Best practice recommendations for the clinical care of spinal bulbar muscular atrophy

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Background: Although rare in the general population, spinal bulbar muscular atrophy (SBMA) is an X-linked recessive neuromuscular condition that is highly prevalent in people identifying as First Nations and Métis in western Canada. The aim of this guideline is to improve and standardize care of SBMA, and to increase awareness of the condition.

Methods: Our interdisciplinary working group conducted a needs assessment survey to aid in the development of guideline topic questions, followed by a literature search, evidence review, and external review by health practitioners and people with lived experience. We followed the ADAPTE framework to evaluate the only pre-existing SBMA guideline (2020 French national protocol) and the 2020 Canadian amyotrophic lateral sclerosis guideline for appropriateness of adaptation. Our process adhered to the Appraisal of Guidelines for Research and Evaluation (AGREE II) tool; used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach; and followed the Guidelines International Network–McMaster Guideline Development Checklist. Indigenous community engagement was led by the Pewaseskwan Indigenous Research Group, who participated in the development of the guideline.

Recommendations: We developed 41 recommendations to address the continuum of care in SBMA, including diagnosis; multidisciplinary teams; management of limb and bulbar symptoms, respiratory and cardiac complications, and multisystem symptoms; female carriers; emotional supports; and considerations for Indigenous people. Spinal bulbar muscular atrophy is best managed by multidisciplinary teams that can address both its motor and nonmotor manifestations, including cardiac involvement, sensory symptoms, and metabolic dysfunction. Concerns for female carriers may include symptom management and genetic counselling. Providers should ensure culturally appropriate care for Indigenous people.

Interpretation: In this guideline, we provide health care professionals with a culturally responsive standard of care for SBMA, and hope this will translate into improved quality of life for people affected by SBMA.

Spinal bulbar muscular atrophy (SBMA), also known as Kennedy disease, is an X-linked recessive neuromuscular disorder. Although considered a rare disorder in the general population with a prevalence of 1–2 per 100 000,[1] a recent study found a substantially elevated prevalence of 14.7 per 100 000 for people in western Canada who identify as First Nations and Métis — the highest estimated worldwide.[2] A subsequent study estimated a very high case incidence for Indigenous people in this region (11 per 100 000 over 5.5 years), suggesting that the true prevalence is likely even higher.[3] These findings make SBMA a high-priority condition for diagnosis and management, and highlight the importance of culturally responsive care.

Males with SBMA usually develop disease between the ages of 30 and 50 years. Progressive spinal and bulbar lower motor neuron dysfunction results in limb weakness, dysarthria, dysphagia, and elevated risk of early mortality (median age 65 yr), from aspiration pneumonia and respiratory dysfunction.[4,5] The multisystem manifestations are becoming increasingly recognized and include symptoms of androgen insensitivity, and effects on cardiac, skeletal muscle, sensory nerves, endocrine, and metabolic systems.[6] Limited evidence in female carriers suggests that some may develop a milder phenotype of the condition.[7–11] No disease-modifying treatments have been approved in Canada. Management is symptomatic.

Spinal bulbar muscular atrophy is caused by an expanded trinucleotide repeat (≥ 38 cytosine, adenine, guanine [CAGs]) in the first exon of the androgen receptor gene (*AR*) on the X chromosome.[12] The resultant polyglutamine expansion is believed to confer both loss of function (androgen resistance) and toxic gain of function of the AR protein. Based on animal models, the presence of androgens is required for development of eventual motor neuron toxicity.[13]

Amyotrophic lateral sclerosis (ALS) is a motor neuron disease with some clinical features similar to SBMA (including limb weakness, dysarthria, dysphagia, and respiratory dysfunction), but without the nonmotor manifestations seen in SBMA. Because both ALS and SBMA are motor neuron diseases, in Canada patients with SBMA are often seen by the same providers and clinics as those with ALS, and principles of SBMA medical management are typically adapted from knowledge on ALS management.

No guideline for care of people with SBMA exists in Canada, and a set of recommendations is needed that takes into account the Canadian health care system, the specific context of high prevalence in Indigenous people in Canada, and the increasingly recognized nonmotor manifestations of SBMA. The literature regarding care for people with SBMA is scant and, as such, development of this guideline was additionally informed by the only existing guideline for SBMA from France,[14] with adaptations for SBMA made from the 2020 Canadian ALS guideline.[15]

Scope

We developed this guideline to provide family physicians, other specialists, and allied health care professionals with standard-of-care strategies for the management of people with SBMA in Canada. The goal is to improve the lived experience of people with SBMA, their caregivers and families, and carriers of SBMA. A national guideline may give health care professionals, health systems, and patient advocacy groups a benchmark to aid in advocacy for quality care. An additional aim is to increase awareness of this rare disease.

Recommendations

Forty-one recommendations address the diagnosis of SBMA, limb and bulbar symptoms, respiratory and cardiac management, multisystem symptoms, female carriers, emotional supports and considerations for Indigenous people, as well as the importance of a multidisciplinary team approach. The recommendations are grouped by topic in Table 1.

We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to determine the certainty of evidence and strength of our recommendations (Box 1),[17,18] taking values, balance of effects, equity, acceptability, and feasibility including cost into account (see Appendix 1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.250180/tab-related-content, for detailed information). We used the ADAPTE process to evaluate the only pre-existing SBMA guideline[14] and the Canadian ALS guideline for appropriateness for adaptation.[15,19]

Because SBMA is rare in the general population, the literature for management is scant, and recommendations are largely based on small and nonrandomized studies, and expert opinion. We provide an overview of the background and context for our recommendations by topic group below. A visual summary of the guideline is available in Figure 1.

