

## Poststroke Fatigue: Emerging Evidence and Approaches to Management A Scientific Statement for Healthcare Professionals From the American Heart Association

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**Abstract**—At least half of all stroke survivors experience fatigue; thus, it is a common cause of concern for patients, caregivers, and clinicians after stroke. This scientific statement provides an international perspective on the emerging evidence surrounding the incidence, prevalence, quality of life, and complex pathogenesis of poststroke fatigue. Evidence for pharmacological and nonpharmacological interventions for management are reviewed, as well as the effects of poststroke fatigue on both stroke survivors and caregivers. (*Stroke*. 2017;48:e159-e170. DOI: 10.1161/STR.000000000000132.)

**Key Words:** AHA Scientific Statements ■ disease management ■ fatigue ■ health care ■ stroke ■ therapeutics

Fatigue is a common and often debilitating sequela of both ischemic and hemorrhagic stroke. Globally, there are ≈33 million stroke survivors,<sup>1</sup> and at least half of these individuals experience fatigue.<sup>2</sup> The goal of this scientific statement is to provide an international perspective on the current understanding of the incidence, prevalence, quality of life (QOL), and complex pathogenesis of poststroke fatigue (PSF). Potential pharmacological and nonpharmacological approaches to management are explored, as well as the effects of PSF on both stroke survivors and caregivers.

### Methods

A critical analysis of published quantitative research and guidelines on fatigue after stroke was conducted. Databases searched included PubMed, CINAHL, MEDLINE, and PsycINFO. Search terms included *poststroke fatigue*, *fatigue*, *chronic fatigue*, *incidence*, *prevalence*, *caregiver*, *biomarker*, *etiology*, *intervention*, *patient education materials*, and *pharmacological interventions*. Analysis involved reviewing titles, abstracts, and full-text articles for relevance to the topic with

the following inclusion criteria: (1) written in the English language; (2) involved human subjects; (3) published from January 2000 through March 2016; (4) used a quasi-experimental, experimental, observational research or randomized clinical trial (RCT) design; (5) involved the subject of fatigue after ischemic or hemorrhagic stroke; and (6) was conducted during any part of the stroke continuum of care (acute hospitalization, inpatient rehabilitation, homecare, long-term care). Additional quantitative research was identified from the reference lists of publications found with the search criteria listed above.

### Overview of PSF

There are many ways in which fatigue is defined and measured. These varying definitions affect the estimates of the incidence and prevalence of PSF. None of the current definitions of PSF are specific to stroke. The most commonly used definitions include the following:

- “Subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities.”<sup>3</sup>

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- “A feeling of early exhaustion developing during mental activity, with weariness, lack of energy, and aversion to effort.”<sup>4</sup>
- “Sense of exhaustion, lack of perceived energy or tiredness, distinct from sadness or weakness.”<sup>5</sup>

These definitions may include both physical and mental energy or be limited only to mental activity. In recent years, fatigue has come to be distinguished from symptoms of depression, but there is no consensus among clinicians or researchers on one definition of PSF.

Given the many and differing definitions of fatigue, estimates of its incidence (first reported fatigue related to stroke onset) and prevalence (number of stroke survivors experiencing fatigue at any given point in time) vary. Reliable reports of incidence are not available in the literature. One of the earliest studies on PSF estimated the incidence to be 75%.<sup>6</sup> This study, however, did not provide a definition of fatigue and evaluated only 44 individuals who were 3 to 24 months after stroke and thus likely gives a better estimate of prevalence than incidence. In reviews, prevalence estimates for PSF range from 23% to 77%.<sup>7–11</sup> Because of the varying definitions and scales used, meta-analyses are limited. One systematic review of individuals with transient ischemic attack and minor stroke estimated the pooled prevalence of PSF to be between 23% and 34%.<sup>7</sup> Another systematic review that included 49 studies reported prevalence rates between 25% and 85%.<sup>12</sup> Although no data were reported on stroke severity, with >3000 subjects represented in the review, it can be assumed that more than transient ischemic attacks and minor strokes were represented, which could be one possible explanation of the wide prevalence.

Lynch and colleagues<sup>13</sup> created case definitions of PSF based on interviews with stroke survivors in the initial and recovery stages. These definitions are as follows:

*For hospital patients: Since their stroke, the patient has experienced fatigue, a lack of energy, or an increased need to rest every day or nearly every day. And this fatigue has led to difficulty taking part in everyday activities (for inpatients this may include therapy and may include the need to terminate an activity early because of fatigue)... For community-dwelling patients: 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. And this fatigue has led to difficulty taking part in everyday activities.*<sup>13</sup>

With this definition, the prevalence of PSF was estimated to be 40% after stroke.<sup>13</sup> PSF was associated with female sex and emotional distress.<sup>13</sup>

In summary, there is no consensus among clinicians or researchers on one best definition of PSF. A consensus definition would lead to more accurate estimates of incidence and prevalence.

