Inflammatory Signaling in Post-Stroke Fatigue and Depression

Hongmei Wen^a Kristianna B. Weymann^b Lisa Wood^c Qing Mei Wang^d

^aDepartment of Rehabilitation Medicine, The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou, China;

^bOregon Health and Science University, Portland, OR, USA; ^cSchool of Nursing, MGH Institute of Health Professions, Boston, MA, USA; ^dStroke Biological Recovery Laboratory, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA, USA

Keywords

Stroke · Fatigue · Depression · Inflammation

Abstract

Background: In the United States, stroke continues to be the cause for long-term disability. Of the patients with a first stroke, up to 75% will experience post-stroke fatigue (PSF) in the first year following stroke. PSF is one of the most disabling symptoms in stroke survivors; it decreases quality of life, increases mortality, and is a barrier to stroke rehabilitation. Given the incidence of stroke and the prevalence and detrimental impact of PSF on quality of life, independent living, and overall survival, efficient management of PSF must be a priority in stroke rehabilitation. The cause of PSF remains unknown. The burden of fatigue in stroke survivors is influenced by other stroke-related symptoms, most notably post-stroke depression (PSD). It is well known that stroke induces a systemic inflammatory response that is the trigger for sickness behavior, of which fatigue and depression are predominant symptoms. **Summary:** To date, only a handful of studies have sought to explore the relationship between stroke-induced inflammation and PSF and PSD. In this review, we describe this evidence, highlight the strengths and

weaknesses of these existing studies, and suggest further experiments that may further support the association between stroke-related inflammatory processes and stroke-related symptoms. **Key Messages:** The current concept and further research are important for a more specific therapeutic intervention for PSF and PSD.

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Background

Although functional recovery from stroke is improving, stroke continues to be the leading cause of adult disability [1, 2]. In the United States, every year about 795,000 end up having a stroke and this costs the nation USD 38.6 billion [3]. With an aging population at increased stroke incidence and improved survival from stroke [2], promoting functional recovery, symptom management, and quality of life after stroke is critically important. Post-stroke fatigue (PSF), defined as a lack of energy, or an increased need to rest on most days, which interferes with normal daily activity, is a very common and often lasting symptom post stroke [4–7]. Of the Americans who will have a first stroke [2], 48–69.5% will have PSF in the first

year following stroke [8, 9]. Although PSF may decline in some by 3 months after stroke [10], it can persist in 38–74% of individuals during the first year following stroke [8, 10, 11], and in 40–58% of individuals several years post-stroke [10, 11]. PSF can occur even after a mild stroke or transient ischemic attack [12, 13] and can persist after there appears to be otherwise full neurological recovery [14, 15]. PSF interferes with recovery from stroke [16], results in decreased function [4, 10, 17, 18], and increases the chance of being dependent in daily activity, especially for those over the age of 65 [2]. PSF decreases quality of life [19] and increases mortality rate due to its association with a sedentary lifestyle [20]. PSF is an independent risk factor for decreased physical health after stroke [21] and is a barrier to stroke rehabilitation [16, 22, 23]. Given the incidence of stroke and the prevalence and detrimental impact of PSF on quality of life, independent living, and overall survival, the effective management of PSF must be a priority in stroke rehabilitation.

Post-stroke depression (PSD) is also highly clinically important. PSD is a dynamic situation with a frequency of 25–79% [24]. A recent systematic review found there was no significant decrease in the percentage of people (31%) affected by depression after stroke as compared with 10 years ago (33%) [25, 26]. Depression severity was an independent predictor of severity of functional impairment. PSD has become a prominent barrier to stroke recovery.

Despite the fact that a high proportion of patients with stroke develop PSF and PSD, and PSD and PSF are more predictive of quality of life than actual neurological disability [27], the mechanisms underlying PSF and depression are very complex and have received little attention from the field of neurobiology until now [28–30]. A better understanding of PSF and PSD may improve patient management and facilitate the development of precise treatments. In this review, we provide evidence that neuroinflammation may be involved in the processes of PSF and PSD.

Post-Stroke Fatigue and Depression

The cause of PSF remains unknown. PSF was first reported in the literature as being a component of depression following stroke [31]. Since then, several studies have documented an association between PSF and PSD [20, 32–36]. The co-occurrence of PSF and PSD could be an indication that they may share a common etiology. Fatigue and depression are major symptoms of cytokine-

induced sickness behavior [37]. In the short term, cytokine-induced sickness behavior is thought to be evolutionarily advantageous for survival following infection or tissue damage because it results in withdrawal from activity, allowing for rest and recovery [38, 39]. Prolonged production of inflammatory cytokines does not appear to serve any evolutionary advantage and is associated with chronic fatigue and depression [38–40]. Although some risk factors of PSF and PSD are similar, such as age, sex, prior history of strokes, physical disability [32, 41–45], other factors associated with PSF and PSD are different. For examples, locations of infarction were associated with PSF but not with PSD [46]. Avoidance was independently related to PSD at 3 months, whereas confrontation was related to PSF [46].

The neural targets that mediate some of the cytokine-induced behavioral changes in rodents have been elucidated [47–49]. A cluster of “fatigue” neurons was recently identified in the perifornical lateral hypothalamus [47]. Under normal conditions, these neurons secrete orexin, a neurotransmitter that stimulates arousal and wakefulness via cholinergic, serotonergic, dopaminergic, and histaminergic pathways in the ascending arousal system [50, 51]. Narcolepsy, characterized by excessive daytime sleepiness, is caused by a loss of orexin-secreting neurons or reduced orexin neuron signaling in the hypothalamus [52]. Grossberg et al. [47] showed that endotoxin-induced fatigue in rodents, as indicated by a decline in locomotor activity, was associated with increased inflammatory signaling in the brain and decreased orexin neuron activity. Importantly, they were able to show that central administration of orexin-A reversed the inflammation-induced fatigue/lethargy in this model [47]. A similar role for inflammation-induced orexin dysfunction has been demonstrated in a rodent model of cancer treatment-related fatigue (CTRF) [53]. Although stroke has long been known to induce neuroinflammation, whether this is associated with a decrease in orexin neuron functioning is not known and is an important area for future research.

