Fatigue in Parkinson Disease, Stroke, and Traumatic Brain Injury

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KEYWORDS

• Fatigue • Traumatic brain injury • Parkinson disease • Stroke
• Cerebrovascular accident • Post-stroke syndrome

Fatigue is a commonly reported symptom after traumatic brain injury (TBI), after stroke, and in persons living with Parkinson disease (PD). Fatigue compounds the underlying impairments of all these neurologic disabilities, leading to greater handicap and lower life satisfaction. Fatigue in neurologic illnesses has serious social and public health implications. One study looking at social security disability insurance (SSDI) in PD found that 82% of patients in their sample felt they were too disabled to work full-time at a mean of 3.4 years after PD diagnosis.[1] The primary debilitating symptom that contributed to applying for SSDI in this study was fatigue.

Merriam-Webster's Collegiate Dictionary defines fatigue as "weariness or exhaustion from labor, exertion or stress; the temporary loss of power to respond that is induced in a sensory receptor or motor end organ by continued stimulation," and tiredness is defined as, "the state of being drained of strength and energy; fatigued often to the point of exhaustion." In laypersons' terms, they are synonyms. Medical literature generally employs yet another similar definition, describing fatigue as a *subjectively* overwhelming sense of tiredness, lack of energy, and feeling of exhaustion. These similar definitions are all irrespective of sleep status.

It is important to note that people with neurologic disorders describe fatigue differently from the way that the general population does. One paramount distinction is that fatigue experienced by individuals with neurologic disorders does not respond to sleep or rest nor is it accompanied by the *desire* to sleep, whereas people in the general population report an amelioration of fatigue symptoms with a nap or a full night's sleep. This important difference in definitions has implications for research, because scales used to quantify fatigue in the general population may not accurately measure fatigue in those with neurologic conditions.

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Although there is no universally accepted definition for fatigue, there is a general distinction between peripheral and central fatigue. Peripheral fatigue, or physical fatigue, is most commonly expressed as musculoskeletal symptoms that impair mobility and the ability to perform activities of daily living (ADLs).

Central fatigue, also known as mental or cognitive fatigue, results from dysfunction of the supratentorial structure involved in performing cognitive tasks. Central fatigue is a difficulty initiating and sustaining mental and physical tasks in the absence of motor or physical impairments.[2,3] The inability to maintain focused attention is a key component of central fatigue, since focused attention is necessary to incorporate the mental, physical, and sensory inputs involved in completing a task. Once focused attention is impaired, integrating the various types of information needed to complete a task becomes more difficult and requires greater effort to complete.

In persons with TBI and stroke, central fatigue predominates, whereas in PD, fatigue complaints are often mixed. In evaluating patients with complaints of fatigue, differentiating between central and peripheral fatigue is an important initial step, as inciting agents and treatments differ between the 2. The goal of this article is to provide the reader with an overview of the etiology, assessment, quality of life (QoL) implications, and treatment of this common symptom in adults with neurologic disabilities.

EPIDEMIOLOGY

Fatigue is reported to be almost ubiquitous in individuals with neurologic disorders. Estimates of prevalence depend somewhat on the specific neurologic disorder in question, the scale used, and the study cited. Additionally, as discussed, the definition of fatigue tends to vary from study to study, so statistics cannot always be directly compared. Regardless, it is accepted that fatigue is an extremely common problem associated with neurologic disorders, which is reported with significantly higher frequency than that in the general population and may significantly affect an individual's return to independent living.

