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# *Canadian Stroke Best Practice Recommendations*: Mood, Cognition and Fatigue following Stroke, 6th edition update 2019

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## Abstract

The 2019 update of the *Canadian Stroke Best Practice Recommendations (CSBPR) for Mood, Cognition and Fatigue following Stroke* is a comprehensive set of evidence-based guidelines addressing three important issues that can negatively impact the lives of people who have had a stroke. These include post-stroke depression and anxiety, vascular cognitive impairment, and post-stroke fatigue. Following stroke, approximately 20% to 50% of all persons may be affected by at least one of these conditions. There may also be overlap between conditions, particularly fatigue and depression. If not recognized and treated in a timely matter, these conditions can lead to worse long-term outcomes. The theme of this edition of the CSBPR is *Partnerships and Collaborations,* which stresses the importance of integration and coordination across the healthcare system to ensure timely and seamless care to optimize recovery and outcomes. Accordingly, these recommendations place strong emphasis on the importance of timely screening and assessments, and timely and adequate initiation of treatment across care settings. Ideally, when screening is suggestive of a mood or cognition issue, patients and families should be referred for in-depth assessment by healthcare providers with expertise in these areas. As the complexity of patients treated for stroke increases, continuity of care and strong communication among healthcare professionals, and between members of the healthcare team and the patient and their family is an even bigger imperative,

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as stressed throughout the recommendations, as they are critical elements to ensure smooth transitions from acute care to active rehabilitation and reintegration into their community.

**Keywords**
Stroke, transient ischemic attack, depression, vascular cognitive impairment, fatigue, guidelines

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## Introduction

Globally, stroke is the second most common cause of all deaths (11.8%), behind ischemic heart disease at 14.8%.[1] In Canada, every year, approximately 62,000 people with stroke and transient ischemic attack (TIA) are treated in Canadian hospitals, representing one patient every 9 min.[2] Not counted in this statistic are the estimated nine silent strokes that occur for each symptomatic stroke, often resulting in subtle mood and cognitive changes.[3] With advancements in acute stroke care interventions and rapid systems response, mortality from stroke is declining. While these achievements are to be celebrated, stroke remains a leading cause of adult disability, with over 400,000 people living with its effects.[4] Access to inpatient rehabilitation varies across regions, with only 19% of people accessing inpatient rehabilitation following an acute stroke inpatient stay. There are also gaps in availability of specialized services outside large urban centers.

Common consequences of stroke, including post-stroke depression (PSD) and anxiety, vascular cognitive impairment (VCI), and post-stroke fatigue (PSF), create challenges that may impede recovery and lead to poor functional outcomes and decreased quality of life. Following stroke, between 20% and 50% of all persons may be affected by at least one of these conditions.[5–7] There can be overlap in the occurrence of these conditions, increasing the complexity of diagnosis and appropriate management. Fatigue and depressive symptoms have been shown to co-exist in up to 30% of stroke survivors, which in turn may be associated with cognitive and mobility impairments.[8] The overall prevalence of depression in persons with mild cognitive impairment (MCI) was 32% in a meta-analysis including the results of 57 studies.[9] Persons with depression may progress more quickly from MCI to dementia.[10] These conditions all have the potential to delay or impede recovery, which may lead to worse long-term outcomes.[11–13] Unfortunately, these conditions may not be obvious to the person who experienced a stroke, their healthcare providers or their informal caregivers, especially if symptoms are mild or manifest slowly and progressively, or are present only later in the recovery process, when care becomes more fragmented in the community. Furthermore, recent reports on the quality of stroke services across Canada have shown that screening and monitoring of patients for PSD, fatigue, and vascular cognitive functioning issues are completed in just over half of people seen in stroke prevention clinics following stroke or TIA.[14] As a result, these conditions may not be recognized and treated in a timely manner, leaving patients and their families overwhelmed and lost as they try to navigate the healthcare system, and underscoring the need for a standardized system of care for addressing these conditions across the continuum.[15]

The 2019 update of the Canadian Stroke Best Practice Recommendations (CSBPR): Mood, Cognition and Fatigue following Stroke is a comprehensive summary of current evidence-based recommendations, focusing on the management of people who have already had an initial stroke or TIA. The theme of this edition of the CSBPR is *Partnerships and Collaborations*, which stresses the importance of integration and coordination across the healthcare system to ensure timely and seamless care of stroke patients to optimize recovery and outcomes. The importance of a coordinated and organized multidisciplinary approach to guide screening, assessment, and management decisions are emphasized throughout these guidelines, which are appropriate for use by clinicians who care for people who have experienced a stroke and their families, across multiple settings.

### *What's new in 2019?*

In areas where insufficient evidence exists, a new section, entitled clinical considerations has been added to each section, representing recommendations based on weaker evidence and/or expert consensus-based practices. In the depression section, new literature has been incorporated which suggests that prophylactic antidepressant medication can be effective in some stroke patients. There is a new, novel therapeutic agent, actovegin, which enhances oxidative metabolism in the brain and may help in the recovery of cognitive function following ischemic stroke. While it is not used currently in clinical practice, it may become more widely used in the future. There is also an updated comparison table of assessment tools for screening for

VCI and updated information on the management of PSF.

## Guideline development methodology

The *Canadian Stroke Best Practice Recommendations* development and update process follows a rigorous framework adapted from the Practice Guideline Evaluation and Adaptation Cycle.[16,17] The methodology has been used in previously published updates[18,19] and can be found on our Canadian Stroke Best Practices website at www.strokebestpractices.ca. An interdisciplinary group of experts in the areas of depression, anxiety, cognition, and fatigue were convened and participated in reviewing, drafting, and revising all recommendation statements. Selected members of the group, considered to be experts in their fields, have conducted clinical trials on the topics addressed in this module and have extensive publication records. The writing group included stroke neurologists, a geriatric psychiatrist, a clinical pharmacologist, neuropsychologists, occupational therapists, a speech-language pathologist, family physician, nurses, people who have experienced a stroke and evidence-based methodology experts. This interdisciplinary approach, which ensured that all perspectives were considered in the development of the recommendations, mitigated the risk of potential or real conflicts of interest from individual members.

A systematic literature search was conducted by experienced personnel to identify evidence for each topic area addressed in the *Mood, Cognition and Fatigue following Stroke* module. The literature for this module was updated up to February 2019. The writing group was provided with comprehensive evidence tables that included summaries of all high-quality studies identified through the literature searches (evidence tables are available at www.strokebestpractices.ca). Systematic reviews, meta-analyses, randomized controlled trials, and observational studies were included, where available. The writing group discussed and debated the quality and value of the evidence and, through consensus, developed a set of proposed recommendations. Through their discussions, additional research may have been identified and included in the evidence tables if consensus on the value of the research was achieved.

All recommendations were assigned a level of evidence ranging from A to C, according to the criteria defined in Table 1. When developing and including "C-Level" recommendations, consensus was obtained among the writing group and validated through the internal and external review process. This level of evidence was used cautiously, and only when there was a lack of stronger evidence for topics considered important system drivers for stroke care (e.g. issues related to screening and assessment). In some sections, the expert writing group felt there was additional information that should be included. Since these statements did not meet the criteria to be stated as recommendations, they were included under the term, *clinical considerations*, with the goal of providing additional guidance or clarity in the absence of evidence.

