An Insight about Fatigue and Sleep In Survivors of Childhood Acute Lymphoblastic Leukemia

Elhamy Rifky Abd El-khalek [1], Laila Metwaly Shrief [1], Eman Roshdy El Safy [2], Marwa Mohamed Elsayed Azab [3]

1 Pediatrics Department, Faculty of Medicine - Zagazig University, Egypt
2 Psychiatry Department, Faculty of Medicine - Zagazig University, Egypt
3 Resident of Pediatrics
Corresponding author: Marwa Mohamed Elsayed Azab
Mail: m.azab2025@gmail.com

Abstract

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, and most affected children (> 90%) will become long-term survivors. Survivors and caregivers have identified fatigue as one of the most prevalent and distressing late effects experienced following childhood cancer treatment. Fatigue can negatively impact the lives of pediatric cancer survivors, increasing levels of depression, diminishing neurocognitive and behavioral functioning, and impacting academic achievement and overall quality of life. Fatigue is characterized by low energy and weariness, whereas sleepiness is the normative experience of feeling that one needs to sleep, and is only considered a disorder when it occurs too frequently (eg, excessive daytime sleepiness) or infrequently (eg, insomnia). Both fatigue and excessive daytime sleepiness occur in children and adolescents who have not been affected by cancer, but rates are higher among pediatric cancer patients and survivors. Sleep disturbances may directly result from cancer and its treatment, as well as from multiple other risk factors, many of which lead to a bidirectional relationship between sleep and physical and psychological distress

Keywords: *Fatigue, Survivors, sleep, childhood, Acute Lymphoblastic Leukemia.*

1. Introduction

Long-term survivors of ALL report significant fatigue and sleep disturbances, including prolonged sleep onset latency, abnormal sleep duration, nighttime and premature awakenings, and daytime sleepiness[1]. Fatigue and poor sleep quality hurt ALL survivors' neurocognitive and behavioral functions. Specifically, fatigue is associated with impairments in processing speed, attention, and memory in adult survivors of childhood cancer[2].

Fatigue is an exceedingly common often treatable problem in cancer patients that profoundly affects all aspects of quality of life. Patients report fatigue as one of the most important and distressing symptoms related to cancer and its treatment, and it is a strong and independent predictor of decreased overall patient satisfaction and health-related quality of life. While expert guidelines now recommend regular screening for cancer-related fatigue, the condition remains consistently underreported and often goes untreated[3]. According to the guidelines of the National Comprehensive Cancer Network (NCCN), cancer-related fatigue is defined as a persistent subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion

related to cancer or cancer treatment that is not proportional to recent activity and that significantly interferes with usual functioning. Prevalence estimates have varied widely, reflecting the variety of populations in which it has been studied as well as the subjective nature of the condition and various screening methods that have been employed. Overall 50%–90% of cancer patients experience fatigue, the latter number corresponding with those undergoing active anticancer chemotherapy or radiotherapy[4].

Prevalence

Among survivors of childhood ALL, prevalence estimates of self-reported sleep disturbances range from 13.4% to 49% [5]. This is evidenced in a study by Zupanec et al., where greater than 80% of ALL patients between the ages of 4 to 18 years old on outpatient maintenance chemotherapy described poor sleep characterized by increased nighttime awakenings and wake time after sleep onset when compared to pediatric norms[6].

Recent research has identified increased fatigue levels in children with leukemias on active treatment. However, findings have been mixed concerning the rate and impact of fatigue symptoms following treatment completion. Studies assessing the early survivorship phase directly following treatment, provide some evidence that fatigue symptoms may improve over time. Yet, elevated fatigue has been reported in approximately half of ALL long-term survivors[7]

Pathophysiology:

Chemotherapy, steroids, and radiation therapy are the mainstays of pediatric cancer therapy and also play a significant role in altering sleep patterns. Changes in sleep during treatment have been observed in a wide array of malignancies, including non-neural solid tumors, hematological cancers, and CNS tumors, despite the differences in the specific chemotherapies administered. Hospitalization is also a component of treatment in which initial or subsequent admissions have been shown to negatively affect sleep in pediatric cancer patients [8].