### Effect of PSF on QOL

PSF exerts a negative impact on a patient's daily activities such as decreased participation in physical activities<sup>14</sup> and rehabilitation.<sup>15</sup> Consequently, patients with PSF are reported to have poor neurological recovery and increased mortality.<sup>16</sup> Patients

with PSF have difficulty in resuming social, familial, and professional activities<sup>4</sup> and have low QOL scores.<sup>16,17</sup> The association between PSF and daily activity is mediated partly by associated depression or neurological deficits, even after controlling for depression.<sup>18</sup> Fatigue is a significant factor associated with low health-related QOL.<sup>17</sup> For example, one study reported that although PSF was strongly associated with low scores on the physical health composites of QOL, depression was related to low scores on nonphysical composite scores.<sup>17</sup>

There is consensus among clinicians, researchers, patients, and caregivers that PSF is important because it affects QOL.<sup>14,19</sup> It is suggested that QOL measures be consistently included in studies of PSF.

### The Multidimensional Aspects of PSF

Evidence indicates that the cause of PSF is multidimensional. Studies have investigated the interactions between demographic factors, neurological/physical deficits, medical comorbidities, smoking, medications, sleep disturbances, pain, prestroke fatigue, depression and anxiety, cognitive impairment, and PSF.

#### Demographic Factors

Seven studies reported that PSF is associated with old age,<sup>16,20–25</sup> and 8 studies reported that PSF was associated with being female.<sup>17,19,20,25–29</sup> Determining the demographic contributions to PSF prevalence is complicated because the prevalence of fatigue is higher in older individuals and women in general. It is important to note that most of the reported studies did not include control subjects (ie, age- and sex-matched individuals without stroke).

Educational level does not appear to be associated with PSF.<sup>14,21,26–28,30–34</sup> PSF may be less common in married people (compared with single people) and in those living at home (compared with those living in an institution),<sup>16</sup> but these findings have not been widely replicated.<sup>20,21,24,30</sup> Patients with PSF are more often unemployed or more likely to change their jobs than those without PSF,<sup>14,21</sup> but cause-and-effect relationships remain unclear. Patients with PSF are less likely to return to their previous work.<sup>21,22,29,34</sup>

#### Neurological/Physical Deficits

Physical impairment and functional deficits are important contributors to PSF.<sup>14,16,21,35,36</sup> Patients who suffer a stroke experience worse fatigue than patients who suffer a transient ischemic attack.<sup>16,37</sup> Infarct volume and functional recovery (as determined by the modified Rankin Scale) do not appear to predict PSF,<sup>38</sup> but because studies generally exclude patients with strokes leading to a decreased level of consciousness or severe aphasia,<sup>14,39</sup> these results must be interpreted with caution. In many of these studies, at least some of the PSF can be attributed to associated depression; for instance, an association between physical disability and PSF in the subacute stage was lost after controlling for the effects of depression and anxiety in the long-term stage.<sup>22,30</sup> Motor dysfunction,<sup>40,41</sup> speech disturbances (aphasia or severe dysarthria),<sup>14,16</sup> facial palsy,<sup>35</sup> and arm weakness<sup>35</sup> are all related to PSF. Systematic investigations of the impact of the multiple diverse neurologic deficits on PSF, however, are rare.

### Medical Comorbidities, Smoking, and Medications

Many patients who suffer a stroke have comorbid medical conditions such as hypertension, diabetes mellitus, heart failure, and kidney disease that may produce fatigue by themselves.<sup>42–44</sup> The influence of such diverse comorbidities on PSF has not been sufficiently investigated. One study reported that PSF was more common in stroke patients with either hypertension or hypotension,<sup>40</sup> but this finding was not replicated in other studies.<sup>14,17,26,45–48</sup> An association between diabetes mellitus and PSF was observed in 1 study<sup>21</sup> but not in 7 other studies.<sup>14,16,26,27,45,46,48</sup> The presence of heart disease was related to PSF in 2 studies<sup>17,27</sup> but not in 4 others.<sup>14,47,49,50</sup> Generally, cigarette smoking is not considered a risk factor for PSF, as reported in 3 studies.<sup>21,24,27</sup> One study reported that smoking cessation was associated with PSF in patients without depression,<sup>14</sup> suggesting that sudden abstinence of smoking may contribute to PSF.<sup>51</sup>

Medications that are commonly used in patients with stroke such as sedatives,<sup>27</sup> antidepressants,<sup>45,52</sup> and hypnotics<sup>17</sup> may cause fatigue. Although studies have not implicated medications as a major cause of PSF,<sup>14,34,47</sup> the potential association should not be ignored.