After a draft set of recommendations had been developed, they underwent an internal review conducted by the Canadian Stroke Best Practices and Quality Advisory Committee, then were sent for external review to several Canadian and international

**Table 1.** Summary of criteria for levels of evidence reported in the *Canadian Best Practice Recommendations for Stroke Care* (update 2019)

| Level of evidence | Criteria[a] |
|---|---|
| A | Evidence from a meta-analysis of randomized controlled trials or consistent findings from two or more randomized controlled trials. Desirable effects clearly outweigh undesirable effects or undesirable effects clearly outweigh desirable effects. |
| B | Evidence from a single randomized controlled trial or consistent findings from two or more well-designed non-randomized and/or non-controlled trials, and large observational studies. Desirable effects outweigh or are closely balanced with undesirable effects or undesirable effects outweigh or are closely balanced with desirable effects. |
| C | Writing group consensus and/or supported by limited research evidence. Desirable effects outweigh or are closely balanced with undesirable effects or undesirable effects outweigh or are closely balanced with desirable effects as determined by writing group consensus. Recommendations assigned a Level-C evidence may be key system drivers supporting other recommendations, and some may be expert opinion based on common, new or emerging evidence or practice patterns. |
| Clinical Consideration | Reasonable practical advice provided by consensus of the writing group on specific clinical issues that are common and/or controversial and lack research evidence to guide practice. |

[a]Adapted from Guyatt GH, Cook DJ, Jaeschke R, et al. Grades of recommendation for antithrombotic agents: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition) (published erratum in Chest 2008; 134: 473). *Chest* 2008; 133: 123S–131S.

experts who were not involved in any aspects of the guideline development. All feedback received was given careful consideration during the editing process. All recommendations are also accompanied by five additional supporting sections devoted to: the rationale (i.e. the justification for the inclusion of the selected topics), system implication (to ensure the structural elements and resources are available to achieve recommended levels of care), performance measures (to monitor care delivery and patient outcomes), a list of implementation resources, and a summary of the evidence on which the recommendations were based. Brief summaries of current research evidence are provided at the beginning of each section below. More detailed evidence summaries and links to all evidence tables, and additional knowledge translation information for the recommendations included in this publication can be found at: http://www.strokebestpractices.ca. For a more detailed description of the methodology on the development and dissemination of the *Canadian Stroke Best Practice Recommendations* please refer to the *Canadian Stroke Best Practice Recommendations* Overview and Methodology documentation available on the Canadian stroke best practices website at: http://www.strokebestpractices.ca.

## Recommendations Section 1: Mood and stroke

Post stroke depression occurs frequently. One of the most current and comprehensive estimates, obtained from a systematic review that included the results of 61 prospective studies, suggests that approximately 30% of all stroke survivors experience depressive symptoms at some point following the event.[5] The prevalence of depressive symptoms among stroke survivors is greater than that in the general population. The estimate obtained from one population-based study[20] indicated that over a two-year period, the development of new-onset depression was over three times greater (25.4% vs. 7.8%; adj HR = 4.09, 95% confidence interval (CI) 4.00–4.18) in persons recovering from stroke compared to a large, age and sex-match community-based sample. Risk factors for the development of PSD include increasing age, living alone, high levels of comorbidity, a history of depression, female gender, physical disability (modified Rankin Scale score >2 at discharge from hospital), increased initial stroke severity, cognitive impairment, and prior history of stroke.[13,20–22] Depression has also been associated with poorer functional outcomes and higher mortality.[13,23]

Since the frequency of depression is highest during the first year following stroke,[5] episodic screening should be conducted during this period. Screening can be performed during the acute inpatient stay, at the point of transition to, or during inpatient rehabilitation, upon discharge to the community and during routine health assessments. Although screening for depression has been shown to be feasible for most patients, it may not be in a sizable minority due to cognitive deficits or unresponsiveness during the early period following stroke. Karamchandani et al.[24] reported that while 70% of patients were eligible for depression screening prior to hospital discharge or transfer to another service, the remaining 30% of patients were not, due to aphasia, other medical condition, hospice/comfort measures, or prolonged intubation. Swartz et al.[11] describes the feasibility of using the two-item version of the Patient Health Questionnaire during routine clinical practice for 1500 outpatients attending a stroke prevention clinic. All patients were able to complete the screen, 89% of whom did so in less than 5 min. While many previously validated screening tools exist, those with the highest sensitivities identified from a recent meta-analysis include the 20-item Center of Epidemiological Studies-Depression Scale, the 21-item Hamilton Depression Rating Scale, and the 9-item Patient Health Questionnaire.[25]

The use of antidepressants is the mainstay of treatment for depression. Once diagnosed, use of antidepressants has been associated with a reduction of depressive symptomatology. Xu et al.[26] included 11 randomized controlled trials in a meta-analysis of patients with a clinical diagnosis of PSD and reported that antidepressant treatment was associated with a significant reduction in depression scores (standardized mean difference $= -0.96$, 95% CI $-1.41$ to $-0.51$, $p < 0.0001$) and better response to treatment (risk ratio = 1.36, 95% CI 1.01–1.83, $p = 0.04$). Similarly, a Cochrane review[27] including the results from 12 RCTs reported the odds of remission of depression (i.e. a reduction of ≥50% in depression scale scores) were significantly higher with pharmacotherapy, although many adverse events were reported. Most of the agents evaluated in these reviews were selective serotonin reuptake inhibitors and, to a lesser extent, tricyclic antidepressants. A longer duration of treatment has been shown to be effective. In one systematic review, Chen et al.[28] observed an almost perfect inverse linear relationship between length of treatment and decrease in depression rating scale scores (Spearman's rho $= -0.93$, $p = 0.001$). The benefit of antidepressants to improve functional recovery and reduce dependency in persons following stroke is uncertain, given the conflicting results of the FLAME trial,[29] which reported improved functional outcome following 90 days of treatment with 20 mg of fluoxetine (vs. placebo), and the recent FOCUS trial,[30] which reported no differences in dependency between

groups (20 mg fluoxetine vs. placebo) at six or 12 months. The use of antidepressants has been associated with reductions in emotional lability,[31] a common consequence of stroke as well as the development of PSD. In pooled analysis, based on 776 observations, the risk for development of PSD was significantly reduced with the use of prophylactic pharmacotherapy (odds ratio (OR) = 0.34, 95% 0.22–0.53, $p < 0.001$).[32,33]

Non-pharmacological interventions for the treatment of PSD include different forms of psychotherapy, physical activity, non-invasive brain stimulation, and acupuncture. While psychotherapy (including problem-solving therapy, cognitive behavioral therapy, and motivational interviewing) is probably one of the most commonly used strategies, it has not been shown to be an effective treatment for depression in person recovering from stroke when used in isolation[27]; however, these same techniques may be effective when used in combination with pharmacotherapy.[34] Behavioral therapy was shown to be effective for the treatment of PSD in persons with aphasia.[35] Although not widely used in clinical practice, acupuncture has been shown to be effective in the treatment of PSD. In a meta-analysis including the results of 15 RCTs,[36] treatment with acupuncture was associated with improved odds of recovery/remission compared with pharmacotherapy (OR = 1.48, 95% CI 1.10–1.97). Non-invasive brain stimulation, using either repetitive transcranial magnetic stimulation or transcranial direct current stimulation (tDCS), is another example of a non-traditional treatment that has been shown to improve symptoms of depression.[37,38] Physical activity

## Section 1: Post-stroke depression update 2019

### Definitions and descriptions

**Depression following stroke:** *Within this module, we consider depression following stroke*. The DSM5 category that applies is *mood disorders due to another medical condition such as stroke with depressive features, major depressive-like episode, or mixed-mood features*. It is often associated with large vessel infarction.[40,41]

- A patient who is a candidate for this diagnosis would present with depressed mood or loss of interest or pleasure along with four other symptoms of depression (e.g. weight loss, insomnia, psychomotor agitation, fatigue, feelings of worthlessness, diminished concentration, suicidal ideation) lasting two or more weeks.
- Several mechanisms, including biological, behavioral, and social factors, are involved in its pathogenesis.
- Symptoms usually occur within the first three months after stroke (early onset depression following stroke); however, may occur at any time (late onset depression following stroke). Symptoms resemble those of depression triggered by other causes, although there are some differences; people who have experienced a stroke with depression following stroke experience more sleep disturbances, vegetative symptoms, and social withdrawal.