Effect of chemotherapy of ALL on sleep;

In terms of specific risk factors and mechanisms, some patients who report sleep disturbances during chemotherapy have been found to have gene polymorphisms in genes encoding Interleukin-6 (IL-6) and tumor necrosis factor (TNF) that lead to elevated cytokine levels in the context of inadequate sleep. As shown by Cheung et al. in a study looking at ALL survivors at a median of 7 years following diagnosis, the effects of chemotherapy on disturbed sleep, such as increased nighttime awakenings, may persist well into survivorship, as a result of an increase in cortisol, cytokines, and the associated physiologic cascade of immune and inflammatory responses[2].

Effects of Steroid Treatment of ALL on Sleep:

Steroids such as dexamethasone and prednisone are commonly used in the treatment of cancer patients and have been found to contribute to insomnia in adolescent acute lymphoblastic leukemia patients, some of whom require sleep aids. Dexamethasone, in particular, is associated with poorer sleep quality compared to those on prednisone, longer time spent napping to compensate for inefficient nighttime sleep than prednisone, and disruption of REM sleep[9].

There is a consensus that steroids lead to increased daytime napping and nighttime insomnia; as they are a mainstay of cancer treatment, practitioners should be aware of the sleep disruption that they can cause. As with chemotherapy, more research is necessary to ascertain the impact of

individual steroid agents on sleep independent of other factors, as well as to better identify patient characteristics that may lead to greater vulnerability to sleep disturbance with steroids[10].

Effects of Radiation Therapy of ALL on Sleep:

Radiation therapy may have direct effects on sleep in pediatric cancer patients. Cranial radiation affects brain structures, such as the suprachiasmatic nucleus that regulates sleep and wakefulness, through direct injury to those structures. Effects of such radiation-induced injuries to the sleep-regulating structures in the hypothalamic-pituitary axis, including the SCN, may persist into adulthood[11]

Effect of chemotherapy on ALL fatigue

Numerous processes may play a role in the onset of cancer-related fatigue, the pathophysiology of which remains poorly understood. Muscle energy metabolism, inflammation and stress mediators, immunological activation, cancer and its treatment-related CNS impacts, sleep and circadian rhythms, and hypothalamic-pituitary axis-related hormonal alterations are all part of this [12]. Radiation therapy patients, as well as almost all patients given the biological modifiers interferon or interleukin 2, often experience fatigue. Diagnosing common reversible reasons for fatigue, such as hypothyroidism, depression, and anemia, requires constant vigilance [13].

Many factors may contribute to the development of cancer-related tiredness [14]. Regardless of this intricacy, most research on cancer-related fatigue has concentrated on immunological and inflammatory variables. It is believed that these variables cause fatigue by affecting brain systems engaged in "sickness behaviors." For example, there are variations in genes that control inflammation (such as IL6, TNFA, and IL1) as well as in inflammatory indicators in the blood (such as IL-1, TNFA, CRP, and IL-6) [15].

Several biochemical and physiological systems can become dysregulated during inflammation. These include both peripheral (in muscles and tissues) and central (in the central nervous system) mechanisms. Fatigue can be caused by changes in cytokine levels, dysfunction in the hypothalamic-pituitary-adrenal (HPA) axis, disruption of the circadian rhythm, changes in adenosine triphosphate (ATP), muscle metabolism, and vagal afferent activation [16].

Although the genetic underpinnings and pathophysiologic pathways are not well understood, these results provide promise for the discovery of new causative processes and possible therapy targets. Furthermore, the intricate psychological, social, and behavioral aspects that can significantly contribute to cancer-related exhaustion are not accounted for in the existing pathophysiological models [16].

