Post-stroke fatigue: a review on prevalence, correlates, measurement, and management

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Background: Post-stroke fatigue (PSF) is a common yet debilitating symptom for the majority of patients post-stroke. However, limited information is available for the management of this disabling condition. This is partly due to our poor understanding of the condition.

Objectives: In this paper, we review the prevalence, predisposing factors, impact, measurement, and management of PSF.

Results: The prevalence of PSF ranged from 29 to 70%, depending on the selected outcome measurement tools and the patient characteristics. Predisposing factors of PSF are multifactorial, including biological, physical, and psychological factors. Further, the relationships between some of the predisposing factors and PSF seem to be indirect.

Conclusions: PSF has an adverse effect on the patient’s quality of life, recovery, and mortality. Its impact on physical function and independence requires further investigation. There are a number of tools available to measure fatigue in neurological conditions. However, very few of them have been validated in stroke. Lastly, single-disciplinary management for PSF was rarely successful. In contrast, evidence suggests that approaches which incorporated both physical and psychological interventions may be beneficial. Further studies are urgently needed to gain a better understanding of the etiology of PSF, such that the development of better management strategies is possible.

Keywords: Cerebrovascular accident, Transient ischemic attack, Infarction, Tiredness, Weariness, Health, Rehabilitation

Introduction

Fatigue is a subjective experience ranging from tiredness to exhaustion. It is a common experience for both healthy and diseased individuals. Most people have experienced ‘normal’ fatigue, for instance, after running a marathon or a long day of work. This type of fatigue is often short in duration and can be alleviated with rest or sleep. It is often deemed as a healthy response from the body. In contrast, “abnormal” fatigue that is often chronic and not alleviated by rest is believed to be pathological. This type of fatigue is devastating and often associated with certain underlying diseases, such as cancer, multiple sclerosis, and stroke.

Post-stroke fatigue (PSF) is a common and distressing symptom for stroke survivors. Previous studies have reported frequency of PSF ranging from 29 to 68%. It was listed as the most disabling symptom in 40% of stroke patients. Furthermore, PSF predicts death, disability, and quality of life. However, our understanding of the phenomenon is limited, therefore hindering the development of strategies to manage the problem. Studying PSF is challenging because of a few barriers. First, the phenomenon is subjective in nature; therefore measuring and quantifying PSF are difficult. Consequently, the field still lacks a gold standard of PSF measurement. Furthermore, the etiology of PSF seems to be complex and multifactorial. This further increases the difficulty to study the phenomenon. However, the increase interest in multidisciplinary research approach and advancement in research methodology have shed light on this complicated issue. In the past few years, interest in the investigations of PSF has increased. The purpose of this review is to summarize the current evidence in PSF and to highlight the gaps in the current literature.

Definition of Fatigue

Fatigue is a multidimensional construct and relates to individual physical, emotional and mental experiences. Fatigue, synonymously known as tiredness or exhaustion, is a normal virtual symptom experienced by living organisms in habitual activities. It is
a feeling of tiredness and decrement of body or mental function from usual performance.\textsuperscript{3,10,11} Fatigue can be classified into two types, objective and subjective fatigue.\textsuperscript{10} Objective fatigue refers to an observable and measurable decrement in performance of physical or mental repetitive tasks. Objective fatigue is considered normal and usually reversible by rest. In contrast, subjective fatigue, also known as pathological fatigue, is a feeling of early and extreme exhaustion which cannot be restored through rest. Pathological fatigue is unrelated to previous exertion levels.\textsuperscript{2,11,12}

Although there is no agreement on the definition of PSF, it is generally deemed as “a subjective experience of extreme and persistent tiredness, weakness or exhaustion after stroke, which can present itself mentally, physically or both and is unrelated to previous exertion levels.”\textsuperscript{13} Kirkevold and colleagues reported that fatigue experienced by stroke survivors was different from normal exhaustion and most likely under the category of pathological fatigue.\textsuperscript{14} Tseng \textit{et al.} also demonstrated that exertion fatigue (normal fatigue) and chronic pathological fatigue were two independent entities that were explained by different variables in patients with stroke.\textsuperscript{15} In this review, we included studies addressing pathological fatigue rather than normal fatigue in patients post-stroke.