Disrupted sleep and wakefulness are also key features of traumatic brain injury (TBI) [54]. Similar to stroke, interleukin-1 β (IL-1 β) is a core mediator of the inflammatory response following TBI, and loss of orexin neurons has been observed in animal models of TBI [55]. Altered inflammatory signaling has also been implicated in clinical depression [56]. Inflammatory cytokines influence the synthesis and activity of serotonin, dopamine, and norepinephrine. Monoamine neurotransmitters are required for mood stability, and their deregulation has

been implicated in clinical depression. Inflammatory cytokines suppress the synthesis of these neurotransmitters by altering the function of 2 key enzymes required for their synthesis: indoleamine 2,3-dioxygenase and tetrahydrobiopterin [57]. Inflammatory cytokines also upregulate the synthesis and activity of serotonin, dopamine, and norepinephrine reuptake pumps at nerve endings, thereby decreasing the concentration of these neurotransmitters in the synaptic cleft [56]. By reducing neurotransmitter synthesis and increasing reuptake, inflammatory cytokines reduce serotonin, dopamine, and norepinephrine signaling, and it is this mechanism that is believed to contribute to depressive symptoms [56].

Stroke Induces Systemic Inflammation and Subsequent PSF and/or PSD

Stroke, whether caused by blood vessel blockage (ischemic) or rupture (hemorrhagic), causes a lack of oxygen (hypoxia) and glucose to brain tissue, interrupting production of ATP. ATP depletion results in cell damage and eventually cell death (Fig. 1i). Molecules released from dead or dying cells, commonly referred to as danger associated molecular patterns (DAMPs), are recognized by pattern recognition receptors belonging to the toll-like receptor (TLR) family located on the surface of microglia, sentinel cells of innate immunity in the brain [58] (Fig. 1ii). DAMP-TLR binding initiates the NF- κ B signaling cascade (Fig. 1iii), which induces the synthesis of the pro-inflammatory cytokine IL-1 β [59, 60]. IL-1 β is synthesized as a precursor (pro-IL-1 β), which is processed to its mature form by an intracellular protein complex called the inflammasome (Fig. 1iv). Several types of inflammasomes have been identified (NLRP1, NLRP3, AIM, etc.), but recent work suggests that the NLRP3 inflammasome plays a primary role in the processing of pro-IL-1 β in activated microglia [61]. Once cleaved by the NLRP3 inflammasome, mature IL-1 β is rapidly secreted into the extracellular space where it is available to bind to IL-1 receptors (IL-1R) located on adjacent cells. Binding to its receptor, IL-1 β induces its own synthesis and that of several other inflammatory cytokines, chemokines, and proteases including IL-6, and tumor necrosis factor alpha (TNF- α), nitric oxide (NO), and reactive oxygen species (Fig. 1v) [62, 63]. The extent of brain injury following stroke appears to depend on the magnitude of this IL-1 β -driven inflammatory cascade, since blockade of IL-1 β signaling through the inhibition of the NLRP3 inflammasome or with the IL-1R antagonist (IL-1RA) reduces

brain inflammation and injury and improves neurologic function in rodent models of ischemic stroke or TBI [64–67]. In human studies, IL-1 β expression has been shown to be elevated in post-mortem brain tissue of adult patients following stroke [68].

Brain injury results in the infiltration of peripheral immune cells to the site of damage (Fig. 1vi). The infiltration of leukocytes into the injured brain greatly exacerbates ischemic brain injury [69]. Migration of monocytes, neutrophils, and T lymphocytes into the injured brain is facilitated by the breakdown of the blood brain barrier and inflammatory cytokines. At the site of brain injury, these cells secrete additional inflammatory cytokines that act in a paracrine and autocrine manner to exacerbate brain inflammation and injury. CD4 $^{+}$ T lymphocytes in particular appear to play an important role in controlling post-ischemic brain injury [69]. In experimental animal stroke models, the infiltration of IL-17-secreting T cells (Th17) exacerbates brain injury [70], while another CD4 $^{+}$ T cell subset, regulatory T cells (Treg), dampen inflammation and protect against post-ischemic brain injury [71]. The anti-inflammatory effect of Treg cells is related to their secretion of anti-inflammatory molecules IL-10 and TGF- β . The disrupted balance between these 2 CD4 $^{+}$ T cell subsets, namely, an excess of pro-inflammatory Th17 cells relative to anti-inflammatory Treg cells, has been implicated in chronic inflammation and autoimmunity [72]. Preliminary evidence of an altered Th17/Treg balance in stroke was recently demonstrated [73]. Brain inflammation alters the functioning of hypothalamic orexin-secreting neurons and decreases the synthesis and activity of monoamine neurotransmitters (Fig. 1vii) to induce PSF and depression respectively (Fig. 1viii).

Whereas inflammation and immune system both exert deleterious effect, they also contribute to the repair of damaged tissue depending on the stage of tissue injury, the magnitude of response, and whether the inflammatory or immune response also activates regeneration and long-term recovery [74, 75]. Immunomodulatory treatment has shown promises in promoting stroke recovery [76].

Concurrent with brain inflammation, immunological changes can also be observed in the circulation, liver, gut, bone marrow, and spleen [77–79]. Marked changes in circulating levels of several inflammatory markers including IL-1 β , IL-1 α , TNF- α , IL-6, IL-8, soluble TNF receptor 1, IL-10, IL-1RA, and C-reactive protein (CRP) have been observed in the acute phase post stroke. In a recent study, Zeng et al. [80] compared circulating levels of CD40L, IFN- γ , IL-1 α , IL-1 β , IL-6, IL-8, IL-17, and

Fig. 1. Proposed mechanism of post-stroke related fatigue and depression. (i) Stroke causes a lack of oxygen and glucose to brain tissue, interrupting production of ATP. ATP depletion results in cell damage and eventually cell death; (ii) Molecules released from dead or dying cells, commonly referred to as DAMPs, are recognized by pattern recognition receptors belonging to the TLR family located on the surface of microglia, sentinel cells of innate immunity in brain tissue; (iii) DAMP-TLR binding initiates the NF- κ B signaling cascade, inducing the synthesis of pro-IL-1 β ; (iv) The NLRP3 inflammasome processes pro-IL-1 β to mature IL-1 β , which is rapidly secreted into the extracellular space where it is

available to bind to IL-1R located on adjacent cells; (v) Binding to its receptor, IL-1 β induces its own synthesis and that of several other inflammatory cytokines and chemokines; (vi) Localized production of inflammatory cytokines and chemokines triggers the infiltration of immune cells into the injured brain; (vii) Brain inflammation alters the functioning of hypothalamic orexin-secreting neurons and decreases the synthesis and activity of monoamine neurotransmitters; (viii) The unknown pathway to induce PSF and depression. DAMPs, danger associated molecular patterns; TLR, toll-like receptor; IL-1 β , interleukin-1 β .