Diagnostic testing and genetic counselling

Our recommendations on diagnostic testing and genetic counselling (Table 1) are based on expert opinion from review articles and adaptation of the French SBMA guideline[14] (Appendix 1). Genetic testing and counselling should be offered to people with clinical features of SBMA for diagnostic confirmation (≥ 38 CAG repeats in *AR*). Clinical manifestations of a CAG repeat number between 35 and 37 are difficult to predict.[1] A higher number of CAG repeats in *AR* may be associated with earlier onset, but associations with disease course are less clear.[20] Inheritance is X-linked recessive; however, the absence of a positive family history does not preclude the diagnosis.

Early symptoms of SBMA are tremor, cramps, and weakness, with dysphagia and dysarthria emerging as the disease progresses, and respiratory dysfunction occurring late in disease course.[4] The natural history of the nonmotor manifestations of SBMA is less well defined.

Genetic testing should be offered to symptomatic family members, preferably in conjunction with neurology specialists who can consider and exclude differential diagnoses. Genetic testing to identify carrier status in asymptomatic family members (females or presymptomatic males) can be undertaken once genetic counselling implications have been explored with that individual, preferably with genetic specialists who have relevant supports available. Use of testosterone levels as a diagnostic marker has not been shown to be useful, as the majority of people with SBMA have hormonal levels within the normal range.[21]

Multidisciplinary care

Once a diagnosis of SBMA has been made, expert opinion suggests that a multidisciplinary care team approach is beneficial,[14,20,22,23] preferably in motor-neuron disease clinics to address both the motor symptoms and nonmotor manifestations.[14] No studies have examined the benefits of multidisciplinary care specifically in SBMA (Appendix 1). However, the Canadian ALS guideline recommends multidisciplinary teams as they are associated with greater use of supportive equipment and fewer hospital admissions,[15] and are well received by patients and caregivers.[24] Health-related quality of life measures and SBMA-specific outcome measures, such as the SBMA Functional Rating Scale, applied virtually, can chart disease progression and impact.[25,26]

Cardiac disease

Cardiac rhythm disturbances should be closely evaluated and monitored regularly throughout the disease course, given the potential for life-threatening dysrhythmias in patients with SBMA. Recommendations are based upon observational and natural history studies (Appendix 1). Spinal bulbar muscular atrophy is associated with cardiac rhythm disturbances, most commonly Brugada syndrome.[27] Brugada syndrome is diagnosed by a spontaneous type 1 Brugada pattern on electrocardiogram (ECG) (i.e., J-point elevation of > 2 mV with coved ST elevation and T-wave inversion in at least 1 right precordial ECG lead, V1 or V2).[28] Although rates of cardiac arrythmias in SBMA, including Brugada syndrome, vary among studies, there is agreement that people with SBMA should be monitored for potentially life-threatening

Table 1 (Part 1 of 3): Summary of recommendations

Recommendation	Strength of recommendation	Certainty of evidence
Diagnostic testing and genetic counselling		
The diagnosis of SBMA should be confirmed with genetic testing to demonstrate an increased CAG repeat number ≥ 38 in the androgen receptor gene.	Strong	High
Formal genetic counselling should outline the range in age of onset, symptoms, natural history, mode of transmission, and risk of SBMA for family members.	Strong	Low
Multidisciplinary care		
SBMA should be managed by multidisciplinary teams that can effectively collaborate to address motor symptoms as well as nonmotor manifestations of the disease. • Teams can include neurologists, physiatrists, pulmonologists, cardiologists, dietitians, endocrinologists, geneticists or genetic counsellors, psychologists, nurses, physiotherapists, occupational therapists, respiratory therapists, speech therapists, social workers, patient-support people — including Indigenous patient navigators or Indigenous cultural support — and family physicians in the community.	Strong	Very low
Virtual care should be considered if travel and mobility concerns exist.	Strong	Low
Assessments by the multidisciplinary team should occur yearly, or as clinically indicated.	Strong	Low
Cardiac disease		
Initial and follow-up cardiac assessments should be provided to all patients. • Initial assessments should include cardiology consultation, 12-lead ECG, ambulatory ECG, and echocardiogram. • Follow-up assessments should occur every 1–2 years and include 12-lead ECG, ambulatory ECG, and additional testing if indicated.	Strong	Low
Rhythm disturbances should be managed according to current cardiology guidelines.	Strong	Moderate
In people with Brugada syndrome, drugs should be avoided that may induce ST-segment elevation in the right precordial leads, as well as use of cocaine, cannabis, and excessive alcohol. Fever should be treated with antipyretic drugs.	Strong	Moderate
Patients with established SBMA and unexplained syncope should be promptly evaluated by a cardiologist or electrophysiologist for ventricular arrhythmias and Brugada syndrome.	Strong	Moderate
Patients with Brugada syndrome and syncope or arrhythmia should have driving restrictions as per Canadian recommendations.[16]	Strong	Moderate
Limb symptomatic management		
Strategies to optimize functional independence, fall prevention, and safety should be implemented, such as individualized home and workplace assessments. This may include property modifications and equipment (i.e., ramps, lifts, bathroom and bedroom modifications, wheelchairs, ambulation aids, and orthoses).	Strong	Very low
If tremor causes distress or limits function, propranolol could be considered. If propranolol is initiated, close monitoring of benefit and adverse effects is advised.	Conditional	Very low
An individual's pain symptoms should be assessed, and a multimodal treatment model should include mechanistic prescribing of medications where appropriate.	Strong	Very low
Muscle cramps should be differentiated from other causes of pain. First-line management of muscle cramps could include ensuring adequate hydration, stretching, tonic water, gabapentinoids, and baclofen.	Conditional	Very low
Fasciculations typically do not need medication management. A trial of gabapentinoids could be considered if fasciculations cause substantial distress.	Conditional	Very low
Exercise should not be discouraged, as movement may have multiple beneficial effects. An individually tailored exercise program is suggested, and should be adjusted if worsening fatigue, pain, or weakness are noted.	Conditional	Very low
Sensory symptoms are common and likely contribute to imbalance. Strategies to prevent fall risk should take into account the contribution of both motor and sensory dysfunction.	Strong	Very low