Fatigue can be conceptualized based on its potential sources as well, including physical, mental, somatic, and psychological fatigue.\textsuperscript{6,12} Physical fatigue refers to muscle exhaustion which causes interruption in physical activity. It can be further divided into peripheral and central fatigue. Peripheral fatigue is defined as a decrease in the muscle force output. Central fatigue refers to the contribution of central nervous system to the decrement in physical activity performance and is often described as “tiredness.”\textsuperscript{11} Mental fatigue refers to inability to sustain a mental effort over a long period of time.\textsuperscript{12,16} Psychological fatigue is related to “lack of interest and poor motivation.”\textsuperscript{12,17} Somatic fatigue is associated with the manifestation of diseases.\textsuperscript{12} These subtypes of fatigue are not mutually exclusive. They can be expressed at a behavioral level (objective fatigue) or as a state of feeling (subjective fatigue) or a mixture of both. PSF is more likely an expression of various subtypes at both subjective and objective levels.\textsuperscript{18} The multifactorial feature of PSF has increased the challenges to determine its prevalence.

**Prevalence of Post-Stroke Fatigue**

Frequency of PSF ranged from 30 to 72\%.\textsuperscript{4,6,7,19–24} Table 1 summarizes the prevalence reported by 16 studies. The prevalence data reported had huge variations. Differences in outcome measures, population characteristics and administration of the measurements may explain the variations. The diagnosis or quantification of PSF varied across studies. Some studies determined frequency by asking questions such as “Do you feel tired?” while other studies utilized validated scales, such as the Fatigue Impact Scale or the Fatigue Severity Scale.\textsuperscript{3,4} Furthermore, each study evaluated different aspects of fatigue, from severity to impact to life. The variations in the measurement tools may contribute to the wide range of frequency.

Patients’ characteristics may explain differences in frequency as well. It has been shown that younger patients and male patients were less likely to suffer from PSF.\textsuperscript{5,22,25} Chronicity seems to play an important role as well. Most of the prevalence studies included patients who were 3–13 months post-stroke.\textsuperscript{3,4,20,22} There were very few longitudinal studies that examined the evolution of PSF.\textsuperscript{8,26,27} Schepers \textit{et al.} found that the frequency of PSF increased with time. They followed up 167 stroke patients and reported the frequency of 52\% at admission, 64\% at 6 months post-stroke and 70\% at 1 year post-stroke.\textsuperscript{24} van de Port \textit{et al.} also demonstrated a similar observation in their cohort of 223 patients. The frequency of fatigue at 6 months post-stroke was 68\%, 74\% at 1 year, and 58\% at 3 years post.\textsuperscript{8} On the other hand, Christensen \textit{et al.} showed that the frequency of fatigue decreased 3 months after stroke and remained stable through the remainder of the two-year follow up.\textsuperscript{27} Similarly, Lerdal \textit{et al.} showed that levels of fatigue remained stable from the acute phase to 18 months post.\textsuperscript{28} These findings highlight the need for monitoring the development of PSF from the acute stage and may explain the variations in reported PSF frequencies.

In summary, PSF is a common complaint among stroke survivors with a huge variation in its prevalence. Nevertheless, it affects the majority of stroke survivors and persists over time; thus, it requires immediate attention. Future studies are recommended to stratify patients and to follow up patients longitudinally in order to have a better estimation of the prevalence.

**Factors Correlated with Post-Stroke Fatigue**

PSF is multidimensional and various factors have been shown to influence its severity or impact on life. This section discusses the factors which have been identified to be associated with the severity of PSF. Exploration of factors associated with
Table 1  Prevalence of post-stroke fatigue