**Vascular depression** is a newer concept incorporating a broader range of depressive disorders. Vascular depression is related to small-vessel ischemia and people experiencing vascular depression may have white matter disease seen on brain imaging. Vascular depression also includes post-stroke depression as a sub-category. People who have experienced a stroke with *vascular depression* have later age at onset, greater cognitive impairment, less family and personal history of depression, and greater physical impairment than geriatric persons with nonvascular depression. They have been found to have different responses to treatment and different prognoses. In addition, persons with vascular depression with executive dysfunction and/or persons who show progression of white matter hyperintensities over time have a poor response to treatment with antidepressants and a more chronic and relapsing clinical course.[42]

**Apathy:** Most commonly defined as a multidimensional syndrome of diminished goal-directed behavior, emotion, and cognition.[43,44] People present with loss of motivation, concern, interest, and emotional response, resulting in a loss of initiative, decreased interaction with their environment, and a reduced interest in social life. It can negatively impact recovery post-stroke. Apathy can occur as an independent syndrome, although it may also occur as a symptom of depression or dementia.[45] Apathy has been reported to occur in 29–40% of people who have experienced a stroke.[46]

**Anxiety:** Anxiety following stroke is characterized by feelings of tension, extreme apprehension and worry, and physical manifestations such as increased blood pressure. Anxiety disorders occur when symptoms become excessive or chronic. In the post-stroke literature, anxiety has been defined both by consideration of the presence and severity of symptoms using validated screening and assessment scales (such as the Hospital Anxiety and Depression Scale) or by defining syndromes using diagnostic criteria (e.g. panic disorders, general anxiety disorder, social phobia).

### Recommendations

**1.0** All people who have experienced a stroke should be considered at risk for post-stroke depression, which can occur at any stage of recovery [Evidence Level A].

i. People who have experienced a stroke and families should be given information and education about the potential impact of stroke on their mood [Evidence level C].

ii. People who have experienced a stroke and families should be provided with the opportunity to talk about the impact of stroke on their lives at all stages of care [Evidence level C]. *Refer to the CSBPR Transitions of Care Module for further information on Patient and Family Education, and Community Follow-up*[47]

**1.1. Screening for post-stroke depression**

i. All people who have experienced a stroke should be screened for post-stroke depression if deemed medically appropriate, given the high prevalence of post-stroke depression and the evidence for treating symptomatic depression post stroke [Evidence Level B]. *Note: "Medically appropriate" excludes people who have experienced a stroke who are unresponsive or who have deficits that interfere with screening for mood disorders. Any pre-stroke mental health or cognitive diagnoses should be taken into consideration during the screening process.*

ii. Screening should be undertaken by trained professionals using a validated screening tool to maximize detection of depression [Evidence Level B]. *Summary of suggested validated screening tools at www.strokebestpractices.ca.*

iii. Stroke assessments should include evaluation of risk factors for depression, particularly a history of depression [Evidence Level C]. *Refer to note below for list of risk factors.*

iv. For people who experience some degree of communication challenge or deficits following stroke, appropriate strategies that do not rely on verbal communication should be implemented for screening of possible post-stroke depression to ensure adequate detection and assessment, and access to appropriate treatment [Evidence Level C]. *Refer to the CSBPR Stroke Rehabilitation Module for further information on communication deficits.*[48]

*Note: Common risk factors associated with post-stroke depression include increasing stroke severity, functional dependence, presence of cognitive impairment, and history of previous depression. Increased functional dependence (e.g. requiring help with activities of daily living) and having a history of pre-stroke depression may be the two most salient risk factors for the development of post-stroke depression. Communication deficits and social isolation may also be considered as possible risk factors for depression. Refer to CSBPR Transitions of Care and Participation Module for information on depression in family and informal caregivers of people with stroke.*

**1.2 Assessment for post-stroke depression**

i. People who have experienced a stroke whose screening indicates a high risk for depression should be assessed in a timely manner by a healthcare professional with expertise in diagnosis, management, and follow-up of depression [Evidence Level C].

**Clinical considerations 1.2: Timing of screening for post-stroke depression (new in 2019)**

i. Screening for post-stroke depression may take place at various stages throughout the continuum of stroke care, especially at transition points, as time of onset for post-stroke depression can vary and include:
   a. At transfer from an inpatient acute setting to an inpatient rehabilitation setting;
   b. From an inpatient rehabilitation setting before return to the community;
   c. During secondary prevention clinic visits;
   d. Following discharge to the community, during follow-up appointments with consulting specialists, and during periodic health assessments with primary care practitioners.

ii. Screening for depressive symptoms could be considered during the initial acute care stay, if deemed medically appropriate, particularly if evidence of depression or mood changes is noted or if risk factors for depression are present, as outlined in Section 1.1, iii.

iii. Repeated screening may be required since the ideal timing for screening for post-stroke depression is unclear.

**1.3 Non-pharmacological management of post-stroke depression**

i. It is reasonable to consider either cognitive-behavioral therapy or interpersonal therapy as one of the first line treatments for depressive symptoms post stroke [Evidence Level B], as a monotherapy.

ii. Treatment for post-stroke depression may include psychotherapy as an adjunct in combination with antidepressants [Evidence Level A], as appropriate to the person who has experienced a stroke's health state and other deficits (e.g. communication and other cognitive deficits).

**Clinical considerations 1.3**

i. Other approaches to adjunctive treatment of post-stroke depression are emerging, with research in very early stages. These include music, mindfulness, and motivational interviewing. These therapies could be considered on an individual basis at the discretion of the treating healthcare professional in consultation with the patient.

ii. Other therapies include deep breathing; meditation; visualization; physical exercise; repetitive transcranial magnetic stimulation; or, for severe refractory depression, electro-convulsive therapy or deep brain stimulation. These have all been suggested in the literature but lack sufficient evidence for routine use and require more research.

**1.4. Pharmacotherapy for post-stroke depression**

i. People who have experienced a stroke with mild depressive symptoms or those diagnosed with minor depression may initially be managed by "watchful waiting"* (Evidence Level B). *See note below for definition of watchful waiting*.*
   a. Pharmacological treatment should be considered and started if the depression is persistent or worsens and interferes with clinical goals [Evidence Level B].

**Note: Watchful waiting is defined as a period when the patient who displays mild depressive symptoms is monitored closely without additional therapeutic interventions to determine whether the mild depressive symptoms will improve. The timeframe for watchful waiting varies in the literature, typically between 2 and 4 weeks. It is often described as including suggestions to the patient for self-help strategies and participation in physical exercise.*

ii. People diagnosed with a depressive disorder should be considered for a trial of antidepressant medication [Evidence Level A].

iii. No one drug or drug class has been found to be superior for post-stroke depression treatment. Side effect profiles, however, suggest that some selective serotonin reuptake inhibitors may be favored in this patient population [Evidence Level A].
   a. Choice of an antidepressant medication will depend upon symptoms of depression, potential known side effects of the medication, particularly in the child or older adult, drug interactions with other current medications and underlying disease conditions. *For a summary table of the efficacy and safety of pharmacologic agents for the treatment of post-stroke depression please see www.strokebestpractices.ca.*

iv. Response to treatment should be monitored regularly by a health professional. Monitoring should include evaluation of any changes in the severity of depression, review of potential side effects, and update of ongoing management plans [Evidence Level C].

v. If a good response is achieved, treatment should be continued for a minimum of six to 12 months. [Evidence Level C].

*Note: Examples of a "good response" may be indicated by positive changes in thoughts and self-perceptions (e.g. hopelessness, worthlessness, guilt), emotional symptoms (e.g. sadness, tearfulness), neurovegetative symptoms (e.g. sleep, appetite), and improved motivation to carry out daily activities.*

   a. If the person mood has not improved 2–4 weeks after initiating treatment, assess patient compliance with medication regime. If compliant, then consider increasing the dosage, adding an additional medication, or changing to another antidepressant [Evidence Level B].
   b. Following the initial course of treatment, maintenance therapy could be considered on an individual basis (consider previous history and risk factors for recurrence of depression). [Evidence Level C].
   c. If a decision is made to discontinue an antidepressant, it should be tapered over one to two months [Evidence level C].

vi. Following initial treatment for post-stroke depression, people who have experienced a stroke should continue to be monitored for relapse or recurrence of depression [Evidence Level C].

vii. *Pseudobulbar affect*: In cases of severe, persistent or troublesome tearfulness, emotional incontinence or lability, a trial of antidepressant medication should be considered [Evidence Level A].
   a. Side effect profiles suggest that some selective serotonin reuptake inhibitors may be preferred over others for this population. There is no evidence for non-pharmacologic interventions for this condition. *For a summary table of suggested pharmacotherapy agents for the treatment of post-stroke depression see www.strokebestpractices.ca.*

**Clinical considerations 1.4**

i. The involvement and feedback of people who have experienced a stroke, family, and caregivers is an important component of ongoing monitoring for post-stroke mood changes and conditions.

ii. Counseling and education should include information about potential relapse or recurrence of symptoms, signs to be aware of, the importance of adherence with prescribed medication regime, and contacting their primary care physician or mental health expert should those signs reappear.

