CANADIAN BEST PRACTICE RECOMMENDATIONS FOR THE MANAGEMENT OF AMYOTROPHIC LATERAL SCLEROSIS

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Amyotrophic lateral sclerosis (ALS) is a debilitating, progressive disease with degeneration of motor neurons in the brain and spinal cord causing weakness, muscle atrophy, fasciculations and spasticity[1]. Onset in the limbs, with extremity weakness and mobility impairments, is the most common presentation, occurring in approximately 70% of patients[2]. Bulbar onset with oropharyngeal muscle involvement affecting swallowing and speech occurs in approximately 25% of cases[2]. In addition to motor impairment, degeneration in the frontal and temporal lobes resulting in cognitive or behavioural impairments occurs in up to 50% of patients[3]. Over time, strength progressively declines, and patients typically die from respiratory failure within 5 years of diagnosis[2]. Despite increased research efforts in recent years, treatment options for ALS remain limited, and patient care is primarily focused on managing symptoms, and optimizing function and quality of life.[2]

An estimated 3,000 Canadians are currently living with ALS.[4,5] Clinicians caring for patients with ALS and advocacy groups have strongly supported the development of best practice recommendations for the care and management of these patients in Canada. Although ALS clinical practice guidelines have been published in the United States[6,7] and in Europe[8,9], to date there have been no published guidelines explicitly for the care of patients with ALS in Canada.

In addition to providing an update on the evolving standard of care in ALS, the best practice recommendations in this guideline serve to address several issues unique to Canada, such as caregiver support, medication alignment and medical assistance in dying (MAiD). Developing the first Canadian ALS guideline is a critical step in an iterative process whereby these recommendations can be updated as evidence evolves, and research priorities can be identified and prioritized to fill knowledge gaps.

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As the rigorous standards of evidence-based medical recommendations are not met in most areas of ALS care, many of the recommendations presented are expert consensus on good practice. Traditionally, symptom management in ALS is extrapolated from evidence in other disease states. The recommendations presented in this guideline are based on best available evidence and expert consensus on best practices, and thus reflect the real-life experiences of Canadian clinicians caring for patients with ALS. This article is a summary of the full guideline which is available on the ALS Canada website (specific URL for guideline).

SCOPE

The purpose of this guideline is to provide ALS clinicians, allied health professionals and primary care providers with best practice recommendations for the care and management of patients living with ALS in Canada, inclusive of all genders, ages and stage of the disease. This guideline is intended to develop a national standard to improve quality of care for patients, families and caregivers living with ALS. Advocacy groups (e.g., ALS Society of Canada [ALS Canada], provincial ALS Societies), health authorities, governments and policymakers will be enabled to establish benchmarks and advocate for standards of care.

METHODS

The concept for this guideline was concurrently fostered by ALS Canada and Canadian ALS clinicians within the Canadian ALS Research Network (CALS; now merged with ALS Canada). The guideline was developed using the Guideline International Network-McMaster Development Checklist [10], for guidance on all aspects of guideline development, including planning, formulation of recommendations, implementation and evaluation.

Guideline panel composition

A working group of 13 Canadian ALS clinicians (the authors), chaired by C.S., led the development of this guideline. Neurologists and physiatrists who were active in the Canadian ALS research network and could represent the geographic diversity of Canada were invited to participate in the working group. Clinicians with previous experience with guideline development were particularly encouraged. The working group also included a gastroenterologist (D.L.) and a respirologist (A.T.) with ALS expertise. Early in the guideline development process, 2 other Canadian ALS clinicians were involved, but they removed themselves from the project because of the time commitments required.

Selection of key questions

In 2014, we selected clinical questions of interest for the guideline by surveying clinicians and staff at all 19 Canadian multidisciplinary ALS clinics via an emailed survey. The survey included a list of the key questions used to develop the American Academy of Neurology (AAN)[6,7] Practice Parameters and European Network for the Cure of ALS (ENCALS)[8] guideline, as well as additional questions that members of the working group had derived based on their own clinical experience. Survey participants were asked to rate the importance of these questions for inclusion in the guideline. The survey tool and results can be seen in Appendix A. Initially, our writing group had referred to the guidelines as “Clinical Practice Guidelines” (CPGs). However, about mid way through the guideline process, we decided to rename the process “Best Practice Recommendations” (BPRs).

Questions included in the literature review were those questions rated highly by participants on the survey; these questions were further refined by the working group. The selected clinical questions were grouped by topic including communication of diagnosis, disease-modifying therapy, multidisciplinary care, respiratory management, nutrition management, symptom management, cognitive impairment, risk of venous thromboembolism (VTE), exercise, palliative care and caregiver support. The final questions that were evaluated are located in Appendix A.

Literature search

In 2015, the Centre for Effective Practice, a consulting firm with substantial guideline development experience, conducted literature searches for the selected clinical questions using MEDLINE, EMBAS, and CINAHL databases. The search terms for each clinical question were developed by the centre through review of the search terms that had been used for the AAN guideline[6,7] and in consultation with the working group. A second literature search was performed by the centre in December 2018 to search for papers published after the initial search in 2015. For clinical questions addressed in the AAN guideline, literature searches were restricted to publications dated from 2007 to December 2018. For new clinical questions that had not been addressed in the AAN guideline or ENCALS guideline, literature searches were restricted to publications dated from 1998 to December 2018. The search strategies can be found in Appendix B.

Quality assessment

The working group was divided into topic groups, with 2 members per group. For questions grouped under a major topic, 2 members of each topic group screened the retrieved abstracts separately based on the inclusion criteria and relevance to the clinical question. Inclusion criteria included published ALS guidelines, ventilation guidelines, randomized controlled trials (RCTs), case-control studies, cohort studies, meta-analyses and systematic reviews. Publications had to be published in English or French and available in full text. Single-case reports, review articles, publications available only in abstract or proceeding forums, and thesis data not published elsewhere were excluded. Publications meeting the inclusion criteria by at least 1 of the abstract reviewers were reviewed in full by the topic group for inclusion criteria and data quality and assigned a class of evidence based on the AAN criteria (Box 1).The evidence tables are available in Appendix C of the full guideline (URL).

Development of recommendations

The working group met regularly at face-to-face meetings at least annually in Toronto, and through regular group teleconferences to discuss the specifics of guideline statements. Each topic group drafted preliminary guideline statements for each clinical question through considering previously published guideline statements[6-8] and updated evidence.

These draft statements were reviewed by the working group and refined on an iterative basis, ideally until consensus was obtained. If consensus could not be reached among the working group, we agreed that a decision would be made based on a two-third majority (66%) vote. However, there was consensus on all statements and so no vote was held.

Each statement was assigned a level of evidence, which included the option of expert consensus (Box 2). The working group felt strongly that in the absence of published evidence, best practice

recommendations based on expert consensus should be included, rather than not providing any recommendation. Given that there is limited evidence from clinical trial to direct care in ALS, the working group members thought it important that the recommendations be a practical guide to the care of patients with ALS, rather than simply a review of the evidence. Expert consensus statements were made based on non-clinical trial literature in ALS, evidence in other diseases or current Canadian ALS clinical practice. The order of the statements in the recommendations table was discussed at length to reflect their clinical importance and the order with which a practitioner would consider interventions when caring for these patients.

After the statements we developed for the respiratory questions had obtained consensus support from our working group, the Canadian Thoracic Society (CTS) published a guideline on the respiratory care of patients with ALS[11]. The working group decided it was important for our recommendations to be consistent with this guideline. To accomplish this, each of the recommendations in the CTS guideline was compared with our draft statements. Most of the CTS recommendations were accepted by our working group without changes, apart from slight wording alterations for consistency. We asked the CTS ALS committee to review our suggested statements, including those expert consensus statements where questions deemed important in our survey had not been addressed by the CTS guideline; their feedback led to some minor changes in our wording.

Review process

An executive summary of the guideline statements was developed and reviewed by the working group for further revisions. When the working group was satisfied with the recommendation statements including the wording, order and evidence ranking, this executive draft summary was emailed to members of the Canadian ALS Research Network (which includes all multidisciplinary ALS clinics in Canada) and topic experts external to the working group (i.e., representing gastroenterology, respirology, palliative care and physiatry) for open-ended feedback. The ALS clinics were asked to share the executive draft summary with their allied health staff and request additional open-ended feedback from them as well. The working group discussed each feedback comment received to determine if changes were required to the recommendation statements and if so, how the statements should be revised.

Using the revised executive draft summary, a second round of external review followed in which key stakeholders within each provincial ALS Society were asked to participate. The revised executive draft summary was emailed to each of the provincial ALS societies along with an attached survey with open-ended questions. Each society was asked to solicit feedback from its members, including one patient living with ALS in their province. All comments received were individually considered by the working group and implemented at their discretion through a robust discussion about the feedback. The changes made with the feedback received mostly involved wording changes. No substantial changes were made.

A complete version of the guideline was prepared and reviewed by all working group members for final approval.

Management of competing interests

All members of the working group performed their tasks voluntarily and were not paid honoraria for their involvement. The development of the

guideline, including travel for face-to-face meetings and preparation of the manuscript for publication, was funded by the ALS Canada and the Canadian ALS Research Network.

ALS Canada is a grassroots donor-funded organization and part of the funding for this project came from donations during the ice bucket challenge. ALS Canada assisted with logistic support but did not contribute to the content of the recommendations. The Canadian ALS Research Network was a non-profit organization of ALS clinicians and researchers formed to increase clinical ALS research in Canada and funded by stipends given by biotechnology companies to review clinical trial proposals for Canadian ALS clinics (it has subsequently merged with ALS Canada). While members of CALS participated in the development of the guideline, CALS had no role in approving guideline recommendations.

