



# Cancer-related Fatigue in Patients with Oncological Diseases: Causes, Prevalence, Guidelines for Assessment and Management

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## Abstract

Fatigue and exhaustion are considered to be the most common complaints of patients with cancer during treatment and upon its completion. The manifestations of fatigue can be physical, cognitive, and emotional. The exact determinants of fatigue, however, are yet unknown. An initial literature review was conducted. Four reference databases were searched (MEDLINE, ELSEVIER – Science Direct, ELSEVIER – SCOPUS, Springer). The initial search yielded 430 articles. We included references consistent with the study design, published between 1993 and 2017, and written in English or German. The 48 remaining articles were assessed for relevance to the area by visually examining their titles for keywords: cancer-related fatigue, assesment, management. Cancer-related fatigue in cancer patients during treatment and in survivors is estimated to have a prevalence in the range of 58% to 90%. This report is a review of the literature relevant to the problem of fatigue in patients with oncological diseases – causes, prevalence, and impact on the lives of affected patients, proposing guidelines for assessment and management. A set of reliable tools have been presented for assessment and measurement of the burden of fatigue. The management strategies include a number of non-pharmacological methods: physically based therapies, psycho-educational and mind-body interventions, methods of managing sleep disorders, methods of increasing physical activity, and pharmacological modalities. Clarification of the causes for fatigue, its detection, a reliable assessment of its severity, the application of appropriate interventions for treatment and the necessary care could support the application of a differentiated approach.

## Keywords

assesment, cancer-related fatigue, management, prevalence

## INTRODUCTION

According to 2013 official statistics, there were 3702.4/100000 cases of malignant diseases in Bulgaria of which 432.4 were newly detected. In 2014, the number of registered cases rose to 3819.0/100000 cases, with the newly detected ones being 461.9.<sup>1</sup> Based on the forecast, the frequency of oncological diseases will reach 234.8/100000 by 2025.<sup>2</sup> The estimated and observed 5-year cancer survival in Bulgaria between 2000 and 2005 was 28%, which

is far below that of the economically developed countries. Bulgaria is at the bottom of the black list of oncological diseases survival. This determines the importance and social damage caused to the society by this disease.<sup>1</sup>

## MATERIALS AND METHODS

An initial literature review was conducted. Four reference databases were searched (MEDLINE, ELSEVIER – Science

Direct, ELSEVIER – SCOPUS, Springer). The initial search resulted in 430 articles. We included references respective of the study design, published between 1993 and 2017, written in English or German. The 48 remaining articles were assessed for relevance to the area by visually examining their titles for keywords: cancer-related fatigue, assessment, management.

## Cancer-related fatigue

The symptoms of fatigue and exhaustion are considered to be the most common complaints among patients with malignant diseases<sup>3-5</sup> and survivors<sup>6</sup> which are related to the disease and its treatment. Fatigue may occur during the treatment, at each stage of the disease<sup>7</sup>, it may last for months and even years after completion of the treatment<sup>8</sup>, with manifestations at physical (reduced working capacity), cognitive (impaired concentration, problems with the short-term memory) and emotional level.<sup>6</sup>

As defined by the National Comprehensive Cancer Network<sup>9</sup>, fatigue is a restriction of physical and mental capacity which has occurred as a result of the medical treatment and significantly affects the activity of the patient and despite the adequate rest and relaxation it does not decrease. Persistent fatigue has a negative effect on the quality of life of the affected patients, reducing their ability to actively participate in personal, professional and social activities and roles that make their lives meaningful<sup>10,11</sup> and impedes the execution of typical cognitive tasks.<sup>12</sup>

Over the last years, increased interest has been shown in the epidemiology, the etiology and the pathogenesis of fatigue among patients with oncological diseases.<sup>1</sup> A number of studies examine the risk factors for the emergence of fatigue and, in particular, the type of fatigue that lasts for months or even years upon the completion of the treatment.<sup>13</sup> The variety of manifestations and symptoms among the individual patients has been determined by the various reasons for its occurrence and this, in turn, impedes the identification of the basic pathogenetic mechanisms of fatigue among patients with oncological diseases. At present, the researchers studying fatigue perceive this notion as a multidimensional concept and assume various reasons for its emergence.

