**ORIGINAL ARTICLE**

**Provincial differences in the diagnosis and care of Amyotrophic Lateral Sclerosis**

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**Abstract**

**Background:** Amyotrophic Lateral Sclerosis (ALS) is a progressive motor neuron disease resulting in muscle weakness, dysarthria and dysphagia, and ultimately respiratory failure leading to death. Half of ALS patients survive less than 3 years, 80% less than 5 years. Riluzole is the only approved medication in Canada with randomized controlled clinical trial evidence to slow the progression of ALS, albeit only to a modest degree. The Canadian Neuromuscular Disease Registry (CNDR) collects data on over 140 different neuromuscular diseases including ALS across 10 academic institutions and 28 clinics including 10 multidisciplinary ALS clinics. **Methods:** In this study, CNDR registry data were analyzed to examine potential differences in ALS care among provinces in time to diagnosis, riluzole and feeding tube use. **Results:** Significant differences were found among provinces, in time to diagnosis from symptom onset, in the use of riluzole, and in feeding tube use. **Conclusions:** Future investigations should be undertaken to identify factors contributing to such differences, and to propose potential interventions to address the provincial differences reported.

**Introduction**

ALS is a devastating rapidly progressive motor neuron disease with an incidence rate of 2 per 100,000 per year. (1) The Canadian health care system is administered and funded independently by each respective province resulting in variations in accessibility to and quality of specialized care. ALS has a tremendous psychological and economic impact on Canadian patients and their caregivers. It has been demonstrated that centralized multidisciplinary ALS clinic care results in improved survival compared to community-based care. (2,3) In Canada, there is a mean annual direct out-of-pocket cost of C$19,574 per patient with a mean annual income loss of C$36,467 per patient per year and C$20,353 per caregiver per year. (4,5)

The exact cause of sporadic ALS remains unclear, and there is no effective cure. However, riluzole, a glutamate antagonist that reduces glutamate-mediated excitotoxicity, modestly slows disease progression and extends median survival by 2 to 3 months. (6,7) However, 5 studies using large databases spanning 5 to 10 years have suggested that treatment with riluzole might be associated with a prolonged survival of 6-, 10-, 12-, 14-, or even 21 months. These cohort studies had longer-term follow-up than the clinical trials, but are subject to greater bias. (8) Riluzole usage has minimal adverse effects, and is prescribed to approximately 60% of patients in both Europe and North America. (3) Clinical care practice guidelines of the American Academy of Neurology recommend that patients should be offered riluzole to slow disease progression. (8)The cost of riluzole in Canada ranges between C$400 to C$600 per month and coverage for riluzole is available through various insurance plans. Prescribing rules for riluzole vary among and within provinces and it may only be prescribed by a neurologist or physiatrist in Canada. During the time of data collection, all 7 provinces in the study, included riluzole on the provincial formulary, and provided additional programs to help cover riluzole costs for those without private insurance. Saskatchewan included riluzole on the provincial formulary during data collection (in 2017). Canadian residents with financial need can be eligible to receive riluzole coverage through the Medicum Rilutek Reimbursement and Co-Pay Assistance program. Yet, patients’ knowledge and/or use of this privately-sponsored coverage may vary province-to-province. Edaravone, an antioxidant with unknown mechanism of action, shown to modestly improve survival in early-stage ALS, was not available in Canada during the time of data collection (9).

While there is currently no known cure for ALS, comprehensive symptomatic management is available. A shortened time to diagnosis allows for timely provision of prognostic information, counselling and institution of a clinical management plan including symptom management (i.e. spasticity, sialorrhea, pain, percutaneous endoscopic gastrostomy (PEG) tube, and non-invasive ventilation). Additionally, shorter time to diagnosis results in improved recruitment into clinical trials. (10,11,12) Individuals with a shorter time to diagnosis are more likely to meet criteria for trial participation such as time from symptom onset less than 24 months or percent predicted forced vital capacity above 80%. Thus, earlier diagnosis would lead to a larger population of patients who are likely to better respond to life prolonging therapy such as riluzole or potentially edaravone. (9, 11-13).

Similarly, a timely and accurate diagnosis can alleviate the anxiety associated with diagnostic uncertainty and enable patient and family planning. (14) Criteria that often contribute to a slower time to diagnosis include (15-17):

• physician lack of familiarity with ALS

• patient comorbidities

• complexity of the referral system

• difficulty of early clinical diagnosis when ALS may be restricted to one region of the nervous system

• hesitancy by a health care provider in communicating the diagnosis of a progressively disabling and fatal disease

Shorter time to diagnosis also prevents unnecessary investigations and treatments that could result in avoidable complications and health care expenditures. Studies have found that approximately 40% of ALS patients receive one or more misdiagnoses prior to a correct diagnosis of ALS. Further investigation demonstrated that a subset of these misdiagnosed patients underwent unnecessary surgery for symptoms later attributable to ALS, resulting in increased health care expenditures and risks of complications. (18-20) Therefore, time from symptom onset to diagnosis is an important measure that can have significant impact on the ALS journey for patients.

