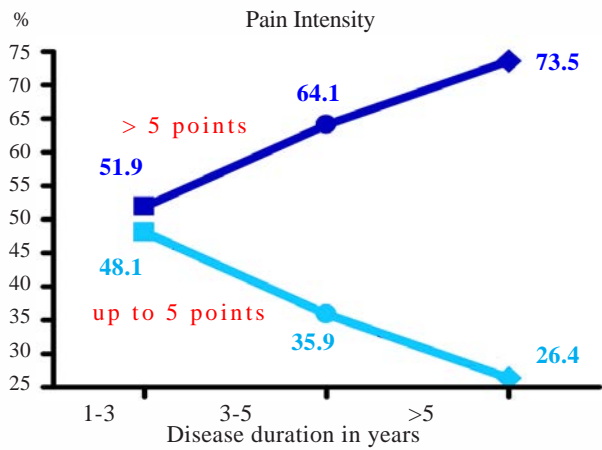


FIGURE 2. Pain intensity in patients with fibromyalgia depending on the duration of the disease.

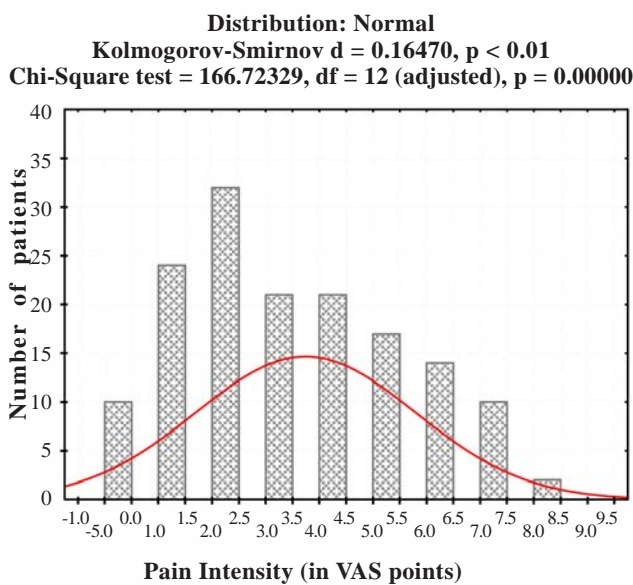


FIGURE 3. Results of the frequency distribution analysis of sleep disturbance index in total sample of patients with fibromyalgia.

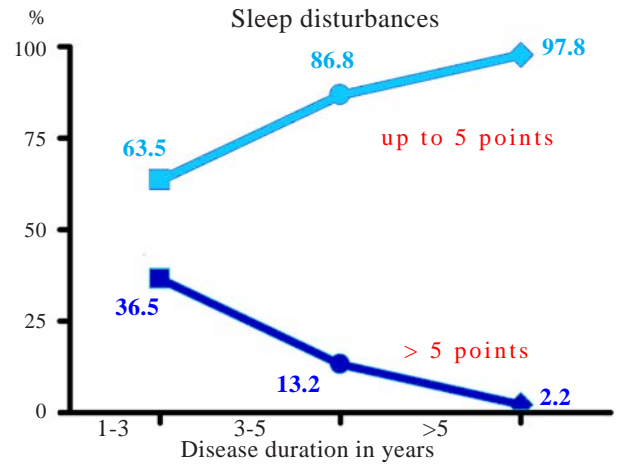


FIGURE 4. Severity of sleep disturbances in patients with fibromyalgia, depending on the duration of the disease.

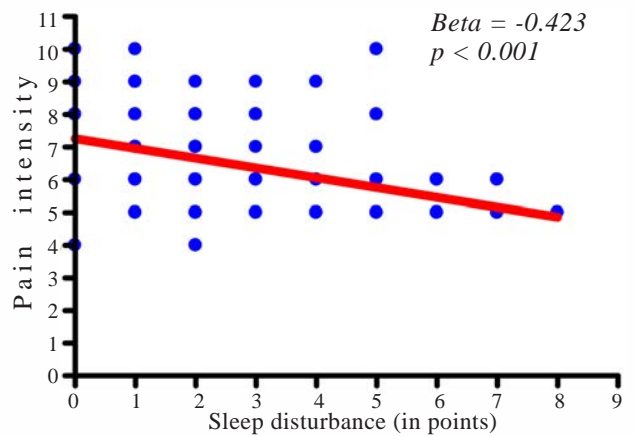


FIGURE 5. The interrelation of pain level and sleep disturbances in patients with fibromyalgia.