<table>
<thead>
<tr>
<th>References</th>
<th>N</th>
<th>Age in years</th>
<th>Mean (SD)</th>
<th>Disease duration</th>
<th>Outcome measure</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stroke</td>
<td>Healthy</td>
<td>Stroke</td>
<td>Healthy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ingles et al. 4, 1999</td>
<td>88</td>
<td>56</td>
<td>66.6 ± 13.4</td>
<td>73.9 ± 7.9</td>
<td>3–13 months</td>
<td>FIS</td>
</tr>
<tr>
<td>Werf et al. 23, 2001</td>
<td>90</td>
<td>50</td>
<td>Range (32–73)</td>
<td>Range (30–72)</td>
<td>≥ 1 year</td>
<td>CIS</td>
</tr>
<tr>
<td>Glader et al. 3, 2002</td>
<td>4023</td>
<td>...</td>
<td>56.4 ± 11.4</td>
<td>...</td>
<td>Admission, 6 months, and 12 months</td>
<td>FSS</td>
</tr>
<tr>
<td>Schepers et al. 24, 2006</td>
<td>167</td>
<td>...</td>
<td>57.3 ± 11.1</td>
<td>6 months, 12 months, and 36 months</td>
<td>FSS</td>
<td>6 months=64.1%</td>
</tr>
<tr>
<td>van de Port et al. 8, 2007</td>
<td>223</td>
<td>...</td>
<td>64.5 ± 11.4</td>
<td>...</td>
<td>Admission, 6 months, and 12 months</td>
<td>FSS</td>
</tr>
<tr>
<td>Christensen et al. 27, 2008</td>
<td>165</td>
<td>1069</td>
<td>47.6 ± 11.4</td>
<td>10 day, 3 months, 1 year, and 2 years</td>
<td>FSS</td>
<td>10 days=59%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Park et al. 59, 2009</td>
<td>40</td>
<td>...</td>
<td>32.7 ± 27.4</td>
<td>...</td>
<td>6 months</td>
<td>FSS</td>
</tr>
<tr>
<td>Winward et al. 37, 2009</td>
<td>76 (TIA) 73 (Stroke)</td>
<td>...</td>
<td>TIA=72.5</td>
<td>...</td>
<td>&gt;6 months</td>
<td>FSS and MFI - 20</td>
</tr>
<tr>
<td>Falconer et al. 25, 2010</td>
<td>91</td>
<td>...</td>
<td>69 ± 11.7</td>
<td>...</td>
<td>&gt;3 months</td>
<td>FSS</td>
</tr>
<tr>
<td>Tang et al. 31, 2010</td>
<td>456</td>
<td>...</td>
<td>66.2 ± 11.7</td>
<td>...</td>
<td>&gt;3 months</td>
<td>FSS</td>
</tr>
<tr>
<td>Chesnut et al. 26, 2010</td>
<td>4 (LVD) 9 (SVD)</td>
<td>...</td>
<td>LVD=74.8 ± 3.4</td>
<td>...</td>
<td>&gt;3 months</td>
<td>FSS</td>
</tr>
<tr>
<td>Vuletic et al. 20, 2011</td>
<td>35</td>
<td>35</td>
<td>61.8 ± 14.2</td>
<td>61.2 ± 12.0</td>
<td>3 months</td>
<td>FSS</td>
</tr>
<tr>
<td>Lerdal et al. 28, 2012</td>
<td>95</td>
<td>...</td>
<td>67.8 ± 13.3</td>
<td>...</td>
<td>Admission, 6 months, 12 months, and 18 months</td>
<td>FSS</td>
</tr>
<tr>
<td>Zedlitz et al. 19, 2012</td>
<td>479</td>
<td>...</td>
<td>52.4 ± 10.8</td>
<td>...</td>
<td>...</td>
<td>FSS</td>
</tr>
<tr>
<td>Naess et al. 9, 2012</td>
<td>377</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>FSS</td>
</tr>
<tr>
<td>Feigin et al. 22, 2012</td>
<td>613</td>
<td>...</td>
<td>69.9 ± 13.0</td>
<td>...</td>
<td>...</td>
<td>SF 36 — vitality score</td>
</tr>
</tbody>
</table>

Note: FIS = Fatigue Impact Scale; FSS = Fatigue Severity Scale; MFI – 20 = Multidimensional Fatigue Inventory 20; VASF = Visual Analogue Scale Fatigue; CIS = Checklist Individual Strength; TIA = Transient Ischemic Attack; SVD = Small Vessel Disease; LVD = Large Vessel Disease.
PSF is valuable in understanding the underlying mechanisms, such that meaningful strategies can be developed to address the problem. As a result of the multifaceted nature of PSF, the identified factors fall into three major groups: biological, psychological, and behavioral correlates. Figure 1 depicts the inter-correlation between these factors and PSF.