TNF- α 72 h after symptom presentation with levels in 105 non-stroke controls matched on age, gender, and cardiovascular risk factors. Circulating levels of IL-6, IL-8, and TNF- α were significantly higher in stroke patients relative to their non-stroke counterparts. IL-17 was found to induce the activation and mobilization of neutrophils to sites of inflammation. In ischemic brain injury, IL-17 could induce blood brain barrier breakdown and allow for an uncontrolled influx of peripheral immune cells, like neutrophils, and lead to the formation of cytokines as a cause of secondary inflammation [81, 82]. In a similar study, Ormstad et al. [83] observed

elevated serum levels of IL-1RA, IL-6, IL-8, IL-10, IL-12, IL-18, and Gro- α at 72 h post ischemic stroke compared to healthy controls matched on age and gender but not cardiovascular risk factors. In general, elevations in circulating pro-inflammatory cytokines such as IL-1 β , TNF- α , and IL-6 have been linked to larger infarct size and worse prognosis, while the opposite is true for circulating levels of anti-inflammatory cytokines like IL-10 and IL-1RA [69, 84]. Becker [27] indicated that overall systemic milieu after stroke, rather than a single cytokine or other biological substrate that cause either PSD or PSF.

Despite evidence that stroke induces systemic inflammation and sickness behavior-like symptoms, few studies have examined the association between stroke-induced inflammation and PSF or PSD. Ormstad et al. [85, 86] investigated whether serum levels of inflammatory markers 72 h post-stroke could predict long-term PSF and PSD. Serum levels of IL-1 β , IL-1RA, IL-2, IL-4, IL-6, IL-8, IL-9, IL-10, IL-12, TNF- α , IFN- γ , Gro- α , and IL-18 were measured in 48 stroke patients within 72 h of symptom presentation. Fatigue (Fatigue Severity Scale) and depression (Beck Depression Inventory) were measured at 6, 12, and 18 months post stroke. Associations between the serum inflammatory analyte and PSF and PSD at 6, 12, and 18 months were then examined. The authors observed a positive correlation between acute IL-1 β levels and fatigue 6 months post stroke, while IL-1RA and IL-9 levels negatively correlated with fatigue level at 12 months. Neither size nor location of infarct was associated with fatigue. While fatigue and depression were correlated at 6, 12, and 18 months post stroke, unlike PSF, an association between the inflammatory analyte and PSD was not found. However, limitations of this study, which included the relatively small sample size, the high number of inflammatory analytes that were measured, and the failure to account for multiple comparisons in the analysis, make research findings difficult to interpret. In a follow-up study, these authors demonstrated that stroke survivors with PSF at 18 months post stroke had higher serum levels of kynurenic acid, a marker of availability of tryptophan for serotonin synthesis than those without [87]. Although depression is linked to reduced serotonin activity, these authors did not observe a similar association between serum kynurenic acid and PSD. In our recent study, we found stroke survivors in the severe fatigue group had greater anxiety and depression than in the low-moderate fatigue group. Serum IL-10 levels negatively correlated with the Th17/Treg ratio, and the latter was associated with the severity of PSF [88]. Kutlubaev et al. [89] reviewed 17 studies and found that one study reported CRP levels associated with fatigue.

The vast majority of studies have focused on inflammatory influences on PSD. Two review papers [90, 91] provided evidence that proinflammatory cytokines, such as IL-1 β , TNF- α , or IL-18, resulting from stroke may lead to an amplification of the inflammatory process, widespread activation of 2,3-dioxygenase, and to a subsequent depletion of serotonin. Spalletta et al. [92] performed an extensive neuropsychiatric evaluation of 48 ischemic stroke patients 72 h after the presentation of stroke symptoms and collected fasting peripheral blood

for measurement of IL-6 at the same time point. Elevated serum IL-6 levels were associated with depressed mood, loss of interest, loss of weight/appetite, and insomnia. Like IL-6, elevated circulating levels of the proinflammatory cytokine IL-18 are associated with major depressive disorder [93]. IL-18 belongs to the IL-1 family of proinflammatory cytokines, and circulating levels are elevated post stroke. To determine whether high IL-18 levels were associated with PSD, Yang et al. [94] measured fasting serum levels of IL-18 in 100 stroke patients on 1 and 7 days post stroke and depressive symptoms (Hamilton Depression Scale) on 3, 7, and 14 days, as well as 6 months post stroke. They found that elevated serum IL-18 on 7 days post stroke was associated with PSD in the acute phase post stroke and 6 months thereafter [94].

Similarly, Su et al. [95] followed 144 ischemic stroke patients for weeks after a first stroke and for 1, 3, 6, 9, and 12 months after discharge. Fasting serum levels of IL-1 β , IL-6, IL-10, TNF- α , and IFN- γ and depressive symptom severity (Hamilton Depression Scale) were assessed at each time point. Only 12% of their cohort developed PSD during the 1-year follow-up period ($n = 12$). Although IL-1 β levels were undetectable in the majority of samples, change in serum levels of IL-6, IL-10, TNF- α , and IFN- γ were significantly higher in the PSD group relative to the non-PSD group. A limitation of this study was the small sample size and the small number of participants who developed PSD during the study period. The incidence of PSD in this cohort was lower than previously reported, which is likely explained by the fact that approximately a third of patients participated in a PSD prevention trial and received selective serotonin reuptake inhibitors (SSRIs). More recently, Yin et al. [96] found that neither homocysteine nor high sensitivity CRP alone was related to PSD. However, the coexistence of higher homocysteine and higher hs-CRP was associated with subsequent PSD in the acute phase of ischemic stroke, independent of established conventional risk factors [96]. In addition, high serum vitamin D levels were found to be protective against PSD [97, 98].

DNA polymorphisms in some inflammatory cytokine genes predict the magnitude of their expression following an inflammatory stimulus [99, 100]. Kim et al. [101] determined whether alleles related to higher expression of pro-inflammatory cytokines (IL-1 β , IL-8, and TNF- α) and lower expression of anti-inflammatory cytokines (IL-4 and IL-10) were associated with PSD. Depression (Mini International Neuropsychiatric Interview) was assessed in 276 patients 9–15 days post stroke, and participants were classified into severe PSD ($n = 29$), all PSD

(minor and severe, $n = 77$), or no PSD ($n = 199$). Study findings revealed that the IL-4 + 33C/C and IL-10 -1082A/A genotypes were associated with severe PSD and all PSD, respectively. In contrast, there was no association between PSD and any of the proinflammatory cytokine alleles. This study suggests that an impaired anti-inflammatory response to stroke increases the risk of acute PSD presumably by enhancing the production and/or activity of proinflammatory cytokines. In summary, there have been few clinical studies that have sought to examine the relationship between inflammation and stroke-related symptoms as a primary aim. Those that have are in general agreement that stroke-induced inflammatory signaling may play a role in the etiology of these symptoms. To our knowledge, only 1 animal study has specifically sought to examine the role of stroke-induced neuroinflammation in PSF or PSD. Craft and Devries [102] examined sucrose consumption as a measure of anhedonia in mice following middle cerebral artery occlusion. They found that middle cerebral artery occlusion mice displayed anhedonia over a 7-day period post treatment. This depressive-like behavior was reversed in mice administered IL-1RA by intracerebroventricular injection, which supports a role for stroke-induced IL-1 β in the etiology of PSD [102].