Eating difficulties related to lower cranial nerve palsy, poor attention, and loss of appetite<sup>53–55</sup> and malnutrition<sup>56</sup> are common in patients who have had a stroke. Although patients with poststroke eating difficulties often report feelings of depression<sup>56,57</sup> and a lack of energy,<sup>58</sup> the association with PSF has not been appropriately studied. One study reported that patients with PSF more often had decreased appetite than those without,<sup>14</sup> suggesting a possible association.

### Sleep Disturbances

Sleep-related breathing disturbances (apnea-hypopnea index  $\geq 10$ ) occur in 50% to 70% of stroke patients.<sup>59</sup> Hypersomnia and excessive daytime sleepiness are observed in 27% of patients,<sup>59</sup> whereas insomnia occurs in 57% of patients in the early months after stroke.<sup>60</sup> PSF is associated with sleep disturbances<sup>21,26,31,35,50,61–63</sup> and daytime sleepiness<sup>46,63–65</sup> in many studies, but these associations have not been consistently demonstrated.<sup>20,24,49</sup> The role of sleep disturbances as they pertain to PSF thus remains uncertain.

### Pain

Poststroke pain impairs patient function<sup>66</sup> and may cause PSF. Two studies reported an association between poststroke pain and PSF,<sup>67,68</sup> but this association was not confirmed in 2 other studies.<sup>33,35</sup> One study reported that fatigue was present in 53% of patients with central poststroke pain and in 61% of those with nociceptive pain and that fatigue was associated with both conditions.<sup>66</sup> Although fatigue, pain, and depression are related conditions, poststroke pain seems to be more closely associated with fatigue than depression.<sup>52,69</sup> Pain may somehow be involved in the persistence of fatigue over time.<sup>26</sup>

### Prestroke Fatigue

Several studies report an association between prestroke fatigue and PSF.<sup>14,16,27,31,45,70</sup> One study reported that in patients with prestroke fatigue, the severity of fatigue increased after stroke,

and PSF was more severe than in patients without prestroke fatigue.<sup>14</sup> Such studies are inherently biased, however, because prestroke fatigue is assessed in a retrospective manner. Prestroke fatigue has been reported to be a risk factor for stroke,<sup>71–73</sup> and patients with prestroke fatigue are more likely to have medical comorbidities than those without prestroke fatigue.<sup>14</sup> It is possible that prestroke fatigue may, at least in part, be attributed to premorbid medical conditions that increase the risk of stroke such as diabetes mellitus or heart disease.

### Depression and Anxiety

Although patients with PSF are often depressed,<sup>4,14,18,31,62,74</sup> the relationship between PSF and depression is difficult to evaluate because many of the tools for assessing depression contain items about fatigue. Fatigue is one of the somatic symptoms that have high discriminative power for predicting poststroke depression.<sup>75</sup> The impact of depression on PSF may differ according to the stage of stroke. Although stroke severity and neurological disability lead to exertional fatigue in the early stage of stroke,<sup>22</sup> depression seems to play a more important role in the long-term stages of stroke.<sup>76</sup> Many studies report an association between PSF and anxiety,<sup>13,16,21,22,30,32,45,46,77</sup> although this association is not uniformly replicated.<sup>28,78</sup> Furthermore, even in those studies that find an association between anxiety and fatigue, the association weakens after controlling for depression.<sup>10</sup> Moreover, poor coping styles are associated with PSF.<sup>20,79</sup>

Although some patients with PSF have depression, others do not.<sup>4,14,16,21,39,40</sup> There are reasons to believe that PSF and poststroke depression are distinct clinical entities. First, PSF is more prevalent than poststroke depression; thus, there are patients with fatigue who are not depressed. One study found that only 38% of patients with PSF were depressed.<sup>40</sup> Second, pharmacological therapy for poststroke depression is ineffective at treating PSF, although it improves depression.<sup>80,81</sup> Finally, PSF appears to be related to tissue injury given that fatigue is more common in individuals with infarction who completely recover, whereas “poststroke” depression occurs similarly among individuals with transient ischemic attack and no tissue injury and those with infarction and complete recovery.<sup>39</sup> This suggests that PSF occurs as a result of biochemical changes precipitated by tissue injury, whereas depression is more likely related to the psychological aspects of the event.

### Cognitive Impairment

Most studies fail to find an association between cognitive impairment and PSF.<sup>21,30,62,77,78</sup> Many of these studies use the Mini-Mental State Examination, a test of global cognitive ability with limited sensitivity and specificity.<sup>82</sup> Moreover, patients with severe cognitive impairment or aphasia are generally excluded in studies of PSF.<sup>14,37</sup>

Evidence suggests that cognitive impairment, mental slowing, and difficulty in concentration may contribute to the decreased mental energy aspect of PSF. A cross-sectional study showed that attention deficits are associated with PSF.<sup>22</sup> Others found that processing speed was correlated with mental fatigue at 3 and 6 months after stroke<sup>34,83,84</sup> and that memory dysfunction was related to PSF at 6 months after stroke.<sup>34</sup> Thus, although PSF is not likely to be associated with general

cognitive impairment, dysfunction in some parts of cognition (attention, executive function, memory, etc) may be related to a certain component (mental) of PSF.