**Biological correlates**
The age of the patients is the most commonly studied factor. However, the findings were controversial. A study showed that young stroke survivors had a higher frequency of fatigue compared to older survivors. However, others reported that PSF increased with age. A recent study published by Lerdal and colleagues revealed that younger (< 60 years) and older (> 75 years) had the highest level of fatigue. The relationship between age and the level of fatigue was U-shaped. Furthermore, they demonstrated that age itself explained very little variance in fatigue. In addition to age, PSF was found to be more frequent in females. However, others reported no gender difference. The perception and expression of fatigue may be different between females and males. Therefore, the inconsistency in the findings may partially be due to different fatigue definition between genders.

The type of stroke is another commonly studied factor. It appears that patients with large vessel stroke experienced greater fatigue than patients with small vessel involvement. Patients with stroke demonstrated greater fatigue than those with TIA even with little to no physical deficits. This suggests a ‘central origin’ of PSF. Involvement of brainstem (especially reticular system) or basal ganglia might be particularly important to the development of PSF because of their contribution to wakefulness, attention and motivation. Right hemisphere stroke was found to associate with PSF in some early studies. However, a recent systematic review revealed that the association between PSF and lesion location was inconclusive. The authors argued that structural neuroimaging techniques (such as MRI) may not be sensitive enough to reveal the association. Functional neuroimaging techniques such as functional MRI or transcranial

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**Figure 1** Illustration of the inter-relationship between predisposing factors, post-stroke fatigue and its impacts.
There is only one study that has examined the association between sleep disturbance and fatigue in chronic stroke. Appelros demonstrated that fatigue measured 1 year after stroke was associated with both physical disability and sleep disturbance. Post-stroke pain is common among stroke survivors and it predicts long term quality of life and mortality. Appelros found no significant association between pain and fatigue, while Naess reported that patients with pain reported higher fatigue scores on the Fatigue Severity Scale. Notably, patients who reported pain also showed high frequency of sleep disturbances and depression. Thus, the association between pain and fatigue is probably more complicated and potentially indirect.

**Psychological correlates**

Psychological factors such as anxiety and depression are associated with PSF. To date, the relationship between fatigue and depression remains controversial. Some studies showed that PSF was not dependent on depression while other studies reported a significant relationship between fatigue and depression. Ingles and associates demonstrated that the presence of PSF was independent from the presence of depression. However, the effect of fatigue on functional abilities was mediated by depression. Thus, the association between fatigue and depression may exist but may not be direct. Further, assessment of depression often includes evaluation of fatigue or lack of energy, or difficulty in concentration. Thus, the mental aspect of PSF may be more closely associated with depression than the physical aspect. The unique relationship may also explain the high variability in PSF prevalence summarized earlier. The prevalence depended on whether patients with depression were included or excluded in the studies. Thus, the evaluation of the relationship between fatigue and depression needs to be considered in the multidimensional nature of each entity and their complex interactions.

In addition to depression, apathy and anxiety have been proposed to exacerbate PSF. Using the Hospital Anxiety and Depression Scale, Vuletic et al. demonstrated that anxiety was significantly associated with fatigue. Radman et al. found that the scores on the Hamilton Anxiety Rating Scale were associated with fatigue measured at 6 months post stroke but not at 12 months. In contrast, the Hamilton Depression Rating Scale remained a strong predictor for fatigue even at 12 months post-stroke. These results suggest that anxiety may also behave as a determinant especially during the acute phase of stroke.
In summary, PSF associates with various biological, behavioral and psychological factors. However, current evidence showed mixed results and further research is warranted. Understanding the contributing factors is critical for the development of management strategies. Most identified factors, such as depression, physical deconditioning, sleep disturbance, and pain, are modifiable. Management of these factors may reduce the severity and impact of PSF.

**Impact of PSF**

PSF significantly impacts the patients’ life. PSF has been identified as one of the worst symptoms, prohibiting patients from living a normal life. In this section, we summarize current findings on the effects of PSF on quality of life, mortality, and rehabilitation outcomes. Figure 1 illustrates the relationship between PSF and its impacts.