Fatigue can be a debilitating symptom of PD, affecting all aspects of life. Although the literature studying fatigue in PD lags behind that of other neurologic entities, it has recently begun to flourish. The prevalence of fatigue in PD varies in the literature from 33% to 81%. Two important studies done in 1993 were among the first to highlight the relationship between fatigue and PD.[4,5] These studies reported for the first time that the rate of fatigue in PD was high. In the study by Friedman and colleagues, more than 50% of their PD patients reported that fatigue was among the 3 most disabling symptoms of their disease. This is important to keep in mind, because physicians on the whole are not doing an adequate job of recognizing fatigue in their PD patients. In 1 study, 42% of patients with PD complained of fatigue, whereas only 25% of the physicians uncovered the symptom.[6]

Fatigue as an *independent* symptom in PD is a relatively new concept. Karlsen and colleagues[7] were the first to present evidence backing the claim that the high prevalence of fatigue seen in PD cannot be explained by comorbid depression, dementia, or sleep disorders alone. Alves and colleagues[8] studied PD patients for 8 years, measuring the prevalence of fatigue at the inception of the study and 4 and 8 years later. They found that the prevalence of fatigue in patients without depression and excessive daytime sleepiness remained high and increased from 32.1% to 38.9% during the 8-year study period.

The prevalence of fatigue after stroke ranges from 30% to 68%.[9] Fatigue is reported both in the acute phase and the late phase after stroke. Ingles and colleagues[10] found that fatigue problems, measured by the Fatigue Impact Scale (FIS), were reported in

68% of subjects between 3 and 13 months after stroke, compared to 36% of age-matched control subjects. Two years after stroke, 51% of survivors have elevated scores on the fatigue subscale of the Checklist Individual Strength compared to 12% of control subjects, and 50% report that fatigue is their main complaint. Controlling for depression, 39.2% of stroke survivors experience significant fatigue independent of reports of depression. In addition, the frequency of fatigue associated with clinically relevant depression was found to be 67% in individuals who had strokes at least 7 years earlier.

A 2006 study tracked the natural history of post-stroke fatigue for 1 year.[11] The authors used the Fatigue Severity Scale (FSS) to measure fatigue at admission, 6 months, and then 1 year after stroke. They found that the incidence of fatigue increased with each subsequent evaluation and that fatigue impact was greater among women, older subjects, and those who exhibited more depressive symptoms.

There is no clear primary etiology of fatigue after TBI. Depression, pain, sleep disturbance, and neuroendocrine abnormalities all have been associated with fatigue after TBI.[12–14] It has also been hypothesized that the injured brain requires more effort to compensate for impairments in attention and processing speed.[15–17] Many individuals with TBI describe mental tasks as being effortful and fatiguing.

Fatigue is a commonly experienced symptom after TBI and occurs at a greater frequency than that in the general population.[15] Fatigue is among the most pervasive symptoms after TBI.[18,19] Estimates of the incidence of fatigue in individuals living in the community range from 50% to 80%.[20] Fatigue after TBI appears to be independent of severity and age at time of injury and is associated with duration after TBI in some studies and not others.[15,21] In a 2-year prospective longitudinal study by Bushnik and colleagues[22] of individuals with moderate to severe TBI, improvements in fatigue were seen in the first year. Further changes were not seen up to 2 years after TBI. The subset of individuals who reported significant increases in fatigue during the first 2 years demonstrated poorer outcomes in multiple domains than did those with stable or decreased fatigue.

EFFECTS ON QUALITY OF LIFE

Parkinson Disease

Patients with PD have worse QoL scores compared with those of the general population, and PD patients with fatigue have even lower scores. A shifting focus from defining the symptoms of this disease to describing their QoL implications is reflected in current literature. It is well known that fatigue is rated among the most disabling symptoms of PD, but it was not until recently that we knew how this symptom compared with other common symptoms. A 2008 British study looked at the *relative* importance of symptoms with respect to QoL in PD patients and found that fatigue was as important as some of the classic motor symptoms, such as shuffling and falls.[23]

A well-done Slovakian study used several scales to measure the effects that fatigue has on QoL in PD patients.[24] The authors found that the existence of fatigue in PD patients was associated with lower scores on all QoL domains, the most affected being bodily discomfort, mobility, and emotional well-being. In addition, a 2003 Norwegian study described the influence of fatigue on health-related QoL in patients with PD.[25] The authors' sample included patients without known depression or dementia, and they used the FSS as a measuring tool. They found that 50% of the patients had significant fatigue and that those with fatigue had a more advanced disease than those without. They also uncovered a strong correlation between fatigue and high distress scores on health-related QoL scales.