In conclusion, more research with rigorous designs is suggested to more fully understand the complex interactions among demographic factors, neurological/physical deficits, medical comorbidities, smoking, medications, sleep disturbances, pain, prestroke fatigue, depression and anxiety, cognitive impairment and PSF. Furthermore, studies that measure the baseline of stroke survivors before the stroke (ie, fatigue or general state of fitness) in an unbiased manner are needed to investigate how these factors play into PSF.

### Pathophysiology of PSF

The pathophysiology of PSF is unknown. Factors discussed include altered cortical excitability, lesion location, inflammation, immune response, and genes.

#### Altered Cortical Excitability and Lesion Location

Lines of inquiry suggest that PSF is centrally mediated and not a manifestation of neuromuscular dysfunction. Some researchers theorize that PSF may be associated with disturbances in cortical excitability. One study examining patients after stroke with minimal neurological deficits<sup>85</sup> found that PSF was explained, in part, by higher motor thresholds measured with transcranial magnetic stimulation. It was suggested that low excitability of both corticospinal output and its facilitatory synaptic inputs from cortical and subcortical sites may contribute to PSF. Some researchers believe that disruption of crucial central pathways leads to the perception of fatigue, although there are few data to support this point of view.

There is little convincing evidence that links PSF with a specific lesion location.<sup>77,86</sup> Some studies suggest an association between PSF and subcortical infarcts<sup>26,74,87,88</sup> and infratentorial infarcts.<sup>30,77</sup> Physiologically, PSF appears to be related to low excitability of corticospinal output and facilitatory synaptic inputs from cortical and subcortical sites.<sup>85</sup> Impaired motor control, as assessed by the Fugl-Meyer test, seems to be predictive of PSF.<sup>41</sup>

#### Inflammation, Immune Response, and Genes

A role for inflammation in the genesis of PSF is implicated by several key observations. First, fatigue is a common symptom in patients with immune-mediated diseases.<sup>89–93</sup> Second, fatigue occurs in otherwise healthy individuals who develop infections.<sup>94,95</sup> Third, administration of proinflammatory cytokines to healthy individuals leads to the perception of fatigue.<sup>96</sup> Finally, modulation of inflammation with cytokine antagonists improves fatigue in several different diseases.<sup>97–102</sup>

Actual data to support a role for inflammation in PSF are more limited. Most attempts at identifying biological markers of PSF are based on small patient cohorts and have serious methodological issues. For example, increased interleukin (IL)-1 $\beta$ , decreased IL-1 receptor antagonist, and decreased IL-9 at stroke onset have been associated with later onset of PSF.<sup>47</sup> These data, however, are based on a cohort of 45 patients and were not controlled for initial stroke severity, age, or other important covariates. More fundamentally, however, if fatigue

is caused by a cytokine, that cytokine should be measured at the time the fatigue is assessed, not at the time of the acute stroke.

When biomarker assessment is done concomitantly with fatigue assessment, C-reactive protein is variably reported to correlate with PSF.<sup>103–105</sup> These studies are quite small, however, and larger studies controlling for baseline comorbidities and stroke characteristics are needed to adequately address the relationship between C-reactive protein and PSF.

The assessment of genetic contributions to PSF is relatively immune to timing, and it appears that single-nucleotide polymorphisms in genes that modulate inflammation are related to PSF. Specifically, PSF is associated with the C allele of *IL1RN* rs4251961.<sup>38</sup> This single-nucleotide polymorphism is commonly associated with a decrease in IL-1 receptor antagonist and an increase in proinflammatory cytokines such as IL-1 $\beta$  and C-reactive protein.<sup>106,107</sup> In addition, functional polymorphisms in the gene for toll-like receptor 4 that render toll-like receptor 4 less responsive to its ligands are associated with less PSF.<sup>38</sup>

Another possible biochemical link to PSF is glutamate.<sup>108</sup> In a small study, plasma glutamate levels in the week after minor stroke correlated with the degree of fatigue at 6 months after stroke.<sup>109</sup> Glutamate is an excitatory neurotransmitter that is released after stroke,<sup>110</sup> but inflammation leads to major changes in the metabolism of neurotransmitters.<sup>111–113</sup> These data suggest that most postulated causes of PSF are related and share a common denominator in the immune system.<sup>114–116</sup> Additional biomarkers measured in the acute phase and linked to the later development of fatigue include glucose<sup>47,48</sup> and homocysteine.<sup>48</sup> Table 1 provides a synopsis of biomarker research that has been conducted to investigate PSF.