Glaus et al. have discussed as possible causes and favourable primary factors for the emergence of fatigue the production of cytokines as a defensive reaction of the body against the emergence of the tumour, immunological, endocrine, neurological, psychological, hematological (anemia, hypokalemia, hypocalcemia) musculoskeletal factors and also nutrition-related factors (for example, dietary).<sup>14</sup>

Glaus et al.<sup>14</sup> regard as secondary causes for the emergence of fatigue sleep disorders, pain, dyspnea as a result of a malignant disease, the anti-tumour therapy and its effect on the patient. Other authors<sup>15</sup> assume that the disintegration of several physiological and biochemical systems significantly affects the development of fatigue. According to them, the disruption of the regulation of serotonin, the ac-

tivation of the vagal afferent pathways, the muscle damages, the disruptions in the metabolism of the adenosine triphosphate (ATP), the disruptions in the hypothalamic–pituitary–adrenal axis, the disorders in the circadian rhythms and the increased production of cytokines contribute to the development of fatigue. The comorbid conditions, including anemia, cachexia, depression, sleep disorders<sup>15</sup> and cognitive dysfunctions<sup>16,17</sup> also play a role in the development of fatigue among patients with oncological diseases.

The problems in the process of determining the etiological factors for the emergence of fatigue result from the fact that usually a number of such factors exist simultaneously and in many cases may have a cumulative effect. Up to now, in scientific literature there has been no firm evidence supporting any of the aforementioned mechanisms, which necessitates continuing the study of this issue.

Despite the fact the most patients with cancer say that fatigue is the main obstacle preventing them from doing their usual daily activities and deteriorating the quality of their lives, it is rarely discussed by the patients and their oncologists.<sup>18</sup> The substantial negative effect on the quality of life of the affected patients, their physical, psychosocial well-being and ability to do everyday activities<sup>19</sup> necessitates focusing on this phenomenon as one of the priorities in the care for patients with oncological diseases. This will allow guidelines to be given in order to assess the burden and effectively manage it.

## Prevalence

Depending on the used methods of assessing fatigue and the features of the groups of examined patients: localization of the process, stage of the disease, type of treatment<sup>20</sup> and others, its spread among patients with oncological diseases, which has been described in scientific literature, varies widely – from 14% to 99%.<sup>9,21</sup> During the stage of diagnosing, up to 40% of the patients complained of fatigue.<sup>22</sup> During the active treatment stage, the registered values of its spread range from 30% to 90%.<sup>23,24</sup> Fatigue is extremely common with patients undergoing cytotoxic chemotherapy, radiation therapy, bone marrow transplantation, treatment with biological response modifiers, including a interferon and interleukins.<sup>25-28</sup> Based on scientific literature data, among patients undergoing chemotherapy and radiation therapy, the level of the burden of fatigue is significantly higher (98.30%) compared to patients undergoing radiation therapy only (78.57%).<sup>29</sup> Other authors<sup>12</sup>, in a telephone inquiry of 379 patients undergoing chemotherapy, have established that 76% of them experienced fatigue for at least several days during the last chemotherapy cycle and 30% of them experience fatigue on a daily basis. According to<sup>30,31</sup> with the treatment-related fatigue, there is usually a clear time connection between the condition and the intervention. For example, with patients undergoing cyclic chemotherapy, fatigue often reaches its peak within several days and decreases by the next cycle of treatment. According to<sup>32</sup>, the values of the spread of fatigue are higher for some ty-

pes of cancer, such as cancer of the pancreas, breast cancer or lymphoma diseases, although it is not clear whether the type of the malignant disease or its related treatment have caused its emergence among these patients.

The fatigue during the process of treatment may become chronic upon its completion<sup>33</sup>, especially in case of conducted combination of chemotherapy and radiation therapy or stem cells transplantation.<sup>34,35</sup>

According to several studies<sup>36-38</sup>, the high levels of fatigue during the treatment may decrease again after its completion but even years after that, the average values among these patients are higher compared to the non-cancer population.<sup>23</sup> In a conducted survey<sup>39</sup> of 649 cancer survivors, it has been established that 36% of them suffer from moderate fatigue and 12% of them suffer from severe fatigue, as the average duration of the fatigue established in this survey was 3.6 years. According to Bower JE et al.<sup>40</sup>, approximately one fourth up to one third of the cancer survivors experience persistent fatigue for a period of 10 years after they were initially diagnosed. In a study of 763 long-term breast carcinoma survivors, the same authors established the existence of fatigue among 35% of them for a period of 1 to 5 years after the completion of the treatment and among 34% of them for a period of 5 to 10 years after the completion of the treatment. Dodd et al.<sup>108</sup> have reported that in case of chronic fatigue after the completion of the treatment, certain co-factors of the conducted therapy can be observed such as sleep disorders, desperation, depression and even pain in some cases. According to<sup>41</sup>, fatigue can also be a predictor of shorter survival among patients with malignant diseases.