Table 1 (Part 2 of 3): Summary of recommendations

Recommendation	Strength of recommendation	Certainty of evidence
Dysarthria, communication, and sialorrhea		
A speech-language pathologist should be consulted when a patient develops dysarthria for assessment of strategies for improving speech clarity, including augmentative and alternative communication devices.	Strong	Low
Sialorrhea typically does not require treatment. Because of the increased risk of cardiac conduction defects in SBMA, cautious use of systemic anticholinergic medication is advised.	Conditional	Low
Dysphagia and nutrition		
Nutritional status should be monitored by measuring weight and BMI yearly or as clinically indicated.	Strong	Very low
A dietitian should regularly review diet and fluid intake, and consider calorie, nutritional, and vitamin supplements. • Providers should be mindful of potential concurrent metabolic disease, including fatty liver, diabetes, and bone health, when providing advice about diet.	Strong	Very low
Swallowing function should be regularly assessed clinically or with VFSS, and behavioural modifications or gastrostomy suggested as clinically indicated.	Strong	Very low
Gastrostomy should be considered if 1) loss 10% of baseline weight; 2) BMI < 18.5 in people aged 18–70 years or < 21 if older than 70 years; 3) high risk of aspiration pneumonia; 4) excessive time to finish meals. Radiologically inserted gastrostomy may be considered with low forced vital capacity (< 50%).	Strong	Very low
Respiratory dysfunction		
Annual respiratory assessment should evaluate for respiratory muscle weakness, sleep-disordered breathing, and airway clearance function. • Measures may include upright and supine forced vital capacity, slow vital capacity, maximal inspiratory and expiratory pressures, sniff nasal inspiratory pressures, peak cough flow, and overnight oximetry.	Strong	Very low
Patients should be counselled on the signs, symptoms, and management of laryngospasm.	Strong	Very low
Airway clearance techniques should be initiated when the peak cough flow is < 270 L/min. Patients should receive appropriate education and training by an airway clearance expert.	Strong	Very low
Noninvasive ventilation should be initiated if chronic respiratory failure is diagnosed.	Strong	Very low
Pharmacotherapy with mucolytics, a β-receptor antagonist, nebulized saline, or nebulized ipratropium should be considered for management of bronchial secretions.	Strong	Very low
Endocrine and metabolic complications		
Patients should be referred to a clinician with appropriate expertise for assessment of endocrinologic and metabolic complications when SBMA is diagnosed (e.g., primary care provider, internist, or endocrinologist). Follow-up should occur annually, or at the judgment of the clinician.	Strong	Low
Screening for metabolic and endocrine complications should be done at the judgment of the expert clinician. • Initial screening may include thorough physical examination (including thyroid, gynecomastia, testes volume). • Blood work may include lipid profile, diabetes screen (glycated hemoglobin, fasting glucose), thyroid screen (TSH, FT_4), bone metabolism markers (parathyroid, calcium, phosphate, and vitamin D if available), and liver enzymes (AST, ALT, GGT). • Imaging screens may include liver imaging (for NAFLD) and bone mineral density. • Follow-up or repeat investigations are at the judgment of the physician or primary care provider. • Hormonal screen may also be considered (LH, FSH, testosterone, prolactin, cortisol, DHEA-S) based on case-by-case clinical judgment.	Strong	Low
Patients should be asked about symptoms, such as sexual dysfunction, lower urinary tract symptoms, and other features of androgen insensitivity, as it may enable identification of symptoms and instigate referral for supportive management.	Strong	Low
Counselling or referrals to support weight loss in patients with elevated BMI may be helpful, to reduce the risk of endocrine complications.	Conditional	Low
Testosterone supplementation should not be used in SBMA, based on data from animal models that demonstrate the relationship between testosterone exposure and disease pathogenesis.	Strong	Low

Table 1 (Part 3 of 3): Summary of recommendations

Recommendation	Strength of recommendation	Certainty of evidence
Emotional supports		
Emotional health, including depression and anxiety, should be evaluated regularly in both multidisciplinary and primary care clinical encounters.	Strong	Very low
Timely access to appropriate counselling, education, and locally available emotional supports should be provided as required.	Strong	Very low
All people affected by SBMA, inclusive of carriers, family, and community members, should be offered education and emotional support, and should be encouraged to seek spiritual and cultural supports appropriate for them. This may be especially important for Indigenous people.	Strong	Very low
Female carriers		
Providers should enquire about neurologic symptoms in carriers to improve ascertainment and allow for consideration of symptom management.	Strong	Moderate
Management of symptoms in carriers, such as cramps and tremor, should be addressed similarly to males with symptoms. Care may occur in primary care or neurologic clinic settings.	Strong	Low
The phenotype of females with homozygous *AR* expansions is not well defined, but appears to be more pronounced than in heterozygous carriers. Clinicians should be aware of potential symptoms in carriers and develop an individualized management approach.	Strong	Very low
Considerations for Indigenous people		
Culturally appropriate care should be implemented with guidance by relevant First Nations and Métis communities.	Strong	Low
Clinic interactions should occur in the preferred language for care, with translation supports available if needed.	Strong	Low
Clinics should encourage and, if needed, provide support so family members can attend clinic appointments.	Strong	Low
Clinic staff should liaise with existing primary care, home care, traditional medicine services, and other providers to ensure appropriate community supports and reduce fragmentation of care. • Providers may include Indigenous health navigators, patient advocates, and Knowledge Holders (Elders).	Strong	Low
The emotional and cultural impact of fertility and family planning should be taken into account, with consideration for appropriate supports. The heritable nature of SBMA, as well as the potential reduction in fertility that can occur as part of the condition, can affect wellness and decisions regarding family planning.	Strong	Low
Providers should be trained in trauma-informed approaches, cultural safety, and cultural responsiveness to ensure respectful and meaningful interactions.	Strong	Low