A Different Approach to Cancer Fatigue: The 3P Factors Model

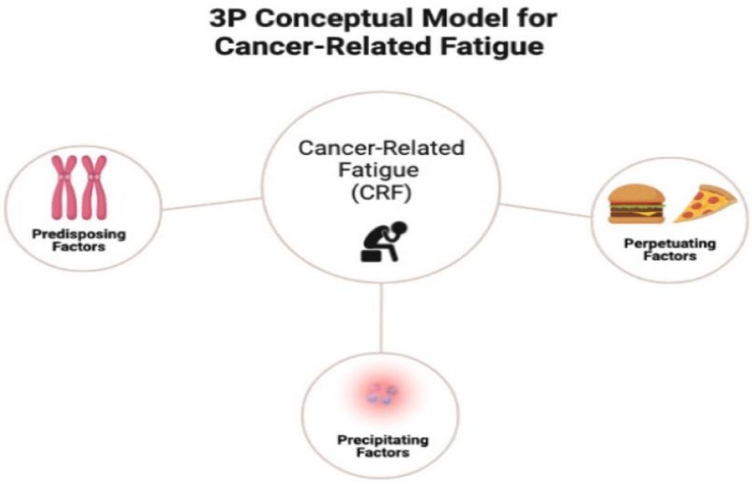

Figure 1: The 3P conceptual model for cancer-related fatigue [16].

The biopsychosocial model stands out among past attempts to explain complicated illness processes. This multi-disciplinary approach considers the interplay between socioenvironmental variables, psychology, and biology [17]. Despite its importance in challenging biological reductionism and advancing a more holistic view of human health, the biopsychosocial model does not provide the level of detail needed to explain the interplay between different risk factors for disease [18].

Conversely, the plethora of psychological and physiological components involved in cancer-related fatigue can be better understood by utilizing the 3P paradigm. The 3P model identifies several risk factors for patients to experience weariness. Among these include biobehavioral elements such as chronological age and biological sex, genetic variations, metabolomics, inflammation, body composition, dietary quality, circadian disturbance, and co-morbidities. Mental health issues such as sadness, worry, sleeplessness, and stress perception are also thought to play a role in increasing the likelihood. Fatigue may set in as a result of metabolic alterations and inflammation brought on by treatment-related variables such as systemic therapy and radiation. Finally, factors like poor sleep, physical inactivity, and unhealthy eating can exacerbate or even cause fatigue to become chronic. Some have proposed the 3P model to help us grasp exhaustion; it has been useful in the past for other chronic problems, such as sleep disorders and pain [16].

Predisposing Factors

Biological sex, heredity, body composition (such as poor muscle mass and body fat), and viral exposures are some of the patient features that are thought to lead to cancer-related fatigue. Also, by controlling wakefulness and slumber, circadian rhythms may have a major impact on the causes of exhaustion [16].

Fatigue from cancer treatment is more likely among people with poor performance status, who are female, who have insomnia, who are neurotic, who have pain, or who suffer from depression [19].

Precipitating Factors

Though the exact causes of cancer-related fatigue are unknown at this time, potential culprits include inflammation (increased production of pro-inflammatory cytokines), cancer treatment-induced metabolic dysregulation (changes in metabolic genes and regulatory pathways), and accelerated cellular aging (e.g., premature telomere shortening and altered DNA methylation). A well-established example is the impact of chemotherapy on the aging process. [20].

Fatigue may be exacerbated by chemotherapy-induced mitochondrial damage and muscular deconditioning [21].

Factors that trigger an event may interact with one another in a multiplicative fashion. Metabolic dysregulation, encompassing energy, lipid, and amino acid metabolism, has been observed in studies examining muscular tiredness in cancer patients [22, 23].

The essential amino acid tryptophan drives the de novo synthesis of niacin and serotonin. While serotonin controls cognitive and behavioral processes, nicotinamide adenine dinucleotide (NAD) is a co-factor necessary for maintaining an equilibrium of energy levels; NAD is also linked to aging and the regulation of circadian rhythms (Sirtuin1) (SIRT1) [24]. There is encouraging evidence that tryptophan can alleviate mental and physical fatigue following an endurance event [16].

