Post-stroke fatigue highlight notice

Background
Fatigue is common after stroke, and can be triggered by both mental and physical activity. A 2016 meta-analysis reported a pooled estimate of fatigue prevalence of 50%, with a range of 25% to 85%.¹ In a 2018 survey of over 11,000 stroke survivors by the Stroke Association, 86% reported that they had experienced fatigue following their stroke.²

There have been few longitudinal studies of post-stroke fatigue and little is known about how long fatigue may persist after stroke, however a 2016 study found a significant proportion of stroke survivors still experienced fatigue six years after their stroke.³ The factors that may help or hinder recovery from fatigue remain unclear.

There are a variety of definitions of post-stroke fatigue used in clinical practice and research, with no universally accepted definition. Common features of these definitions are an increased need to rest, that fatigue is not relieved by rest, and a lack of energy that is not related to previous exertion levels.⁴ Lynch et al.⁵ created a case definition of post-stroke fatigue, covering fatigue experienced by stroke survivors both in hospital and in the community. However it’s not clear how widely this definition is used, and many studies still utilise cut-offs on fatigue scales to judge whether a participant has post-stroke fatigue.

Post-stroke fatigue is a hugely important issue for people affected by stroke, impacting on many aspects of daily life, and research into fatigue has been highlighted as a priority for stroke survivors and healthcare professionals alike.⁶,⁷ The Action Plan for Stroke in Europe (2018-2030) also highlighted research into the management of post-stroke fatigue as a priority.⁸

Stroke survivors with post-stroke fatigue score lower on quality of life measures,⁹ many report fatigue to be one of the worst or the worst symptoms following their stroke,¹⁰ and a significant proportion feel that their fatigue-related needs are not being met.¹¹

Post-stroke fatigue can have a significant impact on recovery. It can affect a stroke survivor’s ability to engage in rehabilitation,¹² their physical and psychological functioning,¹³ and their ability to return to work.¹⁴ Post-stroke fatigue has also been linked to increased mortality.¹⁵
There is little evidence for effective treatments for post-stroke fatigue. Current NICE guidelines do not make any treatment recommendations for adult stroke survivors.\(^{16}\) The Royal College of Physicians National Clinical Guideline for Stroke acknowledge the lack of high quality evidence for fatigue treatments, recommending that management strategies for fatigue should include “the identification of triggers and re-energisers, environmental modifications and lifestyle changes, scheduling and pacing, cognitive strategies to reduce mental effort, and psychological support to address mood, stress and adjustment.”\(^{17}\)

**Research topics**

The areas below highlight some important post-stroke fatigue research topics. These are not exhaustive, but indicate some of the areas in which challenges remain for post-stroke fatigue research. You are not required to address one or more of these topics in this call, they are suggested research areas.

**Measures of fatigue**

Mead et al. identified 52 individual scales that had been used to measure fatigue in stroke survivors\(^{18}\). However, none had been designed for use in stroke and many contained items which could be confused with the neurological effects of stroke. A 2016 meta-analysis found that the most commonly used scale was the Fatigue Severity Scale, which was used in 24 of 49 studies that met their inclusion criteria\(^{1}\). There is currently no consensus among researchers or clinicians about the best scale to use to measure post-stroke fatigue, or when this should be used.

**Pathophysiology**

The pathophysiology of post-stroke fatigue is unclear. White matter lesions and type of stroke are not believed to be linked to post-stroke fatigue, however there may be some association between lesion location and fatigue, particularly for brainstem lesions, however the data is inconclusive.\(^{19}\) Kuppuswamy et al. argue that low excitability of both corticospinal output and its facilitatory synaptic inputs from cortical and sub-cortical sites contribute to post-stroke fatigue.\(^{20}\) Another study by this team, investigating whether transcranial direct current stimulation (tDCS) applied to the motor cortex could reduce levels of fatigue will be reporting soon.\(^{21}\)

Becker et al. carried out the first study investigating a genetic contribution to post-stroke fatigue, implicating single nucleotide polymorphisms in genes that modulate inflammation in post-stroke fatigue\(^{22}\). Other factors including inflammation and glutamate have been implicated in the development of post-stroke fatigue, however more research is needed to confirm their role.\(^{4}\)

Post-stroke fatigue has often been assumed to be a symptom of depression. However, many patients with post-stroke fatigue do not have depression,\(^{13}\) and when
Cumming et al. excluded participants with depression from their meta-analysis the prevalence of post-stroke fatigue changed very little, from 50% to 47%. Other factors independently associated with post-stroke fatigue in a 2018 meta-analysis were female sex, longer time since stroke and greater disability, with stroke survivors in their 40s, 50s and 80s experiencing the highest levels of post-stroke fatigue.