**1.5 Prophylactic treatment for post-stroke depression**

i. While prophylactic pharmacotherapy has been shown to prevent post-stroke depressive symptoms [Evidence Level A], their impact on function is less clear. At this time routine use of prophylactic antidepressants for ALL people who have experienced a stroke is not recommended as the risk—benefit ratio has not been clearly established [Evidence Level B].

ii. Further research is required to define *at risk* people who have experienced a stroke, choice of antidepressant agents, optimal timing and duration of intervention.

iii. Problem-solving therapy (i.e. cognitive-behavior therapy) has been shown to have efficacy for prophylactic treatment for post-stroke depression [Evidence-Level B].

**1.6 Other mood states**

i. Screening for anxiety may be considered in people who have experienced a stroke as increased prevalence has been demonstrated following stroke [Evidence Level B].
   a. A validated screening tool should be used to detect presence of anxiety [Evidence Level B].
   b. People who have had a stroke with resulting communication limitations should be screened for anxiety using appropriate methods validated for aphasic people who have experienced a stroke [Evidence Level B].

ii. Anxiety frequently co-exists with depression following stroke or may appear in people who have experienced a stroke who are not clinically depressed. For people who have experienced a stroke with marked anxiety with or without clinical depression, it is reasonable to offer pharmacotherapy [Evidence level C].
   a. Although evidence is limited in people who have experienced a stroke, psychotherapy may be considered as an adjunct to pharmacotherapy [Evidence Level C].

iii. Problem-solving therapy (i.e. cognitive behavior therapy) has been shown to have efficacy for anxiety post-stroke [Evidence-Level B].

iv. Apathy frequently co-exists with depression following stroke or may appear in people who have experienced a stroke who are not clinically depressed. For people who have experienced a stroke with marked apathy, with or without clinical depression, it is reasonable to offer nonpharmacological intervention such as exercise or music therapy [Evidence level C]. Psychostimulants have been trialed, but evidence remains limited [Evidence Level C].

**1.7 Ongoing monitoring, support, and education**

i. People who have experienced a stroke and families should continue to be given information and education about the potential impact of stroke on mood [Evidence level C].

ii. People who have experienced a stroke and families should be provided with the opportunity to talk about the impact of stroke on their lives at all stages of care. *Refer to the CSBPR Transitions of Care Module for further information on Patient and Family Education, and Community Follow-up.*[47]

was also associated with a small, but significant reduction in depression scores in a meta-analysis that pooled the results of 13 RCTs (SMD = −0.13, 95% CI −0.26 to −0.01, p = 0.03).[39]

## Recommendations Section 2: Cognition following stroke

The reported prevalence of VCI among persons who have experienced a stroke is approximately 20% within the first three months of stroke,[49,50] increasing to 29% over the next five years.[6] In a systematic review including the results of 73 studies, Pendlebury and Rothwell[51] estimated the pooled cumulative incidence of post-stroke dementia increased linearly at a rate of 3.0% per year. Common predictors of post-stroke dementia include older age, lower education level, previous stroke, diabetes, atrial fibrillation, pre-existing cognitive impairment, and stroke severity.[51]

The most commonly used tests for the screening of cognitive function post stroke are the Montreal Cognitive Assessment (MoCA) and the Mini Mental State Examination (MMSE). The sensitivities and specificities of the MMSE to identify MCI using cut-points <26 or <27 out of 30 have been estimated at 82% and 76%, respectively,[52] and to detect dementia or multidomain cognitive impairment, 88% and 62%, respectively.[53] In contrast, the corresponding estimates of the pooled sensitivity and specificity for an MoCA cut-point of <26 were 95% and 45%, respectively.[53] Overall, the MoCA appears more sensitive to detect the presence of VCI compared to the MMSE, particularly with mild deficits.

The use of antihypertensive agents following stroke to reduce cognitive decline has been evaluated in a limited number of trials in which cognition was the primary and not one of the secondary outcomes. In the "Prevention of Decline in Cognition after Stroke Trial",[54] although terminated before recruiting the 600 planned participants, intensive blood pressure management resulted in significant reductions in systolic and diastolic blood pressures, but did not alter cognition outcomes in persons with normal or near-normal cognition at baseline. Blood pressure reduction was one component of a multifaceted intervention program evaluated in the Austrian Polyintervention Study to Prevent Cognitive Decline After Ischemic Stroke trial.[55] Within three months of stroke, 202 patients were randomized to a 24-month intensive intervention program, emphasizing blood pressure control, increased physical activity (goal of moderate or vigorous, 3–5x/week), diet (elements of a prudent diet and Mediterranean type diet), while encouraging weight loss in the obese, cognitive training (home-based exercises), and cessation of smoking; or to a control group, which received care according to standard guidelines. At 24 months, there was no significant difference between groups in the number of patients who experienced cognitive decline (10.5% of patients in the intervention group vs. 12.0% in the control group). Although a recent Cochrane review[56] failed to show a statistically significant effect of blood pressure lowering on dementia in patients with a history of stroke or TIA (HR = 0.88, 95% CI 0.73–1.06, n = 2 trials), control of blood pressure is strongly indicated in this population for the purpose of preventing recurrent stroke, which is one of the strongest risk factors for post-stroke dementia.

Prior evidence from randomized controlled trials is inconclusive regarding whether blood pressure lowering prevents dementia in persons without a prior history of stroke (pooled risk ratio 0.93, 95% CI 0.84–1.02).[57] Most recently, the dementia outcomes of the Systolic Blood Pressure Intervention Trial-Memory and Cognition IN Decreased Hypertension,[58] randomized participants with established hypertension to an intensive blood-pressure lowering arm, with a goal of SBP <120 mm Hg, or to a standard care arm with a goal of SBP <140 mm Hg, for up to six years. After a median duration of treatment of 3.34 years and a median follow-up of 5.11 years, there was no significant difference between groups in the primary cognitive outcome, probable dementia (7.2 (intensive) vs. 8.6 cases (standard care) per 1000 person-years; HR = 0.83; 95% CI 0.67–1.04, p = 0.10); however, the risks of MCI and the composite outcome of MCI or probable dementia were significantly lower in the intensive therapy group (HR = 0.81; 95% CI 0.69–0.95, p = 0.007 and HR = 0.85, 95% CI 0.74–0.97, p = 0.01, respectively).