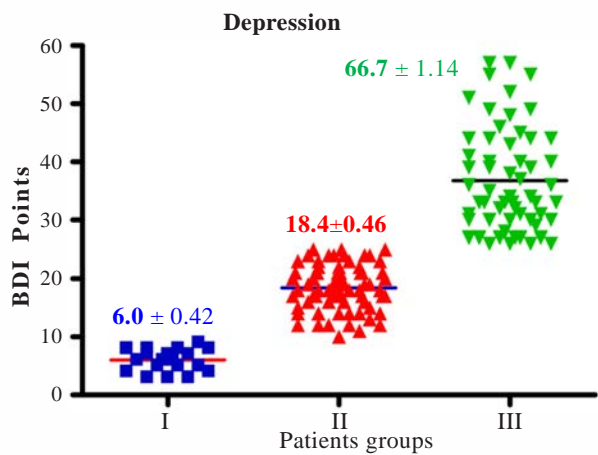


FIGURE 6. Test results of patients with fibromyalgia on the depression scale of BDI. NOTES: I- no signs of depression, II- light level of depression, III- major depression.

number of examined patients with fibromyalgia using BDI questionnaire. From the patients with depressive disturbances a mild level of depression was detected in 54.9% of cases, in 45.1% – major depression (Fig. 6, 7).

These findings are consistent with the results of a number of authors, according to which depressive disturbances are observed in approximately 90% of patients with fibromyalgia and major depression – in 62-86% of cases [Arnold L et al., 2004; Maletic V, Raison C, 2009; Aguglia A et al., 2011; Marangell L et al., 2011]. It is well established that among the group of patients with disease duration of more than 5 years a sharp increase is noticed in the number of patients with major depression and this happens by the reduction of specific proportion of patients with moderate depression (Fig. 8).

Thus, it should be established that with the increase of disease duration in patients with fibromyalgia, parallelism is observed in the escalation of depression and the severity of pain syndrome, which is accompanied by the reduction of sleep disturbances' severity indicator. At the same time, as the data show, it is revealed that the rate of depression fibromyalgia is significantly positively correlated with the indicator of pain level ($r = 0.725$, $p < 0.0001$) and negatively – with the exponent of sleep disturbances ($r = -0.631$, $p < 0.001$), (Fig. 9 a, b).

It should be emphasized that the correlation between depression and pain in fibromyalgia should be regarded as fixed while numerous data suggest that underlying pain symptoms and depression in fibromyalgia are common pathogenic mechanisms. [Williams L et al., 2006; Bigatti S et al., 2008; Ang

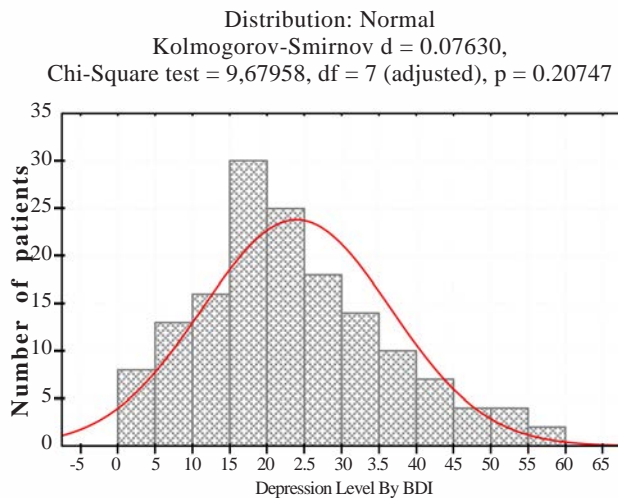


FIGURE 7. Frequency distribution of depression level index in total sample of patients with fibromyalgia.

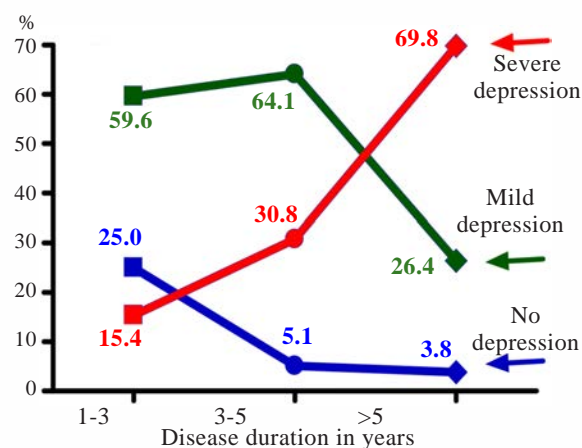


FIGURE 8. Dynamics of changes in the structure of depressive disturbances depending on the duration of the disease.