Competing interest management was discussed during the planning phase of the guideline; competing interests were defined by a financial relationship with a company. At that time, there was only 1 drug approved by Health Canada for the treatment of ALS, riluzole. None of the working group members have conflicts related to the drug riluzole, which has been available for more than 20 years. Other potential conflicts of interest were solicited from the working group at the beginning of this project and no conflicts were present.

In 2017, during the guideline development process, edavarone was approved to treat ALS by the U.S. Food and Drug Administration. Its manufacturer, Mitsubishi Tanabe Pharma (MTP), sponsored scientific advisory committees regarding the use of edaravone in patients with ALS in Canada. The drug was approved by Health Canada in October 2018 and became commercially available in Canada in November 2019. Some working group members were members of the MTP scientific advisory committees for edaravone (C.S., M.C., A.I., W.J., C.O., K.S., L Z.), which they disclosed to the working group. The statements in this guideline regarding edaravone were discussed at length among all members of the working group. During review of the draft guideline, feedback from members of the Canadian ALS Research Network and key stakeholders regarding the edaravone statements were deliberated by working group members who did not have conflicts of interest with MTP, defined as having received any honoraria from MTP. Final decisions regarding the edaravone statements were made by working group members without potential conflicts. Other than edaravone, there are no other potential conflicts with the statements in this guideline.

RECOMMENDATIONS

The care and management of patients with ALS should always be patient focused, with attention to holistic and emotional aspects of wellbeing. It is the patient who ultimately decides on their treatment; this includes the option of declining interventions.

The recommendations for the management of patients with ALS in Canada are in Table 1, grouped by topic, and indicating the level of evidence. If evidence was insufficient or absent for a key question, recommendations were made based on expert consensus through review of the available literature and clinical experience in ALS or extrapolated from treatment of other more common diseases.

The following section lists clinical questions, the recommendations that stem from those clinical questions, followed by the rationale behind the recommendations. Each recommendation is labelled either the level of evidence associated

with the recommendation (Level A, B, and C or EC – expert consensus). The evidence tables in Appendix 3 provide details of supporting evidence for all recommendations listed in Table 1.

Communication of diagnosis

How should a physician tell patients that they have ALS?

- *The approach to communicating the diagnosis should be tailored to the patient's individual needs (EC).*
- *The diagnosis of ALS should be confirmed by a neurologist or physiatrist with training and expertise in ALS (EC). Patients referred for confirmation of an initial diagnosis of ALS should be seen in an ALS specialty clinic within 4 weeks (EC). Timely clinical contact by the specialty ALS clinic after confirmation of diagnosis is recommended (EC).*
- *Discussion about ALS treatments and ALS research should occur. Patients should be provided with written information about ALS resources (paper or internet-based) and encouraged to register with their local and national ALS society (EC).*
- *Discussions on prognosis are important and should be tailored to the individual but need not be discussed at initial diagnosis unless specifically requested. (EC).*

The manner in which the diagnosis of ALS is delivered is a source of discontent for many patients and caregivers.[12,13] Recommendations have been formulated which outline a comprehensive approach to diagnosis delivery in the context of ALS.[8] One of the most important concepts for clinicians to consider is to tailor the diagnosis delivery to the individual needs of the patient. If a patient is overwhelmed by the diagnosis of ALS, then the diagnosis could be delivered in a stepwise fashion, without divulging all of the information at once.[14] Conversely, patients may feel that they did not receive enough information when receiving their diagnosis. Patients and caregivers wish to be informed about current research, treatments and prognosis when receiving a diagnosis of ALS.[15]

In a study of satisfaction with manner of disclosure of the diagnosis of ALS, 41% of patients indicated that they received insufficient information, and one third stated that they were not given a contact for follow up.[12] Furthermore, approximately three quarters of patients and caregivers had questions that arose immediately after the initial diagnosis was given.[13] These findings highlight the need for clinicians to address sources of information, community support and provide timely follow up when the diagnosis is first discussed. Patients report better satisfaction with the delivery of an ALS diagnosis if they believe that the clinician has understood their feelings.[15] An additional source of frustration for patients was the delay in receiving confirmation of a diagnosis including wait times to see an ALS specialist.[12] A reasonable maximum wait time of 4 weeks for a consultation for confirmation of a diagnosis of ALS, was agreed upon by the working group.

Disease-modifying therapies

What is the benefit of medications for ALS approved by Health Canada?

- *Disease-modifying therapies should be prescribed by clinicians with experience in managing patients with ALS (EC).*
- *Riluzole:*
    a. *Riluzole has demonstrated efficacy in improving survival in ALS (level A).*

b. *There is evidence that riluzole prolongs survival by a median duration of 3 months (level A).*

c. *Riluzole should be started soon after the diagnosis of ALS (EC).*

d. *Regular monitoring of potential adverse effects of riluzole is important (EC).*

e. *There is insufficient evidence to suggest that riluzole loses clinical efficacy with progression of disease, including development of respiratory insufficiency (EC).*

- *Edaravone:*

  a. *In a select group of patients, intravenous edaravone has been shown to slow decline on the ALSFRS-R scores compared against intravenous placebo, over a 6-month period of time (level B). (These are patients who have shown benefit from edaravone have disease duration of less than 2 years, FVC >80%, all ALSFRS-R subcomponents scores >2, and have demonstrated steady decline in the ALSFRS-R over a 3-month interval.)*

  b. *Evidence for benefit of intravenous edaravone at other stages of ALS has not been demonstrated (EC).*

  c. *As with any other therapies, individualized goals, risks, and benefits should be carefully considered and discussed before intravenous edaravone is initiated (EC).*

- *Physicians are encouraged to have an open dialogue with their patients about the potential risks and benefits of unapproved therapies (EC).*

Riluzole was approved by Health Canada as a treatment for ALS in 2000. Based on a Class I meta-analysis of 4 RCTs, riluzole has a modest benefit on survival compared with placebo, with a hazard ratio (HR) of 0.84 (95% confidence interval [CI] 0.698 to 0.997), representing a 9% gain in annual probability of survival. This translates to an increase in median survival from 11.8 to 14.8 months.[16] Recent registry-based cohort studies (all Class III) have estimated an improvement in median survival with riluzole treatment of 7.3 months,[17] 10 months,[18] or 12 months,[19] but other studies have found no effect on survival.[20-23] Findings from other Class III cohort studies reported HR estimates of 0.34,[24] 0.71,[25] 0.79,[26] and 0.81,[27] which translates to an estimated absolute increase in annual survival that ranges from 10% to 50%.

There are no controlled trials that have examined whether riluzole extends life at a specific stage or all stages of ALS. A post-hoc analysis of the original dose-ranging study suggests that riluzole may only be effective at prolonging survival at later disease stages (defined by nutritional or respiratory failure sufficient to require intervention),[28] but results from other cohort studies differ, showing that it may be effective only at earlier stages,[29] or that its effect on survival is short-lived.[30] Nevertheless, decades of experience worldwide have shown riluzole to be generally well tolerated with prolonged use and with regular monitoring of liver enzymes and blood counts, as well as screening for nausea and fatigue (Class I).[16]

Edaravone was approved by Health Canada to treat ALS in October 2018. A single Class I study in a generalized ALS population did not demonstrate overall benefit of edaravone in slowing progression of the ALS Functional Rating Score Revised (ALSFRS-R score) over 6 months[31] but did suggest benefit in a subgroup of patients (see Table 1 for

characteristics of this subgroup). This beneficial effect on the slowing of the progression of the ALSFRS-R score was subsequently confirmed in a second Class I study which restricted recruitment to patients with characteristics of the subgroup from the first study[32]. The second study demonstrated a mean reduction in the change in ALSFRS-R score over 6 months of 2.49 (95% CI 0·99 to 3·98). At this time, the available evidence suggests a level B evidence rating of "probably effective" in a select group of patients with ALS.

Multidisciplinary care

Does multidisciplinary management improve outcomes?

- *Patients with ALS should be referred to specialized ALS multidisciplinary clinics for optimized health care delivery (level B).*
- *Patients and health care authorities should be educated on the rationale for patient attendance at a multidisciplinary clinic. Benefits include:*
    a. *Survival benefit (level B).*
    b. *Fewer and shorter hospital admissions than patients not attending such clinics (level C).*
    c. *Increased use of adaptive equipment (level C)*
    d. *Increased use of riluzole, percutaneous feeding tubes and NIV (level B)*
    e. *Enhanced QOL (level C)*

What are the necessary components of multidisciplinary care?

- *Multidisciplinary care should be delivered through a team-based approach, with physicians and other health professionals addressing issues including communication, nutrition, swallowing, mobility, activities of daily living, respiratory care, cognition, psychosocial issues, medical management and end-of-life care (EC).*
- *The frequency of multidisciplinary clinic visits will be dictated by the patient's needs and rate of progression (EC).*
- *A dedicated nurse or other clinic allied health care professional should be available to support patients and their family members for ALS issues between clinic visits (EC).*
- *Telemedicine and telehealth monitoring are feasible and may be able to supplement clinic-based multidisciplinary care (level C).*

Patients with ALS should be regularly followed by a multidisciplinary ALS clinic. Multidisciplinary care should be delivered through a team-based approach, with physicians and other health professionals addressing issues including communication, nutrition, swallowing, mobility, activities of daily living, respiratory care, cognition, psychosocial issues, medical management and end-of-life care. Patients followed through a multidisciplinary clinic have been shown to have better outcomes, including survival, fewer hospital admissions, increased use of adaptive equipment and enhanced quality of life than those not followed in a multidisciplinary clinic.[32-39] One prospective cohort study demonstrated that patients followed in a multidisciplinary clinic lived 7.5 months longer than those followed in a general neurology clinic[34].

Telemedicine and telehealth monitoring are feasible and may be able to supplement clinic-based multidisciplinary care[40-43]. Also, management of patients with ALS should be a

collaborative arrangement between the family physician and the ALS clinic, with the ALS clinic staff available for remote consultation between patient visits.