Few studies have revealed that PSF impacted quality of life negatively. van de Port et al. found that the relationship between quality of life and fatigue were significantly correlated even after taking into account the influence of depression. In another study, fatigue was found to correlate with the physical subscales of SF-36 whereas depression was correlated to the nonphysical components of health related quality of life. These findings highlight the unique yet specific contribution of fatigue to quality of life. Naess and his team further showed that low quality of life due to PSF was associated with an increased mortality rate. In a two-year follow up study, Gleder et al. showed that patients who manifested PSF had higher mortality rates. Naess and Nyland reported that fatigue was an independent predictor of long-term mortality in young stroke survivors after adjustment of age and gender. The authors hypothesized that fatigue linked to mortality in young stroke survivors was probably due to the development of diabetes mellitus, myocardial infarction and psychosocial factors.

PSF has been identified as a barrier to participation in rehabilitation programs and physical activities. It was also associated with poor neurological recovery, partly due to low level of participation in rehabilitation programs. Patients with PSF were more likely to move into institutions rather than living in their own homes even after adjusting for age. They also had more limitations in social participation. In a qualitative study, fatigue was deemed a barrier to participate in social activities and return to work. Fatigue was negatively correlated with the probability of return to work and levels of professional activity. The relationship between fatigue and functional independence remains debated. Glader et al. showed that PSF was associated with an increased level of dependence during daily life activities. However, few studies revealed that stroke survivors functioned independently in daily life regardless of the existence of fatigue. Few studies demonstrated that the relationship between fatigue and functional independence was mediated by depression. This again implicates the complex relationship between depression and fatigue and their connection with functional outcomes. The impact of fatigue on functional independence is believed to particularly accentuate in physical domains. The relationship between physical deconditioning and fatigue is bidirectional as mentioned earlier. Tseng and Kluding showed that there was a negative relationship between fatigue and aerobic fitness in chronic stroke. However, Michael et al. did not find a correlation between aerobic fitness and fatigue in 53 community dwelling stroke survivors but the authors showed that fatigue severity was significantly associated with balance. Miller and colleagues, on the other hand, failed to find significant correlations between fatigue and balance or walking capacity. Their results were consistent with Hoang et al. who also found no relationship between presence of fatigue and walking speed and walking endurance. Patients recruited in Micheal et al. had lower scores on the physical task tests (balance and walking speed) compared to those in Miller et al. and Hoang et al. studies. The difference in physical capacity might contribute to the contradictive findings. Interestingly, both Michael et al. and Miller et al. found a moderate relationship between fatigue and balance self-efficacy. This may suggest that one of the possible causes of limited social participation in patients with fatigue is the lack of confidence in their balance.

In summary, PSF negatively impacts patients’ social participation and quality of life. It also has a negative impact on their rehabilitation outcomes, including participation in rehabilitation therapy, return to work and functional independence. However, the impact seems to be influenced by depression. Though studies suggested that PSF affected the physical components of quality of life, the results of the relationship between physical performance and fatigue were mixed. It appears that fatigue may negatively affect patients’ self-efficacy on physical performance rather than physical performance per se. Further studies are warranted to explore the influence of fatigue on physical performance with patients with various physical limitations.

**Measurement of PSF**

Measurement of fatigue in neurological populations, particularly pathological fatigue, is challenging.
Difficulty has arisen from lack of standardized definition and heterogeneity of populations. Moreover, there are only a few stroke-specific fatigue measures. Table 2 summarizes fatigue assessment tools that are commonly used in stroke literature. A comprehensive review of fatigue measurement has been done elsewhere 11,76-80 and is beyond the scope of the current review. The purpose of any instrument is to diagnose, monitor changes, or evaluate outcomes. Here, we compiled the psychometric property information of these instruments, especially their reliability and validity in stroke. This information is valuable for clinicians and researchers to identify proper tools for their assessment with various purposes.