Hormonal disruptions in chronic fatigue syndrome have also been linked to alterations in twenty metabolic pathways, including those involving sphingolipids, phospholipids, purines, cholesterol, microbial metabolites, proline-5-carboxylate, riboflavin, amino acids, peroxisomal, and mitochondrial metabolism [25]. These processes are directly regulated by the amount of redox or NADPH, which highlights the importance of the mitochondria, which are organelles within cells that produce energy [25]. About 70% of the diversity in metabolic phenotype was attributed to sphingolipids and phospholipids in a study of eighty-four participants with chronic fatigue syndrome. It is worth noting that variations between sexes were also identified in this area. According to the area under the receiver operator characteristic curve analysis, the accuracy in predicting fatigue for males was 94% (95% CI = 84-100%) while for females it was 96% (95% CI = 86-100%). Three further metabolomics studies [26, 27, 28] found that sphingolipids, phospholipids, and energy, amino acid, and nucleotide metabolic anomalies all play major roles in fatigue-associated diseases. Inhibition of PPAR in cancer patients' muscles may influence the changes in sphingolipids, which may be associated with altered lipid metabolism and mitochondrial energetics [29].

Perpetuating Factors

A bad eating pattern, inconsistent meal timing, lack of physical activity, and inadequate sleep are examples of perpetuating variables that may amplify or extend weariness [30, 31]. Previous studies have shown that anti-inflammatory eating habits, like the Mediterranean and sensible diets, can help reduce inflammation and improve body composition, which can help alleviate cancer-related fatigue [16]. Vegetables, fruits, legumes, nuts, and whole grains make up the bulk of a Mediterranean diet, which also calls for modest amounts of fish and red wine and mostly uses olive oil for fat [32]. Metabolic endotoxemia, characterized by a two- to threefold increase in circulation levels of bacterial endotoxin, is reduced and GI microbiota improvements are linked with anti-inflammatory dietary patterns [33]. Daily, people often encounter central tiredness, exercise-induced exhaustion, and pathological fatigue, including chronic fatigue syndrome (CFS) and disease-related fatigue. Studies on rats and people have shown that when tiredness is present, there is a rise in hazardous bacteria and a decrease in helpful bacteria. Exhaustion, which is associated with changes in gut microbiota metabolism, manifests itself in several ways, including an excess buildup of lactate, an energy deficit, and poor central nervous system performance. On the flip side, fatigue causes an imbalance in the gut microbiota, which in turn causes oxidative stress, inflammation, and the breakdown of the intestinal barrier.

Table 1 [34] shows the gut microbiota that are linked to fatigue occurrences.

Table 1. The gut microbiota involved in fatigue-induced damage [34].

Gut Microbiota *	Factor Related to Fatigue	Target	Effect
Escherichia *Streptococcus* *Enterococcus*	5-HT	Brain	Central fatigue
Bifidobacterium breve Yakult *Lactobacillus casei Shirota* *Escherichia coli*	L-lactic acid	Blood	Imbalance of muscle and blood pHs; reduction in muscle function and muscle contractility; exercise-induced fatigue
Lactobacillus acidophilus *Lactobacillus fermentum* *Lactobacillus delbrueckii subsp. Lactis* *Lactobacillus buchneri* *Streptococcus bovis* *Enterococcus*	D-lactic acid	Blood	Metabolic disorders, direct or indirect neurotoxic effects; CFS

* The names of bacteria at the genus or species level are in italics, and those at the phylum or family level are in the normal style.

The Western diet, which is popular in the US, is an example of a pro-inflammatory eating pattern that is defined by a low intake of fresh produce, legumes, and fruits, as well as an abundance of sugary drinks and refined grains [35]. Metabolic endotoxemia can develop in response to changes in the gut microbiota and bacterial fermentation end products, intestinal physiology and barrier function, and the enterohepatic circulation of bile acids, among other things [33]. Moreover, pro-inflammatory markers associated with cancer-related fatigue, including tumor necrosis factor (TNF)-α, C-reactive protein (CRP), interleukin (IL)-6, and IL-8, have been discovered to be correlated with the Western diet, according to researchers [36]. The EDIH and EDIP, which stand for the empirical dietary index for hyperinsulinemia and chronic inflammation, respectively, show that eating habits that promote these conditions greatly affect the risk of obesity, type 2 diabetes, cardiovascular disease, and cancer [37]. The EDIH has gone above and beyond in predicting future cancer risk, while the EDIP has predicted known amounts of insulinemic and inflammatory biomarkers [38].