Respiratory management

What pulmonary tests should be used to detect and monitor respiratory insufficiency?

- *Patients with ALS need regular respiratory monitoring at baseline and every 3 months, or as clinically indicated (EC). Regular respiratory monitoring should include:*
    a. *Symptom review, including dyspnea, orthopnea and morning headaches (level C)*
    b. *Measurement of sitting FVC or SVC (level B)*
    c. *One or more of the following: SNIP, supine FVC or MIP (level C)*
    d. *Arterial blood gases, venous blood gas or transcutaneous CO_2, when hypercapnia is suspected or when bulbar impairment precludes accurate testing (level C)*
    e. *PCF measurement to assess cough effectiveness (level C)*
    f. *Nocturnal oximetry or overnight polysomnography, when symptomatic sleep-disordered breathing is suspected and other daytime indications for NIV initiation are not present (level C)*

When and how should non-invasive ventilation be initiated?

- *NIV is the standard of care to treat respiratory insufficiency in ALS, both to lengthen survival and treat symptoms (level B).*
- *Criteria for NIV initiation are any of the following:*
    a. *Symptoms of respiratory insufficiency, including orthopnea (level B)*
    b. *SNIP <–40 cm H_20 or MIP <–40 cm H_20 (level C)*
    c. *Upright reliable* FVC <65% (EC).*
    d. *FVC sitting or supine <80% with symptoms or signs of respiratory insufficiency (level B)*
    e. *Daytime hypercapnia pCO_2 >45 mm Hg (level B)*
    f. *Abnormal nocturnal oximetry or symptomatic sleep-disordered breathing (level B)*
- *A respiratory specialist should be consulted to initiate NIV (EC).*
- *In any patient with the above indications, NIV should be initiated within 4 weeks. Severely symptomatic patients will need more urgent initiation. An overnight polysomnogram is not required for initiation of NIV (EC).*
- *Ensure in-home** NIV respiratory support for education, titration and troubleshooting (EC).*
- *There should be ongoing assessments by a specialized respiratory therapist who can optimize modes, pressure, and interfaces of NIV. Monitoring should include device download and may include nocturnal oximetry (level C).*

What are the benefits of NIV and what challenges can be encountered with NIV?

- *Patients should be informed that use of NIV may change the survival trajectory in ALS and the end-of-life experience (EC).*
- *NIV enhances QOL in patients with ALS who have respiratory insufficiency (level B).*

What are the indications for using oxygen in patients with ALS?

- *Oxygen should not be considered a treatment for chronic respiratory insufficiency. In patients with ALS with acute hypoxemia, management of respiratory insufficiency with NIV needs to be considered first. If hypoxemia remains after optimal NIV pressure is applied, the etiology of the hypoxia needs to be assessed and supplemental oxygen can be considered. (EC).*

Is diaphragm pacing effective?

- *Diaphragm pacing should not be used in ALS because it is not effective and likely harmful in patients with ALS (level B).*

What are the considerations for invasive ventilation in ALS?

- *NIV is the recommended treatment for ventilation even when ventilation is required 24 hours per day (EC).*
- *Mouth-piece ventilation can be considered in carefully selected patients as a form of NIV during the day in addition to nocturnal NIV (EC).*
- *In patients who cannot be effectively managed by NIV, invasive ventilation is an option in carefully selected patients. Discussions pertaining to goals of care and advanced directives should occur well in advance of respiratory failure (EC).*
- *Patients need to understand that ALS will continue to progress even with ventilatory support (EC).*
- *Advanced care planning discussions should include explicit information about all respiratory interventions. Discussions should include the fact that intubation may be irreversible depending on the disease stage, and palliative options for breathlessness (please refer to the Palliative Care section). Discussions should also include the option of removing any treatment that has been initiated (EC).*

How is airway clearance best managed in ALS?

- *Lung volume recruitment strategies (level C) and manual assisted coughing (EC) should be initiated when patients report difficulty clearing airway secretions.*
- *MIE twice daily should be considered for secretion clearance in patients with ALS who have reduced peak cough flow (PCF <270 L/min). Increased MIE frequency should occur during an acute chest infection (EC).*
- *Ensure in-home** respiratory support of MIE for education, titration, and troubleshooting (EC).*
- *Pharmacotherapy with mucolytics (i.e., guaifenesin or N-acetylcysteine), a β-receptor antagonist (e.g., metoprolol or propranolol), nebulized saline or nebulized ipratropium can be considered (EC).*

What are the indications for tracheostomy for airway clearance in ALS?

- *Tracheostomy can be considered for upper airway obstruction with vocal cord paresis; however, discussions of long-term invasive ventilation should also occur (EC).*

The respiratory management of patients with ALS was recently reviewed by the CTS guideline group on home mechanical ventilation.[11] We decided to have our recommendations on respiratory management (Table 1, Figure 1) be consistent with the CTS guideline. We made a few additions to the CTS recommendations, including a statement on avoiding the use of oxygen for respiratory symptoms in patients with ALS, timing of initiation of interventions and managing secretions. We also thought it was important to adjust the minimum FVC (forced vital capacity) criterion for initiation of non-invasive ventilation in asymptomatic patients to 65% of predicted from the CTS recommendation of 50% because available evidence suggests early initiation improves survival.[44] Patients with an FVC of greater than 65% predicted can be started on non-invasive ventilation if any of the other initiation criteria are met, as consistent with the CTS guideline. Our group also unanimously agreed that if criteria for initiation of non-invasive ventilation are met, patients should be initiated on non-invasive ventilation within 4 weeks.

It is important to acknowledge that non-invasive ventilation can change the natural disease trajectory of ALS. For example, increasing reliance on non-invasive ventilation converts it into life-support technology. In patients reliant on non-invasive ventilation, natural death may not occur while using the technology; death may only occur is there is an active decision to discontinue the ventilation support. Patients should be counselled that they may need to take an active decision as to the timing of discontinuing the ventilatory support, unless they wish prolonged survival.

Difficulty with secretion management is common among persons living with ALS, and is a cause of distress, reduced quality of life and impairment of respiratory function. Airway clearance management was not explicitly addressed in the CTS guideline. Because we thought it was very important to include recommendations on airway clearance, we reviewed available evidence and clinical experience. We recommend that lung volume recruitment techniques be introduced whenever patients present with symptoms of retained airway secretions or difficulty in clearing secretions. Such techniques can be combined with manual assisted coughing and be performed independently by patients or with assistance of care providers. If patients develop impaired peak cough flow (<270L/min), then mechanical insufflation exsufflation twice daily should be considered for secretion clearance, and more frequently during an acute respiratory infection.

We also attained consensus that providing adequate in-home respiratory support of non-invasive ventilation and mechanical insufflation exsufflation for education, titration and troubleshooting is essential, regardless of whether the patient resides in their own home, long-term care facility or hospice.

Nutrition management

How is nutritional status monitored? How should aspiration risk be assessed? What factors should lead to a recommendation for enteral nutrition?

- *Nutritional status should be monitored by weight and BMI every 3 months, or as clinically indicated (level B); consider use of TDEE (level B).*

- *Nutritional interventions, including dietary alteration and consideration of referral for enteral tube insertion, are indicated at diagnosis or at follow-up if there is: (1) increased risk of aspiration despite consistency modifications and compensatory recommendations (EC); (2)≥5-10% reduction in weight from usual or baseline weight (level C); (3) ≥1-point reduction in BMI from usual or baseline BMI (level B); (4) BMI <18.5 (level B); or (5) TDEE exceeds daily energy intake (EC).*

- *Information regarding potential benefits and risks of enteral feeding tubes should be provided early in the course of ALS management (EC).*

- *A decrease in FVC approaching 50% should prompt consideration of referral for enteral tube insertion, even in the absence of dysphagia. An FVC <50% should not necessarily preclude the recommendation of enteral feeding tube insertion as long as respiratory status is carefully monitored during and after the procedure (level C). NIV may improve safety of RIG or PEG insertion in patients with respiratory impairment (EC).*

- *Regular monitoring of swallowing safety should be performed by a certified swallowing clinician (level B). Objective measures of swallowing impairment (MBS or FEES) can be used early and during the course of ALS management (EC).*

Low or falling weight or BMI at the time of ALS diagnosis or at follow-up may be associated with poorer prognosis. A reduction in BMI by more than 1 point over 2 years was found to worsen prognosis, while a stable weight improved prognosis (Class I).[45] In a population-based study, 50.6% of patients had weight loss of more than 5% from diagnosis, and risk of death increased by 14% (range: 5%–23%) for each 5% increment in weight loss (Class I).[46] Another study reported that 30-day mortality was 10.7 times higher in patients who had more than 10% weight loss from diagnosis (Class II).[47] While these studies correlated prognosis with reductions in weight or BMI, having a BMI of less than 18.5 has been shown to be associated with poorer survival (Class I).[48] Multiple Class III studies have shown that weight loss from before symptoms, either at diagnosis, or at PEG insertion, is an independent factor for poor survival.[26,49-51] Collectively, these studies found that as low as a 5% reduction in usual weight, a 1-point reduction in BMI, or a BMI of less than 24 points, were associated with poorer survival. Two Class IV studies[52,53] showed that weight loss of at least 5 kg from baseline or a lower BMI at the time of PEG insertion were associated with poorer survival. There is no definite answer to whether feeding tube insertion affects outcomes. Though most studies have drawn a different conclusion, a causal inference study (Class III)[54] of data from a ceftriaxone trial calculated a 46% decrease in survival time for patients who had a feeding tube inserted during the trial when compared with their estimated survival times had they never received a feeding tube. The study also concluded that having a feeding tube had no benefit in quality of life (QOL).