Cognitive rehabilitation interventions for VCI associated with stroke focus on common deficits of attention, memory or executive function. In general, interventions may be considered to have one of two objectives: (1) to reinforce or re-establish previous behavioral skills or function (e.g. to remediate with computerized exercises) or (2) to teach compensatory mechanisms (e.g. strategy training) that may be either internal or external to the individual.[59] A recent Cochrane review by das Nair et al.[60] included the results of 13 RCTs (n = 514) that examined various memory rehabilitation strategies including computerized memory training, strategy training, the use of external memory aides, and imagery mnemonics. Memory training was associated with significant improvements in short-term *subjective* memory measures (SMD = 0.36, 95% CI 0.08–0.64, p = 0.01), but not *objective* memory measures. Training was also not associated with long-term effects of either subjective or objective memory measures at three to seven months following treatment. Enriched environments improved measures of working memory, but not attention in one RCT that provided a computer-based gaming activity for 600 min over eight weeks targeting five cognitive domains (attention, speed, memory, flexibility, and problem solving).[61] Another Cochrane review[62] pooled the results of six RCTs evaluating interventions designed to either restore attentional functions or provide compensatory strategies for persons with attention deficits post stroke. Cognitive rehabilitation resulted in significantly greater improvement on assessments of divided attention, but not global attention function or functional outcome (activities of daily living). Evidence for the effectiveness of the rehabilitation of executive function and problem solving is less compelling. The results of two systematic reviews suggested that neither restorative nor compensative approaches using a variety of techniques were effective.[63,64] Given that cognitive deficits may be evident across all cognitive domains (including attention, memory, and executive function), a proposed systematic review will evaluate the evidence from non-randomized trials for cognitive rehabilitation

that targets all forms of cognitive impairment, using psychological interventions.[65]

Other interventions, such as physical activity, achieved through aerobic activity, resistance training or physiotherapy, have been associated with small, but statistically significant improvements in measures of cognitive impairment post stroke.[66,67] Non-invasive brain stimulation using tDCS has also been associated with improvements in cognitive function following stroke.[68]

In terms of pharmacological treatments, cholinergic agents, including donepezil and galantamine, have been investigated in the treatment of post-stroke cognitive deficits. Donepezil, a selective acetylcholinesterase inhibitor, has been the subject of three large randomized controlled trials.[69–71] In these trials, patients with possible or probable dementia following stroke were randomized to receive 5 or 10 mg of the agent or placebo for 24 weeks. In all trials, participants in the donepezil groups demonstrated significantly greater improvement on the Vascular Alzheimer's Disease Assessment Scale cognitive subscale or the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog), compared with those in the placebo group. In one of these trials,[70] 11 participants (1.7%) in the donepezil group died during the study period, with three deaths determined to be possibly related to the use of donepezil. There were no deaths in the control group. Treatment with 24 mg galantamine for 24 weeks was associated with significantly greater improvements in ADAS-cog scores compared with placebo in two trials that included patients with probable or possible post-stroke dementia.[72,73] The use of the N-methyl-D-aspartate (NMDA) receptor antagonist, memantine has also been reported to improve cognitive function in persons with vascular dementia.[74,75]

## 2. Vascular cognitive impairment (update 2019)

### Definitions and descriptions

**Vascular cognitive impairment** includes the cognitive and behavioral disorders associated with cerebrovascular disease and risk factors, from mild cognitive deficits to frank dementia. Vascular cognitive impairment is a syndrome with cognitive impairment affecting at least one cognitive domain (e.g. attention, memory, language, perception, or executive function) and with evidence of clinical stroke or subclinical vascular brain injury. Vascular cognitive impairment encompasses a large range of cognitive deficits, from relatively mild cognitive impairment of vascular origin to Vascular Dementia, the most severe form of vascular cognitive impairment. Vascular cognitive impairment also plays an important role in people with Alzheimer's disease pathology who have coexisting vascular lesions. *Diagnostic criteria for vascular cognitive impairment following stroke has been defined by Gorelick et al.,[80] with further revisions by Sachdev et al. for the VASCOG society.*[81]

**Cognitive deficits:** The pattern of cognitive deficits in vascular cognitive impairment may encompass any cognitive domain.[81] The most common areas are attention, processing speed, and frontal-executive function (which includes functions such as planning, decision making, judgment, error correction, impairments in the ability to maintain task set, inhibit a response, or shift from one task to another) and deficits in the ability to hold and manipulate information (e.g. working memory). Other cognitive domains that could be affected include learning and memory (immediate, recent, and recognition memory), language (expressive, receptive, naming, grammar, and syntax), visuoconstructional-perceptual ability, praxis-gnosis-body schema, and social cognition.

**Vascular pathology**: Cognitive impairment can result from a range of vascular pathologies (see Sachdev et al.,[81] Table 3), including large or multiple cortical infarcts, multiple subcortical infarcts, covert ("silent") infarcts, strategic infarcts, small-vessel disease (ischemic white matter changes, multiple lacunar infarcts, dilatation of perivascular spaces, cortical microinfarcts, and microhemorrhages), and brain hemorrhage. Risk factors such as hypertension, diabetes and focal or global cerebral hypoperfusion are also associated with cognitive impairment.

### Recommendations

**2.0** All patients with clinically evident stroke or transient ischemic attack should be considered at risk for vascular cognitive impairment [Evidence Level B].

*Note: Screening and assessment of vascular cognitive impairment must be nuanced by multiple factors. In the current version of these recommendations we have included a section called "clinical considerations", where we present a brief discussion of issues identified in the evidence review or by expert consensus that impact performance or interpretation of cognitive screening and assessment information—please see below.*

**2.1 Screening for vascular cognitive impairment**

i. Patients with stroke and transient ischemic attack should be considered for screening for vascular cognitive impairment [Evidence Level C]. This may occur prior to discharge from acute care if concerns with cognition are identified; during inpatient rehabilitation, and during post-stroke follow-up in outpatient and community settings [Evidence Level C].

ii. People who have experienced a stroke with other significant risk factors for vascular disease and vascular cognitive impairment, such as neuroimaging findings of covert stroke or white matter disease, hypertension, diabetes, atrial fibrillation, or other cardiac disease, may be considered for screening for vascular cognitive impairment, particularly those people who have experienced a stroke with cognitive, perceptual, or functional changes that are clinically evident or reported during history taking [Evidence Level B].

iii. Screening for vascular cognitive impairment should be conducted using a validated screening tool, such as the Montreal Cognitive Assessment screen [Evidence Level B]. *A summary of suggested VCI screening and assessment tools, and their psychometric properties can be found at www.strokebestpractices.ca.*

*Note: Screening of global cognitive functioning using a validated tool can be administered to objectively understand the functional impact of vascular cognitive impairment.*

Stages of care across the continuum may include:

- during acute care stay, particularly if cognitive, perceptual, or functional concerns, in the absence of delirium is noted;
- during rehabilitation in inpatient, outpatient, and home-based settings, according to client progress;
- following hospital discharge from the emergency department or inpatient setting to follow-up in an outpatient or community-based healthcare setting.

**2.2 Assessment for vascular cognitive impairment**

i. The diagnosis of vascular cognitive impairment requires confirmation of cerebrovascular disease. Brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is useful to evaluate cerebrovascular disease [Evidence Level B].
   a. MRI is more sensitive than CT to vascular changes.
   b. Clinical history and examination findings consistent with stroke can be used as objective evidence of cerebrovascular disease if imaging is not available

ii. People who have experienced a stroke and who demonstrate cognitive impairments (either clinically, by history, by report of the individual or family, or detected in the screening process) should be assessed by healthcare professionals with the appropriate expertise in neurocognitive functioning, ideally by a clinical neuropsychologist [Evidence Level C].

iii. The impact of deficits on function and safety in activities of daily living, instrumental activities of daily living, occupational function, and/or academic functioning should be considered as part of a cognitive assessment (e.g. driving, home safety) [Evidence Level C].

iv. People who have experienced a stroke with suspected cognitive impairment should also be screened for depression, given that depression has been found to contribute to vascular cognitive impairment [Evidence Level B] *Refer to Recommendation 1.0 on Post-stroke Depression for additional information.*

v. Prior to discharge or transfer from acute care or inpatients rehabilitation, people with acute cognitive problems following stroke should receive an assessment for any safety risks from persisting cognitive impairments and this should be communicated to their primary care team [Evidence Level C].

vi. The results of these assessments should be considered to guide selection and implementation of appropriate remedial, compensatory, and/or adaptive intervention strategies according to person-centered needs and goals [Evidence Level C].

vii. People who have experienced a stroke should have a full assessment of their cognitive strengths and weaknesses when undergoing rehabilitation or prior to returning to cognitively demanding activities such as driving or work [Evidence Level C].