Nutritional metabolomics, the study of food-related metabolites in a biofluid, can supplement self-reported questionnaires for assessing dietary patterns in cancer-related fatigue [39], and it can provide an objective estimate of recent or regular dietary intake. Using untargeted metabolomics, a discovery technique for small molecules affected by dietary behavior and associated with disease, we can better understand the body's natural reaction to food and find metabolic targets for dietary intervention in disease prevention. To the best of our knowledge, nutritional metabolomics studies examining cancer-related fatigue have not yet been conducted. There is a wealth of evidence linking the microbiota to human illness, and numerous studies conducted over the past decade have examined how these microorganisms aid the host. The microbiome, and especially bacterial metabolites, have been linked to oxidation and inflammation [40].

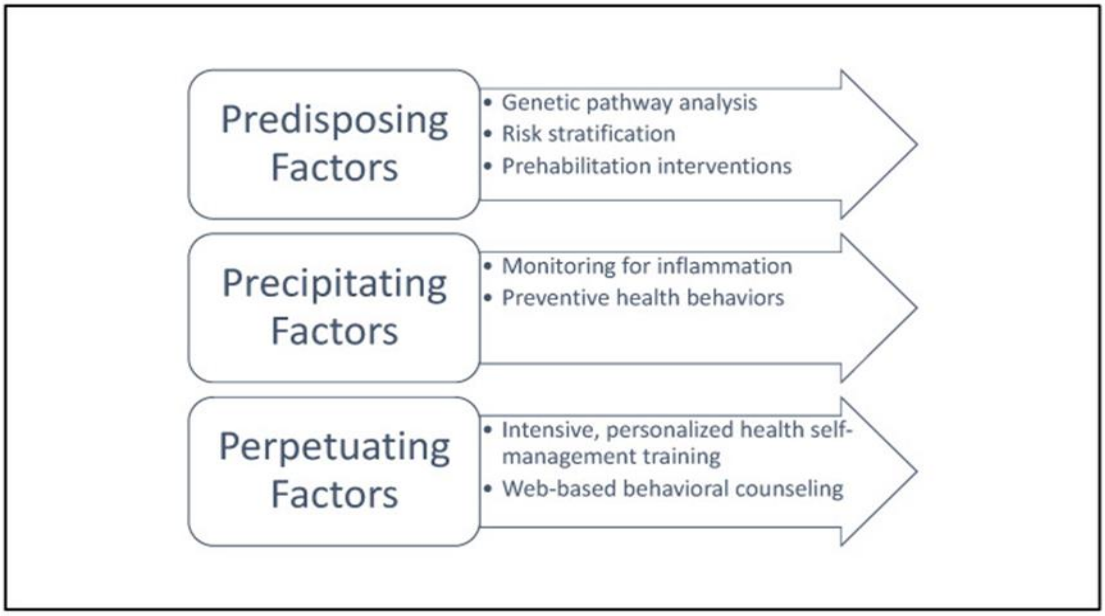

Figure 2: Recommended clinical actions to address each 3P factor [16].

Depression and Fatigue

Children with cancer feel not only the effects of physical treatment but also effects on their mental and social health. Depression is one of the most common psychiatric disorders in children and adolescents with cancer Depression and fatigue have a close relationship. Even though the mechanism of fatigue occurrence is not yet known, it is suspected that cancer and its treatment affect serotonin and cytokine dysregulation. Depression and fatigue that are not immediately treated can cause children to become uncooperative in cancer treatment; cause an inability to make treatment decisions; and disrupt daily activities, social interactions, and, ultimately, their quality of life [41].

Screening and assessment of fatigue

The National Comprehensive Cancer Network (NCCN) recommends screening for cancer-related fatigue at both the initial visit after an advanced cancer diagnosis and each treatment appointment for all cancer patients. However, there are obstacles to treatment from both doctors and patients. Patients may view fatigue as an inevitable and irreversible side effect, and they may be afraid that voicing their concerns will lead to a shift toward less aggressive cancer treatment [42]. Meanwhile, doctors may lack adequate knowledge about fatigue and its treatments, or they may fail to recognize the extent to which fatigue impacts quality of life.