Potential Treatment of PSF and Depression

As mentioned above, the exact mechanisms of origin and persistence of PSF and PSD are still elusive, and evidence-supported treatment for PSF and PSD is still lacking. A few studies explored whether the serotonin reuptake inhibitor (SSRIs) and modafinil was effective in reducing PSF and PSD [103–110] (Table 1). Results indicate that the effect of antidepressants is not ascertained, while Modafinil seems to improve fatigue in a specific subgroup of stroke patients. Further multicenter, random controlled clinical trials are needed to provide evidence-based practice for the anti-inflammatory treatment of PSF and PSD. McGeough et al. [111] reviewed 3 trials that recruited a total of 239 stroke patients to 3 treatments (fluoxetine, tirilazad, chronic disease self-management program). At follow-up, there was no difference in fatigue levels between the treatment and control. However, the trials were too small to draw firm conclusion and further studies are warranted. A meta-analysis showed that citalopram shows a faster action than the other SSRIs, though their efficacy on PSD treatment is similar [112]. Besides SSRIs, noradrenaline reuptake inhibitor and tricyclic an-

tidepressant are also associated with decrease of PSD [113]. Kang et al. [114] found that increased levels of IL-6 and IL-18 were correlated with depression within 2 weeks and 1 year following stroke. There was an interaction between statin use and IL-6 in patients with depressive disorder at 1 year. Recently, a systematic review [115] reported anti-inflammatory treatment; in particular, cerceceib alleviates depressive symptoms. The identification of the optimal population that could benefit from the treatment might be warranted. In a recent ACTION trial, 161 patients with acute ischemia stroke were treated by placebo or natalizumab, an antibody against the leukocyte adhesion molecule $\alpha 4$ integrin. Results showed that natalizumab administered up to 9 h after stroke onset did not change infarct growth but might have beneficial effects in cognitive and functional recovery [76].

Conclusions and Future Research

PSF is a common and often debilitating consequence of stroke. It reduces quality of life, is a barrier to stroke rehabilitation, and increases stroke-related mortality. There is a critical need to understand the etiological mechanisms underlying PSF, as this knowledge will facilitate the development of timely, targeted interventions to manage this disabling symptom effectively. An immune system response, characterized by secretion of IL-1 β and other inflammatory cytokines and chemokines, and the infiltration of immune cells into the damaged area, occurs rapidly after an ischemic or hemorrhagic event in the brain. Understanding the role of this inflammatory response on infarct size and functional recovery from stroke has been the focus of review. The role that inflammation plays in the initiation and perpetuation of post-stroke symptoms has received less attention. Yet, research accumulated over the past 20 years has provided compelling evidence of the role of inflammatory cytokines in the genesis of these symptoms. The neural targets that mediate some of the cytokine-induced behavioral changes have been elucidated in experimental studies. For instance, decreased activity of hypothalamic orexin neurons is associated with cytotoxic chemotherapy-induced fatigue/lethargy [53]. This connection was made possible by modeling cytokine-induced sickness behavior in rodents. A similar approach could be used to model stroke-related symptoms, thus allowing the neural biological basis of PSF to be defined, which in turn, would allow the identification of new drug targets for the management of PSF and related symptoms.

Table 1. Studies of PSF and PSD treatment

Participants	Study design	Fatigue/depression assessments	Interventions	Outcomes	Reference
First-ever stroke <12 months after onset (<i>n</i> = 60)	Randomized control trial	FSS HAM-D	Duloxetine (60–120 mg/day) Citalopram (20–40 mg/day) Sertraline (50–200 mg/day) For 3 months	No significant change in FSS Improvement of depression in all study groups	103
Stroke patients Average 14 months after onset (<i>n</i> = 83)	Double-blind, placebo-controlled trial	VAS FSS	Fluoxetine (20 mg/day) Placebo For 3 months	Fluoxetine does not improve post-stroke fatigue although depression improved	104
Stroke patients 12–48 months after stroke (<i>n</i> = 23)	Case control study	FAI	Modafinil (50–200 mg/day) For 3 months	Modafinil seems to improve fatigue in patients whose lesions located in brainstem and/or diencephalon but not in cortical	105
Stroke patients (<i>n</i> = 41)	Randomized double-blinded, placebo-controlled trial	MFI-20 GF FSS	Modafinil (400 mg/day) Placebo For 90 days	No significant differences in MFI-20 GF Patients in the modafinil group had better scores on the FSS	107
Stroke patients At least 3 months after stroke (<i>n</i> = 36)	Randomized double-blinded placebo-controlled cross-over trial	Multidimensional fatigue inventory The DASS	Modafinil (200 mg/day) or placebo for 6 weeks 1-week washout period Swap treatment arms for 6 weeks	Modafinil significantly decrease fatigue. DASS was not improved with modafinil therapy	108
Stroke patients Acute stroke within 21 days (<i>n</i> = 478)	Placebo controlled double-blind trial	MADRS	Escitalopram (10 mg/day) Placebo For 3 months	Escitalopram did not significantly reduce moderate or severe depressive syndromes	109
Stroke patients At discharge and 3, 6, and 9 months after discharge (<i>n</i> = 274)	Single-blind randomized controlled trial	HAMD Bech-Rafaelson MES	Placebo and general discussion Citalopram and general discussion Placebo and cognitive behavioral therapy	Citalopram has similar effect as rehabilitation alone for early-onset PSD Rehabilitation and citalopram are more effective than rehabilitation alone for delayed-onset PSD	110

FSS, fatigue severity scale; VAS, visual analogue scale; FAI, fatigue assessment inventory; DASS, depression, anxiety, and stress scale; MADRS, montgomery-asberg depression rating scale; MFI-20 GF, multidimensional fatigue inventory-20 general fatigue score; MES, melancholia scale; HAMD, hamilton depression rating scale; PSF, post-stroke fatigue; PSD, post stroke depression.