Monitoring nutritional status in patients and intervening when there is evidence of worsening nutritional status may be beneficial for survival. Institution of a multidisciplinary protocol with standardized referral for nutrition consultation has been shown to result in a higher BMI at the time of the initial nutritional encounter (Class III).[55] Though not a widely used method, a formula for estimating TDEE using height, weight, gender, age, and ALS Functional Rating Scale Revised (ALSFRS-R) data has been shown to correlate well with measured

energy expenditure in 2 Class I studies.[56,57] As such, TDEE could be used to monitor patients for indications of insufficient nutrition prior to the development of falling weight or BMI.

Dysphagia and choking are issues that overlap with nutritional insufficiency in ALS. Swallowing assessment and counseling regarding safe swallowing techniques can be initiated when symptoms develop, but it is apparent from objective measures that swallowing dysfunction precedes patient awareness of swallowing impairment. Video fluoroscopy, or MBS, has been used to demonstrate risk of aspiration in patients with no bulbar symptoms and in patients with dysphagia who have normal eating habits (Class III[58] and Class IV[59]). A Class II study[60] compared video fluoroscopy with the Volume-Viscosity Swallow Test (V-VST), which does not involve radiation, and found that the two methods had similar sensitivity and specificity in detecting oropharyngeal dysphagia. FEES has also been shown to detect evidence of aspiration before symptoms of swallowing impairment (Class IV).[61] Patient awareness of symptoms was studied using a questionnaire, the Eating Assessment Tool-10 (EAT-10), which was determined to be a good screening tool for risk of penetration and aspiration (sensitivity: 85.7%–88%; specificity: 56.7%–71.9%; Class II).[62] Ultimately, certified swallowing clinicians, including speech-language pathologists, dietitians, and ENT specialists (for FEES), are essential to the follow-up care of patients.

Enteral nutrition is an important intervention for the management of ALS. Enteral nutrition can reduce aspiration and choking risk, as well as provide necessary nutrition when oral feeding is insufficient. Barriers to the introduction of enteral nutrition include limited availability of resources and attitudes of patients and families regarding the intervention. A Class IV study[63] showed that the best predictor of whether a patient will eventually have PEG is their initial attitude toward PEG. As such, it is important that information about the procedure be provided to patients before it is absolutely necessary, or too late, to introduce.

Respiratory status influences the approach and potential complications of enteral tube insertion in patients with ALS. An early Class III study[64] demonstrated poor prognosis for patients following PEG insertion when their FVC was less than 50%. However, with careful management of patients during the procedure, and the use of various methods of tube insertion, patients with a lower FVC can still receive tubes for nutrition. A Cochrane review[65] reported 2 uncontrolled studies[66,67] that demonstrated that PEG can be performed at low FVC. Two Class III studies[68,69] and 5 Class IV studies[52,66,67,70,71] showed PEG was safe in patients with low FVC. PEG has been shown to be safe in a small study, specifically in patients with an FVC of <30% (Class III).[72] Four Class III studies[73-76] and 3 Class IV studies[77-79] showed that RIG was safe in patients with low FVC. In one of these studies,[73] RIG was more often successful and associated with better survival compared with PEG.

In patients with respiratory impairment, NIV may improve safety of specific enteral tube insertion procedures. Open gastrostomy was demonstrated to be safe with NIV In patients with low FVC (Class IV).[80] In addition, NIV was deemed to improve safety for RIG in 2 Class IV studies[76,77] and PEG in 4 Class IV studies,[66-68,70] and there was no difference in markers of desaturation when compared with no NIV according to a Class III study.[81] The state of respiratory function will influence counseling to patients regarding recommendations for timing of enteral nutrition as well as the method of insertion. An FVC <50% should not preclude the

consideration of a feeding tube, but warrants extra caution with the procedure.

What is the maximum allowable delay for PEG/RIG insertion, after it has been clinically recommended?

- *Once a decision is made to insert an enteral feeding tube, insertion should be performed within 4 weeks. The ALS team should have access to endoscopists or radiologists who have interest and expertise in tube insertion (EC).*

There are no studies that address the maximum allowable delay for enteral tube insertion once the decision has been made to insert a tube; nevertheless, the delay should be no more than 4 weeks. ALS progresses steadily and delaying tube insertion may negatively influence prognosis and the success of the procedure. Success in limiting the delay is most likely if alliances can be established with endoscopists and radiologists who have interest and expertise in tube insertion. These alliances are also important for ensuring appropriate care of the tube after insertion.

What is the recommended procedure for feeding tube insertion?

- *There is insufficient evidence to recommend PEG or RIG as the usual procedure for gastrostomy insertion (level C). There is weak evidence that RIG may be safer in patients with ventilatory impairment, as RIG does not require substantial sedation (EC).*

- *Once a feeding tube is placed, an experienced clinician (endoscopist or radiologist) should be readily available to address immediate and late tube complications. There should be regular support by a registered dietician with respect to the enteral feeds prescribed (EC).NG feeding is not a preferred long-term option and should be reserved for those patients where no other procedure is possible and enteral nutrition is still desired (level C).*

Various methods for tube insertion have been developed. Most centres use PEG or RIG, though other methods have been developed, such as per-oral image-guided gastrostomy (PIG), a hybrid technique of PEG and RIG. A Cochrane review[65] did not find any randomized controlled trials (RCTs) that addressed which procedure was better. This review found 4 case control studies with poor methodology that did not demonstrate a consistent advantage to either procedure. A meta-analysis[82] included 9 studies (some of which were published before the analysis period of this guideline), although no RCTs were included and the evidence class was variable. The meta-analysis compared outcomes between PEG and control groups that could include RIG, nasogastric tube (NG), percutaneous radiologic gastrostomy (PRG), or other, and found a higher survival for PEG at 20 months, but not at 30 days, 10 months or 30 months. Another meta-analysis[83] analyzed 5 Class III studies and 1 Class II study and found no difference between PEG and PRG in the ALS subgroup with regard to complications or 30-day survival. Another study also found that 30-day survival was not different among PEG, RIG and PIG, however the patient characteristics of the groups were not equivalent, with patients in the PIG group having a lower mean FVC than those in the other 2 groups (Class II).[47] Three Class III studies reported that RIG was superior to PEG,[73,84,85] reporting improved success rates, safety, and survival when RIG was used. However, 4 Class III papers reported PEG and RIG have equivalent results.[74-76,86] One of these studies[86] stated that RIG was better than PEG, but the results were not statistically significant. In some studies, stratification of

patients with low FVC to the RIG group hampers interpretation of the results. A Class III study[87] reported that PIG had a similar outcome to PEG. Because PEG insertion under sedation can cause apnea or hypoventilation, newer methods that do not require sedation have been investigated. A Class IV study[88] compared standard sedated or unsedated PEG insertion with unsedated PEG insertion using an ultrathin endoscope (UTE) and reported no failures or episodes of apnea and/or hypoventilation or aspiration pneumonia with the UTE method. A Class IV study[89] described the use of nasal unsedated, seated PEG (nuPEG) and reported a high success rate with rare serious complications. The evidence does not provide a clear conclusion of which tube insertion procedure is ideal. Respiratory function should be considered when recommending a specific procedure. In the absence of high-level evidence at this time, RIG or PIG should be considered when respiratory function is very poor, though concern may be low with PEG in this circumstance. When there is impaired respiratory function, NIV support during the procedure may be considered.

Whether tube insertion should be performed as an outpatient or inpatient procedure has not been studied. Patient status and prediction of potential complications from the procedure should guide decisions on the setting for tube insertion.

NG feeding is an alternative enteral feeding support. Although there is insufficient evidence comparing NG feeding with other methods, it is not considered a good option under most circumstances. NG feeding was compared to PEG and RIG in 2 Class III studies,[75,76] but NG-fed patients were dissimilar to those in the other groups at the time of insertion, with more advanced disease and shorter post-insertion survival.

What type of supplements/enteral feeds should be suggested? Should hyperalimentation be used in ALS?

- *High-calorie diets can be used to improve nutritional indicators (level B) and possibly survival (level C). High-calorie/high-carbohydrate diets may be better than high-calorie/high-fat diets (level B).*
- *Parenteral nutrition is a potential source of nutrition in patients who cannot successfully have an enteral nutrition source; its use should be reserved for exceptional circumstances (EC).*

Dietary content and amount may influence outcomes in patients with ALS. A Class I (Class II for some endpoints) study[90] demonstrated that a high-carbohydrate/high-calorie diet for 4 months was associated with fewer adverse events and better survival compared with a high-calorie/high-fat diet or a control diet. However, survival was an exploratory endpoint in this study and requires further investigation to strengthen the evidence. A supplement with high protein content (70% milk whey protein isolate [WPI] and 30% modified starch [MS]; 70%WPI:30%MS) was found to improve nutritional markers to a small degree compared with a control supplement (maltodextrin) over a 4-month period (Class III).[91] Another study showed that 2 different high-calorie diets, high fat and high carbohydrate, increased weight during the 4-month intervention (Class III).[92] Weight gain was higher in the high-fat diet group, but this was not a statistically significant difference. A Class IV study[52] showed survival was longer with a diet of greater than 1500 kcal/d compared with a diet of less than 1500 kcal/d in patients who survived beyond 12 months.

Home parenteral nutrition is not a first-line management for nutritional support in ALS. One Class III[93] and 1 Class IV study[94] reported successful nutritional management with home parenteral nutrition in a high percentage of patients, however infectious complications occurred on 1.34/1000 catheter days in one study (leading to death in half of those affected) and were reported in 4/30 patients in the other study (leading to death in 2 patients).

The nutrition recommendations (Table 1, Figure 2) largely follow those outlined in the AAN guideline.[6] Differences from the AAN recommendations include the addition of an expert consensus statement on the 4-week maximum allowable delay for a feeding tube insertion after criteria have been met, and a statement on the availability of appropriate follow up post-insertion for immediate or late complications. The recommendations also include a statement about nutritional components, and note that high-calorie diets can be used to improve nutritional indicators and possibly survival.[91,92] High-calorie/high-carbohydrate diets may be better than high-calorie/high-fat diets.[90]

Venous thromboembolism

What is the risk of VTE in patients with ALS?