Symptom management in ALS includes nutritional management, as both malnutrition and body weight are independent prognostic factors for survival. (22-24) Dysphagia impairs swallowing and occurs secondary to bulbar involvement in ALS. This can be compounded by limb weakness affecting the ability to prepare and feed oneself. Without adequate nutrition, patients will become malnourished, leading to respiratory distress and reduced quality of life. (25)

Some studies have demonstrated that feeding tube use can improve survival, however there is some debate regarding this, as well as the optimal timing of PEG tube intervention. (26-29) However, it is clear that PEG tube use can improve body weight and subsequent quality of life. (30-31) Based on these findings, the AAN clinical care guidelines for ALS recommend placing of a PEG tube to supplement nutrition. (8)

Patient registries, such as the CNDR, are an important tool for healthcare planning through the collection of real-world patient data enabling comparative analyses among different countries and regions.

The purpose of this study was to assess provincial differences in care delivery, by assessing time to diagnosis and interventions including riluzole, ventilation, and feeding tube use, for ALS patients across Canada.

**Methods**

The Canadian Neuromuscular Disease Registry (CNDR) collects prospective clinical data at ALS clinics in 8 of 10 Canadian Provinces and 0 of 3 Canadian territories (Supplementary Table 1). Dataset elements were derived by the consensus of a disease working group encompassing expert clinicians, geneticists, and scientists from across Canada as previously published. (32)

The CNDR is administered through a national office with affiliated multi-disciplinary neuromuscular and ALS clinics throughout Canada. Patients are required to have a diagnosis of ALS according to World Federation of Neurology EI Escorial - Revised criteria (33), and must provide informed consent in order to be entered into the registry. Patient recruitment to the registry is ongoing in affiliated ALS clinics and through the national office. In Canada, patients are first referred from a primary care practitioner to a specialist (general neurologist, neuromuscular specialist or other) for diagnosis by EMG, and then re-referred to a neuromuscular specialist and/or ALS speciality clinic (Figure 1). All patients analyzed in this study were seen in hospital-based multi-disciplinary clinics.

 Patient data are collected prospectively at routine clinic visits by the attending physician and trained data entry staff taking information from medical charts. Recruitment and data collection across different clinics is expected to be highly comparable due to rigorous research assistant training, the availability of a comprehensive data dictionary defining each data item in detail, regular CNDR project manager teleconferences with data entry staff. Data integrity is ensured through auditing at the National Office.

Data collected are itemized in supplementary figure 1 and include items such as:

• date of diagnosis

• date of symptom onset

• riluzole usage

• feeding tube usage

• use of ventilation

• ALS revised functional rating scale (ALSFRS-R, a questionnaire based disability scale)

• genetic testing.

Data were collected between 2010 and 2017 from both prevalent and incident cases. All data are collected in compliance with local research ethics board approvals. Parameters analyzed in this study include:

• time to diagnosis (from first symptom onset)

• disease progression (ALSFRS-R progression rates, calculated as a decrease is ALSFRS-R scores divided by time between assessments)

• riluzole use at any point following the diagnosis

• feeding tube use at any point following the diagnosis

• ventilation use (either non-invasive or invasive) at any point following the diagnosis

• survival (from first symptom onset)

Statistics were calculated utilizing IBM SPSS Statistics for Macintosh, Version 24, with p<0.05 considered significant. Descriptive statistics were calculated from the patient’s first recorded clinic visit. Descriptive statistics are described as mean +/- standard deviation (SD). Mean descriptive statistics were compared to reported United States means utilizing a paired one-way Student’s t-test.

Time from symptom onset to diagnosis was calculated for each patient and means for each province were compared using a one-way ANOVA, followed by a post-hoc pairwise Tukey Honest Significant Difference (HSD).

Riluzole usage is recorded on the CNDR ALS physician form as one of the following; yes, no, past, stopped, declined or unknown. Riluzole usage was calculated as “yes” if patients had recorded present usage, usage in the past or whether they stopped during any clinic visit. Riluzole usage per province was compared using a chi-square test.

Survival analysis was calculated as the amount of time in months from symptom onset to death. Cases were excluded for absence of date of death. Survival analysis per province was compared using a Log Rank chi-square test, and median survival presented with a 95% confidence interval (CI). This is derived from log transform of the survival (Kaplan-Meier) function.

Mean ALSFRS-R progression rates were calculated as mean difference per month, utilizing a total score of 48 at time of symptom onset as a baseline value and calculated to the first recorded clinic visit. A score of 48 is considered normal; 0 severely impaired; with lower scores indicating increased impairment. Progression rates, assumed to be on a continuous scale, were compared using a one-way ANOVA with post-hoc, pairwise Tukey HSD.

Feeding tube usage was recorded as “yes” if the patient had used a feeding tube at any point during the course of disease. Feeding tube usage per province was compared using a chi-square test.

Ventilation usage was recorded as “yes” if the patient had ever used either non-invasive or invasive ventilation at any point during the course of disease. Ventilation usage per province was compared using a chi-square test.