Given the limitations of research done to date, it is apparent that definitive biomarkers for PSF have not been identified. Furthermore, it seems unlikely that there will be a single biomarker linked to PSF. The data suggest, however, that perturbations in the immune response after stroke may contribute to the perception of PSF.

### Clinical Implications

Areas of importance to clinicians include patient assessment and pharmacological and nonpharmacological interventions. In the realm of patient assessment, there is concern about the best tool to measure patient reports of PSF. The pharmacological and nonpharmacological management of PSF is complex.

#### Patient Assessment

Many tools have been used to measure PSF. All of the instruments were originally developed to measure fatigue in conditions other than stroke. Measures that include a question about general weakness may not be valid for stroke because weakness after a stroke is generally attributable to hemiparesis rather than to fatigue.<sup>117</sup> Table 2 provides a description and assessment of the reliability and validity of common fatigue measures and examples of studies in which these measures have been used with patients after stroke.<sup>17,117–120</sup>

Although clinicians acknowledge the need to assess for PSF, there is no consensus on which tool to use and when to use it. A systematic review reported that the Fatigue Severity Scale has been used in 24 studies of PSF (Table 2).<sup>12</sup> The review of 24

**Table 1. Summary of Biomarker Research Conducted to Investigate PSF**

Biomarker	Biomarker Description/Properties	Timing of Blood Sample	Fatigue Scale	Relationship to PSF	n	Comments
Glutamate	Excitatory amino acid/neurotransmitter, immunomodulator	At acute stroke (within 1 wk)	Chalder Fatigue Scale	Increased PSF at 6 mo after stroke	38	Small cohort; published only in abstract form <sup>109</sup>
IL-1 $\beta$	Proinflammatory cytokine	At acute stroke (within 72 h)	FSS	Increased PSF at 6 mo after stroke	45	Small cohort; not controlled for stroke severity, depression <sup>47</sup>
IL-1ra	Endogenous inhibitor of IL-1; inhibits inflammation	At acute stroke (within 72 h)	FSS	Decreased PSF at 12 mo after stroke	45	Small cohort; not controlled for stroke severity, depression <sup>47</sup>
IL-9	Proinflammatory T-cell cytokine	At acute stroke (within 72 h)	FSS	Decreased PSF at 12 mo after stroke	45	Small cohort; not controlled for stroke severity, depression <sup>47</sup>
Glucose	Blood sugar	Concomitant with PSF assessment (10–15 d after stroke onset)	FSS	Increased PSF in the 10–15 d after stroke onset	214	Early time frame for determining the presence of PSF; not controlled for stroke severity <sup>48</sup>
		At acute stroke (within 72 h)	FSS	Increased PSF at 6 and 12 mo after stroke	45	Small cohort; not controlled for stroke severity, depression <sup>47</sup>
Homocysteine	Amino acid; elevated levels associated with vascular disease	Concomitant with PSF assessment (10–15 d after stroke onset)	FSS	Increased PSF in the 10–15 d after stroke	214	Early time frame for determining the presence of PSF; not controlled for stroke severity <sup>48</sup>
CRP	Nonspecific marker of inflammation	Concomitant with PSF assessment	FAS	Increased PSF in the year after stroke	40	Small cohort <sup>104</sup>
		Concomitant with PSF assessment	FAS	Increased PSF in the 3 mo after stroke	28	Significant only after excluding those with prestroke fatigue and mood disorders; small sample size <sup>103</sup>
		Concomitant with PSF assessment	FAS	No association in the year after stroke	65	Part of a larger study <sup>48</sup>
VCAM-1	Adhesion molecule expressed on blood vessels; binds lymphocytes	Concomitant with PSF assessment	FAS	Decreased PSF in the year after stroke	40	Small cohort <sup>104</sup>
<i>IL1RN</i> rs4251961 C allele	Gene for IL-1ra; C allele associated with decreased production of IL-1ra and increased inflammation	NA	FAS	Increased PSF in the year after stroke	39	Small sample size; no correlation with IL-1ra <sup>38</sup>
<i>TLR4</i> (1063 A/G [Asp299Gly] rs4986790 and 1363 C/T [Thr399Ile] rs4986791)	Cosegregating genes for TLR4; render TLR4 less responsive to inflammatory stimuli	NA	FAS	Decreased PSF in the year after stroke	39	Small sample size; few patients with polymorphisms <sup>38</sup>

CRP indicates C-reactive protein; FAS, Fatigue Assessment Scale; FSS, Fatigue Severity Scale; IL, interleukin-1; IL-1ra, interleukin 1 receptor antagonist; NA, not applicable; PSF, poststroke fatigue; TLR4, toll-like receptor 4; and VCAM-1, vascular cell adhesion molecule 1.

studies revealed that when PSF was measured varied widely, but several studies provided comparison data at 3 and 6 months.<sup>12</sup>

The link between PSF and depression is acknowledged in the national stroke guidelines from Scotland, which state that patients with PSF should be screened for depression, but there is no mention of exact frequency and timing.<sup>15</sup> Lynch and colleagues<sup>13</sup> created case definitions for PSF based on interviews with hospitalized and community-dwelling patients. These case definitions may be useful for clinicians.