There is currently no diagnostic technique for cancer-related fatigue, however, multiple validated instruments exist for screening and assessment. The diagnosis can be reached by integrating the patient's medical history and physical examination with pertinent test results, consulting with family members and caregivers, and utilizing standardized evaluation instruments. The VAS and BFI are the most basic and easy-to-understand ones. Although these instruments are more comprehensive and hence more commonly used in clinical research, they have also been validated in other languages, including the Functional Assessment of Cancer Therapy and the Multidimensional Fatigue Symptom Inventory-Short Form [43].

When diagnosing cancer-associated fatigue, it is common practice to rule out reversible treatable

factors such as hypothyroidism, anemia, sleep disturbance, pain, emotional distress, climacteric, adverse medication events, electrolyte or metabolic disturbances, or organ dysfunction caused by conditions like heart failure, myopathy, or pulmonary fibrosis. Short self-assessment instruments for fatigue, such as the Visual Analog Scale (VAS) or the Beck Depression Inventory (BFI), should be given to patients once these potential causes have been addressed or excluded [44].

Nonpharmacologic strategies can treat minor fatigue that does not significantly influence daily functioning; however, those with moderate to severe fatigue may benefit from a combination of pharmacologic and nonpharmacologic approaches. Typically, it's necessary to regularly assess the level of exhaustion and its impact on daily functioning and quality of life [45].