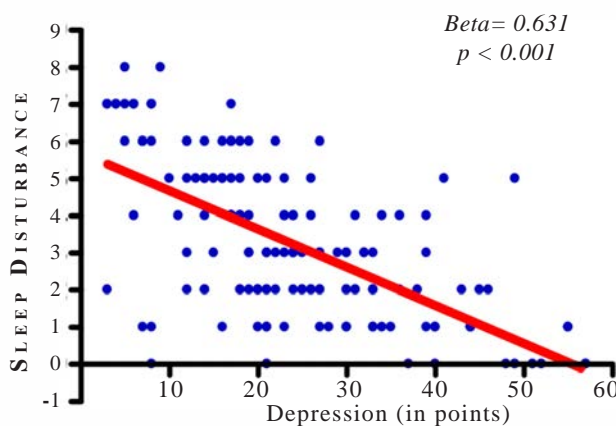
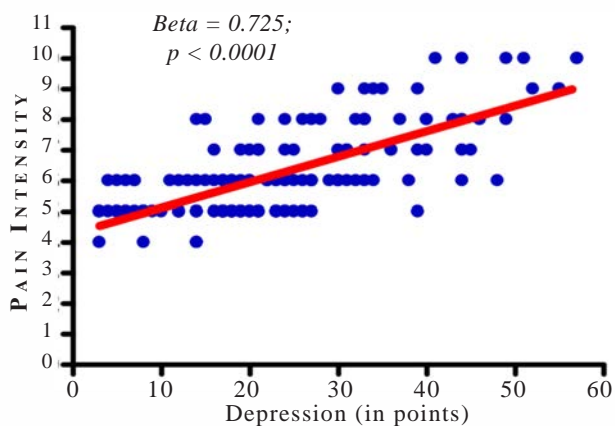


FIGURE 9. The interrelation of depression: a) with indicators of pain level, b) the degree of sleep disturbances.

D et al., 2011; Marangell L et al., 2011]. Taking into account that according to the test results using questionnaire (by Beck Depression Inventory), a major depression was identified in 45.1% of patients from studied sample the indicators such as OR and RR were calculated with the aim of studying the role of pain symptoms, sleep disturbances and duration diseases in the development of major depression in fibromyalgia. OR and RR values between 0 and 1.0 correspond to the reduction, and >1.0 – to the increase of relative risk [*Robbins A et al., 2002; Viera A, 2008*].

The results of these studies suggest that the relative risk of major depression in patients with fibromyalgia during pain intensity in the range of 1-5 points is significantly lower (OR = 0.119, RR = 0.182), than at the level of pain greater than 5 points (OR = 0.830, RR = 0.889), although in both cases they are lower than in total sample. It is noteworthy that with increasing duration of the disease in patients with fibromyalgia marked increase in the risk of developing major depression. So, if in groups of patients with a disease duration of fibromyalgia up to 1-3 years, the studied indices are: OR = 0.283, RR = 0.393, and 3-5 years – OR = 0.693, RR = 0.787, in patients with “experience”

of more than 5 years the relative risk of major depression increases dramatically: OR = 3.577, RR = 1.782.

Sufficiently interesting pattern was revealed during the study of sleep disturbances’ role as a relative risk factor for major depression. As the present data testify, the relative risk of major depression revealed the severity of sleep disturbances in the 1-3 score (OR = 1.871, RR = 1.396), whereas in sleep disturbances exceeding 3 points relative risk is lower than for the total sample, accounting at 3-5 points: OR = 0.415, RR = 0.538, >5 points: OR = 0.129, RR = 0.196 (Table).

Over the past few decades the widely used term “quality of life” was acquired as an interdisciplinary concept, an area of researchers’ interest representing different branches of medical and humanitarian discipline. It has entered into scientific turnover in the 1960s as a reaction to the dominance of objective indicators for the assessment of the usefulness of such life factors as income level, disease and others. In contrast to objective criteria it became necessary to develop and use subjective indicators of well-being.

The term “quality of life” in medical literature which was firstly used by Elkinton J. (1966) is in

Characteristics of relative risk factors in patients with major depression of fibromyalgia

TABLE.

Indicators	Odds Ratio	Relative Risk	Sensitivity	Specificity
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 to 0.570	0,196** 0.051 to 0.756	0,032 0.051 to 0.756	0,793 0.708 to 0.862

NOTES: * – $p < 0.05$, ** – $p < 0.01$, *** – $p < 0.001$.

the focus of researchers and is widely used in all areas of clinical medicine. The assessment of physical and mental components of life quality plays an important role considering the polymorphism of fibromyalgia pathogenesis, as well as the escalation in patients with signs of psychosomatisation, domestic and psychosocial deadadaptation, induced spectrum of stressful factors, along with the monitoring of main clinical symptoms of the disease and, especially, depression. The principle of multimodality, intending a transition from univariant representations into the multivariant approach providing a variation of different individual categories including data plane, data sources, methods of inspection, constructs and others lies on the basis of modern trends for the development of psychometric studies.