Among the commonly used fatigue assessment tools, only the Neurological Fatigue Index-Stroke 86 and Case Definition of Fatigue 101 were developed specifically for PSF. Hence, the psychometric testing of other tools in the stroke population is by far limited. Evaluation of the reliability and responsiveness of the fatigue measurement tools is particularly important for clinical intervention trials. However, the reliability and responsiveness of some commonly used tools in stroke trials such as Fatigue Severity Scale 89 have not been reported. Most measurement tools, except for the Multidimensional Assessment of Fatigue 93, evaluate single dimension (severity or impact) of fatigue. Thus, a combination of more than one assessment tool may be required in order to comprehensively measure PSF.

Management of PSF
Most PSF investigations focused on prevalence, correlates and effects, and measurements. Investigations on the management of PSF are very limited, 81 possibly due to our poor understanding of the etiology. There are a few recent clinical trials that have investigated the effectiveness of different interventions. Table 3 summarizes both pharmacological and non-pharmacological intervention studies.

Pharmacological management
Pharmacological management of PSF assumes that fatigue resulted from the disruption of cortical connection, 82 alteration of the neurotransmitter receptor sensitivities, 83,84 or involvement of the reticular activating system. 85 Overall, the pharmacological management of PSF is far less than satisfactory. The two randomized control trials 83,84 found no differences between the intervention and placebo groups. Both studies administered serotonin reuptake inhibitors (Fluoxetine and Duloxetine, respectively). Serotonin reuptake inhibitors are commonly used to treat post-stroke depression. Interestingly, Karaisko et al. found that antidepressants effectively improved post-stroke depression symptoms but had no effect on fatigue. This finding implies that depression and fatigue may be two distinct impairments among stroke survivors.

Two other pharmacological studies did not include a control group 85 or included a small sample. 82 Notably, Brisoichi et al. demonstrated that Modafinil, a wakefulness-promoting molecule that increases the excitatory glutamate transmission and the cortical serotonin release, was effective to improve fatigue severity in brainstem and/or dienecephalic stroke patients, but had no effect on cortical stroke. 85 The findings provided support for the ‘brain fatigue generator’ model in which dysfunction of reticular formation is hypothesized to result in central fatigue. 85 However, this study did not include a placebo control group and the sample size was small. Further investigations of the effect of Modafinil on PSF are needed.

Non-pharmacological management
Given the multifactorial nature of PSF, it is reasonable to hypothesize that non-pharmacological approaches, such as education, nutrition, exercise, sleep intervention, relaxation and meditation, biofeedback, music therapy, and recreational therapy could be potentially beneficial. 61,66 There is relatively little evidence on the effectiveness of non-pharmacological management of PSF. We summarize two recently published trials in Table 3. In both studies, beneficial effects of group-based interventions were demonstrated.

In their pilot trial, Clarke et al. showed that a group education program that targeted fatigue management were effective in improving fatigue symptoms. Though the improvement was not statistically different from the control group, there was a trend that the fatigue management group education was superior to the stroke group education (the control). 86 The fatigue management education was comprised of introduction to fatigue, fatigue management strategies, sleep hygiene, relaxation exercise, physical exercise education, nutrition, and mood. Zedlitz et al. reported that the combination of graded physical activity training and cognitive treatment was superior to cognitive treatment alone in improving fatigue. 13 In this study, both combined treatment and cognitive treatment alone led to similar improvement on the Checklist Individual Strength-subscale Fatigue but more patients in the combined treatment group demonstrated a clinically important improvement. Part
Table 2  Measures of fatigue