- *There is likely an increased risk of VTE in patients with ALS. The risk appears heightened in ALS with leg onset and in patients with poor mobility (EC).*
- *Clinicians are encouraged to consider VTE as a potential cause for new leg pain or new leg swelling in patients with ALS (EC).*
- *There is no evidence to suggest screening for thromboembolism in asymptomatic patients with ALS (EC).*

Should VTE prophylaxis be considered in patients with ALS?

- *VTE prophylaxis has not been evaluated in patients in ALS and is not recommended at this time in non-hospitalized patients (EC).*
- *If VTE occurs in a patient with ALS, they should be anticoagulated as per standard VTE guidelines (EC).*

There is likely an increased risk of VTE in patients with ALS[95,96]. The risk appears heightened in ALS with leg onset and in patients with poor mobility[95]. Even though there is likely an elevated risk of VTE in patients with ALS, there are no studies to support primary VTE prophylaxis. At this time, primary VTE prophylaxis is not recommended because the risk-benefit ratio of potential adverse consequences from falls versus VTE prevention in patients with ALS is uncertain.

Medication alignment

Should medication reviews occur regularly?

- *Primary care physicians and specialists should perform intermittent medication reviews and consider discontinuing any non-essential medications (EC).*
- *Symptom management medications should be continued (EC).*
- *Primary prevention medications should be discontinued if duration of effect is longer than the expected survival (EC).*

Should statins be discontinued in patients with ALS?

- *Patients and health care professionals can be reassured that pre-morbid statin administration does not appear to contribute to the development of ALS (level B).*

- *There is insufficient evidence to recommend discontinuation of statins in all patients with ALS. Discontinuation of statins may be considered based on the patient's expected survival and their cardiovascular risk (EC).*

When patients come to the ALS clinic, they are often on multiple medications. Some of these medications may be considered nonessential, particularly considering the average survival of patients with ALS. Through expert consensus, we developed several statements that address the need for regular review of the medications that a patient is taking and suggest discontinuation of any nonessential medications that are not providing symptomatic relief or appropriate therapeutic benefit in the context of an individual patient's expected survival.

Symptom management

What is the prevalence and type of pain in ALS patients?

- *Pain is a recognized consequence of ALS, with many potential causes (EC).*
- *Patients must be queried regularly about pain symptoms. Pain should be regularly assessed and treatments should be tailored towards the specific cause (EC).*

Pain is a recognized consequence of ALS and there are many potential causes. The types of pain in ALS have not been well described. Pain should be regularly assessed and managed in patients with ALS and treatments should be tailored towards the specific cause. Pain is frequent in ALS[97]. There are no evidenced-based guidelines on treatment of pain in ALS. There is a single small study that found THC was not effective in the treatment of pain in ALS[98].

What are the most effective treatments for fasciculations?

- *In most patients, fasciculations do not need medication management (EC).*
- *If fasciculations cause substantial distress, gabapentin can be considered (level C).*

In most patients, fasciculations do not need medication management (EC). Fasciculations have been studied as a secondary outcome measure in clinical trials testing Gabapentin[99] and THC[98]. Gabapentin was found to reduce fasciculations (Class III) but THC had no benefit (Class III). In patients who are bothered by frequent fasciculations, gabapentin can be considered (Level C). Clinicians should be aware that patients may become concerned about their fasciculations reflecting disease progression. In patients who have difficulty sleeping secondary to fasciculations, gabapentin can be considered (EC).

What are the most effective treatments for sialorrhea?

- *Anticholinergic medications are the first-line therapy of sialorrhea. Individual medication choices should be tailored to patient factors (EC).*
- *If one anticholinergic medication is ineffective, switching to another anticholinergic medication should be considered (EC).*
- *Oral suction can be used as an adjunct therapy in managing sialorrhea (EC).*
- *Botulinum toxin is effective for management of sialorrhea in ALS (level A). It can be used as second-line therapy and should be considered after feeding tube insertion because of the*

theoretical risk of worsening swallowing or airway integrity (EC).

- *Focal salivary gland radiation is an option for management of sialorrhea (level C) as second- or third-line therapy.*

Sialorrhea or drooling is common in ALS patients who have bulbar symptoms. In patients with ALS, anticholinergic medications are generally first line treatments to reduce sialorrhea (EC), although their effectiveness is unproven. Second line therapy would be to switch to another anticholinergic medication (EC). Options include sublingual atropine drops (1% atropine ophthalmic drops, 1-2 drops q4h prn); amitriptyline (start at 10-25mg at hs and titrate up to max 100mg/d divided); scopolamine patch (1.5mg q 72 hr); glycopyrrolate (0.1mg-1mg orally up to qid). Anticholinergics were selected over botox because experience tells us they are effective, cheaper, titratable, easily accessible, non-invasive, and reversible (EC).

In patients with ALS who have medically refractory sialorrhea, BTxB should be considered (Level B) and low-dose radiation therapy to the salivary glands may also be considered (Level C). Several studies have shown improvement with botulinum toxin[100-105]. BTxB injections into the parotid and submandibular glands are probably effective, while there are inadequate data on the effectiveness of BTxA and amitriptyline. Botulinum toxin injection poses the theoretical risk of worsening swallowing or worsening airway integrity. Low-dose irradiation to the salivary glands is possibly effective for sialorrhea (2 Class III studies) for patients with symptoms refractory to medical treatment[106,107] .

What pharmacologic measures reduce pseudobulbar affect?

- *Patients and families should be educated that pseudobulbar affect is a symptom of ALS and does not necessarily represent a symptom of depression or impaired cognition (EC).*
- *Pseudobulbar affect does not require treatment unless it is distressing to the patient (EC).*
- *If treatment is warranted, medications that may co-treat concomitant symptoms (e.g., amitriptyline for sleep and mood effect, SSRI for depression) may be considered (EC).*
- *Dextromethorphan (20 mg) combined with quinidine (10 mg) can be used for treatment of pseudobulbar affect (level B).*

Pseudobulbar affect, excessive laughing or crying, or involuntary emotional expression disorder is common in patients with ALS. Patients and families should be educated that pseudobulbar affect is a symptom of ALS and does not necessarily represent a symptom of depression or impaired cognition (EC). Pseudobulbar affect does not need to be treated unless it is distressing to the patient (EC). Although these symptoms are not considered a mood disorder, antidepressants such as amitriptyline and SSRI's are frequently employed. A fixed-dose combination of 30 mg dextromethorphan (DM)/30 mg quinidine (Q) BID for treatment of pseudobulbar affect in ALS (1 Class I study) reduced the frequency and severity of laughing and crying behaviors[108]. DM/Q should be considered for symptoms of pseudobulbar affect in patients with ALS (Level B), although side effects and access may limit its usefulness (currently in Canada this can be made by a compounding pharmacist). There in insufficient

evidence to support the use of amitriptyline or SSRI's, although they are frequently used.

What interventions reduce spasticity?

- *Stretching can be useful for managing spasticity (level C).*
- *If pharmacological management of spasticity is required, baclofen, tizanidine, botulinum toxin, benzodiazepines and cannabinoids could be considered (EC).*
- *There is insufficient evidence to recommend intrathecal baclofen for spasticity management in patients with ALS (EC).*

Spasticity is a frequent complaint in patients with ALS affecting the upper motor neuron. Careful consideration of individual factors is required with addressing spasticity in ALS (EC). Stretching can be useful for managing spasticity (EC). Vitamin E (5,000 mg daily) plus riluzole had no beneficial effect on spasticity as a secondary outcome measure in a Class III clinical trial[109]. Baclofen pumps were found effective in reducing spasticity in one class III[110] and one class IV study[111] . There is insufficient evidence to recommend intrathecal baclofen for spasticity management in patients with ALS (EC). Two small case series have looked at using botulinum toxin to treat spasticity in ALS[112,113]. Due to the non-randomized nature of these studies, there is insufficient evidence to suggest botulinum toxin to treat spasticity in ALS.

At this point, there is insufficient evidence to recommend a specific medication for treating spasticity in ALS, although benzodiazepines, baclofen, tizanidine and gabapentin are frequently used (EC). Antispasticity agents may unmask lower extremity weakness and may impact a patient's ambulatory or standing ability. Cannabinoids have an approved indication for spasticity in MS and spinal cord injury, but there is no expert consensus at this point on the use of cannabinoids for management of spasticity symptoms in ALS (EC).

What interventions reduce cramps?

- *Muscle cramps need to be differentiated from other causes of pain (EC).*
- *First-line management could include tonic water, gabapentin and baclofen (EC).*
- *Second-line treatment could include quinine, levetiracetam and mexiletine (EC).*

Muscle cramps are common in ALS and need to be differentiated from spasticity and fasciculations. Cramps have been a secondary outcome measure in ALS clinical trials testing gabapentin[99] (Class III); vitamin E[114] (Class III) and riluzole[115] (Class III), and none showed any significant benefit observed versus placebo. There are no studies in ALS on the use of quinine, and Health Canada has warned against using quinine for leg cramps. One class III trial on the use of THC in cramps found no evidence of efficacy[98]. One class III trial on the use of mexiletine in cramps found evidence of efficacy[116]. A phase II double-blind randomized controlled trial of 60 ALS patients (Class I study) using mexiletine 300 mg/d, or mexiletine 900 mg/d and followed for 12 weeks resulted in large dose-dependent reductions in muscle cramp frequency (300 mg per day; 31%; p=0.047) and intensity (300 mg per day; 45%, p=0.08). Mexiletine was well tolerated at a dose of 300 mg per day. A higher dosage (900 mg per day) led to frequent discontinuation due to adverse effects and was therefore not recommended. A multicenter, double-blind, placebo-controlled crossover trial was conducted in 20 ALS patient with mexiletine (150 mg twice daily) showed a significant reduction in muscle cramp frequency (an average reduction of 1.8 cramps per day; $P < 0.05$) and severity (estimated

reduction of 15 units on a 100-unit scale (P = 0.01) from a baseline average of 46)[117].There are insufficient data to support the use of any specific medication for the treatment of cramps in ALS.