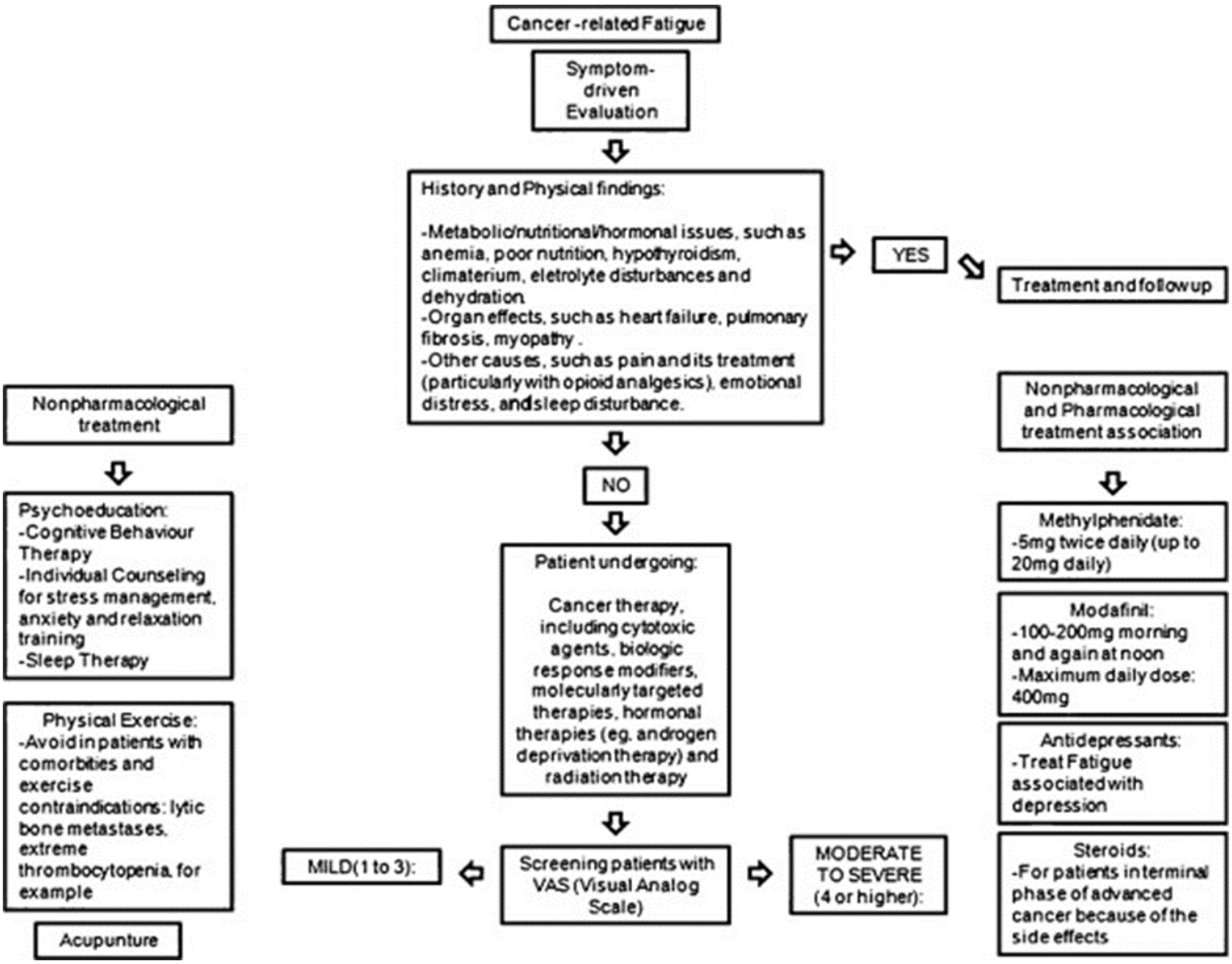

Figure 3: Diagnosis and treatment of cancer-related fatigue [43].

The Pediatric Multidimensional Fatigue Scale (PedsQL MFS), developed by James W. Varni, is a validated tool designed to assess fatigue in children and adolescents aged 5 to 18 years. It measures fatigue across three dimensions: General Fatigue, Sleep/Rest Fatigue, and Cognitive Fatigue, using an 18-item questionnaire. Each item is scored on a 5-point Likert scale, with scores

transformed to a 0–100 range, where higher scores indicate lower levels of fatigue. The PedsQL MFS includes both child self-reports and parent proxy reports, making it versatile for clinical and research settings. Originally validated for pediatric rheumatology populations, it has since been widely adopted to evaluate fatigue in various conditions, including cancer and chronic illnesses, with proven reliability (Cronbach's alpha ranging from 0.77 to 0.92). Its use has been instrumental in understanding the multidimensional impact of fatigue on pediatric quality of life and guiding tailored interventions [46].

Clinical Relevance

The PedsQL MFS is particularly valuable in assessing fatigue in survivors of childhood acute lymphoblastic leukemia (ALL), where fatigue significantly impacts neurocognitive functioning, sleep quality, and overall quality of life. The scale is useful for tracking fatigue over time, identifying specific areas of concern, and tailoring interventions to meet the unique needs of pediatric patients [47].

Assessment of sleep disturbance in ALL survivors:

Polysomnography and wrist actigraphy represent two objective measures of sleep, while sleep diaries and surveys are influenced by subjective input. While polysomnography is considered the gold standard for diagnosing SDB and sleep limb movement disorders, it may not be feasible in some settings because of the expense, the need for a child-friendly sleep laboratory, and the inability to diagnose sleep disorders associated with behavior[48].

Wrist actigraphy provides sleep data through a continuous monitor that measures activity such as sleep/wake cycles and sleep efficiency, but it is poorly equipped to evaluate the stages of sleep. When used alongside a sleep diary, the data from both modalities are effective at assessing sleep quality. Although it is a subjective measure, sleep diaries maintained by the parent or child provide insight into sleep quantity and timing on a consistent nightly basis[49].

Self-reported questionnaires are imperfect but valuable and convenient tools for categorizing and quantifying the presence and severity of sleep disturbances. As a testament to the usefulness of sleep surveys, the American Academy of Sleep Medicine used data from parent- and child-reported sleep questionnaires to develop consensus recommendations for sleep duration in children and adolescents
[49].

A variety of sleep questionnaires, such as the Children's Sleep Habits Questionnaire and Sleep Disturbance Scale for Children, are reliable surveys for assessing multiple components of sleep, including duration of sleep and disorders of initiating and maintaining sleep; they have also been used to measure sleep in studies of pediatric cancer patients. However, the Patient-Reported Outcomes Measurement Information System pediatric sleep scale is the only measure that has been validated specifically in the pediatric cancer population[50].