Note: ALT = alanine aminotransferase, *AR* = androgen receptor gene, AST = aspartate aminotransferase, BMI = body mass index, CAG = cytosine, adenine, guanine, DHEA-S = dehydroepiandrosterone sulfate, ECG = electrocardiogram, FSH = follicle-stimulating hormone, FT_4 = free thyroxine, GGT = γ-glutamyl transferase, LH = luteinizing hormone, NAFLD = nonalcoholic fatty liver disease, SBMA = spinal bulbar muscular atrophy, TSH = thyroid-stimulating hormone, VFSS = videofluoroscopy swallowing study.

rhythm disturbances.[14] A European study of 30 patients found abnormal ECGs in 21 (70%), including early repolarization or fragmented QRS; only 2 patients had a Brugada ECG pattern.[29] A Japanese study of 144 patients found abnormal ECGs in 48.6% of participants and "Brugada-type ECGs" in 12%; 1 patient had recurrent syncope, and 2 died suddenly.[27]

The prevalence of cardiomyopathy is not clear. The literature consists of rare case reports,[30,31] 1 of which identified an alternate cause of cardiomyopathy.[32] A small case series, in which magnetic resonance imaging (MRI) showed no cardiomyopathy beyond what was expected for age and hypertension for some patients,[33] conflicts with the findings of another that showed most patients had diffuse fibrosis on cardiac MRI.[29]

The mechanism for cardiac involvement in SBMA has not been fully elucidated, but the *AR* gene is expressed in cardiac muscle,[34] and autopsy has shown nuclear accumulation of mutant androgen receptor protein and decreased expression of SCN5A in myocardium despite absence of mutation of the *SCN5A* gene.[27]

Arrhythmias should be managed according to existing cardiology guidelines[28] in conjunction with an electrophysiology cardiologist,[35] with driving restrictions as per local policy.[16] People with Brugada syndrome should avoid medications and drugs that may unmask ST-segment elevation and thus cause arrhythmias (such as tricyclic antidepressants, mexiletine, or cocaine).[36] For patients who are on statins for cardioprotection, no evidence exists on their safety in SBMA; however, the Canadian ALS guideline states that there is insufficient evidence to support discontinuation of statins in that condition.[15]

Box 1: GRADE approach and interpretation of grading[17,18]

The GRADE approach assigns a rating for certainty of evidence and strength for each recommendation.

Certainty of evidence

Initial estimates of certainty are based on a traditional hierarchy of evidence, whereby meta-analyses of RCTs are assigned the highest score, followed by individual clinical trials, quasi- or nonrandomized trials, observational studies and reports, and expert opinion, which is assigned the lowest score. Factors that lowered confidence in the estimated effect of an intervention included risk of bias, inconsistency across the RCTs, indirectness and publication bias; factors that increased confidence included large effect sizes and an observed dose–response effect. The final certainty ratings are reflective of the estimated effect of an intervention, as reported in the literature, with consideration of biases and limitations of the evidence base as identified by the guideline committee, as described below:

- **High:** Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very low:** Any estimate of effect is very uncertain.

Strength of recommendation

To determine strength of recommendations, the GRADE system takes into account the quality of evidence and additional factors, such as clinician, patient, and policy-maker's values and preferences, costs and cost-effectiveness, risk–benefit ratios and feasibility.

A strong recommendation indicates the following:

- **For patients:** Most patients in the given situation would want the recommended course of action and only a small proportion of patients would not.
- **For clinicians:** Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
- **For policy-makers:** The recommendation can be adapted as policy in most situations, including for use as performance indicators.

A conditional recommendation indicates the following:

- **For patients:** Most patients in the given situation would want the recommended course of action, but many would not.
- **For clinicians:** Clinicians should recognize that different choices will be appropriate for different patients, and that they must help each patient arrive at a management decision consistent with the patient's values and preferences. Decision aids may well be useful to help individuals make decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.
- **For policy-makers:** Policy-making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to acknowledge that adequate deliberation about the management options has taken place.

Note: GRADE = Grading of Recommendations Assessment, Development, and Evaluation, RCT = randomized controlled trial. Reproduced from Wood E, Bright J, Hsu K, et al. Canadian guideline for the clinical management of high-risk drinking and alcohol use disorder. *CMAJ* 2023 Oct 16;195(40):E1364-E1379, https://www.cmaj.ca/content/195/40/E1364.

Limb symptoms

Our recommendations for limb symptoms address gait, progressive weakness, tremor, cramps, fasciculations, numbness, pain, and the role of exercise. A few randomized controlled trials (RCTs) have studied gait and exercise in SBMA, but we gathered most evidence on gait and exercise from reviews and observational and nonrandomized studies (Appendix 1). We found no publications evaluating management of cramping, fasciculations, sensory symptoms, or pain in SBMA; therefore, our recommendations on the management of these symptoms were made by expert consensus and informed by previous recommendations on SBMA and ALS which, in turn, were based on limited evidence.[14,15]

Currently, no pharmacologic interventions can be confidently recommended to delay progression of muscle weakness. Tremor in SBMA shares clinical characteristics of essential tremor (although the pathology may differ), as tremor in SBMA is suspected to have peripheral origins.[37,38] One study used propranolol for treatment, but the response was not quantified.[37] Reassuringly, use of propranolol has been shown to be safe in conjunction with careful observation, even in patients with Brugada syndrome.[39] Sensory neuropathy or neuronopathy is common[40–42] and can contribute to imbalance.[43] Fatigue can be substantial, with need for energy conservation strategies.