Stroke

Fatigue in a post-stroke patient can have significant QoL-lowering effects. Van de Port and colleagues[26] were the first to show that fatigue is an independent variable in post-stroke patients. They also found that post-stroke fatigue is more closely related to instrumental activities of daily living (IADLs), such as shopping and cleaning, than to simple ADLs. Another study found that health-related QoL in patients who survived an ischemic stroke was lowest in the domain of physical mobility.[27] It is not surprising that fatigue is predictive of mobility decline 1 year after stroke,[28] yet the relationship between ambulatory activity and post-stroke fatigue is complex. Several other studies have shown no relationship between mobility and fatigue or daily step activity and fatigue,[29,30] yet it is clear to all that the 2 have a relationship. It is likely that more salient variables such as hemiparesis or social isolation become the primary obstacles to mobility after stroke.

Traumatic Brain Injury

Cantor and colleagues studied community dwelling individuals who had suffered a range of severity of TBI to examine the relationships between post-TBI fatigue and comorbid conditions, participation in activities, QoL, and demographic and injury variables. A noninjured control group was also examined. Fatigue was more severe and prevalent in individuals with TBI and more severe among women. It was not correlated with other demographic and injury variables. Fatigue was correlated with health-related QoL and overall QoL but was not generally related to participation in major life activities.[31]

DIFFERENTIAL DIAGNOSIS

Fatigue should always be suspected and inquired about when encountering a patient with a neurologic condition, yet it is critical to keep in mind that the patient's fatigue may not be due to that neurologic condition. It is important to determine whether the fatigue is primary or in fact secondary to another condition. The differential diagnosis for fatigue is vast, but **Table 1** provides a summary of the most common non-neurologic causes of fatigue.

The issues of fatigue and disordered sleep are closely intertwined, and differentiating the 2 is often a problem for physicians. Although sleep disorders are common in many neurologic conditions, it is believed that fatigue itself is an independent symptom, often unexplained by a comorbid sleep disorder. Though they share common symptomatology, the treatments are quite different. It is a challenge to the physician to disentangle this perplexing constellation of symptoms and determine the root of the problem so that proper therapy can then be administered. Depression is another entity common in both the general population and among those with neurologic diseases. As with sleep disorders, it is possible that a patient's fatigue is not primary but secondary to comorbid depression. Another important thing to remember is that dementia occurs in 10% to 15% of PD patients, so it is important not to neglect this possibility in your differential diagnosis of fatigue.[32]

ASSESSMENT

When evaluating any patient with symptoms of fatigue, it is crucial to conduct a thorough diagnostic workup looking for underlying causes that may be unrelated to any known neurologic diagnoses. Initially, the clinician should attempt to differentiate between central and peripheral origins as well as primary versus secondary causes.

Table 1
Differential diagnosis of fatigue

Neuropsychiatric
Depression
Sleep disorders
Dementia
Infectious
Endocrine
Hypothyroidism
Anterior pituitary dysfunction
Hypogonadism
Growth hormone deficiency
Adrenal insufficiency
Chronic disease
Diabetes
Cardiac disease
Pulmonary disease
Anemia
Cancer
Hepatorenal disease
Rheumatologic disease
Medications
Antispasticity agents & muscle relaxants
Analgesics
Anticonvulsants
Antihistamines
Anti-inflammatories
Antipsychotics
Antidepressants
Gastrointestinal drugs

Central fatigue questioning and examination typically focus on the presence of fatigue when attempting to perform cognitive tasks that require 1 or more steps. Peripheral fatigue questions focus on fatigue with physical activities such as walking, lifting, or completing ADLs.