The terms “multimodality” and “constructs” mean that rational choice of construct is defined by the actual level of research, with the distinction of traditional, integrated global and multidimensional constructs, for example, the test for the assessment of life quality level – HRQOL The SF-36, by which the life quality of patients with fibromyalgia were studied.

As the test results show, a reduced level of life quality was revealed in patients with fibromyalgia regardless of age, gender and duration of illness, wherein the reduction of its total level is equally the result of a reduced level of physical and mental component of life quality which is mainly inherent to psychosomatic pathology. Data from the study of various indicators of life quality in patients with fibromyalgia are presented below, which shows that the lowest levels are detected on the scale of physical activity, physical pain, emotional factor and mental health. (Fig. 10, 11).

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

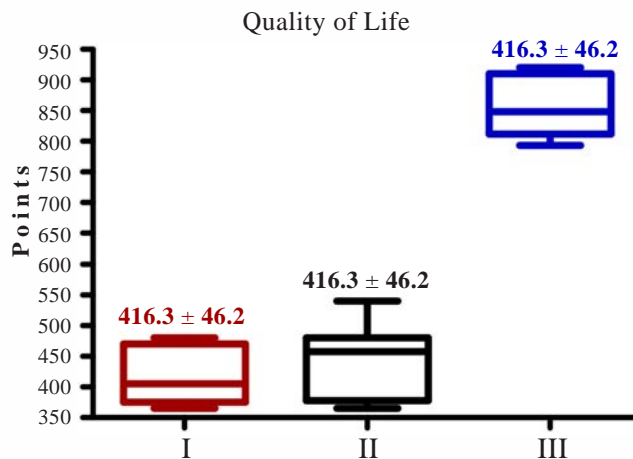


FIGURE 10. Physical (I), mental (II) components and total level (III) of life quality in patients with fibromyalgia (based on SF-36).

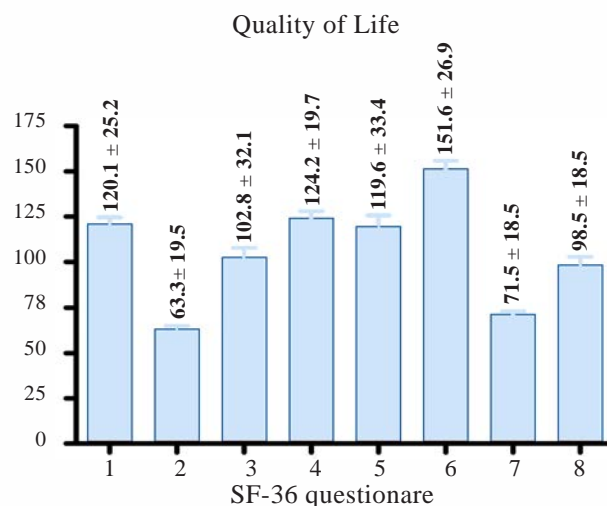


FIGURE 11. Level of various life quality indicators in patients with fibromyalgia.

NOTES: 1 – physical activity, 2 – physical activity, 3 – physical pain, 4 – general health, 5 – viability, 6 – social activity, 7 – emotional factor, 8 – mental health (by SF-36).

CONCLUSION

It is well known from the study of various aspects of fibromyalgia that depression is considered as an unchanged diagnostic criterion and a target of pharmacological intervention. Taking into account that depression was detected in 86.8% of patients suffering from fibromyalgia, special attention was paid to the study of major depression (according to DSM-IV “major depression”), found in patients in 45.1% of cases and occurring almost twice as often in women, which is comparable with data of a number of authors. Presented published

data with the results of this study convincingly show highly informative indicators of physical and mental components of life quality, especially in the study of various aspects of fibromyalgia as functional-somatic pathologies.

This approach was dictated by the fact that in some cases, major depression, acting as dominant clinical manifestations of fibromyalgia is characterized by severe symptoms, high risk of suicides wherefore the group of patients needs to provide more specialized mental health care. Commonality

of neuro-immune mechanisms underlying on the basis of phenomenon identified in fibromyalgia with pronounced correlation of depression with pain, gives reason to believe that after the diagnosis of fibromyalgia the quantitative indicators of depression and pain along with the assessment of indicators of physical and mental components of patients' life quality are reliable criterion for the development of tactics of effective management and further monitoring of disease course.

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