Despite the fact that the spread rate of fatigue significantly differs in these studies, the results show that it is quite common among patients in a period of active treatment and survivors as well, as a large percentage of them have suffered from fatigue for years. In relation to this, the routine screening and assessment in the very beginning of the treatment are crucial in order to apply the most appropriate and effective practices of coping with fatigue in the early stages and minimize its negative effects. In accordance with the recommendations of<sup>42</sup>, the patients have to undergo screening for the fatigue during their first visit, when diagnosing an advanced disease and every time they go to chemotherapy.<sup>43</sup>

## Fatigue assessment

As a subjective condition, the most appropriate way of measuring fatigue is the use of self-assessment tools. In practice, an easy and reliable method of making a prompt assessment of fatigue is the application of a simple numerical scale ranging from 0 to 10. The patient is usually asked: "How would you assess your fatigue over the last seven days from 0 to 10?". In accordance with the recommendations of the National Comprehensive Cancer Network<sup>9</sup>, when the values range from 0 to 3, the intensity of fatigue is classified as being insignificant or weak and requires periodic assess-

ment to be made, when they are within the ranges of 4-6 and 7-10, respectively, fatigue is classified as being moderate and severe, in which case an additional diagnostic assessment needs to be made.<sup>43</sup>

The fact that fatigue is a subjective experience determines the variety of developed tools applied in the assessment of this symptom. Its frequency may vary widely depending on the type of measurement tool to be used, as up to now there has been no certain agreement as to how it should be measured. A number of scales have been developed in order to give this phenomenon a quantitative manifestation. They vary in terms of the quality of the psychometric features, easy application, the dimensions of fatigue covered and the extent of use in studies of patients with oncological diseases.

## One-dimensional tools for assessing fatigue

### *BFI - Brief Fatigue Inventory*<sup>45</sup>

The questionnaire is used for making a prompt assessment of the burden and the effect of fatigue on the everyday functioning of the patients during the last 24 hours. It consists of 9 positions (sub-scales). The first three questions are intended to assess fatigue based on a scale from 0 (no fatigue) to 10 (the worst fatigue you can imagine). For the next six questions, the patients are assessed based on a scale from 0 (does not bother me) to 10 (it bothers me significantly) insofar as fatigue has affected the various activities. When the values are within the range of 4-6 and  $\geq 7$ , the intensity of fatigue is classified as being moderate and severe, respectively. The studies of fatigue among patients with malignant diseases show a considerable reduction of the physical function when the levels of the burden of fatigue are equal to 7 or higher, which means that 7 is the threshold value for identifying severe fatigue.<sup>45</sup> The questionnaire allows the measurement of six different dimensions: activity, mood, ability to walk, work, relations with the other people and joyfulness. Internal consistency ( $\alpha=0.96$ )

## Multidimensional tools for assessing fatigue

### *MFI-20 – Multidimensional questionnaire for fatigue*<sup>46</sup>

A multidimensional tool for assessing fatigue. MFI-20 has been presented in five scales: general fatigue; physical fatigue; reduced activeness; reduced motivation; mental fatigue. It contains 20 questions and is intended to be used for patients with oncological diseases. The instrument has good internal consistency ( $\alpha=0.84$ ).

### *FQ - Chalder Fatigue Scale/Fatigue Questionnaire*<sup>47</sup>

A questionnaire for measuring fatigue, which was initially validated for general use but now it is mainly used in sur-

veys related to the chronic fatigue syndrome. The questionnaire contains 11 sub-scales, it is short and easy to administer and covers two aspects of fatigue (physical and mental). Internal consistency ( $\alpha = 0.88-0.90$ ).