It is also important to think in terms of primary and secondary causes for fatigue. Primary fatigue is caused by the neurologic disorder itself, whereas secondary fatigue can be due to multiple factors such as anemia, lack of conditioning, depression, side effects of medications, infection, endocrine dysfunction, or sleep disturbance (**Table 2**). Many medications can cause fatigue as a side effect, and examples are listed in **Table 1**. Checking serum levels of some medications and review of medications for interactions should be a part of the compulsory evaluation of fatigue. In assessing for secondary causes of fatigue, inquiring about current medications, difficulties sleeping, and depression can also yield useful information.

Evaluation for sleep disturbance is a core component in evaluating the etiology of the fatigue. High rates of sleep disturbance have been shown to be associated with

Table 2
Patient assessment of fatigue

Ascertain type of fatigue
• Mental fatigue: Fatigue with cognitive tasks
• Physical fatigue: Fatigue with walking, lifting, and other activities of daily living
Evaluate for secondary causes of fatigue (See **Table 1**)
• Assess for depression
• Sleep dysfunction
Sleep onset
Staying asleep
Nightmares
• Infection
Fever
Chills
Sweats
Urinary symptoms
• Underlying malignancy
Weight loss
Loss of appetite
Anemia
Careful review of medications
• Side effects
• Drug–drug interactions
Laboratory and imaging studies when appropriate

all neurologic disabilities, although for varying reasons. Management of sleep impairment through sleep hygiene, treatment of comorbid illness, or through pharmacology can decrease fatigue. Depression is often associated with disturbances in sleep, appetite, concentration, as well as fatigue.

Hematologic, infectious, endocrine, cardiac, rheumatologic, and metabolic causes of fatigue should be considered. History and physical will help guide the workup, but laboratory testing for metabolic and endocrine function should be standard.

Anterior pituitary dysfunction has been documented after TBI, stroke, and diagnosis of PD. Endocrine dysfunction has been shown to be as high as 59% after TBI.[33] Growth hormone deficiency and hypogonadism are associated with decreased bone mineral densities, aerobic capacity, muscle strength, lower QoL, cognitive impairments, as well as fatigue.[34] Basic screening for endocrine dysfunction should include a thyroid panel, AM cortisol, testosterone, facioscapulohumeral dystrophy, and luteinizing hormone as appropriate, and insulin-like growth factor-1 as a marker of growth hormone. The relationship between fatigue and neuroendocrine dysfunction is still evolving.

A driving assessment should be a routine part of any patient encounter when fatigue is an issue. Driving safety is a controversial issue without clear guidelines in this population, and specific recommendations are often left to the careful discretion of physicians. There is a small but important body of literature looking at the effects that fatigue in PD has on driving. One study assessed the effects of auditory-verbal distraction on driving performance in PD, showing that drivers with PD made more errors

during baseline and with distraction than did their counterparts without the disease.[35] In this study, daytime sleepiness predicted worsening of driving due to distraction. Another study questioned PD patients about occurrences of sudden onset of sleep at the wheel (SOS).[36] Their alarming results showed that of the patients holding a driver's license, 15% had experienced SOS at the wheel in the past 5 years, and in 11% of cases, the episode led to an accident. The risk of accidents in this study was correlated with an increased score on the Epworth Sleepiness Scale (ESS).

Parkinson Disease

When evaluating already-diagnosed PD patients, it is important not to allow their motor symptoms, including bradykinesia, resting tremor, rigidity, and postural instability, to monopolize an office visit. Studies have shown that nonmotor symptoms of PD, such as fatigue, can have just as negative an impact on QoL as motor symptoms.[37] It is also important to keep in mind that there is no clear correlation between the severity of motor symptoms and the presence or severity of fatigue, so the clinician must ask about nonmotor symptoms even in PD patients without severe motor symptoms. There is evidence that the presence of nonmotor symptoms may actually predict the development of PD. In fact, fatigue is usually encountered early in the disease, often before an official diagnosis of PD is made.[38]