To our knowledge there has been only one pre-clinical study aimed at understanding the role of stroke-induced IL-1 β in the etiology of depression. The development of a clinically relevant animal model of PSF would facilitate future experiments. Development of such a model was critical for understanding the role of inflammatory signaling in the etiology of CTRF [53, 116]. There have been only a handful of studies in which stroke-related immune changes were correlated to symptom severity in stroke survivors. Many studies measured only PSF, PSF and PSD, or only PSD; yet, we know that stroke survivors experience a cluster of symptoms including PSF, PSD, anxiety, and changes in sleep and cognitive function. Rothenburg et al. [117] found that a post-stroke inflammatory response (serum CRP, but neither IL-6 nor IFN-gama) may be important in subacute, post-stroke cognitive impairment. Nemeth et al. [118] reported that inflammatory mechanisms contribute to microembolism-induced anxiety-like and depressive-like behaviors. Pro-inflammatory cytokines, such as TNF, IL-1, and IL-6, have been associated with sleep dysfunction [119]. It is unclear from existing clinical studies whether these symptoms cluster together over time in stroke survivors. Indeed, we would expect this to be the case if they share an underlying etiology. A symptom cluster approach would increase our understanding of the interrelationship between these symptoms and PSF. A similar approach has been used extensively to understand the relationship between CTRF and other cancer-related symptoms [120]. The investigation of fatigue/depression in other chronic neuroinflamma-

tory disease, such as multiple sclerosis (MS), has provided important insights to understand the relationship between neuroinflammation and PSD/PSF. Both depression and fatigue are common in patients with MS. Cytokines such as IL-1 and TNF-alpha play a role in MS fatigue by paracrine. Immunotherapeutic can stabilize and meliorate fatigue in parallel to their damping effects on the neuroinflammation process [121]. While findings from prior studies are generally consistent with a role for inflammatory signaling in the etiology of post-stroke related symptoms, several limitations, including insufficient sample size; lack of a non-stroke control group matched for age, gender, and cardiovascular risk factors; the fact that many instruments that measure fatigue do not clearly differentiate fatigue from depression; and heterogeneity in the timing of symptom and cytokine measurement, weaken study conclusions. Future studies are needed to address these limitations in order to generate robust evidence of an association between stroke-related inflammatory processes and stroke-related symptoms. The elucidation of the association between stroke-related inflammatory processes and depression and fatigue would be very important to demonstrate the potential target to minimize the inflammatory effect in the management of PSF and depression.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

References

- 1 Joo H, George MG, Fang J, Wang G: A literature review of indirect costs associated with stroke. *J Stroke Cerebrovasc Dis* 2014;23:1753–1763.
- 2 Go AS, Mozaffarian D, Roger VL, et al: Heart disease and stroke statistics – 2014 update: a report from the American Heart Association. *Circulation* 2014;129:e28–e292.
- 3 American Heart Association. Heart Disease and Stroke Statistics 2014 Update, 2014.
- 4 Appellos P: Prevalence and predictors of pain and fatigue after stroke: a population-based study. *Int J Rehabil Res* 2006;29:329–333.
- 5 Lynch J, Mead G, Greig C, Young A, Lewis S, Sharpe M: Fatigue after stroke: the development and evaluation of a case definition. *J Psychosom Res* 2007;63:539–544.
- 6 Skaner Y, Nilsson GH, Sundquist K, Hassler E, Krakau I: Self-rated health, symptoms of depression and general symptoms at 3 and 12 months after a first-ever stroke: a municipality-based study in Sweden. *BMC Fam Pract* 2007;8:61.
- 7 Mead G, Lynch J, Greig C, Young A, Lewis S, Sharpe M: Evaluation of fatigue scales in stroke patients. *Stroke* 2007;38:2090–2095.
- 8 Schepers VP, Visser-Meily AM, Ketelaar M, Lindeman E: Poststroke fatigue: course and its relation to personal and stroke-related factors. *Arch Phys Med Rehabil* 2006;87:184–188.
- 9 Crosby GA, Munshi S, Karat AS, Worthington E, Lincoln NB: Fatigue after stroke: frequency and effect on daily life. *Disabil Rehabil* 2012;34:633–637.
- 10 Christensen D, Johnsen SP, Watt T, Harder I, Kirkevold M, Andersen G: Dimensions of post-stroke fatigue: a two-year follow-up study. *Cerebrovasc Dis* 2008;26:134–141.
- 11 van de Port IG, Kwakkel G, Schepers VP, Heinemans CT, Lindeman E: Is fatigue an independent factor associated with activities of daily living, instrumental activities of daily living and health-related quality of life in chronic stroke? *Cerebrovasc Dis* 2007;23:40–45.
- 12 Radman N, Staub F, Abouafia-Brakha T, Berner A, Bogousslavsky J, Annoni JM: Post-stroke fatigue following minor infarcts: a prospective study. *Neurology* 2012;79:1422–1427.
- 13 Moran GM, Fletcher B, Feltham MG, Calvert M, Sackley C, Marshall T: Fatigue, psychological and cognitive impairment following transient ischaemic attack and minor stroke: a systematic review. *Eur J Neurol* 2014;21:1258–1267.
- 14 Bogousslavsky J: William Feinberg lecture 2002: emotions, mood, and behavior after stroke. *Stroke* 2003;34:1046–1050.
- 15 van der Werf SP, van den Broek HL, Anten HW, Bleijenberg G: Experience of severe fatigue long after stroke and its relation to depressive symptoms and disease characteristics. *Eur Neurol* 2001;45:28–33.