### **FSI - Fatigue Symptom Inventory<sup>48</sup>**

A scale containing 13 questions, which is intended to make a prompt assessment of fatigue – intensity, duration and effect on the everyday life of the patients during the previous week. The first 4 questions assess the intensity of fatigue during the last week based on a scale from 0 (not at all) to 10 (extreme fatigue). The following questions assess the interference of fatigue based on a scale from 0 (no interference) to 10 (extreme interference). It was initially validated for patients with mammary gland carcinoma. The subsequent validation was in a study of 342 patients with various tumour localizations.<sup>49</sup> It has been used in a number of studies but with a relatively small number of patients. The spheres of application have been minimized to patients undergoing active treatment and survivors.

### **PFS - Piper Fatigue Scale<sup>50</sup>**

A revised shorter version of the original scale. It has been validated among patients who have survived mammary gland carcinoma. It is mainly applied among patients with mammary gland carcinoma undergoing active treatment and survivors. It is a subjective multidimensional tool for assessing the level of fatigue, the level of stress, the effect of fatigue on the daily activities. It contains 4 sub-scales (behavioural – 6 questions, affective – 5 questions, sensory – 5 questions, cognitive – 6 questions) with 22 questions in total. Each of the questions is assessed from 0 to 10. The higher result means a higher burden of fatigue. The total result is a sum of the values of each sub-scale (0-none); (1-3-slight); (4-6-moderate); (7-10-severe fatigue). Internal consistency ( $\alpha=0.97$ ). Total result ( $\alpha=0.96$ ) and for the separate scales for behavioural, affective, sensory and cognitive measurement ( $\alpha=0.89$ ); ( $\alpha=0.96$ ); ( $\alpha=0.96$ ) and ( $\alpha=0.91$ ), respectively.<sup>51</sup>

### **SCFS - Schwartz Cancer Fatigue Scale<sup>52</sup>**

A scale for assessing fatigue over the last 2-3 days. It contains 4 sub-scales (physical, emotional, cognitive and temporal) with 28 components. The assessment is made on the grounds of a five-degree scale from 0 (not at all) to 5 (extreme fatigue). Internal consistency ( $\alpha = 0.96$ ).

### **FAQ - Fatigue Assessment Questionnaire<sup>53</sup>**

A standardized measurement tool for studying and assessing fatigue. It contains three sub-scales – physical, affective and cognitive, with 23 components for assessing the intensity and the effect of fatigue over the last two weeks. The first 20 questions have a scale for assessment from 0 (not at all) to 3 (very much). The questions 1–11 study the physical dimensions of fatigue, 12–14 - the cognitive dimensions, 15–19 – the affective dimensions. Question No 20 – “Do you have problems sleeping at night?” cannot be

added, in terms of content, to any of the aforementioned questions. When making an assessment, the points of the separate questions are added up and the larger their sum, the higher the level of fatigue. The next 3 questions represent a linear-analogue scale. In the first two scales, the patient marks the burden of fatigue during the last week and the last month, respectively. The third scale allows the patient to mark the burden of the suffering caused by fatigue. The manifestation of the burden of fatigue increases in the three scales from the left to the right. The measurement is in millimeters and starts from the left to the mark placed by the patient. Values within the range of 0–33 mm a slight manifestation of fatigue; values within the range of 34–66 mm and 67–100 mm a substantial manifestation of fatigue. Internal consistency ( $\alpha=0.88$ ).

### **CFS - Cancer Fatigue Scale<sup>54</sup>**

A scale for assessing fatigue over the last week among patients undergoing treatment. It has been validated in a study of 307 patients with oncological pathology. It contains three sub-scales – physical, cognitive and affective manifestation of fatigue with 15 components in total and a five-point scale for assessment from 1 (no) to 5 (very much).

The CFS had good stability (average test-retest reliability  $r=0.69$ ,  $p<0.001$ ) and good internal consistency (Cronbach's alpha coefficient for all 15 items= $0.88$ ).

## **Management of fatigue**

The effective management of fatigue among patients with oncological diseases requires the application of an interdisciplinary approach owing to the fact that different clinical, psychological and social factors interact and affect its features. It would be good to make an assessment first and correct the other existing contributing factors, if possible, which, in turn, may significantly improve the quality of life of the affected patients.