The literature regarding exercise in SBMA is conflicting. One small nonrandomized trial showed that moderate-intensity aerobic exercise was ineffective and may cause muscle damage.[44] However, in a small RCT (n = 10), high-intensity aerobic training using an ergometer bike appeared well tolerated and improved VO_2 max (mean ± standard deviation 1.9 ± 2.3 mL/min/kg; p = 0.04).[45] One RCT (n = 54) showed no significant improvements in the Adult Myopathy Assessment Tool scores in the functional exercise versus the stretching control group; however, post-hoc analysis showed possible improvement in people with low baseline function.[46] Case reports of robotic-assisted gait training suggest improvement in ambulatory function,[47,48] but the degree of improvement versus cost was not defined. One review suggested that shorter-duration exercise may reduce exercise-induced fatigue.[49] However, given the presence of dysfunctional androgen receptors in skeletal muscle, SBMA may respond differently from other neuromuscular disorders to transient elevations in testosterone after exercise.[49]

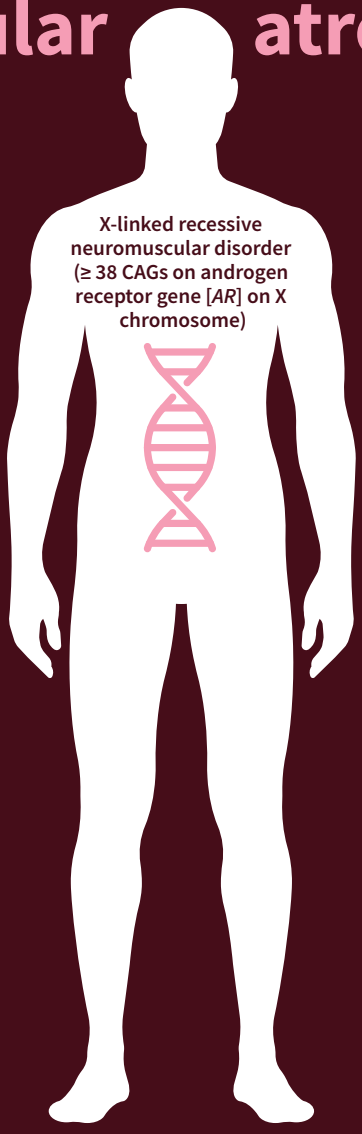
Dysarthria, communication, and sialorrhea

Communication challenges are not well studied in SBMA, and evidence for recommendations consists largely of observational studies and expert opinion (Appendix 1). Hypernasality is common,[50] and dysarthria can become substantial later in disease.[4] Speech-language pathologists should be consulted when dysarthria occurs, although it does not always require intervention.[51] Case reports of palatal lifts suggested improvements in hypernasality, but swallowing dysfunction can be exacerbated.[52] The French SBMA guideline suggested that speech-language pathology should follow patients over time, based on expert consensus.[14]

Manifestations of spinal bulbar muscular atrophy

Bulbar
- Dysphagia
- Dysarthria
- Hypernasal speech
- Peri-oral fasciculations
- Facial weakness

Endocrine and metabolic complications
- Insulin resistance
- Diabetes mellitus
- Nonalcoholic fatty liver disease
- Dyslipidemia
- Gynecomastia
- Reduced fertility
- Testicular atrophy
- Sexual dysfunction
- Lower urinary tract symptoms
- Reduced bone mineral density

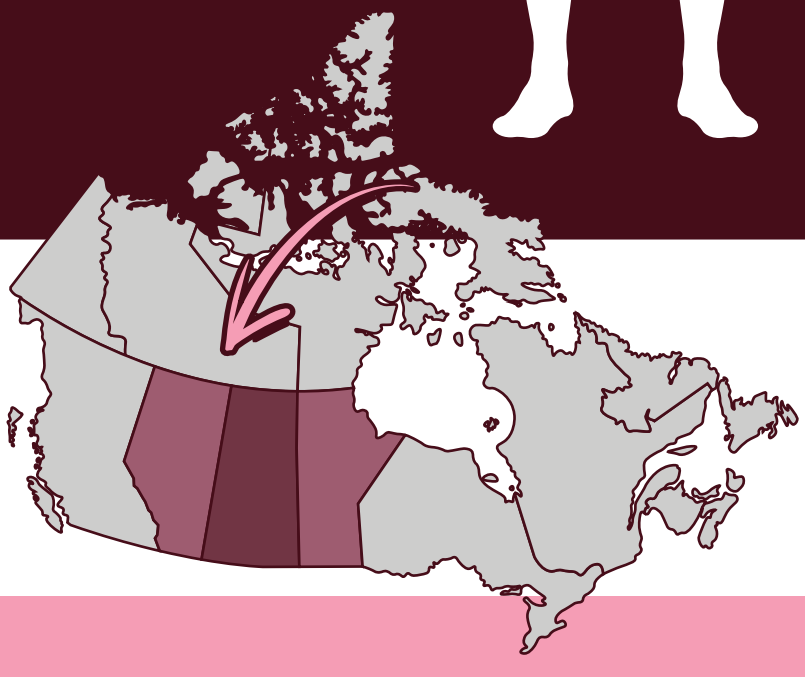


Emotional issues
- Anxiety
- Depression
- Lack of social participation

Cardiac manifestations
- Arrhythmias (e.g., Brugada syndrome)
- Possible cardiomyopathy

Respiratory dysfunction
- Laryngospasm
- Aspiration pneumonia
- Respiratory muscle weakness
- Increased bronchial secretions
- Obstructive sleep apnea
- Chronic respiratory failure

Limb symptoms
- Cramps
- Tremor
- Progressive weakness
- Fasciculations
- Gait dysfunction
- Numbness
- Pain



- Highest prevalence in Indigenous people of prairie provinces in western Canada
- Affected males usually develop disease between ages 30 and 50 years
- Female carriers may develop a milder phenotype
- Management is symptomatic

Figure 1: Summary of the guideline recommendations. See Related Content tab for accessible version. Note: CAG = cytosine, adenine, guanine.

Minimal discussion of sialorrhea exists in the literature, but natural history studies suggest it is rare and mild.[51,52] Caution is suggested with use of systemic anticholinergics to address sialorrhea, given the possibility of potential cardiac rhythm disturbances.[36] Although sublingual atropine drops are sometimes used by clinicians for sialorrhea, there is no literature to guide this.