It is well known that patients with PD already walk at a slower speed, have increased episodes of fall, and have less of an ability to multitask while walking than those without the disease. Contributing to this body of knowledge, 1 study showed that performance of additional tasks while walking resulted in a reduction of walking speed and mean step length in PD patients over the general population.[39] Physical fatigue showed a significant relationship with gait speed in this study; however, it was balance that accounted for most of the variance in walking speed. Another study found that increased levels of fatigue were associated with decreased levels of leisure physical activity, lower frequency of vigorous physical activity, and less time performing ADLss.[40] This relationship between activity and fatigue in PD patients remains unclear, however. One study showed that although PD patients experience significantly greater levels of fatigue than those of controls for a given amount of physical activity, this was not associated with a decrease in physical activity when given the opportunity.[41] These data underscore the fact that an assessment of physical activity level and exercise tolerance should be part of every fatigue evaluation.

Stroke

Assessment of fatigue in post-stroke patients is perhaps the most difficult of all neurologic entities because many patients will have trouble distinguishing peripheral fatigue from muscle weakness secondary to the stroke. Careful use of language and good communication are especially important while conducting this interview.

Lynch and colleagues[42] propose case definitions of post-stroke fatigue, which correlated well with substantially higher fatigue scores on 4 common FSSs. They differentiated between patients in the community and hospitalized patients. Their proposed case definition for post-stroke fatigue in community patients is ''Over the past month, there has been at least a 2-week period when patient has experienced fatigue, a lack of energy, or an increased need to rest every day or nearly every day. This fatigue has led to difficulty taking part in everyday activities.''

It is important not to neglect the possibility of post-stroke fatigue in patients who have had mild strokes. Carlsson and colleagues[43] showed that after mild stroke involving minimal or no motor or cognitive impairments, 75% of their subjects still stated that their stroke affected everyday life. Astheno-emotional disorder (AED),

with fatigue being the most important symptom, was found in 72% of the sample. Carlsson and colleagues[44] went on to further characterize AED the following year and concluded that although fatigue was a pervasive element of this syndrome, it was often hidden to others. This finding highlights the importance of asking about this symptom during office visits.

Traumatic Brain Injury

In the assessment of fatigue after TBI, high yield correlates that require evaluation and treatment include sleep disturbance, hormonal disorders, and pain.

Insomnia, or difficulty initiating or maintaining sleep, is reported with a frequency of 27% to 70% or higher in those with higher frequencies early post injury.[45,46] Disordered sleep can have adverse behavioral, physical, and cognitive consequences. Endocrine dysfunction has been shown to be as high as 59% after TBI.[33] Growth hormone deficiency and hypogonadism are associated with decreased bone mineral densities, aerobic capacity, muscle strength, lower QoL, and cognitive impairments as well as fatigue.[34] The relationship between fatigue and neuroendocrine dysfunction is still evolving.

Scales

Several scales are available to help quantify the magnitude and impact of fatigue in general. Some of the more commonly used scales include the FSS (see **Table 3**), the ESS, the FIS, and the Modified Fatigue Impact Scale (MFIS). In the FSS, the patient is asked to rate 9 statements about fatigue on the degree of agreement, and then the score is averaged. People with depression alone score about 4.5, but people with fatigue related to multiple sclerosis (MS), for example, average about 6.5. The ESS measures the likelihood of a subject dozing during certain mundane daily activities, such as watching television or being a passenger in a car ride lasting for 1 hour. The test subjects must rate each activity based on how likely they feel they would be able to doze off while engaged in that activity. The FIS is a 40-item questionnaire that separates functional categories into physical, cognitive, and psychosocial subsets. Each question is rated 1 to 4. The MFIS is a shorter, 21-item derivative of the FIS and has most frequently been used in the MS population.

One possible reason for the slow pace of research on fatigue in PD is the lack of simple tools available to measure fatigue in this population. The Parkinson Fatigue

Table 3
Fatigue severity scale

Each statement is rated 1 to 7. 1 indicates strong disagreement, and 7 indicates strong agreement
1. My motivation is lower when I am fatigued.
2. Exercise brings on my fatigue.
3. I am easily fatigued.
4. Fatigue interferes with my physical functioning.
5. Fatigue causes frequent problems for me.
6. My fatigue prevents sustained physical functioning.
7. Fatigue interferes with carrying out certain duties and responsibilities.
8. Fatigue is among my 3 most disabling symptoms.
9. Fatigue interferes with my work, family, or social life.