The initial approach for managing fatigue requires an overall assessment, training of the patients and their families and determining an individual plan for treatment based on the clinical status of the patient.<sup>55</sup> It is important to keep the patients informed that as a result of the conducted treatment: chemotherapy, radiation therapy or treatment involving biological agents, fatigue may occur, which will not necessarily indicate progression of the disease.<sup>56</sup> The training of patients and their families in the nature of fatigue, the strategies for its management and the provision of information about the possibilities for treatment and the expected results is a crucial aspect of the therapy.<sup>57</sup> Non-pharmacological interventions and pharmacological treatment can be additionally included<sup>58</sup> in a number of cases as well as a combination of approaches.

## **Non-pharmacological treatment**

The guidelines of the National Comprehensive Cancer Network<sup>59</sup> recommend using various integrated non-pharma-

colological behavioural interventions which could be applied in order to achieve effective management of fatigue in three categories: increasing activity (physical exercise), physical-based therapies (massage) and psychosocial interventions (cognitive and behavioural therapy).

There is some scientific evidence supporting the use of physical exercise and psychosocial interventions, sleep therapy, energy preservation – achieving a balance between relaxation and activity<sup>60</sup> in order to manage fatigue effectively. The results from the examination of 77 randomized surveys studying the effectiveness of a number of integrative non-pharmacological behavioural therapies for management of fatigue are also encouraging.<sup>61</sup>

## Physical exercise

The physical exercise, as an integrative non-pharmacological behavioural intervention, shows promising results regarding the relief of severe fatigue observed with patients with cancer during the active treatment and persistent fatigue upon its completion. According to<sup>62</sup>, when providing consultations to patients with fatigue, the attention has to be focused mainly on increasing physical activity. In relation to this<sup>63</sup>, report that the regular physical exercise can increase the functional capacity of the patients, thus reducing the efforts necessary for doing the everyday activities.

The most comprehensive current meta-analysis of the effect of physical exercise on the burden of fatigue includes 70 studies with a total number of 4881 examined patients during their treatment and after its completion.<sup>64</sup> The results show that the exercise reduces the levels of burden of fatigue with an average effect of 0.32 (95% CI, 0.21–0.43) during the treatment and 0.38 (95% CI, 0.21–0.54) after its completion.

Another meta-analysis<sup>65</sup> including 16 studies with 1426 examined people in total (experimental group – 759; control group – 667) showed that the use of physical exercise significantly reduces the burden of fatigue (SMD 0.26;  $p < 0.001$ ). Based on the substantial collected scientific evidence<sup>66</sup>, a conclusion has been made that the moderate physical activity (50% - 90% of the prognosticated maximum cardiac frequency) effectively reduces fatigue among patients with breast cancer during their treatment and after its completion. In addition, there is more and more evidence about the substantial effect of the physical exercise on the burden of fatigue among patients diagnosed with another type of cancer.<sup>67,68</sup>

Following the guidelines of the National Comprehensive Cancer Network<sup>69</sup>, physical exercise shall be applied cautiously among patients with bone metastases, thrombocytopenia, anemia, fever or acute infection, limitations as a result of metastases and other comorbid diseases. The exercise programme and the regime of its application has to be strictly individual, taking into account factors like the age and gender of the patients<sup>56</sup>, the stage of the disease, the type of the disease, the level of physical activity before the treatment and the accompanying diseases.<sup>70</sup> Berger et

al. recommend that in the beginning, the intensity of the physical activity should be lower and the duration should be shorter, as both can gradually increase depending on the patient's condition, with a maximum duration of no more than 30-45 minutes.<sup>71</sup> All types of exercise reducing fatigue are recommended, but it is believed that aerobic activities such as walking, swimming, cycling, running, rowing have a better effect.<sup>72</sup>

Data of the meta-analyses show that aerobics significantly reduces the burden of fatigue<sup>64,73</sup> in case of moderate activity of about 150 minutes per week, allocated in series of 30-45 minutes for each training session<sup>71</sup>, depending on the individual tolerance and the respective diagnosis.

The daily notes or the keeping of a diary of the exercise could be very useful for setting realistic goals, registering the progress and supporting the motivation of the patient to improve their general condition and reduce the burden of fatigue.<sup>66</sup>

## Psychosocial interventions

A number of studies related to the application of this wide array of psychosocial interventions for overcoming fatigue – group therapy<sup>74</sup>, individual consultations<sup>75</sup>, training to reduce stress and relaxation, cognitive-behavioural therapy<sup>76</sup> have shown quite promising results, mainly with patients in a period of active treatment.