- 16 De Groot MH, Phillips SJ, Eskes GA: Fatigue associated with stroke and other neurologic conditions: Implications for stroke rehabilitation. *Arch Phys Med Rehabil* 2003;84:1714–1720.
- 17 van de Port IG, Kwakkel G, Schepers VP, Lindeman E: Predicting mobility outcome one year after stroke: a prospective cohort study. *J Rehabil Med* 2006;38:218–223.
- 18 Carlsson GE, Moller A, Blomstrand C: A qualitative study of the consequences of 'hidden dysfunctions' one year after a mild stroke in persons <75 years. *Disabil Rehabil* 2004;26:1373–1380.
- 19 Haacke C, Althaus A, Spottke A, Siebert U, Back T, Dodel R: Long-term outcome after stroke: evaluating health-related quality of life using utility measurements. *Stroke* 2006;37:193–198.
- 20 Glader EL, Stegmayr B, Asplund K: Post-stroke fatigue: a 2-year follow-up study of stroke patients in Sweden. *Stroke* 2002;33:1327–1333.
- 21 Lerdal A, Gay CL: Fatigue in the acute phase after first stroke predicts poorer physical health 18 months later. *Neurology* 2013;81:1581–1587.
- 22 Yang SY, Kong KH: Level and predictors of participation in patients with stroke undergoing inpatient rehabilitation. *Singapore Med J* 2013;54:564–568.
- 23 Morley W, Jackson K, Mead GE: Post-stroke fatigue: an important yet neglected symptom. *Age Ageing* 2005;34:313.
- 24 Ayerbe L, Ayis S, Rudd AG, Heuschmann PU, Wolfe CD: Natural history, predictors, and associations of depression 5 years after stroke: the South London Stroke Register. *Stroke* 2011;42:1907–1911.
- 25 Hackett ML, Pickles K: Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. *Int J Stroke* 2014;9:1017–1025.
- 26 Hackett ML, Yapa C, Parag V, Anderson CS: Frequency of depression after stroke: a systematic review of observational studies. *Stroke* 2005;36:1330–1340.
- 27 Becker KJ: Inflammation and the silent sequelae of stroke. *Neurotherapeutics* 2016;13:801–810.
- 28 Choi-Kwon S, Kim JS: Poststroke fatigue: an emerging, critical issue in stroke medicine. *Int J Stroke* 2011;6:328–336.
- 29 Pascoe MC, Crewther SG, Carey LM, Crewther DP: Inflammation and depression: why poststroke depression may be the norm and not the exception. *Int J Stroke* 2011;6:128–135.
- 30 Sandu RE, Buga AM, Uzoni A, Petcu EB, Popa-Wagner A: Neuroinflammation and comorbidities are frequently ignored factors in CNS pathology. *Neural Regen Res* 2015;10:1349–1355.
- 31 Fedoroff JP, Starkstein SE, Parikh RM, Price TR, Robinson RG: Are depressive symptoms nonspecific in patients with acute stroke? *Am J Psychiatry* 1991;148:1172–1176.
- 32 Kutlubaev MA, Shenkin SD, Farrall AJ, et al: CT and clinical predictors of fatigue at one month after stroke. *Cerebrovasc Dis Extra* 2013;3:26–34.
- 33 Naess H, Nyland HI, Thomassen L, Aarseth J, Myhr KM: Fatigue at long-term follow-up in young adults with cerebral infarction. *Cerebrovasc Dis* 2005;20:245–250.
- 34 Park JY, Chun MH, Kang SH, Lee JA, Kim BR, Shin MJ: Functional outcome in poststroke patients with or without fatigue. *Am J Phys Med Rehabil* 2009;88:554–558.
- 35 Tang WK, Chen YK, Mok V, et al: Acute basal ganglia infarcts in poststroke fatigue: an MRI study. *J Neurol* 2010;257:178–182.
- 36 Vuletic V, Lezaic Z, Morovic S: Post-stroke fatigue. *Acta Clin Croat* 2011;50:341–344.
- 37 Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW: From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 2008;9:46–56.
- 38 Adelman JS, Martin LB: Vertebrate sickness behaviors: adaptive and integrated neuroendocrine immune responses. *Integr Comp Biol* 2009;49:202–214.
- 39 Dantzer R, Kelley KW: Twenty years of research on cytokine-induced sickness behavior. *Brain Behav Immun* 2007;21:153–160.
- 40 Ferrari F, Villa RF: The neurobiology of depression: an integrated overview from biological theories to clinical evidence. *Mol Neurobiol* 2017;54:4847–4865.
- 41 Delva M, Lytvynenko N, Delva I: Factors associated with the time-based phenomenology of post-stroke fatigue over the first year after stroke occurrence. *Georgian Med News* 2018:92–97.
- 42 Choi-Kwon S, Han SW, Kwon SU, Kim JS: Poststroke fatigue: characteristics and related factors. *Cerebrovasc Dis* 2005;19:84–90.
- 43 Meng G, Ma X, Li L, et al: Predictors of early-onset post-ischemic stroke depression: a cross-sectional study. *BMC Neurol* 2017;17:199.
- 44 Shi Y, Yang D, Zeng Y, Wu W: Risk factors for post-stroke depression: a meta-analysis. *Front Aging Neurosci* 2017;9:218.
- 45 Guiraud V, Gallarda T, Calvet D, et al: Depression predictors within six months of ischemic stroke: The DEPRESS Study. *Int J Stroke* 2016;11:519–525.
- 46 Wei C, Zhang F, Chen L, Ma X, Zhang N, Hao J: Factors associated with post-stroke depression and fatigue: lesion location and coping styles. *J Neurol* 2016;263:269–276.
- 47 Grossberg AJ, Zhu X, Leininger GM, et al: Inflammation-induced lethargy is mediated by suppression of orexin neuron activity. *J Neurosci* 2011;31:11376–11386.
- 48 Harden LM, du Plessis I, Poole S, Laburn HP: Interleukin (IL)-6 and IL-1 beta act synergistically within the brain to induce sickness behavior and fever in rats. *Brain Behav Immun* 2008;22:838–849.
- 49 Scarlett JM, Zhu X, Enriori PJ, et al: Regulation of agouti-related protein messenger ribonucleic acid transcription and peptide secretion by acute and chronic inflammation. *Endocrinology* 2008;149:4837–4845.
- 50 Saper CB, Scammell TE, Lu J: Hypothalamic regulation of sleep and circadian rhythms. *Nature* 2005;437:1257–1263.
- 51 Kukkonen JP: Physiology of the orexinergic/hypocretinergic system: a revisit in 2012. *Am J Physiol Cell Physiol* 2013;304:C2–32.
- 52 Hara J, Beuckmann CT, Nambu T, et al: Genetic ablation of orexin neurons in mice results in narcolepsy, hypophagia, and obesity. *Neuron* 2001;30:345–354.
- 53 Weymann KB, Wood LJ, Zhu X, Marks DL: A role for orexin in cytotoxic chemotherapy-induced fatigue. *Brain Behav Immun* 2014;37:84–94.
- 54 Baumann CR: Traumatic brain injury and disturbed sleep and wakefulness. *Neuromolecular Med* 2012;14:205–212.
- 55 Baumann CR, Bassetti CL, Valko PO, et al: Loss of hypocretin (orexin) neurons with traumatic brain injury. *Ann Neurol* 2009;66:555–559.
- 56 Ormsbee MJ, Carzoli JP, Klemp A, et al: Efficacy of the repetitions in reserve-based rating of perceived exertion for the bench press in experienced and novice benchers. *J Strength Cond Res* 2017, Epub ahead of print.
- 57 Yang CH, Choi SH, Kim JS, et al: The effects of acupuncture stimulation for brain activation and alcohol abstinence self-efficacy: functional MRI study. *Evid Based Complement Alternat Med* 2017;2017:2850124.
- 58 Kaur C, Ling EA: Periventricular white matter damage in the hypoxic neonatal brain: role of microglial cells. *Prog Neurobiol* 2009;87:264–280.
- 59 Yao L, Kan EM, Kaur C, et al: Notch-1 signaling regulates microglia activation via NF- κ B pathway after hypoxic exposure in vivo and in vitro. *PLoS One* 2013;8:e78439.
- 60 Yao L, Kan EM, Lu J, et al: Toll-like receptor 4 mediates microglial activation and production of inflammatory mediators in neonatal rat brain following hypoxia: role of TLR4 in hypoxic microglia. *J Neuroinflammation* 2013;10:23.
- 61 Hanamsagar R, Torres V, Kielian T: Inflammasome activation and IL-1 β /IL-18 processing are influenced by distinct pathways in microglia. *J Neurochem* 2011;119:736–748.
- 62 Rothwell NJ, Luheshi G, Toulmond S: Cytokines and their receptors in the central nervous system: physiology, pharmacology, and pathology. *Pharmacol Ther* 1996;69:85–95.
- 63 Moskowitz MA, Lo EH, Iadecola C: The science of stroke: mechanisms in search of treatments. *Neuron* 2010;67:181–198.
- 64 Abulafia DP, de Rivero Vaccari JP, Lozano JD, Lotocki G, Keane RW, Dietrich WD: Inhibition of the inflammasome complex reduces the inflammatory response after thromboembolic stroke in mice. *J Cereb Blood Flow Metab* 2009;29:534–544.