Dysphagia and nutrition

Nutritional status and dysphagia should be regularly monitored in patients with SBMA; our recommendations are based on observational studies and expert opinion (Appendix 1). Pharyngeal muscle weakness leads to dysphagia later in the disease course, and aspiration pneumonia is a common cause of death.[4] Many patients, but not all, can be managed with conservative measures rather than use of feeding tubes.[51] Although the impact of nutritional monitoring and gastrostomy has not been studied in SBMA, decreased body mass index is associated with faster progression of motor symptoms and decreased survival[53] in ALS, with survival benefit seen for those whose weight is maintained by gastrostomy.[54] Radiologically inserted gastrostomy can be considered in those with low respiratory function, as there may be less need for sedation and potential for subsequent respiratory depression during the procedure. Our recommendations for gastrostomy placement are adapted from existing SBMA and ALS guidelines.[14,15] Leuprorelin shows no clear benefit on videofluorography or head lift exercises on functional swallow.[55,56]

Respiratory dysfunction

Respiratory status should be evaluated at baseline and annually, with management strategies for laryngospasm, airway clearance, and noninvasive ventilation suggested as need arises. Our recommendations are adapted from the Canadian ALS guideline[15] and informed by small cohort and case series (Appendix 1). Respiratory involvement is generally mild until later in the disease course, and ventilatory support is not usually required.[51] Aspiration pneumonia and respiratory failure are reported to be the most common causes of death.[4] Respiratory compromise may be subclinical, and routine objective testing (Table 1) is needed in addition to symptom review (e.g., orthopnea, exertional dyspnea, morning headaches, excessive daytime somnolence, and reduced cough strength).

No guidance in the literature suggests optimal parameters for initiation of noninvasive ventilation in SBMA and, as such, our recommendation does not specify criteria for intervention. However, the Canadian ALS guideline recommends that noninvasive ventilation should be considered if there is 1 or a combination of the following: upright forced vital capacity < 50%; daytime hypercapnia with an arterial CO_2 > 45 mm Hg; sniff nasal inspiratory pressure < 40 cm H_2O or maximal inspiratory pressure < 40 cm H_2O; or an overnight oximetry that is abnormal and concerning for hypoventilation.[15,57] Reliance on orthopnea as a symptom of respiratory insufficiency in SBMA may be challenging, as pharyngeal weakness can contribute to a sensation of throat closure when supine. Sniff nasal inspiratory pressure may be a more accurate alternative to traditional spirometry if facial weakness prevents an adequate lip seal.

As adapted from the Canadian guidance on managing patients with ALS, management of secretions using pharmacotherapy with mucolytics (e.g., guaifenesin or N-acetylcysteine), a β-receptor antagonist (e.g., metoprolol or propranolol), nebulized saline, or nebulized ipratropium can be considered.[15]

Assessment and management of airway clearance is important to reduce aspiration risks. Laryngospasm is a distressing complication occurring in close to half of people with SBMA.[58] Management is primarily targeted at the patient keeping calm and slowing their breathing. It has been observed that treating gastroesophageal reflux may reduce laryngospasm in some patients.[58] Sleep disorders are common, including poor sleep quality and obstructive sleep apnea. In particular, detecting obstructive sleep apnea in SBMA may require a high index of suspicion, as it often presents without typical risk factors.[59,60]

Endocrine and metabolic complications

Monitoring for endocrine and metabolic complications of SBMA should occur at baseline and on regular follow-up. Supporting evidence for these recommendations is based on observational studies and expert opinion (Appendix 1). Endocrine and metabolic derangements are numerous in SBMA, and often precede the development of neurologic symptoms.[61] Androgen insensitivity may lead to gynecomastia, reduced fertility, testicular atrophy, sexual dysfunction, and lower urinary tract symptoms.[62,63] Other endocrine disturbances are likely indirectly related to androgen insensitivity and include nonalcoholic fatty liver disease (NAFLD), dyslipidemia, insulin resistance and diabetes mellitus, and reduced bone mineral density.[62,64,65]

Almost all people with SBMA have some degree of NAFLD,[64] but the implications and management strategy are unknown. Evaluation of liver function can be complicated by the fact that SBMA results in muscle breakdown, which can cause elevations in creatinine kinase (CK) and liver enzymes (aspartate transaminase [AST] and alanine transaminase [ALT]); these latter enzymes are released by both liver and muscle. In the largest natural history study of SBMA, CK levels were typically elevated (range 31–4955 U/L, mean 863.5 U/L) with mild elevations of AST (range 17–238 U/L, mean 44.3 U/L), and ALT (range 12–248 U/L, mean 52.6 U/L).[4]

The prevalence and risks related to reduced bone mineral density (BMD) are unclear, with reduced femoral BMD but normal or elevated lumbar BMD in 1 study. Vitamin D deficiency is common, but did not correlate with BMD measurements.[62] In one study, fat deposition in SBMA preferentially occurred in a visceral pattern, which may be associated with increased health risks,[66] but this was contradicted in another study using a different imaging modality.[67] Prior data on the natural history of SBMA suggest that endocrine dysfunction may not be a major contributor to mortality in SBMA,[4] but endocrine dysfunction may have been underrecognized previously. Although the evidence in SBMA is meagre, we consider that addressing complications from common endocrine disorders such as diabetes, osteopenia, and dyslipidemia is likely to have an important long-term health benefit.

We do not recommend testosterone supplementation for SBMA, based on data from animal models that show the relationship between testosterone exposure and disease pathogenesis.[13]

Specifically, disease in mice is strongly androgen dependent,[68–70] which is also supported by experiments in drosophila.[71] Although some case reports suggest a possible benefit of androgen therapy for SBMA,[72] others have reported deterioration,[73] and the balance of evidence would seem to suggest testosterone therapy is not likely to benefit patients.