A systemic review with a meta-analysis<sup>77</sup> on the effect of the psychological interventions on the burden of fatigue has identified 24 randomized studies. The data show significant improvement of fatigue with a substantial scope of the effect ( $d\text{-sub}(w) = 0.10$ , 95% CI = 0.02–.18). Another meta-analysis<sup>78</sup> including 57 randomized studies has shown that the application of a cognitive-behavioural therapy has a significant effect on fatigue reducing its burden. According to<sup>79</sup>, the cognitive-behavioural therapy is especially suitable for patients with chronic or persistent fatigue, focusing on the following factors affecting its burden: maladaptive coping strategies<sup>34</sup>, dysfunctional fatigue-related thoughts<sup>80</sup>, sleep disorders<sup>23</sup>, weak social support.<sup>81</sup>

The data from the randomized study<sup>82</sup> of 273 survivors reporting the existence of fatigue, who were included in a 12-week web-based individual programme on the grounds of the fatigue guidance of NCCN (National Comprehensive Cancer Network), presenting information about fatigue: physical activity, sleep hygiene, distress management, nutrition and fight with the pain, have shown a substantial decrease of the burden of fatigue among the patients included in the group compared to the control patients.

## Physically based therapies

The physically based therapies include acupuncture and massage. The effect of these methods on the burden of fatigue remains unclear owing to the lack of sufficient randomized clinical studies. In scientific literature, there are data from a randomized clinical study<sup>83</sup> on the effect of acu-

puncture on the burden of fatigue, which was conducted after the completion of the chemotherapy treatment. The results show a positive effect of the application of acupuncture for reducing the levels of burden of general fatigue ( $p < 0.001$ ), physical fatigue ( $p = 0.016$ ), activity ( $p = 0.004$ ) and motivation ( $p = 0.024$ ). A randomized clinical study<sup>84</sup> and a retrospective review<sup>85</sup> report a positive effect of the massage therapy on the burden of fatigue among patients in a period of active treatment.

## Mind-body interventions

According to the definition of the National Institutes of Health Center for Complementary and Alternative Medicine<sup>86</sup>, the mind-body interventions are “various techniques intended to improve the capacity of the mind to affect the body functions and symptoms”. Their scope ranges from placing hands, energy therapy, different meditation practices, yoga<sup>79</sup>, relaxation, hypnosis<sup>87</sup> and others. The effect of the mind-body interventions on reducing the burden of fatigue has been assessed in a small number of studies.

The data from a meta-analysis<sup>88</sup> assessing the effect of the application of the yoga techniques on the burden of fatigue have shown a weak but positive effect (SMD=0.27, 95% CI=0.23-0.31) for reducing its burden.

Other authors<sup>89</sup> in a randomized control study of women who have survived breast carcinoma, which assesses the effect of the application of yoga for 12 weeks, have detected a reduction of the burden of fatigue ( $p = 0.032$ ) and a significant increase of the energy ( $p = 0.011$ ) in the yoga groups compared to the control group.

Although the patients practising yoga report a subjective reduction of the burden of fatigue and improvement of their quality of life, the currently available evidence of the effectiveness of the application of the yoga techniques on the reduction of the level of fatigue is to be considered insufficient or insufficiently convincing.<sup>90</sup>

## Non-pharmacological methods of affecting sleep disorders

Sleep disorders are quite common with patients who have cancer and may significantly increase the burden of fatigue.<sup>79</sup> Most of the studies assessing the sleep and the fatigue of these patients have established a positive correlation between fatigue and the different sleep parameters: poor quality of the sleep, disrupted beginning of the sleep, waking up at night, uneasy sleep and excessive drowsiness during the day.<sup>91</sup> In relation to this<sup>79</sup> report that the detailed anamnesis of sleep has to be part of the initial assessment of fatigue and is necessary to plan the subsequent rehabilitation.