What pharmacologic interventions reduce depression?

- *Depression should be treated in ALS, since it has a substantial impact on patient well-being (EC).*
- *SSRIs or SNRIs can be used to treat depression in ALS (EC).*
- *Consider non-pharmacological supports such as offered through psychology, social work, psychiatry or spiritual care support (EC).*

There have been no controlled trials of treatment for depression in ALS. There are thus insufficient data to support or refute specific treatments for depression in ALS. Depression should be treated in ALS, since it has a significant impact on patient well being (EC). Citalopram may be preferred to venlafaxine since its intake is easier in patients with dysphagia, while amitriptyline would be used when sialorrhea is present. Mirtazepine qhs is frequently used for depression and insomnia as a favourable side-effect is weight gain.

What pharmacologic interventions reduce anxiety?

- *Anxiety should be treated in ALS since it has a substantial impact on patient well-being (EC).*
- *It is important to determine if anxiety is related to respiratory insufficiency and if present, treat appropriately (EC).*
- *If depression is concurrently present, an SSRI should be prescribed. (EC).*
- *Benzodiazepines can exacerbate respiratory insufficiency (EC).*
- *Non-pharmacological supports can be considered, such as those offered through psychology, social work, psychiatry or spiritual care support (EC).*

There have been no trials of treatment for anxiety in ALS. Thus, there are insufficient data to support or refute specific treatment for anxiety in ALS. Anxiety should be treated in ALS, since it has a significant impact on patient well being (EC). In treating anxiety in ALS, one should consider non-pharmacological support such as offered through psychology, social work, psychiatry, or spiritual care. SSRIs should be prescribed in the context of concurrent depression. Benzodiazepines are often used empirically, although they may exacerbate respiratory insufficiency.

What pharmacologic interventions reduce insomnia?

- *There are multiple causes of insomnia such as respiratory insufficiency and depression that should be appropriately investigated (EC).*
- *Respiratory investigations and sleep studies could be considered to determine the type and cause of insomnia (EC).*
- *Pharmacological management of insomnia will depend on the cause (EC).*

There have been no studies of treatment for insomnia in ALS. Thus there are insufficient data to support or refute specific treatment for insomnia in ALS. There are multiple potential causes of insomnia such as respiratory insufficiency, sleep apnea, muscle cramps or spasticity. Sleep studies can be arranged to determine the type and cause

of insomnia which can then be managed by the most appropriate intervention.

What pharmacologic interventions reduce fatigue?

- *Reversible causes of fatigue should be considered, such as respiratory insufficiency, sleep disorders, depression, medication side effects, and riluzole use (EC).*
- *In patients developing fatigue while taking riluzole, reducing or discontinuing the drug may be considered (level C).*
- *Consider having an OT discuss energy conservation techniques with patients (EC).*

There are no controlled studies of pharmacologic agents for the treatment of fatigue in ALS. Thus, there are insufficient data to support or refute specific treatment for fatigue in ALS. Reversible causes of fatigue such as respiratory insufficiency, sleep disorders, depression, or side effects of medication should be investigated. In patients developing fatigue while taking riluzole, withholding the drug may be considered once the side effect versus the modest survival benefits have been discussed (Level C). Modafinil[118] and Mestinon[119] (citing post-polio syndrome) are occasionally used based on evidence from other neurological diseases.

Patients with ALS often experience multiple uncomfortable symptoms that severely impair quality of life including pain, fasciculations, sialorrhea, pseudobulbar affect, spasticity, cramps, depression, anxiety, insomnia and fatigue. Several clinical trials have explored treatment options for sialorrhea[102] and pseudobulbar[108] affect. However, management of most ALS symptoms has not been rigorously evaluated. As a consequence, most of the recommendations for symptom management were decided by expert consensus and supported by treatment suggestions made in the ALS and palliative care literature. Cost and access to treatments affected our ordering of the recommendations and were weighted more highly than direct evidence if an evidence-supported treatment was expensive. Our recommendations did not include the option of cannabis to treat specific ALS symptoms, because of lack of evidence in the literature. However, the working group is aware that cannabis is being used to manage several ALS symptoms.

Dysarthria

What treatments for dysarthria optimize communication in ALS?

- *Patients with dysarthria should be regularly followed by SLP to ensure timely communication interventions (EC).*
- *Use of augmentative and alternative communication devices should be offered to eligible patients in early disease stages (EC). Patients in later disease stages will also benefit from communication devices and strategies (EC).*
- *The choice of communication devices should be tailored to the patient's needs and abilities (EC). Patients with cognitive impairment may need individualized strategies for communication (EC).*
- *Augmentative and alternative communication strategies may reduce caregiver stress (EC).*
- *Voice amplification should be offered to patients with reduced vocal projection (EC).*
- *Voice banking should be offered to appropriate patients (EC).*
- *Providing access to different modes of communication, including social media, can*

allow independence, participation and better QOL (EC).

The ability to communicate thoughts and needs to others is vitally important to individuals. ALS often impairs the ability to communicate verbally because of dysarthria[2]. There are multiple available interventions that can be initiated to support communication, including low-tech options, such as letter- or picture-boards, and high-tech options, such as speech synthesizers and eye-gaze tracking. As individuals with ALS experience loss of function, some modes of communication may no longer be viable. Providing access to different modes of communication, including social media, can allow independence, participation and better quality of life.[120] Communication devices may also benefit caregivers, as the burden on caregivers was found to be reduced when patients used an eye-tracking assistive device.[121]

Multiple studies have shown altered articulatory kinematics in patients with ALS,[122-126] and issues around communication can lead to a reduced QoL.[127] A wide array of communication strategies are available, including low-tech options, such as letter- or picture-boards, and high-tech options, such as speech synthesizers, and eye gaze tracking. Human–computer interfaces are an area of active research in ALS.[128] Brain–computer interfaces can be of value,[129] however their use may be limited in patients with cognitive dysfunction.[130,131] Other strategies include the use of portable voice amplifiers to increase the volume of the patient's voice, and recording the patient's own voice for later playback (voice banking).[132] Commonly used devices include tablets, smartphones, laptops, and desktop computers.[133] The use of a communication device has been found to improve QoL in patients with ALS,[120,134,135] while speech therapy exercises were found to have comparatively less impact on QoL.[135] Communication devices may also benefit caregivers, as the burden on caregivers was found to be reduced when patients used an eye-tracking assistive device.[121]

As individuals with ALS experience loss of function, some modes of communication may no longer be viable. Providing access to different modes of communication, including social media, can allow independence, participation, and better QoL.[120] Most patients are able to use a communication device,[136] and even severely affected patients, including those with tracheostomy, have been shown to use communication devices effectively.[137,138] However, one study found that in a population of ALS patients with tracheostomy, the majority were unhappy with their current device.[139]

Assessments by speech language pathology and referrals for AAC devices should be made early in the disease course.[140,141] The area of symptom onset should be considered, since patients with bulbar onset have more rapid deterioration of speech than patients with spinal onset.[142] Some experts recommend referral to AAC when the speaking rate falls below 120 words per minute.[143] Nordness et al. found that late referrals for communication devices tended to be patients with significant bulbar dysfunction who had difficulty obtaining a referral from a physician (family physician or non-ALS clinic neurologist) and who resided in a rural area.[144] It should be noted that there are currently no pharmacological therapies approved for the treatment dysarthria in ALS. Although a combination of dextromethorphan and quinidine was shown to improve some objective measures of speech dysfunction in patients with ALS, there was no effect on physician ratings or self-reported measures of speech.[145] These studies highlight the need for early and ongoing

communication assessments through multidisciplinary clinics to ensure that appropriate devices are utilized by patients.

Exercise

What level and type of physical exercise is recommended in patients with ALS?

- *In early ALS, regular moderate-intensity exercise is probably beneficial for function and QOL (level B). A personalized exercise program, including strength and aerobic training, should be suggested to patients who are able to participate (EC).*
    a. *Submaximal effort for resistance should be encouraged.*
    b. *Moderate-intensity physical activities are those that will cause adults to sweat a little and to breathe harder.*
- *Moderate-intensity exercise is well tolerated and not harmful in ALS (level B).*
    a. *Post-exercise fatigue or pain should resolve in 30 minutes and not interfere with daily activities; adjust the exercise program otherwise*
- *A regular stretching and range of motion program is recommended for management of spasticity (level C), pain (EC) and prevention of contractures (EC).*
- *Stretching and range of motion exercise can be done independently (active), with assistance (passive) or in combination (active-assist)*

The benefits of exercise are well established among the general population, with national guidelines established for physical activity[146]. Among persons living with ALS, lack of physical activity can be detrimental, resulting in deconditioning, increasing weakness and contracture risk. However, despite association with improved health and well-being, persons living with ALS may be cautioned against exercise, due to fears of causing further weakness or disease aggravation. This sentiment may be further perpetuated by epidemiological reports of higher ALS incidence associated with pre-diagnosis history of intense physical activity[147]. Although there have been few large controlled trials of exercise in person with ALS, the evidence available supports that exercise is not harmful in ALS and should be recommended.