Emotional supports

Emotional health should be regularly evaluated, with supports offered to people with SBMA and their families and caregivers. The literature is very limited, and our recommendations are based on 3 surveys and expert opinion (Appendix 1). An emotional impact of the diagnosis of SBMA is reported in most patients, with some experiencing substantial distress with anxiety, depression, and lack of social participation.[25,74] Disclosing the diagnosis should be undertaken as for any serious medical condition. Supports should be offered to people with SBMA, their families, and to the wider community affected by SBMA, and may include counselling and other mental health supports as locally available.

Female carriers

Health providers should be aware that female carriers of SBMA (≥ 38 CAG repeats in *AR*) may develop a milder version of the symptoms experienced by males with SBMA, particularly in later years, and an individualized approach to management is needed. Spinal bulbar muscular atrophy is an X-linked recessive disorder, and as such, females are carriers for the condition, but only males develop the full spectrum of symptoms. The phenotype of SBMA carriers is not well defined, is based on cross-sectional studies and case series with few participants, and varies from being mainly asymptomatic[7,8,20] to more symptomatic with muscle cramps, tremor, subclinical muscle weakness, and rare reports of bulbar findings in older age.[9,10] Homozygous female carriers may develop a range of symptoms from minor to more pronounced than heterozygous carriers, but broader conclusions based on these small case series cannot be made.[11,75] Because no studies have addressed symptom management in carriers (Appendix 1), our recommendations suggest extrapolation from strategies for males with SBMA.

Considerations for Indigenous people

Health care practitioners should be mindful of providing culturally appropriate care to people with SBMA who identify as Indigenous. Because this is a specific circumstance that has not yet been studied in the literature, our recommendations are based on input from people with lived experience, informed by recommendations in other diseases,[76] and guided by the Pewaseskwan Indigenous Wellness Research group (Appendix 1).

Spinal bulbar muscular atrophy is highly prevalent in people identifying as First Nations and Métis within western Canada, and in particular, people identifying as Cree, Saulteaux, and Métis.[2,3] Historically, health care has been used as a tool of colonialism.[77] Many Indigenous people are still challenged in accessing medical and supportive care because of coloniality, which perpetuates both interpersonal and systemic racism, as well as the drivers of sociostructural inequities.[78] The Truth and Reconciliation Commission of Canada Calls to Action (in general but especially numbers 18–24) identified the need for changes within the health care system to better address the needs of Indigenous people.[79] Increasing the awareness of this rare disease and educating health care professionals about its optimal care may be a step toward this end. Health care professionals should strive to improve the therapeutic relationship by cultivating cultural safety and patient-centred care. Indigenous cultures should be seen as strength based, supportive, and therapeutic.

Methods

Community concerns regarding lack of health provider knowledge and awareness of SBMA led to the conceptualization of this guideline (K.S.). The work was funded by Muscular Dystrophy Canada, along with a grant obtained through the Saskatchewan Health Research Foundation. The Pewaseskwan Indigenous Wellness Research Group at the University of Saskatchewan provided in-kind support.

We followed the GRADE framework for evidence review[80] and used the Appraisal of Guidelines for Research and Evaluation (AGREE II) tool to ensure the guideline achieved international standards for methodological rigour.[81] The Guidelines International Network–McMaster Guideline Development Checklist informed the process.[82] We used the ADAPTE process to identify and evaluate existing guidelines (AGREE II global rating scales for included guidelines are in Appendix 2, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.250180/tab-related-content).[19]

The University of Saskatchewan biomedical ethics research board granted an ethics exemption for the needs assessment and external feedback surveys. The guideline work began in January 2024 and ended in December 2024.

Composition of participating groups

The committee chair (K.S.) provided leadership and direction for the guideline process. The steering committee (K.S., G.P.) developed a working group of 14 content experts with experience in treating SBMA to represent the geographic diversity of Canada, and the multidisciplinary nature of SBMA care. Previous experience with guideline generation and experience with Indigenous patient populations were taken into consideration. The working group comprised specialists in neurology (W.J., L.K., C.S., K.S. [chair]), neurogenetics (G.P., O.S., J.W-C.), physiatry (B.K., C.O'C., S.W.), respirology (C.E.), cardiology (A.L.), endocrinology (G.C-B.), and rural family medicine (R.McG.). A neurology trainee (J.N.) assisted with the literature search and manuscript preparation.

The leaders of the Pewaseskwan Indigenous Wellness Research Group (A.K., M.K.) and the Community Guiding Circle, composed of people with lived experience in SBMA and a Knowledge Holder (Elder), provided direction for culturally relevant matters. The Community Guiding Circle has experience in providing collective feedback and direction for several previous Canadian SBMA research projects. The circle's concerns regarding lack of health care provider awareness of SBMA was the impetus for this guideline. Both the Community Guiding Circle and Pewaseskwan research group participated in selecting priority

topics, provided leadership for the writing of the section on considerations for Indigenous people and supporting tables, and gave advice and feedback on all the draft recommendations.

Selection of priority topics

A needs assessment survey was created on Research Electronic Data Capture (REDCap)[83] and a link was distributed to the working group, to clinicians affiliated with the Neuromuscular Disease Network for Canada, and to all Canadian ALS clinic sites[84] (often where patients with motor neuron diseases, including SBMA, are seen in Canada). Physicians and multidisciplinary teams with experience in treating SBMA were asked to rank topics in order from the existing French SBMA guideline[14] and the Canadian ALS guideline[15] to determine which components should be included in this guideline development, and to decide which additional components would be helpful, including clinical care in an Indigenous context (Appendix 3, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.250180/tab-related-content).

We developed a list of topics that were ranked highly by participants on the survey, and further refined the list by discussion, with unanimous consensus achieved by the working group. This list was then presented to the Pewaseskwan research group, who provided feedback (e.g., suggested a section name change, from Psychologic Supports to Emotional Supports) and ratified the topics chosen by the working group.