*Note: Experts in neurocognitive assessment may include neuropsychologist, psychologist, occupational therapist, speech-language pathologist, clinical nurse specialist, psychiatrist, physiatrist, geriatrician, neurologist, memory specialist, and developmental pediatrician. Experts require specific qualifications to administer many of the identified assessments.*

**Clinical considerations for screening and assessment of vascular cognitive impairment**

i. Vascular cognitive impairment can be associated with a range of deficits. Further assessment could be considered to evaluate impairments in arousal, alertness, sensorimotor function, attention, orientation, memory, language, agnosia, visual-spatial/perceptual function, praxis, information processing speed, and executive function.
   a. Attention, speed of processing and executive function domains are commonly affected post stroke. Executive function abilities to be assessed may include initiation, inhibition, shifting, insight, planning and organization, judgment, problem solving, abstract reasoning, and social cognition.

ii. *Assessment tool selection*: Cognitive evaluation may be conducted using standardized assessments to determine the nature and severity of cognitive impairments, as well as the presence of remaining cognitive abilities and strengths.
   a. Therapeutic activities and/or functional observations may provide additional information by showing the impact of impairments.
   b. The tools used to assess vascular cognitive impairment may be unique to different settings, geographical areas, professions and timelines encountered along the continuum of care. Consider the validity and standardization of the selected tools with regard to factors such as age, sex, language, aphasia, and education levels.

iii. *Comorbidities:* Screening or assessment for vascular cognitive impairment should take into account any immediate factors that may impact interpretation of results, such as communication and sensorimotor deficits (speech and language, vision, hearing), delirium, hypo-arousal, neuropsychiatric symptoms (e.g. depression, apathy, and anxiety) and other medical conditions that may have temporary impact on cognition.

iv. *Timing:* The impact and presentation of vascular cognitive impairment can evolve over time. Screening and assessment of people who have experienced a stroke and considered at risk for cognitive impairment should be undertaken at different stages of care (rehabilitation, transition points, community follow-up) as indicated by the severity of clinical presentation, comorbidities, history and/or imaging abnormalities, and needs or goals of the person with stroke and their caregiver.

v. *Multiple assessments*: Although screening or conducting assessments at different stages of care is important for guiding diagnosis and management, it is also important to be aware of the potential impact of multiple assessments on both the validity of the results as well as on the person following stroke (e.g. practice effects, test fatigue). To avoid practice effects, the use of different equivalent assessment forms is recommended when available (e.g. MoCA has three versions).

vi. *Life stage:* Effects of age, developmental stage, or pre-stroke function should be considered when deciding when and what to assess. Decisions about what to assess should always take into consideration person-centered goals which may differ by life stages.

vii. *Capacity:* Professionals should consider the capacity of the person with stroke for making informed choices and decisions. Capacity-related provincial legislation should be reviewed, and appropriate substitute decision makers should be identified if the person is deemed incapable of making specific decisions regarding their personal healthcare or self-management following discharge. In special circumstances, when abilities are in question, an individual can be referred to a third party, designated Capacity Assessor to determine a person's mental capacity to make decisions about property, finances, and personal care.

**2.3 Management of vascular cognitive impairment following stroke**

i. Vascular risk factors (e.g. hypertension, diabetes and atrial fibrillation) should be managed to achieve maximum risk reduction for recurrent stroke [Evidence Level A] as these are associated with cognitive impairment [Evidence Level B]. *Refer to the CSBPR Secondary Prevention of Stroke module for additional information*[82]
   a. Treatment of hypertension may reduce cognitive decline, even in the absence of stroke events and should be addressed for all people with elevated blood pressure who are either at high risk [Evidence Level B] or have already experienced a stroke [Evidence Level A].

ii. Interventions for cognitive impairment should be tailored according to the following considerations:
   a. Goals should be person-centered and sensitive to the values and expectations of person with stroke, family, and caregivers [Evidence Level B].
   b. Goals and interventions should take into account the strengths and weaknesses of the affected person's cognitive profile and communication abilities [Evidence Level C].
   c. People with stroke and with communication and/or cognitive issues may require additional support (e.g. family involvement) to optimize participation in goal-setting and/or engagement in rehabilitation [Evidence Level C].
   d. Interventions should be individualized, based on best available evidence, and have the long-term aim to facilitate resumption of desired activities and participation (e.g. self-care, home and financial management, leisure, driving, return to work) [Evidence Level C].
   e. Severity of impairments: If the level of impairment has reached the moderate dementia stage (when the person is unable to live independently), it is reasonable for interventions to be more focused on providing education and support for the caregiver in addition to, or in lieu of, cognitive rehabilitation with the effected person [Evidence Level C].

iii. Interventions that may be considered for rehabilitation for vascular cognitive impairment may include compensation strategies and direct remediation/cognitive skill training [Evidence Level B]. The choice of strategies should be individualized to the person's clinical profile.

a. *Compensation strategy training* should focus on teaching strategies to manage impairments and is often directed at specific activity limitations to promote independence [Evidence Level B]. It can include changes in the physical and or social environment or changing the way one performs an activity [Evidence Level B].
b. *Direct remediation/cognitive skill training* should focus on providing intensive specific training to directly improve the impaired cognitive domain. It can include drill and practice exercises, mnemonic strategies (e.g. acronyms, songs), or computer or tablet-based tools directed at specific deficits [Evidence Level B].

iv. Memory impairments may be treated with compensation using external strategies (e.g. assistive electronic and non-electronic devices) and using internal strategies (e.g. encoding and retrieval strategies, self-efficacy training, and errorless learning), with some evidence for benefits to activity limitations [Evidence Level B].
   a. Targeted computerized skill training directed by a therapist may be considered for working memory deficits [Evidence Level B].

v. Executive function deficits may be treated with metacognitive strategy training and/or formal problem-solving strategies, under the supervision of a trained therapist [Evidence Level B].

vi. Internal strategy training may be considered and includes strategies to improve goal management, problem solving, time management, and metacognitive reasoning [Evidence Level B].

vii. Aerobic exercise can be considered as an adjunct therapy for cognitive impairment including attention, memory, and executive function [Evidence Level B]. *Refer to CSBPR Stroke Rehabilitation module for additional information on exercise.*[48]

viii. People who have experienced a stroke with cognitive impairment and evidence of changes in mood (e.g. depression, anxiety) or other behavioral changes on screening could be referred to and managed by an appropriate mental healthcare professional [Evidence Level B]. *Refer to Section 1.3 on Post-stroke Depression for additional information.*

**Clinical consideration for management of vascular cognitive impairment**

i. The learning abilities of people with vascular cognitive impairment following stroke should be considered when determining the intervention, and how best to provide education to maximize benefits of the intervention (e.g. teach tasks using demonstration, verbal instruction, slow pace, and repetition as needed).

ii. Computer-based interventions may be considered as an adjunct to clinician-guided treatment—research in this area continues to evolve rapidly.

iii. Evidence for impact on activity or participation limitations is limited and requires more research.

iv. Emerging cognitive interventions that may be of potential benefit include repetitive transcranial magnetic stimulation or transcranial direct current stimulation, the use of virtual reality environments, and application of constraint-induced approaches for the impaired cognitive domain. These strategies require more research before recommendations can be developed on their use.

*Refer to CSBPR Stroke Rehabilitation module*[48] *for additional information related to treatment of other domains, including communication, visual-perceptual disorders, and neglect in people who have experienced a stroke and vascular cognitive impairment.*

**2.4 Pharmacotherapy for vascular cognitive impairment following stroke**

i. For people with evidence of vascular cognitive impairment following stroke, a referral to a healthcare professional or team with expertise in vascular cognitive impairment may be considered for further assessment and recommendations regarding pharmacotherapy [Evidence Level C].

ii. Cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine may be considered in individual persons with vascular or mixed dementia following stroke, based on randomized trials showing small magnitude benefits in cognitive outcomes [Evidence Level A]. *Refer to Clinical Consideration iv below for additional information.*

*Note: These medications are currently approved by Health Canada for the treatment of Alzheimer's disease. They have not received approval for the indication of vascular cognitive impairment.*[83]

**Clinical considerations related to pharmacotherapy for vascular cognitive impairment**

i. It should be noted that most of the available evidence is based on people who meet the criteria for vascular dementia or mixed dementia. Thus, evidence for pharmacological treatment effects in vascular cognitive impairment is limited at this time.

ii. Severity of cognitive impairment should be considered in decisions for pharmacological management.

iii. People demonstrating vascular cognitive impairment following stroke may be susceptible to adverse events given the frequent presence of medical comorbidities and concomitant medications.

iv. The clinical relevance of benefits of cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine remains controversial particularly in view of the risk of adverse events and a potential increased risk of mortality; therefore, the use of these medications should be based on clinical judgment that small improvements in cognition would have a meaningful impact on the quality of life of the person following stroke.