Scale (PFS) attempts to fill that niche by providing a quick and reliable tool physicians can use to assess fatigue, specifically in PD patients. The PFS is a 16-item questionnaire arising from statements made by PD patients with fatigue, such as, ''I get tired more quickly than other people I know,'' and ''Everything I do is an effort.'' Although the full scope of this scale's utility is yet to be determined, the PFS will certainly facilitate future research on this topic.

There are 4 scales that are commonly used to measure post-stroke fatigue: The Fatigue Assessment Scale (FAS), the general subscale of the Multidimensional Fatigue Symptom Inventory, the fatigue subscale of the Profile of Mood States, and the Brief Fatigue Inventory. A recent comparison of these fatigue scales determined that although all 4 were valid and feasible to use in stroke patients, the FAS was most highly recommended, because it had the best test-retest reliability.[47] The FAS is a 10-item, self-administered questionnaire consisting of statements describing aspects of fatigue, which the subject must rate according to their agreement. Examples include ''Physically, I am exhausted,'' and ''I have problems thinking clearly.''

The Newcastle Stroke-Specific Quality of Life Measure (NEWSQOL) was recently developed to specifically measure QoL in stroke patients across 11 domains.[48] Among these domains are sleep, cognition, and fatigue. The NEWSQOL is an interviewer-administered multiple-choice questionnaire, with questions varying according to domain. Examples of the fatigue questions include ''Do you doze off during the day because of the stroke?'' and ''Because of the stroke, are there days when you feel you could sleep all the time?'' The subjects are then asked to respond with, ''no, occasionally, sometimes, or always.'' This scale has shown evidence of reliability and validity and is a promising tool for quantifying QoL after stroke.

The Global Fatigue Index is a widely used measure of fatigue in multiple populations including TBI.[31] It is derived from 15 of 16 items of the Multidimensional Assessment of Fatigue (MAF).[49] The MAF covers 4 domains: severity, distress, impact on ADLs, and timing.

TREATMENT

The treatment of fatigue can be broadly divided into pharmacologic and nonpharmacologic interventions. Pharmacologic interventions include medications, hormone replacement, and herbal remedies. These are discussed below. Nonpharmacologic treatments include patient and caregiver education, psychological approaches, osteopathic manipulative therapy, and physical exercise.

Pharmacologic Interventions

Several classes of medications have been demonstrated to be effective for the treatment of fatigue after neurologic disease or injury. Primarily among these are the classic neurostimulants, other wakefulness-promoting agents, and antidepressants. Many anecdotal reports exist for other medications for fatigue. However, as with most issues regarding the pharmacologic treatment of symptoms following neurologic disorders, there is scant objective research studying the effects these medications have on fatigue. The information below is not intended to be a comprehensive list but rather to offer some broad information about typical prescribing practices for this problem.

Classic neurostimulants are probably the most widely studied medications for fatigue following a multitude of disorders, including cancer, PD, TBI, and stroke. In a comparison study with sertraline, methylphenidate was found to be more efficacious for daytime sleepiness on the ESS in patients with TBI.[50] Another recent study showed

that methylphenidate improves fatigue scores on the FSS in PD following a 6-week treatment period.[51] An additional benefit of methylphenidate in the PD population is its ability to potentiate the effects of L-dopa, thus increasing the "on" time.[52] Other neurostimulants that have been used clinically include dextroamphetamine, pemoline, and mixed amphetamine-dextroamphetamine salts. Most of these medications have broad effects of increasing the activity of, or stimulating receptors of, endogenous adrenergic or cholinergic receptors. This has a general effect on patient's subjective feeling of wakefulness and may also have other cognitive effects, such as improving attention and concentration.