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Developed by</th>
<th>Construct tested</th>
<th>No. of items</th>
<th>Response format</th>
<th>Cut-off score</th>
<th>Reliability</th>
<th>Validity</th>
<th>Responsiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue Severity Scale</td>
<td>Krupp et al., 1989</td>
<td>Impact of fatigue</td>
<td>9</td>
<td>7-point Likert scale (1–7)</td>
<td>&gt;36</td>
<td>NO</td>
<td>YES³⁹</td>
<td>NO</td>
</tr>
<tr>
<td>Fatigue Impact Scale</td>
<td>Fisk et al., 1994</td>
<td>Impact of fatigue</td>
<td>21</td>
<td>5-point Likert scale (0–4)</td>
<td>N/A</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Fatigue Assessment Scale</td>
<td>Michielsen et al., 2004</td>
<td>Impact of fatigue</td>
<td>10</td>
<td>5-point Likert Scale (1–5)</td>
<td>N/A</td>
<td>YES⁷⁸</td>
<td>YES⁷⁸</td>
<td>NO</td>
</tr>
<tr>
<td>Multidimensional Assessment of Fatigue</td>
<td>Belza et al, 1993</td>
<td>Severity, impact and timing of fatigue</td>
<td>16</td>
<td>Numerical and categorical responses A global fatigue index can be determined by converting responses from item 1 to 15 to a numeric score that ranges from 1 to 50</td>
<td>Global fatigue index &gt; 21</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>SF-36 Vitality subscale</td>
<td>Qualimetric</td>
<td>Severity of fatigue</td>
<td>4</td>
<td>6-point Likert (1–6)</td>
<td>N/A</td>
<td>YES³⁸</td>
<td>YES³⁸</td>
<td>YES³⁹</td>
</tr>
<tr>
<td>Multidimensional Fatigue Inventory</td>
<td>Smet et al., 1995</td>
<td>Impact of fatigue</td>
<td>20</td>
<td>5-point Likert (1–5)</td>
<td>&gt;12 on general fatigue dimension</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
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<tr>
<td>Neurological fatigue index for stroke</td>
<td>Mills et al. 2012</td>
<td>Experience of stroke</td>
<td>22</td>
<td>4-point Likert scale (0–3)</td>
<td>N/A</td>
<td>YES⁹⁵</td>
<td>YES⁹⁵</td>
<td>NO</td>
</tr>
<tr>
<td>Visual Analog Scale for Fatigue</td>
<td></td>
<td>Severity of fatigue</td>
<td>...</td>
<td>10 cm VAS</td>
<td>N/A</td>
<td>YES⁹⁶</td>
<td>YES⁹⁶</td>
<td>NO</td>
</tr>
<tr>
<td>Checklist of Individual Strength</td>
<td>Vercoulen et al., 1994</td>
<td>Phenomenology and severity of fatigue</td>
<td>8</td>
<td>7-point Likert (1–7)</td>
<td>&gt;40</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
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<tr>
<td>Multidimensional fatigue symptom inventory-General</td>
<td>Stein et al., 1998</td>
<td>Severity of fatigue</td>
<td>6</td>
<td>5-point Likert (0–4)</td>
<td>N/A</td>
<td>YES⁷⁸</td>
<td>YES⁷⁸</td>
<td>NO</td>
</tr>
<tr>
<td>Profile of Mood States-fatigue subscale</td>
<td>McNair et al., 1964</td>
<td>Phenomenology and severity of fatigue</td>
<td>6</td>
<td>5-point Likert</td>
<td>N/A</td>
<td>YES⁷⁸</td>
<td>YES⁷⁸</td>
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</tr>
<tr>
<td>Case Definition of fatigue</td>
<td>Lynch et al., 2011</td>
<td>Presence of fatigue</td>
<td>7</td>
<td>Categorical responses</td>
<td>Yes on all seven questions</td>
<td>YES¹⁰⁰</td>
<td>YES¹⁰⁰</td>
<td>NO</td>
</tr>
</tbody>
</table>

Note: Responsiveness was examined on SF-12
Table 3  Management of post-stroke fatigue