There are various objective and subjective tools available to clinicians to investigate sleep disturbances in children. These tools can generally be used together to provide a more complete picture of sleep issues and their impact on daily functioning. However, there is a need to develop questionnaires and validity studies that specifically target pediatric cancer patients, while taking into account cancer-specific factors, such as treatment and cancer type. Regardless of their crude nature, sleep surveys are an efficient and valid way for clinicians to identify sleep disturbances that may lead to the faster initiation of intervention strategies to mitigate the negative functional and quality-of-life impacts of sleep problems in this population [10].

For the children's Sleep Habits Questionnaire (**CSHQ**) based on child sleep disturbances and sleep behaviors in the past week. The measure includes 33 items, such as “child falls asleep within 20 minutes after going to bed” and “child sleepwalks during the night,” and is composed of eight subscales, which include bedtime resistance, sleep duration, and night wakings. Parents respond to items on a scale of either 3 [“usually” (5-7 nights per week), 2 [“sometimes” (2-4 nights per week)], or 1 [“rarely” (0-1 night per week)]. Several items were reverse scored and the total score ranged from 33 to 99. Higher scores indicated higher rates of sleep disturbances with scores above 41 indicating the presence of a sleep disorder[51].
The Arabic Version used in the present work was developed through a translation and re-translation process by Asaad and Kahla (2001) [52].

Treatment

Nonpharmacologic treatment

Cognitive–behavioral interventions

Psychological interventions have shown promise for many cancer patients experiencing fatigue, and numerous modalities have been investigated in various groups. Group therapy, individual counseling, stress reduction and relaxation training, formal cognitive behavioral therapy, psychoeducation on tiredness, and supportive interventions are some of the interventions that have demonstrated encouraging outcomes, primarily in cancer patients who are currently receiving treatment [53].

Exercise

Counseling for cancer-related fatigue should mainly focus on increasing activity levels, according to current standards. Some patients do get this kind of counseling, but it's still quite rare. Efficacy in reducing fatigue, quality of life, functional capacity, emotional distress, and other symptoms has been consistently shown in studies of exercise conducted either during or immediately following cancer treatment [54]. Exercising regularly may boost functional capacity, which in turn may make it easier to do everyday tasks with less effort. Since no one kind of exercise has been proven to be more beneficial than any other, the selection of exercise should be based on the patient's desire. Better results may be achieved if patients are given the freedom to pick their fitness program in addition to printed instructions and incentive tools like a step pedometer [5].

Pharmacologic treatment

Pharmacologic treatments, in addition to nonpharmacologic therapy, may be beneficial for patients with moderate-to-severe cancer-related fatigue, particularly if the quality of life or ability to perform daily tasks is impaired [55].

Psychostimulants like methylphenidate and dexamethylphenidate have demonstrated potential as an auxiliary treatment for cancer-related weariness [56].

As Merz et al., detail, sleep medications in the pediatric cancer population may inadvertently perpetuate sleep disturbances by not treating the root cause, such as altered circadian rhythms, poor sleep hygiene, maladaptive sleep habits and behaviors, and a non-conducive sleep environment. Moreover, the researchers explain that pediatric patients who habitually use sleep aids during treatment and survivorship may be at risk of suppressing their natural sleep cycle and falsely assume that medication is necessary to sleep[57].

Educating families on sleep hygiene (e.g., appropriate wake and sleep times and activities before sleep) has also been used to mitigate sleep issues during cancer treatment. Based on the understanding that sleep habits change during cancer treatment and parenting behaviors play a role in influencing patients' sleep, investigators educated families of pediatric ALL outpatients on sleep issues and provided them with relaxation techniques to influence family behavior and promote good sleep hygiene. This program resulted in longer nighttime sleep duration and shorter wake time after nighttime awakening, indicating that education and relaxation techniques are viable management strategies in other pediatric cancer and survivor populations[58].

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