Four recent randomized controlled trials (RCT) [148-151]and a case series study[152] have provided evidence consistent with earlier studies[153,154] that resistance (strengthening) and endurance (aerobic) programs are feasible, generally well-tolerated, and are associated with better outcomes in function as evaluated by less deterioration on the ALSFRS-R, as well as positive outcomes in quality of life. Most protocols used submaximal resistance for strengthening activities. Aerobic exercise is activity performed for an extended duration at a moderate intensity during which oxygen use meets the energy demands. Few studies have used physiologic data to determine aerobic performance; one study (class II) reported that a strictly monitored moderate exercise program may significantly reduce motor deterioration in ALS patients, and another small class II[150] trial found improved muscle power and fatigue measures in a group performing moderate aerobic and strengthening exercises over a 5 week period. One recent RCT[155] found improved maximum expiratory pressure with an expiratory strength training program, in keeping with earlier smaller trials[156]. In an extension of the 2012 study, the authors report longitudinal outcomes of improved survival in the expiratory muscle training

group in reference to historical controls. Importantly, based on the studies to date, aerobic, strengthening and range of motion or stretching exercises all appear to be safe and well tolerated in persons with ALS. with no evidence to suggest disease or symptom aggravation.

Although there is insufficient evidence to support one form of exercise over another, the expert consensus follows general fitness and exercise principles of including strengthening, aerobic and range of motion activities. Exercise recommendations should be individualized, and in consideration of the patients physical and cognitive capacity, preferences, and supports.

There are certain limitations in the studies that future work could address; several studies excluded non-ambulatory patients, the majority reported on exercise protocols of 3 to 6 months duration, and most were conducted on patients at early disease stage. While the current research is promising, particularly over the past five years, further research on type, frequency and intensity of exercise throughout the disease trajectory would help clinicians target exercise prescription to maximize benefit and tolerability for patients of varying exercise capacity and disease stage.

Cognition and behaviour

How is cognitive or behavioral impairment in ALS diagnosed?

- *Screening for cognitive and behavioral impairment should be performed in patients with ALS early in their disease (level B).*
- *If there is concern about cognition or behaviour at any point, specific assessments should occur with the person and their family members or caregiver, as appropriate (EC).*

What treatments are effective for cognitive or behavioral impairment in ALS?

- *There are no studies on the use of pharmacological agents to manage cognitive or behavioural impairment in ALS.*
- *Since the presence of FTD negatively affects survival, advance care planning should be done early in the disease (EC).*
- *The presence of cognitive or behavioural impairment should not necessarily preclude the recommendations for NIV or gastrostomy insertion. However, the challenges of intervention compliance with cognitive or behavioural impairment should be discussed with the patient and family prior to deciding to proceed with an intervention (EC).*
- *A multidisciplinary approach can be considered to manage particularly problematic behaviours. Involving a behavioural specialist (such as an OT or psychologist) or psychiatrist for assistance may be considered (EC).*

Detectable frontotemporal dysfunction can occur in about 50% of patients with ALS[3]. The frontotemporal dysfunction can present with cognitive impairment or behavioural impairment, which in 20% is severe enough to reach criteria for dementia[3]. Although there are many tools available to screen for cognitive or behavioural impairment, there is no standard tool to use. At this time, there are no effective drug treatments for cognitive or behavioural impairment in ALS. A multidisciplinary approach can be considered to manage particularly problematic behaviours.

The presence of executive dysfunction or dementia in ALS is associated with poor survival[157]. The presence of cognitive or behavioural impairment

should not necessarily preclude implementing the recommendations for non-invasive ventilation or gastrostomy insertion. However, the challenges of intervention compliance with cognitive or behavioural impairment should be discussed with the patient and family prior to deciding to proceed with an intervention.

Caregivers

What is the best approach for addressing burden of care for caregiver(s)?

- *Health care providers should be attentive to the needs and emotional well-being of caregivers. Caregivers should be involved in planning for the impact of ALS on both the patient and themselves (EC).*
- *Multidisciplinary clinics should be aware of the financial strain on caregivers and provide information on existing relief programs where possible (EC).*
- *Assessment of caregiver burden, coping strategies, mood and family dynamics would assist in identifying caregivers and families in need of respite and supportive services. Local ALS society may have resources for family members and caregivers (EC).*

Informal caregivers are affected by caring for the person with ALS. Many studies have demonstrated the impact of ALS on caregiver quality of life and the correlates of caregiver burden[158] but also the value of caregiving[159]. Advanced disability (a low ALSFRS score) and cognitive impairment increase caregiver strain[160]. Interventions to mitigate the impact on caregivers have been insufficiently studied to make specific recommendations. Persons with ALS are aware of and affected by the burden on their caregivers[161]. Healthcare providers, therefore, need to be attentive to the physical and emotional well-being of the carers, and have them involved in planning for the impact of ALS on both the patient and themselves.

Palliative care

When should palliative care be offered?

- *Palliative care of patients with ALS can be provided throughout the disease course by ALS clinic staff, palliative care practitioners and family physicians (EC).*
- *Palliative care should be introduced if there is severe physical (i.e., pain, dysphagia or dyspnea), psychosocial or existential distress (EC).*
- *To ensure integrated continuity of care, community palliative care services could be introduced before advanced-stage ALS (EC).*

Expert opinion supports early integration of palliative care for patients with ALS.[8,162] However, palliative and end-of-life care are sensitive topics and variably received by patients.[163] Therefore, early introduction of palliative care must also be done with consideration of the patient's evolving needs and expectations.[164] At the very least, experts have advocated that it is appropriate to initiate discussions about palliative care if the topic is raised by patients or caregivers, and if there are indications of advanced disease or disability.[162]

However, without controlled trials that define the optimal timing for introducing early palliative care, this lack of definition may be a barrier to delivering palliative care in some regions.[165]

What treatments reduce dyspnea in the terminal phase of ALS? How can palliative care, spiritual

intervention, or advanced directives improve quality of life in the terminal phase of ALS?

- *Clinicians must clarify with their patient who is experiencing breathlessness, whether the goal of care is prolonging life versus comfort-focused care for a good death (EC).*
- *Clinicians should assess and relieve factors contributing to breathlessness such as oral secretions and anxiety (EC).*
- *Opioids can be titrated to relieve breathlessness (EC).*
- *Air flow across the face to help with breathlessness may be considered (EC).*
- *Conversations about ACP should be initiated early in the disease or whenever the patient inquires. Ongoing discussions about ACP and goals of care should be part of routine ALS follow-up (EC).*
- *Patients should be encouraged to discuss their preferences about end-of-life care with family members and caregivers (EC).*
- *Palliative care should be integrated into routine patient management prior to the terminal phase of ALS (EC).*
- *Use of NIV and PEG tubes should be continued in palliative care for symptom relief and QOL as dictated by patient preference (EC).*

Dyspnea is the physical discomfort of shortness of breath, and can be a significant source of psychological and spiritual distress.[166] Anxiety and oral secretions may cause or result from dyspnea itself, and require separate and targeted treatment. Therefore, the treatment of dyspnea must be nuanced and holistic.

Ventilation supports such as Bilevel Positive Airway Pressure (BiPAP) or tracheostomy may reduce dyspnea (see respiratory section) but have a life-sustaining effect, which may or may not be consistent with the patient's goals of care, and discussed in that context. Beyond ventilation support, there are no controlled trials comparing different methods of managing dyspnea in terminal ALS. Therefore, many recommendations in the literature are drawn from clinical experience and expert opinion. The use of opioids in terminal ALS is derived from its central role in palliative care, and optimum dosage can vary widely between patients.[167] Other strategies, such as airflow to the face or use of nasal prong airflow with or without low fraction of inspired oxygen (fiO_2), may also be effective.

There are no controlled trials evaluating the efficacy or even the availability of spiritual support and hospice care in Canada, but is felt to be generally an unmet need in other regions.[168,169] This lack of data on efficacy may be due to the regional variations in what these interventions entail.

There is variable utilization of PEG and NIV within hospice, despite guideline recommendations.[170] Removal of NIV in order to access hospice or palliative care would poorly impact quality of life since NIV is effective at alleviating dyspnea, even while respiratory function continues to decline. Therefore it is appropriate to continue the use of NIV, and similarly the use of PEG, to maximize comfort in this setting.

ACP helps establish care preferences before the patient can no longer participate in these discussions. There is evidence to suggest that ACP discussions are best initiated when the patient has accepted that death will occur.[171] However, there is a general reluctance among clinicians to broach the topic, as it may be perceived to indicate the

imminence of death.[172] Standardized tools for ACP are felt to be useful for stimulating these discussions, rather than for generating specifics of an advanced directive.[171,173,174] Thus, discussions may be integrated into routine ALS follow-up to invite open conversation, and should take into account the patient's readiness and style of decision-making.

What is the optimal method of withdrawing ventilation (non-invasive or invasive) in ALS?

- *Withdrawal of continuous ventilatory support should only be performed after consultation and planning with a healthcare professional with expertise in ventilation withdrawal and palliative sedation (EC).*
- *Adequate anticipatory symptom control with opioids and benzodiazepines should be achieved before withdrawal of ventilation occurs (EC).*
- *Debriefing and psychosocial support for family and healthcare providers should be offered (EC).*

Ventilation support prolongs survival in patients with ALS with declining respiratory function, but brings the additional burden of deciding if and when to withdraw this support. Coordinating the resources required for withdrawal of ventilation may be challenging technically, emotionally, and ethically.[175] Thus, the withdrawal process should be carried out by a physician experienced with navigating these challenges.[162] Patients may require higher than routine dosages of benzodiazepines and opioids to achieve adequate symptom relief.[176] Since severe dyspnea can be expected when ventilation is withdrawn, these medications should be initiated beforehand to ensure uninterrupted symptom relief once withdrawal occurs. Debriefing should be available for healthcare providers and family caregivers to help with the grieving process afterwards.

How should bereavement be addressed for caregivers of patients with ALS?