- 65 de Rivero Vaccari JP, Lotocki G, Alonso OF, Bramlett HM, Dietrich WD, Keane RW: Therapeutic neutralization of the NLRP1 inflammasome reduces the innate immune response and improves histopathology after traumatic brain injury. *J Cereb Blood Flow Metab* 2009;29:1251–1261.
- 66 Relton JK, Martin D, Thompson RC, Russell DA: Peripheral administration of Interleukin-1 receptor antagonist inhibits brain damage after focal cerebral ischemia in the rat. *Exp Neurol* 1996;138:206–213.
- 67 Garcia JH, Liu KF, Relton JK: Interleukin-1 receptor antagonist decreases the number of necrotic neurons in rats with middle cerebral artery occlusion. *Am J Pathol* 1995;147:1477–1486.
- 68 Hopkins SJ, Rothwell NJ: Cytokines and the nervous system. I: expression and recognition. *Trends Neurosci* 1995;18:83–88.
- 69 Shichita T, Sakaguchi R, Suzuki M, Yoshimura A: Post-ischemic inflammation in the brain. *Front Immunol* 2012;3:132.
- 70 Shichita T, Sugiyama Y, Ooboshi H, et al: Pivotal role of cerebral interleukin-17-producing gammadeltaT cells in the delayed phase of ischemic brain injury. *Nat Med* 2009;15:946–950.
- 71 Liesz A, Suri-Payer E, Veltkamp C, et al: Regulatory T cells are key cerebroprotective immunomodulators in acute experimental stroke. *Nat Med* 2009;15:192–199.
- 72 Noack M, Miossec P: Th17 and regulatory T cell balance in autoimmune and inflammatory diseases. *Autoimmun Rev* 2014;13:668–677.
- 73 Hu Y, Zheng Y, Wu Y, Ni B, Shi S: Imbalance between IL-17A-producing cells and regulatory T cells during ischemic stroke. *Mediators Inflamm* 2014;2014:813045.
- 74 Chamorro A, Dirnagl U, Urra X, Planas AM: Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. *Lancet Neurol* 2016;15:869–881.
- 75 Iadecola C, Anrather J: The immunology of stroke: from mechanisms to translation. *Nat Med* 2011;17:796–808.
- 76 Elkins J, Veltkamp R, Montaner J, et al: Safety and efficacy of natalizumab in patients with acute ischaemic stroke (ACTION): a randomised, placebo-controlled, double-blind phase 2 trial. *Lancet Neurol* 2017;16:217–226.
- 77 Meisel C, Schwab JM, Prass K, Meisel A, Dirnagl U: Central nervous system injury-induced immune deficiency syndrome. *Nat Rev Neurosci* 2005;6:775–786.
- 78 Denes A, McColl BW, Leow-Dyke SF, et al: Experimental stroke-induced changes in the bone marrow reveal complex regulation of leukocyte responses. *J Cereb Blood Flow Metab* 2011;31:1036–1050.
- 79 Brambilla R, Couch Y, Lamberts KL: The effect of stroke on immune function. *Mol Cell Neurosci* 2013;53:26–33.
- 80 Zeng L, Wang Y, Liu J, et al: Pro-inflammatory cytokine network in peripheral inflammation response to cerebral ischemia. *Neurosci Lett* 2013;548:4–9.
- 81 Waisman A, Hauptmann J, Regen T: The role of IL-17 in CNS diseases. *Acta Neuropathol* 2015;129:625–637.
- 82 Candelario-Jalil E, Gonzalez-Falcon A, Garcia-Cabrera M, Leon OS, Fiebich BL: Post-ischaemic treatment with the cyclooxygenase-2 inhibitor nimesulide reduces blood-brain barrier disruption and leukocyte infiltration following transient focal cerebral ischaemia in rats. *J Neurochem* 2007;100:1108–1120.
- 83 Ormstad H, Aass HC, Lund-Sorensen N, Amthor KF, Sandvik L: Serum levels of cytokines and C-reactive protein in acute ischemic stroke patients, and their relationship to stroke lateralization, type, and infarct volume. *J Neurol* 2011;258:677–685.
- 84 Bodhankar S, Chen Y, Vandembark AA, Murphy SJ, Offner H: Treatment of experimental stroke with IL-10-producing B-cells reduces infarct size and peripheral and CNS inflammation in wild-type B-cell-sufficient mice. *Metab Brain Dis* 2014;29:59–73.
- 85 Ormstad H, Aass HC, Amthor KF, Lund-Sorensen N, Sandvik L: Serum cytokine and glucose levels as predictors of poststroke fatigue in acute ischemic stroke patients. *J Neurol* 2011;258:670–676.
- 86 Ormstad H, Aass HC, Amthor KF, Lund-Sorensen N, Sandvik L: Serum levels of cytokines, glucose, and hemoglobin as possible predictors of poststroke depression, and association with poststroke fatigue. *Int J Neurosci* 2012;122:682–690.
- 87 Ormstad H, Verkerk R, Amthor KF, Sandvik L: Activation of the kynurenine pathway in the acute phase of stroke and its role in fatigue and depression following stroke. *J Mol Neurosci* 2014;54:181–187.
- 88 Liu X, Kenkare K, Li S, et al: Increased Th17/Treg ratio in poststroke fatigue. *Mediators Inflamm* 2015;2015:931398.
- 89 Kutlubaev MA, Duncan FH, Mead GE: Biological correlates of post-stroke fatigue: a systematic review. *Acta Neurol Scand* 2012;125:219–227.
- 90 Spalletta G, Bossu P, Ciarabella A, Bria P, Caltagirone C, Robinson RG: The etiology of poststroke depression: a review of the literature and a new hypothesis involving inflammatory cytokines. *Mol Psychiatry* 2006;11:984–991.
- 91 Fang J, Cheng Q: Etiological mechanisms of post-stroke depression: a review. *Neurol Res* 2009;31:904–909.
- 92 Spalletta G, Cravello L, Imperiale F, et al: Neuropsychiatric symptoms and interleukin-6 serum levels in acute stroke. *J Neuropsychiatry Clin Neurosci* 2013;25:255–263.
- 93 Merendino RA, Di Rosa AE, Di Pasquale G, et al: Interleukin-18 and CD30 serum levels in patients with moderate-severe depression. *Mediators Inflamm* 2002;11:265–267.
- 94 Yang L, Zhang Z, Sun D, Xu Z, Zhang X, Li L: The serum interleukin-18 is a potential marker for development of post-stroke depression. *Neurol Res* 2010;32:340–346.
- 95 Su JA, Chou SY, Tsai CS, Hung TH: Cytokine changes in the pathophysiology of post-stroke depression. *Gen Hosp Psychiatry* 2012;34:35–39.
- 96 Yin J, Zhong C, Zhu Z, et al: Elevated circulating homocysteine and high-sensitivity C-reactive protein jointly predicts post-stroke depression among Chinese patients with acute ischemic stroke. *Clin Chim Acta* 2018;479:132–137.
- 97 Shaffer JA, Edmondson D, Wasson LT, et al: Vitamin D supplementation for depressive symptoms: a systematic review and meta-analysis of randomized controlled trials. *Psychosom Med* 2014;76:190–196.
- 98 Wang Q, Zhu Z, Liu Y, Tu X, He J: Relationship between serum vitamin D levels and inflammatory markers in acute stroke patients. *Brain Behav* 2018;8:e00885.
- 99 Iacoviello L, Di Castelnuovo A, Gattone M, et al: Polymorphisms of the interleukin-1beta gene affect the risk of myocardial infarction and ischemic stroke at young age and the response of mononuclear cells to stimulation in vitro. *Arterioscler Thromb Vasc Biol* 2005;25:222–227.
- 100 Jerrard-Dunne P, Sitzler M, Risley P, Buehler A, von Kegler S, Markus HS: Inflammatory gene load is associated with enhanced inflammation and early carotid atherosclerosis in smokers. *Stroke* 2004;35:2438–2443.
- 101 Kim JM, Stewart R, Kim SW, et al: Associations of cytokine gene polymorphisms with post-stroke depression. *World J Biol Psychiatry* 2012;13:579–587.
- 102 Craft TK, DeVries AC: Role of IL-1 in post-stroke depressive-like behavior in mice. *Biol Psychiatry* 2006;60:812–818.
- 103 Karaiskos D, Tzavellas E, Spengos K, Vassilopoulou S, Paparrigopoulos T: Duloxetine versus citalopram and sertraline in the treatment of poststroke depression, anxiety, and fatigue. *J Neuropsychiatry Clin Neurosci* 2012;24:349–353.
- 104 Choi-Kwon S, Choi J, Kwon SU, Kang DW, Kim JS: Fluoxetine is not effective in the treatment of post-stroke fatigue: a double-blind, placebo-controlled study. *Cerebrovasc Dis* 2007;23:103–108.
- 105 Brioschi A, Gramigna S, Werth E, et al: Effect of modafinil on subjective fatigue in multiple sclerosis and stroke patients. *Eur Neurol* 2009;62:243–249.
- 106 Villa RF, Ferrari F, Moretti A: Post-stroke depression: mechanisms and pharmacological treatment. *Pharmacol Ther* 2017:131–144.
- 107 Poulsen MB, Damgaard B, Zerahn B, Overgaard K, Rasmussen RS: Modafinil may alleviate poststroke fatigue: a randomized, placebo-controlled, double-blinded trial. *Stroke* 2015;46:3470–3477.
- 108 Bivard A, Lillicrap T, Krishnamurthy V, et al: MIDAS (modafinil in debilitating fatigue after stroke): a randomized, double-blind, placebo-controlled, cross-over trial. *Stroke* 2017;48:1293–1298.