In review, it is suggested that clinicians use the most commonly used scale, the Fatigue Severity Scale, or the case

definitions created by Lynch and colleagues<sup>13</sup> to screen for depression when assessing for PSF. It makes sense to assess at the time of discharge from acute care and then on a regular basis such as at 3 months, 6 months, and 1 year and then yearly. This will not only help with case finding but advance research and provide comparison data for these time points.<sup>12</sup>

### Pharmacological Intervention

As a result of the multifaceted nature of PSF, the pharmacological management of PSF is far from satisfactory. Ogden and colleagues<sup>121</sup> reported that tirilazad mesylate, a

**Table 2. Summary of Commonly Used Fatigue Measures**

Measure	Description	Reliability	Validity	Specific to Stroke
FAS	10-Item self-rating scale for how a person usually feels with a 5-point Likert scale from 1 (never) to 5 (always)	Cronbach $\alpha=0.58-0.62$ <sup>117</sup>	Construct validity=0.71 (<0.001), n=52 <sup>117</sup>	Systematic review reported FAS used in 4 studies of PSF <sup>12</sup>
Fatigue Impact Scale	Self-report measure of the presence and severity of fatigue and its impact on cognitive, physical, and psychosocial functions <sup>118</sup>	Internal consistency=0.93 <sup>119</sup>	Concurrent: sickness impact profile Discriminative: significant difference between scores of patients with MS and hypertensives <sup>119</sup>	Tested in 60 community-dwelling patients after stroke <sup>118</sup>
FSS	10-Item self-rating scale for how a person has felt in the past week using a 7-point Likert scale	Internal consistency=0.88-0.95 <sup>119</sup>	Construct: factor analysis using oblique rotation verified Convergent: Pearson correlation with MAF ( $r=0.74$ , $P<0.05$ ), VAS-F ( $r=0.37$ , $P<0.05$ ), and Rhoten Fatigue Scale ( $r=0.03$ , $P>0.05$ ) <sup>119</sup>	
Vitality scale of 36-item Short Form	4-Item self-rating scale for how a person has felt in the past 4 wk	Cronbach $\alpha=0.76-0.78$ <sup>117</sup>	Construct validity=0.58 (<0.001), n=55 <sup>117</sup>	Tested in 55 patients with stroke <sup>117</sup>
Multidimensional Fatigue Symptom Inventory	Total=16 items; 14 items=100 mm VAS; 2 items=multiple choice	Cronbach $\alpha=0.91-0.93$ <sup>117</sup>	Construct validity=0.47 (<0.001), n=55 <sup>117</sup>	Tested in 55 patients with stroke <sup>117</sup>
Fatigue domain from Profile of Mood States	6-Item self-rating scale for how a person has felt in the past week	Cronbach $\alpha=0.88-0.89$ <sup>117</sup>	Construct validity=0.75 (<0.001), n=55 <sup>117</sup>	Systematic review reported use in 1 study <sup>12,117</sup>

FAS indicates Fatigue Assessment Score; FSS, Fatigue Severity Scale; MAF, Multidimensional Assessment of Fatigue; MS, multiple sclerosis; PSF, poststroke fatigue; and VAS-F, Visual Analog Scale-Fatigue.

neuroprotective agent, was effective in treating fatigue in a randomized controlled trial. However, the generalizability of the study is limited because it included only female patients with subarachnoid hemorrhage and the method of allocation concealment was doubtful.<sup>121,122</sup>

Modafinil, a drug originally used for patients with hypersomnia or narcolepsy to promote wakefulness, relieved PSF in patients with brainstem-diencephalic strokes better than in patients cortical stroke.<sup>123</sup> The differential effect of modafinil in brainstem stroke may have been attributable to the fact that fatigue in these patients resulted from a dysfunctional reticular activating system. This study, however, was not placebo controlled, and the number of patients included was small (n=40).