The non-pharmacological approaches intended to improve the quality of sleep have been organized in four general groups of interventions: cognitive-behavioural therapy, supplementary therapies, psycho training, information and exercise.<sup>92</sup> In most cases, the cognitive-behavioural therapy includes control stimulation, limitation of sleep and sleep

hygiene.<sup>93</sup> The control of the stimulation includes going to bed when feeling drowsy, going to bed at approximately the same time every evening and getting up at the same time every morning. A key aspect of the control of stimulation is getting out of bed 20 minutes after going to bed if the patient cannot sleep after initially going to bed and when waking up at night. The limitation of sleep requires avoiding long or late afternoon naps and limitation of the total time spent in bed.<sup>93</sup>

In a randomized study<sup>94</sup> conducted among women with breast cancer and sleep disorders, it was established that the sleep improved after 8-week sessions in a group, with combined use of a stimulating control, limitation of sleep, a cognitive therapy, sleep hygiene and sleep management. Subsequent assessments are made 3, 6 and 12 months after the treatment. The same authors state that the therapeutic effects were well maintained up to 12 months after the intervention and were clinically significant as a whole.

## Pharmacological treatment

For patients with moderate and severe fatigue, the non-pharmacological treatment may be supplemented with pharmacological treatment, especially if there are disruptions of the quality of life or the ability to do everyday activities.<sup>44</sup> Based on data from scientific literature, over the last years some quite promising approaches have been used for the purpose of exercising a better effect on fatigue, but up to now no agreement has been reached as to its best pharmacological treatment among patients with malignant diseases.<sup>42</sup>

A number of studies have attempted to assess the effect of different medicines from various pharmacological groups (methylphenidate, donepezil, erythropoietin and corticosteroids)<sup>95,96</sup> on the burden of fatigue. The effect of all of them, with the exception of erythropoietin, has been assessed mainly with patients in an advanced stage of the disease.

There is a comprehensive meta-analysis<sup>97</sup> containing a synthesis and a review of 27 studies of the effect of psychostimulants, antidepressants, erythropoietin and anabolic steroids on fatigue, which show a small overall effect of all classes of medicines. The data show that methylphenidate significantly reduces the burden of fatigue compared to placebo (SMD=0.30, 95% CI=-0.54 to -0.05,  $p = 0.02$ ). There is a more recent meta-analysis<sup>98</sup> containing a review of 31 studies of 7104 examined people. The results show that methylphenidate manifests a slight but significant improvement of fatigue compared to placebo ( $Z = 2.83$ ;  $p = 0.005$ ), and the treatment with hematopoietic agents relieves the fatigue caused by anemia induced by chemotherapy. The data of a meta-analysis of 10 other studies, ( $n = 2226$  patients) assessing the effect of erythropoietin on patients with oncological diseases and anemic syndrome undergoing chemotherapy, show a significant effect of erythropoietin compared to placebo (SMD=-0.30, 95% CI=-0.46 to -0.29;  $p = 0.008$ ). In four studies, it has been established

that darbepoetin used for patients with cancer and anemic syndrome significantly improves the level of fatigue compared to placebo (SMD = -0.13, 95% CI = -0.27 to 0.00;  $p = 0.05$ ). With reference to the use of erythropoietin and darbepoetin<sup>97</sup>, say that the optimum dose as well as the duration of the treatment related to relief of fatigue and maintaining a better quality of life are not clearly established.

In a randomized study of patients with fatigue, other authors<sup>99</sup> say that donepezil does not show any effect compared to placebo for reducing the burden of fatigue.

According to<sup>100</sup>, corticosteroids may have a short-term effect reducing fatigue and increasing activity in palliative care. The National Comprehensive Cancer Network (NCCN) and the European Association for Palliative Care (EAPC) recommend considering the possibility for including corticosteroids in palliative care but only for a limited period of time, as the continuous use of steroid-induced myopathies may deteriorate fatigue.<sup>56,101</sup>

The scientific evidence supports the effectiveness of the corticosteroids prednisone and its derivatives and dexamethasone for providing a short-term relief of fatigue and improving the quality of life of the affected patients.<sup>102</sup> A randomized control study<sup>103</sup> of patients in an advanced stage of the disease shows a significant improvement of fatigue among patients taking dexamethasone ( $n=43$ ) compared to those receiving placebo ( $n=41$ ) for a period of 14 days ( $p=0.008$ ) but the long-term effects have not been assessed.