Wu et al. developed a model accounting for the many biological, psychological and behavioural factors that underpin post-stroke fatigue. In this model factors such as pre-stroke fatigue may predispose someone to developing fatigue, with the stroke triggering various biological factors that contribute to early fatigue. Contributors to late fatigue include affective factors (e.g. depression and anxiety), physical factors (e.g. disability), psychological factors (e.g. self-efficacy) and behavioural factors (e.g. reduced physical activity).

**Fatigue management**

While the amount of research being carried out into post-stroke fatigue has increased dramatically over the last 15-20 years, this has not translated into significant developments in its treatment and management. This is in part due to our lack of understanding of the mechanisms underlying post-stroke fatigue.

A Cochrane review of interventions for post-stroke fatigue looked at five pharmacological and two non-pharmacological interventions. The review concluded that “there was insufficient evidence on the efficacy of any intervention to treat or prevent fatigue after stroke”, reporting that trials to date had been small and heterogeneous and that some had a high risk of bias. The authors recommended that in future the efficacy of interventions should be investigated in high quality randomised controlled trials with adequate sample sizes.

There are several ongoing studies investigating a variety of potential treatments for post-stroke fatigue, including a cognitive behavioural intervention, remote ischaemic conditioning, and a personalised physical activity programme. In addition to these, the recently funded NoTFAST2 study will co-create a fatigue management programme with people affected by stroke and healthcare professionals.

Since the 2015 Cochrane review of interventions for post-stroke fatigue other studies investigating treatments have reported. A phase two randomised controlled trial investigated Modafinil, a wake-promoting agent, as a pharmacological treatment for post-stroke fatigue. Participants treated with Modafinil reported a significant decrease in fatigue and improved quality of life compared to participants who received a placebo.
Wu et al. also reported on the development and feasibility evaluation of the development of a psychological intervention for post-stroke fatigue. While this study only tested the intervention in twelve participants, the eight who completed the course of six treatment sessions reported lower fatigue levels at the end of the study compared to baseline.

**Scope**

We would particularly welcome research that aims to develop and test interventions to treat or manage post-stroke fatigue. These may be pharmacological or non-pharmacological. We expect researchers to follow the recommendation made in the review by Hinkle et al. and include measures of quality of life in any studies assessing the effectiveness of interventions to treat fatigue. We would also encourage researchers to learn from the limitations of previous research highlighted in the Cochrane review of interventions for post-stroke fatigue.

Fatigue is not an issue unique to stroke survivors. Zedlitz et al. reported that stroke survivors with fatigue had similar psychosocial profiles to people with other chronic conditions in which fatigue is also prevalent, such as multiple sclerosis, cancer, chronic fatigue syndrome and rheumatoid arthritis. As such, it’s possible that fatigue treatments and management strategies that have worked for patients with these conditions may also be effective for post-stroke fatigue.

Several reviews have been conducted investigating the efficacy of treatments for fatigue in conditions other than stroke, and have found potentially promising results for various forms of exercise therapy or physical activity, psychosocial interventions, and education interventions. We encourage researchers to learn from other conditions and consider what may work in stroke.

However, it’s clear that post-stroke fatigue is a multi-faceted issue. We would be keen to see applications that take a holistic view of treating post-stroke fatigue, recognising that the causes of and contributors to fatigue will vary between stroke survivors, and which aim to develop personalised approaches to management and treatment.

More research is required to develop our understanding of the various factors that may cause, predispose and perpetuate post-stroke fatigue. This will help healthcare professionals to identify those at higher risk of developing post-stroke fatigue more easily. However, understanding these is only one step – we also need an improved understanding of why it is that these particular factors may pre-dispose someone to, or maintain, fatigue after a stroke, how these factors may interact with one another, and how we may be able to limit their influence to prevent fatigue developing.
We would welcome applications for basic, applied and clinical research. All applications must include a clear pathway to impact. We expect that all research teams will have involved people affected by fatigue in developing their application and will continue to do so should the application receive funding. We don’t expect to receive applications for research into epidemiology as this is out of scope for this highlight notice.


34 Cramp, F. et al. (2013). Non-pharmacological interventions for fatigue in rheumatoid arthritis. Cochrane Database of Systematic Reviews, 8: CD008322.