An additional randomized, double-blinded, placebo-controlled trial of PSF treatment with 400 mg modafinil for 90 days was conducted.<sup>124</sup> Although the primary end point, the Multidimensional Fatigue Inventory-20 general fatigue score, did not differ between groups, the modafinil group obtained better scores on the Fatigue Severity Scale ( $P=0.02$ ), which was the secondary outcome. No serious adverse reactions were observed. The trial, however, was relatively small (41 patients included, 21 received modafinil) and must be interpreted as a pilot study.<sup>124</sup>

Other agents have been investigated. OSU6162 is a compound acting as a partial agonist at both dopamine D2 receptors and serotonin receptors and has been tested for treating PSF in patients with mental fatigue after stroke.<sup>125</sup> It acts as a dopamine stabilizer that may counteract the effects of

excessive or insufficient dopaminergic transmission. Although the patients with PSF in this study exhibited tolerance to it, this drug obviously needs further study because the sample size was small (n=6) and it was not a randomized controlled trial.<sup>125</sup>

Selective serotonin reuptake inhibitors have been tried but do not appear to be effective in treating PSF on the basis of the results of 2 RCTs. One group of researchers investigated the efficacy of fluoxetine in patients with PSF.<sup>80</sup> A double-blind, placebo-controlled trial conducted in 83 patients with PSF found that fluoxetine was not effective in improving PSF, although it improved depression and other emotional disorders in these patients. Similarly, another study showed that duloxetine, citalopram, and sertraline did not relieve PSF (although duloxetine was more effective in treating anxiety than the other 2 drugs).<sup>81</sup> These results suggest that the serotonergic system may not be as closely related to PSF as it is to emotional disorders and imply that PSF and emotional disorders such as depression and anxiety may be distinct phenomena.

Vitamin supplementation has been reported to be effective in relieving PSF, although the data are insufficient to draw firm conclusions.<sup>126-129</sup> Candidate vitamins are vitamin B<sub>12</sub>, vitamin B<sub>1</sub>, and idebenone, a synthetic coenzyme Q10 analog. One observational study reported that vitamin B<sub>12</sub> deficiency was related to fatigue in lacunar stroke and that vitamin B<sub>12</sub> supplementation may be effective in treating fatigue in these patients.<sup>126</sup> The efficacy of vitamin B<sub>1</sub> was reported. One small trial reported that enerion, a synthetic derivative of vitamin B<sub>1</sub>, was effective

in reducing PSF,<sup>127</sup> and a recent case report revealed the efficacy of high-dose vitamin B<sub>1</sub> in relieving PSF, although the sample size was very small (n=3).<sup>128</sup> Antioxidant idebenone, a synthetic coenzyme Q10 analog, was reported to be effective in managing PSF.<sup>122,129</sup> None of these trials were powered adequately, nor were any of them randomized controlled trials.

Traditional Chinese herbs such as *Astragalus membranaceus* may be effective in treating PSF.<sup>130</sup> *Astragalus membranaceus* contains a variety of substances, including saponin, polysaccharide, and flavonoid, that have been reported to have anti-inflammatory, antioxidative stress, immunoregulation, and cardioprotective effects via numerous signaling pathways in vital organs and systems.<sup>131</sup> The efficacy of *Astragalus membranaceus* for treating PSF is being assessed in an ongoing randomized, placebo-controlled, double-blind trial.<sup>130</sup>

To sum up, there are a number of promising pharmacological agents for PSF. More randomized, placebo-controlled, double-blind trials with adequate sample sizes are needed.

### Nonpharmacological Interventions

There is no evidence for nonpharmacological interventions in patients with PSF. Interventions include general advice to patients and caregivers for dealing with PSF and patient education materials.

#### Interventions

Several international guidelines include the subject of PSF. An American Heart Association/American Stroke Association statement notes that PSF may be aggravated by a sedentary lifestyle and encourages regular physical activity.<sup>132</sup> Exercise programming recommendations for stroke survivors are outlined in the guideline, and it is noted that regular exercise may help decrease PSF.<sup>132</sup> The guidelines for adult stroke rehabilitation and recovery recommend aerobic exercise as a way to decrease PSF.<sup>133</sup> An Australian guideline notes that therapy for stroke survivors with PSF should be organized for periods of the day when they are most alert.<sup>134</sup> Furthermore, these guidelines state that stroke survivors and their caregivers should be provided with information about and education on fatigue, including potential management strategies such as exercising, establishing good sleep patterns, and avoiding sedating drugs and excessive alcohol.<sup>134</sup> A Cochrane review provided a comprehensive review of PSF interventions. Trials included 2 non-pharmacological interventions, a fatigue education program, and a mindfulness-based stress reduction program.<sup>122</sup> There was insufficient evidence on the efficacy of any intervention to treat or prevent PSF. It was noted that trials have been small and heterogeneous, and some have had a high risk of bias. In clinical practice, modifiable factors such as depression and anxiety, sleeping or eating disturbances, pain, and fatigue-provoking drugs should be identified and appropriately managed. Although many of the interventions described in the review were noted to be feasible in people with stroke, their efficacy needs to be investigated in research with robust study designs such as RCTs and powered with adequate sample sizes.<sup>122</sup>

#### Patient Education Materials

When patients and caregivers bring up the topic of PSF, having evidence-based education materials to give them would be helpful to clinicians. Three sets of patient education

materials on PSF were located. One was from the American Heart Association/American Stroke Association,<sup>135</sup> another from the National Stroke Association,<sup>136</sup> and the third from the UK Stroke Association.<sup>137</sup> All of the patient education materials contained a date, and the one from the American Heart Association/American Stroke Association has been updated every 2 years since 2012. However, none of the 4 are evidence based because none listed any sources or references. Although all 3 give practical advice for patients (it is normal to feel tired, avoid alcohol, take naps, etc) and can be easily accessed on the Internet, none can be suggested for use because they are not evidence based.