## CONCLUSIONS

Fatigue is one of the most common symptoms among patients with malignant diseases<sup>3</sup> and survivors<sup>12</sup>, which is related to the disease and its treatment and often causes significant disruptions in their functioning and quality of life.

The application of short tools for assessing fatigue can be appropriate for determining its existence and burden, but the initial approach to the treatment usually requires a more comprehensive assessment which shall clarify other features, determine the extent to which fatigue disturbs the implementation of the everyday activities of the affected patients, identify the potential reasons, including the main disease, its treatment, the psychological disorders and others and make an individual plan for treatment. In this sense, the overall assessment of fatigue is crucial for the better clinical management of this symptom.

In accordance with the guidelines of the National Comprehensive Cancer Network<sup>69</sup>, it is recommended to conduct a periodic screening for the existence of fatigue among patients in a period of active treatment and patients who have completed their active treatment and are currently in a period of observation, owing to the fact that fatigue may exist upon the completion of the initial treatment.<sup>104</sup>

The patients and their families need to be informed that the management of fatigue is an integral part of the general health service.<sup>105</sup> The training of patients in relation to fati-

gue, the application of a cognitive-behavioural therapy for managing the symptoms of fatigue, the inclusion of physical exercise have a favourable effect on its burden during the treatment and after its completion. The interventions aimed at affecting fatigue after the completion of the active treatment, regardless of whether they are in direct contact or are web-based, may have an effect on its burden among cancer survivors. With reference to patients with moderate or severe fatigue, medicinal and non-medicinal interventions can be applied and for those patients with moderate burden of fatigue, the treatment can involve only non-medicinal methods that have shown good results – cognitive-behavioural therapy, physical exercise, training, individual consultations, relaxation techniques.

The early diagnosis of fatigue, the identification of the vulnerable patients, the development of target interventions and guidelines for its management in accordance with the instructions for clinical practice will allow the improvement of the quality of life and the well-being of patients with malignant diseases and survivors. This, in turn, could help the patients adhere to their treatment, when an element is needed to ensure effectiveness.

Although additional studies are needed in order to further identify the reasons and the respective treatment of fatigue, the practitioners should regularly assess and treat patients who can use the interventions identified at present, as fatigue may significantly disrupt the quality of their lives.

Subsequent in-depth studies may lead to important conclusions for the better understanding, the determination of suitable objectives and the effective, complex treatment of fatigue in the different stages of the trajectory of the oncological disease as early as possible and, if appropriate and necessary, the patients will be referred to mental health specialists.<sup>1</sup>

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# Общая слабость, связанная с раком, у пациентов с онкологическими заболеваниями: причины, распространённость, рекомендации по оценке и лечению

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## Резюме

Общая усталость и истощение считаются наиболее частыми жалобами больных раком во время и по окончании лечения. Проявления общей усталости могут быть физическими, когнитивными и эмоциональными. Однако точные факторы, определяющие общую усталость, еще не известны. Был проведен первоначальный обзор литературы. Поиск был проведен в четырех базах данных (MEDLINE, ELSEVIER – Science Direct, ELSEVIER – SCOPUS, Springer). При первоначальном поиске появилось 430 статей. Мы выбрали литературу, связанную с дизайном исследования, опубликованную в период с 1993 по 2017 год и написанную на английском или немецком языках. Остальные 48 статей были оценены на предмет соответствия предметной области путём визуального просмотра их заголовков в поисках ключевых слов: общая усталость, связанная с раком, оценка, лечение. Общая усталость, связанная с раком у онкологических больных во время лечения и у выживших имеет распространённость в диапазоне от 58% до 90%. Этот доклад представляет собой обзор литературы, посвящённой общей усталости у онкологических больных – причинам, распространённости и влиянию на жизнь больных, и предлагает рекомендации по оценке и лечению. Были представлены надёжные инструменты для оценки и измерения степени общей усталости. Стратегии борьбы включают ряд нефармакологических методов: физиотерапию, психо-образовательные и психологические вмешательства, методы борьбы с нарушениями сна, методы повышения физической активности и фармакологические методы. Выяснение причин общей усталости, её выявление, надёжная оценка степени тяжести, применение соответствующих лечебных вмешательств и необходимого ухода будут способствовать применению дифференцированного подхода.

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## Ключевые слова

оценка, утомляемость, связанная с раком, лечение, распространённость

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