Other pharmacological agents have been evaluated in the treatment of post-stroke dementia. Citicoline was associated with higher odds of being dementia free among persons recovering from first-ever ischemic stroke with persistent neurological deficit.[76] Antidepressants have also been associated with improvements in executive function[77] and problem solving[78] in persons recovering from stroke. The use of actovegin, a novel therapeutic agent that may enhance oxidative metabolism in the brain, was recently evaluated in persons following acute ischemic stroke with an MoCA test score of ≤25 points.[79] At three, six, and 12 months, significantly more patients in the actovegin group met the definition of responder (≥4-point improvement in ADAS-cog from baseline).

## Recommendations Section 3: Post-Stroke Fatigue

PSF is a common consequence that interferes with recovery, frustrates people experiencing it and is often overlooked. The underlying cause(s) of PSF are poorly understood, but is likely composed of biological, psychosocial, and behavioral factors.[84] Persons experiencing PSF report having less capacity and energy, abnormal tiredness, and an overwhelming need for long-lasting sleep. They also report being easily fatigued, and experience fatigue for which there was no obvious cause or explanation, and increased stress sensitivity.[85] Estimates of the incidence and prevalence vary depending on when fatigue is assessed in the recovery process and which assessment tool was used. A review by Cumming et al.[7] included the results from 22 studies in which a cut-off level of ≥4 or >4 on the Fatigue Severity Scale (FSS) was used. The prevalence of PSF was 50%, when assessed up to six years post stroke. Since the clinical course of PSF is unclear, it is not known whether PSF increases or decreases over time. The results from one systematic review, which included the results of nine studies, indicated that the percentage of patients reporting fatigue both increased and decreased between the initial and second assessment period.[86] In contrast, the estimates of fatigue have been reported to be relatively stable across time (55% within three months of stroke, 46% at one to six months and 53% beyond six months).[7]

Few treatments for PSF have been evaluated. Using the results from seven trials (five pharmacological, two non-pharmacological), a Cochrane review[87] found that overall, treatment resulted in a significant reduction in fatigue scores (weighted mean difference (WMD) = −1.07, 95% CI −1.93, −0.21, $p = 0.014$). Pharmacological agents that have been evaluated in the treatment of PSF include selective serotonin reuptake inhibitors (fluoxetine) and modafinil. In the Modafinil in Debilitating Fatigue After Stroke (MIDAS) trial, 36 participants with PSF received 200 mg modafinil or placebo for six weeks.[88] Active treatment with modafinil was associated with a significantly greater decrease in measures of fatigue (total Multidimensional Fatigue Inventory (MFI)-20 scores (MD = −7.38, 95% CI −21.76 to −2.99; $p < 0.001$), mean FSS scores (MD = −6.31, 95% CI −10.7 to −1.9, $p = 0.048$) and a significantly greater increase in total mean Stroke-Specific Quality of Life scores (MD = 11.8, 95% CI 2.3–21.3, $p = 0.015$). In another RCT, 41 persons with PSF were randomized to receive 400 mg modafinil for 90 days. The results were ambiguous. At 90 days, there was no significant difference between groups in the median MFI-20 GF score (11 modafinil vs. placebo 14, $p = 0.32$), or in the median score of other MFI domains (physical fatigue, reduced activity, reduced motivation); however, median FSS and FSS-7 were significantly lower at 90 days for patients in the modafinil group (36 vs. 49.5, $p = 0.02$ and 22 vs. 37.5, $p = 0.042$).[89] Fluoxetine was examined in a trial including 83 participants with post-stroke emotional disturbances, an average of 14 months after stroke onset.[90] Patients were randomized to receive 20 mg/day of fluoxetine or placebo, for three months. At the end of treatment, there were no significant differences in the number of patients with PSF. At six months, 34 patients (85%) in the fluoxetine group reported PSF compared with 40 (93%) in the control group. However, at three months, fewer patients in the fluoxetine group reported excessive or inappropriate crying (40% vs. 62.8%, $p = 0.038$), and at six months

fewer patients in the fluoxetine group were identified with depression (12.5% vs. 30.2%, p = 0.05).

Among trials evaluating non-pharmacological treatments for PSF, two reported significant improvements in symptoms. Zedlitz et al.[91] randomized 83 participants with severe fatigue >4 months post stroke to participate in a 12-week program consisting of group cognitive treatment (control condition) or group cognitive treatment combined with graded activity training (COGRAT). Cognitive treatment consisted of cognitive behavioral therapy and compensatory strategy teaching. Those in the COGRAT group also received 24 sessions, each 2 h in duration of graded activity training, including treadmill walking, strength training, and homework assignments. Participants who received COGRAT were significantly more likely to experience clinically relevant improvement in fatigue severity (57.9% vs. 24.4%, p = 0.002). Johansson et al.[92] reported that patients recovering from stroke with symptoms of mental fatigue who participated in an eight-week program of mindfulness-based stress reduction had a significantly greater decrease in Mental Fatigue Scale scores compared to a wait list control group. Continuous positive airway pressure was found to significantly reduce Epworth Sleepiness Scale scores compared with usual care in the Sleep Apnea Cardiovascular Endpoints (SAVE) trial.[93] Some non-pharmacological interventions that have been evaluated for the treatment of PSF and found not to be effective include a fatigue management education program,[94] and a six-month chronic disease self-management program.[95]

## Section 3: Post-stroke fatigue update 2019

### Definitions and descriptions

**Post-stroke fatigue**: Fatigue following stroke is a multidimensional motor-perceptive, emotional, and cognitive experience characterized by a feeling of early exhaustion with weariness, lack of energy, and aversion to effort that develops during physical or mental activity and is usually not ameliorated by rest. Fatigue can be classified as either objective or subjective; objective fatigue is defined as the observable and measurable decrement in performance occurring with the repetition of a physical or mental task, while subjective fatigue is a feeling of early exhaustion, weariness, and aversion to effort.[96–99]

**Characteristics** of post-stroke fatigue may include: overwhelming tiredness and lack of energy to perform daily activities; abnormal need for naps, rest, or extended sleep; more easily tired by daily activities than pre-stroke; unpredictable feelings of fatigue without apparent reason.

### Recommendations

**3.0** Post-stroke fatigue is a common condition and can be experienced following a stroke at any point during the recovery process. Post-stroke fatigue is often under-recognized; thus, healthcare professionals should anticipate the possibility of post-stroke fatigue and prepare people who have experienced a stroke and families to mitigate fatigue through assessment, education, and interventions throughout the stroke-recovery continuum [Evidence Level B].

*Note: Post-stroke fatigue does not appear to be correlated to the severity of stroke. People who experience very mild stroke may still experience post-stroke fatigue.*

**3.1 Screening and assessment**

i. Prior to discharge from acute care or inpatient rehabilitation, people who have experienced a stroke, their families and informal caregivers, should be provided with basic information regarding the potential experience of post-stroke fatigue [Evidence Level C].

ii. Following return to the community, people who have experienced a stroke should be periodically screened for post-stroke fatigue during follow-up healthcare visits (e.g. primary care, home care, and outpatient prevention or rehabilitation clinics) [Evidence Level C]. *A summary of suggested validated screening tools is available at www.strokebestpractices.ca.*

iii. People who experience post-stroke fatigue should be screened for common and treatable post-stroke co-morbidities and for medications that are associated with and/or exacerbate fatigue [Evidence Level B].
   a. These may include: signs of depression or other mood-related conditions; sleep disorders or factors that decrease quality of sleep (e.g. sleep apnea, pain); other common post-stroke medical conditions and medications that increase fatigue, e.g. systemic infection such as urinary tract infections, dehydration, sedating drugs, hypothyroidism.