Modafinil has been widely used as an agent to combat fatigue. Modafinil is indicated for the treatment of narcolepsy and daytime somnolence. Although anecdotal reports suggest that it is helpful in treating fatigue in TBI, a controlled study by Jha and colleagues[53] failed to show consistent patterns of relief of fatigue in a brain-injured population. Modafinil has also been studied in PD, although in a recent study it failed to significantly improve excessive daytime sleepiness in this population.[54] Despite this lack of scientific evidence, it remains a widely used drug for treatment of fatigue in stroke, TBI, and PD.

Dopaminergic medications, especially amantadine, have been used as medications for arousal following TBI, PD, MS, and stroke. Amantadine has garnered significant research attention in the MS population and has been shown to be clinically effective in combating fatigue when compared with placebo.[55] Dopamine agonists are also becoming increasingly more important in the treatment of PD, though there is no clear evidence of their effect on fatigue. In fact a recent study found that fatigue in PD was not influenced by dopamine agonists.[56] Case reports have found amantadine to be useful in mutism, apathy, inattention, and impulsivity after TBI. Amantadine appears to have positive effects on arousal, agitation, and cognition after TBI but studies of its use in fatigue after TBI are lacking.[57]

Levodopa is likely the most effective medication in controlling the motor symptoms in PD, yet its effects on fatigue are not well studied. There is 1 study, however, that indirectly demonstrates that levodopa is actually effective in reducing physical fatigue as measured by finger tapping, a commonly used measure of PD severity.[58]

Traditional antidepressant medications, especially selective serotonin reuptake inhibitors, have also been medications of interest. Paroxetine has been reported as an agent to combat fatigue following TBI, MS, and stroke; however, its use has not been strongly identified for the treatment of fatigue in the absence of depressive symptoms. In addition, in that class, a recent double-blind, placebo-controlled study done in South Korea showed that although decreasing post-stroke depression, Fluoxetine was not effective in lessening post-stroke fatigue.[59]

The tricyclic antidepressants, mainly amitriptyline, have also been reported to be effective for fatigue, although the effects noted are more likely a result of improved sleep patterns and decreased vegetative symptoms of depression, rather than the true dampening of the primary effects of fatigue. Like Paroxetine, their use to treat fatigue in the absence of depression has not been formally assessed. Due to their propensity to cause increased confusion, use of tricyclic antidepressants in patients with cognitive impairment must be handled carefully, and routine use in this population is not typically recommended.

Atomoxetine is an agent that has also been promoted as a medication for arousal. Although most clinicians would associate this medication with the traditional neurostimulants, it is more similar pharmacologically to antidepressant drugs. Although no study has been conducted to evaluate its effects as a treatment for combating fatigue, anecdotal reports suggest that it may have a beneficial effect at higher doses.[60]

In patients with fatigue complicated by depression, the nature of their symptoms should be taken into account when choosing an appropriate treatment. When 1 symptom predominates, management should be tailored to treat that symptom along with the depression. For example, Trazodone can help with sleep initiation as seen with depression, whereas stimulants would be appropriate when fatigue or impaired concentration predominates.

Recent research has focused on endocrine abnormalities, especially growth hormone deficiency, as a potential cause for fatigue following TBI. However, the research has had mixed results. To date, a controlled study evaluating the effects of growth hormone replacement therapy on fatigue has not been completed. There is also some evidence that men with PD may have testosterone deficiency, though a study in 2006 that looked at testosterone therapy in this population found that the intervention had no effect on sleep or fatigue.[61]

Many herbal preparations have been promoted for use in fatigue. Among these are Ginkgo biloba, St. John's wort, and Panax ginseng. Although there is mounting anecdotal evidence that these herbal preparations are helpful in fatigue, there is no clear evidence. Caffeine, also considered a herbal remedy due to its widespread over-the-counter use, has been promoted as an agent to combat fatigue, both in its typical liquid form and as a tablet. Although caffeine is a potent stimulant, it can also cause unwanted side effects, such as anxiety and difficulty sleeping, so its recommended use should be in moderation only.