- *Psychosocial support for bereaved caregivers should be provided. Early discussion and support about the bereavement process could be initiated even before the patient's death (EC).*

Caregivers of patients with ALS experience a complex range of emotions, and this impact can last well beyond the immediate bereavement period.[177,178] In spite of this, bereavement support remains an unmet need.[168] A review of ALS clinics across the United States reported that the majority of the clinics found delivery of this bereavement support to caregivers to be below average, and lacking in standardization.[179,180] Some have suggested that palliative care involvement before the terminal phase of disease helped with caregiver bereavement.[181] Similarly, it has been suggested that caregivers who had the opportunity to plan and prepare for their loved one's death may be better able to positively construct the grieving process.[163]

Nonetheless, there are no controlled trials that looked at when and how bereavement support should occur, and this represents an area requiring further study. It has been shown that such research is feasible and not necessarily harmful for participants, and may offer an opportunity for caregivers to reflect and discuss their experience.[182]

How should inquiries about medical assistance in dying (MAID) be addressed?

- *Discussions around MAID should be directed to a physician or nurse practitioner, abiding by regional guidelines (EC).*

- *Physicians caring for patients with ALS are required to provide access to information about MAiD when requested (EC).*
- *Clinicians should not assume questions about MAID constitute a request for MAID. However, questions about MAID should also open a discussion about end-of-life care and ACP (EC).*
- *Patients pursuing MAID should be provided concurrent palliative and supportive care (EC).*

In Canada, the intentional hastening of death sooner than would naturally occur (i.e. in the absence of any treatment or intervention) in the context of disease and/or suffering is legally referred to as *medical assistance in dying (MAID)*. Canada's federal MAID legislation was passed in 2016, in response to the 2015 Supreme Court of Canada ruling that parts of the Criminal Code that prohibited MAID (paragraph 241(b) and section 14) limited the rights of life, liberty, and security of the person, under section 7 of the Canadian Charter of Rights and Freedoms.[183] Provincial and territorial healthcare authorities have developed procedures and rules to provide MAID in accordance with the federal legislation. MAID in Canada is available to persons who have a grievous and irremediable medical condition with a reasonably foreseeable death; who are over the age of 18; who are eligible for health services in Canada; who make a voluntary, uncoerced request for MAID; and who are mentally competent to give informed consent to receive MAID.[184]

It is important to note that regions outside of Canada use different terminology than *MAID*, such as *physician-assisted suicide* or *voluntary-assisted dying*, which do not necessarily have the same legal implications that *MAID* has in Canada. This variation in terminology is reflected in the medical literature; the terminology used depends on the region in which the study was conducted. For simplicity, the term *MAID* is used throughout the following discussion, regardless of the terminology used in the studies described.

Many patients with ALS express interest in MAID and up to half of patients have considered it. However, among those who go on to request it, the desire to die is not necessarily strong.[185,186] Interest in MAID appears not to be associated with physical symptoms,[164,185,187] but rather with current or anticipated loss of autonomy, enjoyment in daily living, and bodily functions, as well as hopelessness and the sense of being a burden.[164,177,185,188-192] Some patients see MAID as an opportunity to exert control over the course the disease.[185,189]

Conversely, improved social support and quality of life were associated with lower interest towards MAID.[190] Religiosity is also associated with less interest in MAID; patients draw strength from their religious beliefs, or use their spirituality to reframe their disease in a positive light.[186,191,193,194]

Some have noted an association between contemplating MAID and depression, thus recommending depression screening in those who request MAID.[188,195,196] Others have not found this association, instead cautioning against conflating depression with hopelessness, which can occur independently of one another.[186,191,197,198]

Therefore, although patients with ALS have often considered MAID, inquiries may also reflect underlying existential suffering or a desire to discuss end-of-life, and should be met with an open and sensitive discussion.

How should a clinician respond to a question from a patient about whether they can donate their organs?

- *Patients with ALS may be accepted as solid organ donors, as determined by their local organ donation organization (EC).*

- *Patients with ALS cannot donate tissue, such as corneas, skin or bone (EC).*
- *Clinics should direct inquiries about donation to their provincial organ donation organization (EC).*
- *Patients may be able to donate their tissues upon death for ALS research (EC).*

Expert opinion supports early integration of palliative care for patients with ALS.[8,162] However, palliative and end-of-life care are sensitive topics and variably received by patients.[163] Therefore, early introduction of palliative care must be initiated with consideration of the patient's evolving needs and expectations.[164] At the very least, experts have advocated that it is appropriate to initiate discussions about palliative care if the topic is raised by patients or caregivers, and if there are indications of advanced disease or disability.[162]

Advance care planning helps establish care preferences before the disease is advanced and communication is impaired. There is evidence to suggest that these discussions are best initiated when the patient has accepted that death will eventually occur.[171] However, there is a general reluctance among clinicians to broach the topic, as it may be perceived to indicate the imminence of death.[172] Standardized tools for advance care planning are thought to be useful for stimulating these discussions, rather than for generating specifics of an advanced directive.[171,173,174] Thus, discussions may be integrated into routine ALS follow-up to invite open conversation, and should take into account the patient's readiness and style of decision-making.

Medical assistance in dying (MAID) was legalized in Canada in 2016. We have made specific recommendations as to how requests for MAID should be addressed, both to support patient choice at end of life, and to provide guidance in this new practice which may be a source of clinical uncertainty and discomfort to practitioners.

We also present recommendations on the potential option of organ donation at the time of death and the process that should be followed for donation.

IMPLEMENTATION

These best practice recommendations are a resource to guide the care of patients with ALS across Canada. The guideline will be made publicly accessible through the ALS Canada website (https://www.als.ca/). ALS Canada will also support the dissemination of the guideline among members of the ALS community, including clinicians, allied health professionals, researchers, patients and their caregivers, through distribution to provincial ALS societies, the Canadian ALS Research Network and attendees of the annual ALS Canada Research Forum. Directors of ALS clinics and ALS clinicians will be encouraged to present the guideline to their clinic teams and relevant stakeholders within their communities. ALS Canada will assist the guideline authors on producing 1-page summary documents of some key clinical areas of the guideline for dissemination to stakeholders.

The working group would support a health impact project assessing patient survival, patient perceived quality of life and other specific outcomes after the implementation of the guideline as compared to prior its publication.

The working group expects that evidence to support ALS management will evolve over time and anticipates that the recommendations will have to be revised approximately every 5 years.

OTHER GUIDELINES

Several ALS clinical practice guidelines have been published in countries other than Canada, including the AAN Practice Parameters (2009),[6,7] the European Federation of Neurological Societies (EFNS) Guidelines on the clinical management of amyotrophic lateral sclerosis (2012),[8] and the motor neurone disease assessment and management guideline developed by England's National Institute of Health and Care and Excellence (2016).[9]

One of the goals for the Canadian guideline was to update the existing North American guidelines, specifically the 2009 AAN recommendations[6,7]. As described in the Methods, literature searches for this Canadian guideline on clinical questions addressed in the 2009 AAN recommendations were restricted to new evidence only (i.e., after 2007), and all evidence was classified using AAN criteria.

In the AAN guideline, recommendations had to be supported by evidence; thus, no guidance was provided in the absence of evidence (e.g., using expert consensus). In contrast, the EFNS guideline provided consensus recommendations in the absence of evidence, we also resolved to offer guidance based on expert consensus in the absence of evidence.

Another goal for the Canadian guideline was to address ALS issues not covered in other guidelines. The EFNS guideline did not address several issues for patients with ALS that are particularly important in Canada, such as medication alignment and MAID. Similarly, guidance on some ALS issues, such as disease-modifying treatments and exercise, was not provided in the NICE guideline.

As discussed earlier, the CTS published a guideline on HMV for patients with ALS in early 2019.[11] In collaboration with the CTS, we ensured that our recommendations for respiratory management were consistent with recommendations in the CTS guideline, but added some consensus recommendations (e.g., on airway clearance).

GAPS IN KNOWLEDGE

This guideline confirms that high-quality evidence is lacking for most topics in ALS management; most recommendations provided are based on expert consensus among the working group. The need for further research in ALS management remains, and more evidence-based recommendations will be critical for improving the standards of patient care in Canada and internationally. This guideline can help point the clinical research community, nationally and internationally, to areas of research prioritization on disease management.

We acknowledge that we were not able to cover all topics of ALS management in this guideline and that subsequent revisions could include topics not currently covered.

CONCLUSION

We hope that the development of the first Canadian ALS guideline is an important step forward for improving the lives of patients with ALS living in Canada. The predominance of expert consensus statements relative to evidence-based statements in this guideline not only highlights the need for more research in ALS management but also emphasizes the challenges ALS clinicians face in managing patients with a severe disabling disease. This guideline will encourage ALS clinics across Canada to meet a common national standard, and to adapt as this standard continues to evolve over time. In doing so, ALS clinicians can offer the best possible care to their patients and

help them to navigate this exceedingly complex and devastating disease.

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APPENDIX

BOX 1. AAN criteria for rating therapeutic studies[199]

Class	Description
I	- Randomized, controlled clinical trial (RCT) in a representative population - Masked or objective outcome assessment - Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences - Also required: a. Concealed allocation b. Primary outcome(s) clearly defined c. Exclusion/inclusion criteria clearly defined d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias
II	- Cohort study meeting criteria a–d (see Class I) or an RCT that lacks one or two criteria b–d (see Class I) - All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences - Masked or objective outcome assessment
III	- Controlled studies (including well-defined natural history controls or patients serving as their own controls) - A description of major confounding differences between treatment groups that could affect outcome** - Outcome assessment masked, objective, or performed by someone who is not a member of the treatment team
IV	- Did not include patients with the disease - Did not include patients receiving different interventions - Undefined or unaccepted interventions or outcome measures - No measures of effectiveness or statistical precision presented or calculable

Box 2. Criteria for levels of evidence in guideline recommendations*.

Level	Type of evidence
A	At least 2 consistent Class I studies
B	At least 1 Class I study or 2 consistent Class II studies
C	At least 1 Class II study or 2 consistent Class III studies
Expert consensus (EC)	Consensus among Canadian ALS clinical experts where evidence meeting criteria for Level A through Level C is lacking

*See Box 1 for definitions of study classes