**3.2 Management of post-stroke fatigue**

i. People who have experienced a stroke should be cared for by healthcare professionals who are knowledgeable in the symptoms of fatigue and its management [Evidence Level C].

ii. There is limited evidence suggesting that pharmacological treatment for post-stroke fatigue with modafinil may be considered in some people who have experienced a stroke [Evidence Level C]. More research is required to fully understand the benefits of this treatment.

iii. There is currently insufficient evidence to recommend antidepressant treatment for post-stroke fatigue [Evidence Level B].

iv. Psychotherapy (cognitive behavioral therapy) may be considered as an adjunct treatment for post-stroke fatigue [Evidence Level B].

v. Mindfulness-based stress reduction may be considered as an adjunct treatment for post-stroke fatigue [Evidence Level B].

vi. Counseling on graduated exercise schedules with increasing physical demands appropriate to tolerance level to improve deconditioning and physical tolerance is recommended [Evidence Level C].

vii. Counseling on energy conservation strategies that consider optimizing daily function in high priority activities is recommended (e.g. daily routines and modified tasks that anticipate energy needs and provide a balance of activity/rest) [Evidence Level C]. *Refer to Box 3 below for examples of energy conservation strategies.*

viii. Counseling on the establishment of good sleep hygiene behaviors is recommended [Evidence Level B].

ix. Provide education to people who have experienced a stroke, their families and informal caregivers, on daily time management and planning a balance of activities with rest periods [Evidence Level C].

x. Encourage people who have experienced a stroke and are experiencing post-stroke fatigue to communicate energy status and rest needs to healthcare providers, family members, caregivers, employers, and social groups [Evidence Level C].

**Box 3: Examples of specific energy conservation strategies**

*The following list includes energy conservation strategies described across a broad literature base. These are provided as helpful information and guidance in counseling people who have experienced a stroke; they should not be regarded as evidence-based recommendations.*

- Structuring day to include a balance of activity and scheduled periods of rest; anticipating energy requirements for each task and for completion of high priority activities;
- Keeping an agenda of daily activities, planning higher energy activities immediately following a period of rest, planning activities a day in advance, anticipating energy requirements for each task, prioritizing tasks and energy requirements;
- Organizing physical environment to minimize efforts to move around, reduce stair climbing, and have ready access to the most frequently used items;
- Sitting rather than standing when possible when doing chores (such as washing dishes or ironing);
- Teaching people who have experienced a stroke to use appropriate body mechanics, posture and sitting positions and locations (i.e. rest in bed, rather than chair);
- Establishing good sleep hygiene patterns, and avoiding sedating drugs and excessive alcohol;
- Using energy saving equipment and technology to reduce physical efforts (e.g. electric can opener, online shopping);
- Engaging in enjoyable vocational and leisure activities that are planned in advance to ensure the person with stroke is well rested prior to activities;
- Delegating activities that are low priority or can be done by someone else, such as family members;
- Developing a plan for healthy diet or proper nutrition to help with energy levels.

## Future directions

Mood changes and disorders, cognitive impairment and fatigue are significant challenges following stroke. They negatively impact recovery and lead to worse outcomes when they are present. Screening, assessment, and appropriate management of these three conditions are imperative. Consideration for their presence must begin in the acute care phase, especially if a prior history of these conditions exists. The impacts are not just felt in the ability to recover, we are now seeing societal impacts as well. For persons of working age, stroke can represent the further burden of loss of employment and decreased earnings. A recent Canadian study reported that 19.8% fewer people who were admitted to hospital following an acute stroke were working three years later, and had experienced a mean decline in annual earnings of $13,278.[100]

With our aging population and the expected increase in stroke, we need to take an aggressive stand upstream.

Primary prevention measures aimed at vascular risk reduction using multidomain interventions for diet and lifestyle may be effective in older adults. In the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER),[101] a primary prevention trial, which included a cognitive training component, in addition to diet and lifestyle, there was significantly greater improvement in a composite score of tests for cognitive functioning after two years in the intervention group. However, similar trials including the Multidomain Alzheimer Preventive Trial[102] and the Prevention of Dementia by Intensive Vascular care[103] (which did not include a cognitive training component), did not prevent cognitive decline or the development of dementia in older adults. A Mediterranean diet supplemented with extra-virgin olive oil significantly reduced the risk of MCI in persons at increased cardiovascular risk in the PREDIMED trial.[104] However, adherence to a healthy lifestyle (maintaining a normal weight, consuming a healthy diet, not smoking, engaging in regular physical activity, and maintaining cholesterol, blood pressure, and fasting glucose at goal levels) beginning in young adulthood has been shown to preserve cognitive function later in life.[105]

Other developments in the diagnosis and treatment of dementia include monoclonal antibodies, such as aducanumab, which selectively targets and binds aggregated amyloid-β (Aβ) plaques, and has been shown to reduce their concentrations in the brains of persons with mild Alzheimer's disease.[106] In the future, if more specific genetic biomarkers for dementia can be identified, they have the potential to refine the diagnoses, provide better prognostic information, and develop more targeted therapies.

## Summary

The 2019 update of the *Canadian Stroke Best Practice Recommendations for Mood, Cognition and Fatigue following Stroke* provides a set of evidence-based statements developed for healthcare professionals and system leaders to help guide the management of three common conditions post stroke, and ensure the necessary structures and resources are in place. While depression, cognitive impairment, and fatigue are all prevalent following stroke and have the potential to negatively impact the course of recovery, they are often neglected aspects of care. The recommendations emphasize the importance of screening and assessment practices, and encourage their integration into existing stroke protocols, especially in the post-acute stages of care. To accomplish this goal, increased capacity is required within the healthcare system to ensure people living with the effects of stroke have access to appropriate specialists to detect and address these issues. While there are fewer effective treatments currently available for these conditions, compared with other aspects of stroke care, there are new pharmacological and non-pharmacological therapies mentioned within this document that may find their way into routine clinical practice if the evidence of their safety and benefit continues to grow.

The Canadian Stroke Best Practice Recommendations continue to be a work in progress. They are regularly updated every two to three years, whereby new recommendations are created, and old ones revised or deleted, in response to new evidence.

## Authors' contributions

Krista L Lanctôt and Richard H Swartz are co-chairs of the Management of Mood, Cognition and Fatigue following Stroke expert writing group and lead authors contributing to all aspects of the development, data analysis, writing, editing, and final approval of this manuscript; M Patrice Lindsay is corresponding author, senior editor of the guidelines and this manuscript, involved in all aspects of scientific literature review, writing group deliberations, external review process, manuscript preparation, and a writer of supplementary documentation. Demetrios J Sahlas, Melissa Austin, Kristyn Ball, Treena Blake, Nathan Herrmann, David Hogan, Aisha Khan, Stewart Longman, Andrea King, Carol Leonard, Tricia Shoniker, Trudy Taylor, and Moira Teed are all members of Management of Mood, Cognition and Fatigue following Stroke expert writing group and contributed by reviewing, analyzing, and discussing the evidence and collectively finalizing the wording of all included recommendations. Andrea de Jong supported the external review process and the final revisions of the guidelines and manuscript. Gord Gubitz and Eric E Smith are senior advisors to the writing group and contributed significantly to the methodology and recommendation development and provided review and edits to the overall documents. Norine Foley and Sanjit Bhogal conducted the evidence searches and completed the evidence tables and evidence summaries supporting this guideline update and contributed to writing of this manuscript. Leanne K Casaubon, Anita Mountain, and Dar Dowlatshahi are senior leaders of the stroke best practices and quality advisory committee and provided inputs throughout development of the recommendations, reviewed the manuscript, and provided inputs and feedback.

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