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient characteristics</th>
<th>Treatment</th>
<th>Fatigue outcome</th>
<th>Results</th>
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<td><strong>Pharmacological</strong></td>
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<td>Ogden et al., 1998</td>
<td>Treatment= 9 Placebo=9</td>
<td>Subarachnoid hemorrhage Age=47.4 years</td>
<td>100 ml of 1.5 mg/ml tirilazad mesylate versus 100 ml of sterile solution for 10 days</td>
<td>Semistructured interview At 3 months Fatigue Severity Scale Visual Analog Scale At baseline, 3 and 6 months</td>
<td>Intervention group reported less incidence of fatigue (44% versus 90%). The study analyzed a subset of data of a larger therapeutic trial.</td>
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<td>Choi-Kwon et al., 2007</td>
<td>Treatment=50 Placebo=43 Age=56.8 years Time since stroke = 14.5 months</td>
<td>Infarction and intracerebral hemorrhage</td>
<td>20 mg/day fluoxetine versus placebo for 3 months</td>
<td></td>
<td>No differences in the number of patients with fatigue between the groups at 3 and 6 months</td>
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<td>Brioschi et al., 2009</td>
<td>Treatment=42 Placebo=0</td>
<td>17 multiple sclerosis (mean age 43.3)</td>
<td>50 mg/day modafinil increased up to 100 mg/day and 200 mg/day at 2 months for 3 months</td>
<td>Fatigue Assessment Inventory At baseline, 3 months and 4 months</td>
<td>A significant improvement on fatigue severity was found in MS and brainstem stroke, but not in cortical stroke groups at 3 months.</td>
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<td>Karaiskos et al., 2012</td>
<td>Treatment=20 Control 1=20 Control 2=20</td>
<td>Ischemic or intracerebral hemorrhagic stroke with post-stroke depression Mean age=52.6 years</td>
<td>Duloxetine 30 mg/day and gradually increased to 60-120 mg/day over 3 months</td>
<td>Fatigue Severity Scale At baseline, 1st, 2nd, and 3rd month</td>
<td>No change in fatigue across the treatment duration and no differences among groups. The active control groups were given Citalopram and Sertraline respectively. Duloxetine was more effective than the controls for treatment of anxiety symptoms.</td>
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<td><strong>Non-pharmacological</strong></td>
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<td>Clarke et al., 2012</td>
<td>Treatment=9 Control=7</td>
<td>Ischemic and hemorrhagic Mean age=72.8 years 3-18 months post-stroke with fatigue</td>
<td>Educational fatigue management that consisted of 6 sessions (60 minutes per week). Each session had a different topic.</td>
<td>Fatigue Severity Scale Visual Analog Scale for Fatigue Checklist of Individual Strength Short Form-36 At baseline, post treatment and 3 months</td>
<td>Both groups showed a similar improvement on Fatigue Severity Scale. The treatment group showed greater reduction in fatigue, but was not significantly different from the controls. The control group received 6 psychoeducation sessions on stroke management. The study was a feasibility study for a larger phase 3 trial.</td>
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</table>
of PSF may arise from physical deconditioning (physical fatigue). Therefore, improving physical endurance through physical activity training could potentially reduce fatigue complaints. However, it does not seem like physical exercise alone is sufficient.

Based on the current evidence, a multidisciplinary approach appears to be more promising management strategy for PSF than that of single-disciplinary approaches. Previous studies that adopted single-disciplinary approach, such as cognitive behavioral therapy or graded activity training, has been shown to be effective. However, our poor understanding of the underlying etiology of PSF may have hindered the development of such a strategy. Better-designed studies that shed light on the underlying etiology of PSF are needed to further our understanding of the nature of PSF. These efforts will hopefully facilitate the development of strategies to prevent and manage this disabling condition.

Conclusion

In conclusion, PSF is a multidimensional phenomenon commonly experienced by most stroke survivors. While the etiology of PSF remains unclear and seems to be complicated, its influences on patients' outcomes are profound. Exacerbating factors of PSF arise from various sources, ranging from biological to psychosocial origins. Therefore, evaluation and management of PSF should reflect the multifaceted nature of PSF.

Assessment of PSF which includes more than one measurement tool covering physical, mental, and psychological fatigue and evaluates both severity and impact of fatigue will provide more comprehensive information than a single measurement tool. Similarly, a single-disciplinary approach for PSF management has been shown to be ineffective. Although it appears that multidisciplinary management would be more effective, our poor understanding of the underlying etiology of PSF may have hindered the development of such a strategy. Better-designed studies that shed light on the underlying etiology of PSF are needed to further our understanding of the nature of PSF. These efforts will hopefully facilitate the development of strategies to prevent and manage this disabling condition.
**Conflicts of interest**
The authors declare no conflicts of interest.

**Ethics approval**
This study was approved by University of Malaya Medical Centre Ethic Committee.

**References**

42. Harbison JA, Walsh S, Kenny RA. Hypertension and day-time hypotension found on ambulatory blood pressure is associated with fatigue following stroke and TIA. *QJM.* 2009;102(2):109–115.