Literature review and quality assessment

Under the direction of a research librarian at the University of Saskatchewan and content expertise from the working group, we conducted a literature search, which was completed in February 2024. Our search terms were patterned after those developed for the Canadian ALS guideline[15] where appropriate (search strategies are in Appendix 4, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.250180/tab-related-content). We searched MEDLINE and Embase databases for full-text articles, published in English or French, from 1946 to February 2024. Because SBMA is rare, with limited literature and very few RCTs, we included cohort, cross-sectional and observational studies, case reports, systematic reviews, guidelines, and review articles.

Two members of the working group were assigned to each topic and separately reviewed all abstracts identified to determine inclusion criteria and relevance. If 1 member labelled an abstract as relevant, then both members reviewed the full article. Agreement from both topic group members was required to add relevant articles for evidence review, including those where findings could be extrapolated from other diseases. All working group members reviewed the French SBMA and the Canadian ALS guideline for relevancy for their allocated topics.[14,15]

Each topic group summarized the available evidence in topic certainty review tables and appraised the data to develop evidence-to-decision tables following the GRADE criteria (Appendix 1).

Development of recommendations

The working group conferred at regular intervals via email and held 5 virtual meetings by videoconferencing, spaced at approximately 2-month intervals. After creating the evidence tables (Appendix 1), each topic group drafted recommendations for their topic, determined the level of evidence for each recommendation according to the GRADE criteria, and developed supporting text. We considered the French SBMA guideline in developing our draft recommendations, and adapted Canadian ALS guideline recommendations where relevant for symptoms in common with SBMA (i.e., multidisciplinary care, limb symptomatic management, dysarthria, communication and sialorrhea, dysphagia and nutrition, and respiratory dysfunction).[14,15,19]

The evidence tables, draft recommendations, and supporting text were reviewed by the working group for each topic, discussed, and edited. Unanimous consensus was achieved through discussion. The draft recommendations for all topics were presented to members of the Community Guiding Circle, who expressed unanimous approval for the guideline as a whole, which highlights considerations for Indigenous people and supports education and awareness. The final draft was approved by consensus of the working group before circulation for external review.

The topic on considerations for Indigenous people had a different process, to maximize input by people with lived experience. After reviewing a summary of the literature developed by the topic group, the Pewaseskwan team, with representation from the Community Guiding Circle (consisting of people with lived experience and a Knowledge Holder [Elder]), edited the relevant evidence-to-decision table and drafted the guideline recommendations and related text to ensure cultural appropriateness.

External review

We solicited key partner feedback via REDCap survey from non-Indigenous people with SBMA, female carriers, physicians and allied health care professionals at Canadian ALS centres, Neuromuscular Disease Network for Canada investigators, Kennedy's Disease Association, Muscular Dystrophy Canada, and additional content experts identified by the working group. The steering committee and topic groups reviewed and incorporated the feedback, which resulted in minor changes to wording and content (Appendix 5, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.250180/tab-related-content). We distributed a revised version of the guideline to all working group members for final approval.

Management of competing interests

Management of competing interests was informed by the Guidelines International Network principles.[85] Honoraria were not provided to any working group members. We reviewed conflict of interests for working group members at the outset and at subsequent meetings. No member declared a competing interest relevant to the publication.

Muscular Dystrophy Canada provided funding for the publication costs, and a grant obtained through Saskatchewan Health Research Foundation covered costs related to administrative support, medical writing, and small honoraria for Indigenous people with lived experience for their participation. Muscular Dystrophy Canada was a funder, but also a key partner, and as such provided feedback on feasibility of implementation but did not contribute to content development.

Implementation

All Canadian partners who provided external feedback stated that they believed the expected costs of implementation were reasonable. We also asked these partners to list barriers and facilitators to implementation (Appendix 5). We will be working with the community and key partners to determine best methods of implementation and evaluation. Initial steps include promoting awareness of the guidelines through presentations for health care practitioners, meetings with community organizations, and further activities for people with lived experience, as directed by the Community Guiding Circle.

The working group members will update the guideline when additional developments occur, such as potential treatments.

Other guidelines

There is only 1 other guideline for SBMA (France),[14] which we considered during the process of topic and recommendation generation. Our Canadian recommendations are closely aligned with the French guideline, but provide more specific recommendations in a Canadian context. Our guideline also introduces new topics whose importance is becoming increasingly recognized, including sensory dysfunction, SBMA carriers, and care in an Indigenous context. The Canadian guidance on managing patients with ALS[15] also informed topic generation and literature search strategy. Although ALS and SBMA are distinct motor neuron diseases, they share many clinical characteristics. Amyotrophic lateral sclerosis is much more common than SBMA, with more robust literature, and we adapted management recommendations from the ALS guidance where appropriate.

Gaps in knowledge

High-quality evidence for management of most topics in SBMA is lacking. Most recommendations are made on low quality of evidence, based on minimal studies, and there are very few randomized placebo-controlled trials. Recommendations often relied on consensus, expert opinion, and extrapolation from management of related conditions. Additional studies are needed to determine how symptoms in SBMA are best managed, which may uncover unique care considerations.

Limitations

The geographic diversity of Canada was not entirely represented in the working group; however, members were preferentially considered if they had experience in caring for patients with SBMA, and particularly if they had additional experience in caring for people with SBMA who identified as Indigenous. As a result, the provinces of Saskatchewan and Alberta are over-represented, which we felt was an appropriate allocation, given SBMA prevalence data. An additional limitation is the low quality of existing literature on which to base the recommendations, which required us to use the ADAPTE process for existing SBMA and ALS guidance.[14,15,19]

Conclusion

This guideline is intended to promote awareness of this rare medical condition in Canada. Our process sought community guidance for cultural considerations, given the high prevalence of SBMA in people who identify as First Nations and Métis in western Canada. The aim of this guideline is to provide health care professionals with a standard of care that we hope will translate into improved quality of life for people affected by SBMA.

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