- 109 Kim JS, Lee EJ, Chang DI, et al: Efficacy of early administration of escitalopram on depressive and emotional symptoms and neurological dysfunction after stroke: a multicentre, double-blind, randomised, placebo-controlled study. *Lancet Psychiatry* 2017;4: 33–41.
- 110 Gao J, Lin M, Zhao J, Bi S, Ni Z, Shang X: Different interventions for post-ischaemic stroke depression in different time periods: a single-blind randomized controlled trial with stratification by time after stroke. *Clin Rehabil* 2017;31:71–81.
- 111 McGeough E, Pollock A, Smith LN, et al: Interventions for post-stroke fatigue. *Cochrane Database Syst Rev* 2009;CD007030.
- 112 Cui M, Huang CY, Wang F: Efficacy and safety of citalopram for the treatment of poststroke depression: a meta-analysis. *J Stroke Cerebrovasc Dis* 2018;27:2905–2918.
- 113 Deng L, Sun X, Qiu S, et al: Interventions for management of post-stroke depression: a bayesian network meta-analysis of 23 randomized controlled trials. *Sci Rep* 2017;7: 16466.
- 114 Kang HJ, Bae KY, Kim SW, et al: Effects of interleukin-6, interleukin-18, and statin use, evaluated at acute stroke, on post-stroke depression during 1-year follow-up. *Psychoneuroendocrinology* 2016;72:156–160.
- 115 Kohler O, Benros ME, Nordentoft M, et al: Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA psychiatry* 2014;71:1381–1391.
- 116 Smith LB, Leo MC, Anderson C, Wright TJ, Weymann KB, Wood LJ: The role of IL-1 β and TNF- α signaling in the genesis of cancer treatment related symptoms (CTRS): a study using cytokine receptor-deficient mice. *Brain Behav Immun* 2014;38:66–76.
- 117 Rothenburg LS, Herrmann N, Swardfager W, et al: The relationship between inflammatory markers and post stroke cognitive impairment. *J Geriatr Psychiatry Neurol* 2010;23:199–205.
- 118 Nemeth CL, Miller AH, Tansey MG, Neigh GN: Inflammatory mechanisms contribute to microembolism-induced anxiety-like and depressive-like behaviors. *Behav Brain Res* 2016;303:160–167.
- 119 Khanijow V, Prakash P, Emsellem HA, Borum ML, Doman DB: Sleep dysfunction and gastrointestinal diseases. *Gastroenterol Hepatol (N Y)* 2015;11:817–825.
- 120 Kirkova J, Aktas A, Walsh D, Davis MP: Cancer symptom clusters: clinical and research methodology. *J Palliat Med* 2011;14: 1149–1166.
- 121 Patejdl R, Penner IK, Noack TK, Zettl UK: Multiple sclerosis and fatigue: a review on the contribution of inflammation and immune-mediated neurodegeneration. *Autoimmun Rev* 2016;15:210–220.