In summary, there are a few promising nonpharmacological interventions and some existing patient education materials for PSF. Both areas need to be investigated using research with robust study designs such as RCTs and powered with adequate sample sizes.

### Influence of Fatigue on Caregiver Burden

Although caregivers identify that dealing with PSF is a top priority for further research,<sup>19</sup> no studies were found that examined the extent to which PSF affects informal caregiver burden. Caregivers play an instrumental role in the rehabilitation and day-to-day care of the stroke survivor. Well-designed research powered with adequate sample sizes is needed to describe how PSF contributes to caregiver burden and to develop and evaluate interventions to help caregivers better understand and help their loved ones manage PSF. For example, caregivers can be taught to help the stroke survivor space activities out throughout the day to conserve energy if this is found to be an effective intervention.

### Summary

In this critical review of quantitative research concerning PSF, the overall quality of the research was found to be poor. Few RCTs were identified, and many studies had sample sizes of  $\approx 40$  or less.

It is known that PSF is common and a cause of concern to clinicians, researchers, patients, and caregivers after ischemic and hemorrhagic stroke. PSF and poststroke depression are distinct clinical entities, and PSF contributes to decreased QOL. Many reliable and valid tools are available to measure PSF. It is apparent that the pathophysiology of PSF is multidimensional and most likely multifactorial. Medications influence PSF, and caregivers are concerned about PSF in stroke survivors.

Despite what is known about PSF, many areas still need further research. It is suggested that clinicians and researchers come to a consensus on one best definition of PSF because current definitions are not specific enough. Unambiguous suggestions are needed for which tool to use and when to measure PSF.

The multidimensional aspects of PSF need to be more fully described in well-designed research. With various demographic, physical, and psychological components, it is difficult to determine the exact influence that these components have on PSF. It is especially important to conduct research on how neurological deficits after stroke contribute to PSF. Another area for research is related to medical comorbidities. Do diabetes mellitus, hypertension, and other fatigue-causing conditions have an effect on PSF? How can a researcher determine which of these may truly affect PSF?

Patients discharged from the hospital after a stroke may be prescribed medications such as anticonvulsants that induce fatigue. It is important to determine which medications are more likely to contribute to PSF. Further study should examine the impact of medications on PSF. Other areas for research include the effect of eating difficulties, sleep disturbances, pain, and prestroke fatigue. Although research has indicated that all of these may have an impact on a patient after stroke, it is not apparent how they affect PSF.

PSF and depression may exist concurrently. The relationship between PSF and depression needs to be examined more thoroughly. Does depression lead to fatigue, or does fatigue lead to depression? Until there is an agreed-on definition of PSF and identification of a strong tool to accurately diagnose depression in stroke, there is much to be done. A better understanding of the pathophysiology of PSF is foundational to identifying treatment. Current research suggests that PSF is centrally mediated, whereas others believe that disruption of pathways is the cause. Because these are 2 different mechanisms, research is needed to further our understanding and to provide information to patients and their family members.

Inflammation, cytokines, and biomarkers are important considerations in PSF. These areas of research provide many avenues of exploration. The number of biomarkers and cytokines that might contribute to PSF makes these areas complex to evaluate

because it may not be obvious which or how many influence PSF. The effect of fatigue on the caregivers of patients who have had a stroke is another suggested area in need of further research.

### Clinical Considerations

Clinicians need to have a better understanding of the entity of PSF to provide appropriate treatment. This comprehension can be gained by consistently gathering data to assess short- and long-term outcomes and engaging in high-quality research such as RCTs on PSF. Evidence-based education materials on PSF need to be provided to the patients and family members so that when symptoms occur, the family unit can support the patient. Some education materials are available through stroke associations and should be provided at discharge from the acute care hospital and rehabilitation.

Although much work needs to be done, much has already been completed. Researchers and clinicians can build on this foundation in efforts to improve the QOL for patients and family members after stroke.

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\*Modest.

†Significant.

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\*Significant.

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## Poststroke Fatigue: Emerging Evidence and Approaches to Management: A Scientific Statement for Healthcare Professionals From the American Heart Association

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