Nonpharmacologic Interventions

Although there is little literature on its efficacy, patient and caregiver education has become perhaps the most important rehabilitation intervention we have for combating fatigue. Patients should be educated on the underlying causes of fatigue and their potential impact and then be taught practical strategies to minimize and manage their symptoms (See **Table 4**.) This will give patients a sense of control and help diminish their frustration. Cognitive-behavioral therapy, which is based on teaching patients how to manage thoughts and behaviors, has been successful in decreasing fatigue as well.

Table 4
Behavioral modifications to minimize fatigue

1. Take frequent rests
2. Schedule breaks
3. Break up tasks
4. Avoid multitasking
5. Prioritize tasks
6. Delegate tasks
7. Focus on completing tasks rather than completing tasks quickly
8. Sleep hygiene strategies
9. Know side effects of medications
10. Do not operate heavy equipment or drive when fatigued
11. Recognize warning signs of fatigue
a. Irritability
b. Making mistakes
12. Custom-designed exercise protocol (when appropriate)

Post-stroke fatigue has significant impact on psychological and social functioning. A Polish study investigating the psychological aspects of stroke patients with fatigue showed that the patient's style of coping with stress can be predictive of fatigue.[62] Specifically, patients who use emotional-style coping showed a lower level of fatigue than did those who used task-oriented coping. This concept has implications for the development of psychologically based therapies focused on stress management.

Some traditional osteopathic techniques can also help treat fatigue in the neurologic population. One of the 4 central principles of osteopathic philosophy is that structure and function are reciprocally inter-related.[63] After a neurologic event such as a stroke, however, the function of key structures often becomes impaired, increasing the energy requirements for ADLs and the fatigue burden on a patient. Osteopathic physicians can employ various techniques to restore alignment and function, which may decrease the energy costs associated with normal activities, thus decreasing fatigue. There are also cranial manipulation techniques that have been successful anecdotally in decreasing fatigue and improving arousal.

Exercise training is another promising strategy for decreasing both physical and cognitive fatigue in persons with neurologic disorders. Because fatigue will intuitively diminish the amount of daily physical activity a person will engage in, it can hasten deconditioning and promote a further decrease in exercise tolerance. Onset of this cycle is a risk encountered by patients after the structured phase of their rehabilitation has ended. Patients should be educated as to the benefits of exercise and what precautions they should adhere to. Several studies have shown that a modest cardiovascular exercise routine can decrease overall fatigue in patients with PD. As with MS and diseases of the neuromuscular junction, patients and therapists should be cautioned not to exercise to the point of exhaustion, as this may have a paradoxical effect and actually increase overall fatigue. Emphasis should be on maintenance of function while decreasing general debility. Maximizing passive and active range of motion is critical to any muscular fitness program, and programs should be tailored to the appropriate neurologic and functional deficits at hand.

Aerobic exercise is well known to improve cognition, mood, and QoL in the general population. Cognitive functioning demonstrated improvement on neuropsychological tests for those individuals who were aerobically trained, compared with that of those who received strength and flexibility training as well as with that of those who did not exercise. Although research examining the effects of aerobic exercise on individuals with TBI, stroke, and PD is limited, exercise has been shown to be effective in improving cognition and depression in individuals with cancer, MS, fibromyalgia, dementia, chronic fatigue syndrome, and chronic obstructive pulmonary disease. In addition, studies have found aquatic therapy to result in strength gains. The gravity-eliminating conditions are beneficial to patients with neurologic weakness as well as many musculoskeletal conditions.

SUMMARY

Fatigue is a serious, QoL-limiting symptom of many neurologic conditions. Physicians should be thorough and consistent in their assessment for this problem and not let motor symptoms monopolize an office visit. Although the use of pharmacology to treat this problem has predominantly only anecdotal evidence of efficacy, several nonpharmacologic interventions may prove helpful. The directions of future research should aim to create clear treatment guidelines using the pharmacologic agents available.

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