An estimate of the number of living ALS patients in Canada at this time was calculated using the upper limit of international prevalence rates of 10 in 100,000 adults and a Statistics Canada 2016 Canadian population at risk estimate of 28,388,100 of adults over the age of 20 years. (34)

 **Results**

A total of 1085 ALS patients were registered in the CNDR at the time of analysis through participating clinics (Supplementary Table 1). After excluding individuals with incomplete data in the registry due to absence of a recorded date for symptom onset, absence of date of birth, or lack of data regarding riluzole usage, 1006 patients remained for analysis (Table 1, Figure 1). Using international prevalence data and Canadian population figures, we estimate that there are currently approximately 2800 living ALS patients in Canada. We report data on our cohort of 1006 patients (453 living patients). Mean age at onset (defined as first symptoms) was 60.1 (±12.0) years and mean age at diagnosis was 61.8 (±11.9) years. Median survival from onset was 36.5 months (95% CI 33.6-39.3). The population analyzed had more males than females, with males representing 60%. These statistics are comparable to available published data for survival (36 months), age at diagnosis and gender prevalence in the United States. (35,36)

Mean time of symptom onset to diagnosis was significantly different among provinces (F=3.395, p = 0.003). It was longest in Saskatchewan (27.0 months), and shortest in Nova Scotia (15.1 months). A comparison of inter-province differences is represented in Table 2. There was no significant difference among time to diagnosis across provinces for males compared to females (F=1.295, p=0.255; data not shown).

Riluzole usage was also significantly different among provinces, (p = 0.000; χ2 = 151.44), with the lowest usage in British Columbia (18.1%) and highest in Quebec (79.7%) (Figure 2). The national average (68%) was close to the expected usage rate of 60 % globally. (9)

Feeding tube usage was significantly different across provinces, (p = 0.000; χ2 = 35.54) (Figure 3), with the lowest usage in British Columbia (16.0%) and highest in Nova Scotia (52.6%).

Ventilation usage was not significantly different across provinces; mean usage across Canada was 31.7% (p=0.437; χ2 = 5.88) (data not shown).

Mean ALSFRS-R progression rates in our cohort (0.75 units per month) are slightly slower than the reported mean progression rate of 0.9 units per month (26, 27). Importantly, there was no significant difference (F=1.672, p=0.125) in disease progression rates across provinces as measured by ALSFRS-R scores (data not shown).

Despite the differences in time to diagnosis, riluzole use, and feeding tube use, median survival of ALS patients (370 deceased patients) in Canada was 36 months (95% CI 33.6-39.3) from symptom onset and did not demonstrate any significant differences among provinces (p=0.167, χ2=9.113) (Figure 4).

**Interpretation**

We report the first nationwide Canadian data on time from symptom onset to diagnosis and treatment with riluzole in patients with ALS. Along with a recent paper, (37) we also report nationwide Canadian data on feeding tube use. Time to diagnosis was significantly different among provinces, with Saskatchewan having the longest (27.0 months) and Nova Scotia having the shortest (15.1 months). Interestingly, population-based registries report time from symptom onset to diagnosis from 10-14 months (38,39,40) whereas our consent-based registry reports a mean time to diagnosis of 21 months. It is possible this discrepancy may partially be explained by patient recruitment to the registry in speciality ALS hospital-based clinics, resulting in slight underrepresentation of faster progressing patients, who are in turn diagnosed more rapidly. This is supported by mean ALSFRS-R progression rates in our cohort slightly slower than the reported mean (41,42).

 While there are some promising therapies for ALS on the horizon, the rapid disease progression and delayed time to diagnosis often result in patients being ineligible for clinical trials. (10,11, 14, 43) An increasing number of studies in animal models have demonstrated that those earlier in the course of ALS symptom progression respond better to treatment.(44-47) Similarly, post-hoc analyses of riluzole trials have demonstrated increased efficacy in those with milder symptomology.(48). Time to diagnosis is impacted by several components of the ALS journey including barriers to obtaining a primary care assessment, lack of knowledge of ALS symptomatology by primary care providers and other specialists, and delayed referral to a neurologist. Further delays often occur when patients are re-referred to a neuromuscular subspecialist from a general neurologist or directly to a multidisciplinary ALS clinic for confirmatory evaluation.

Furthermore, it is known that geographic remoteness can affect access to care. (49, 50, 51) Existing Canadian and American studies evaluating inequality in health care based on geographic variation identified factors contributing to such variation including patient need, patient preferences, illness burden, insurance coverage and community wealth/poverty. (52-55). Further research is required into possible medical practice and health system barriers, such as referral wait times, misdiagnoses, geographic distance to clinic, and urbanity that may result in longer times to diagnosis.

While riluzole use averaged across provinces (68%) was consistent with recent studies in other countries (60%), (3) it was found to be statistically different among provinces with British Columbia, Saskatchewan, and Alberta all below the Canadian average (Figure 2). This may relate to several factors including the treating physician’s opinion on the benefit of riluzole, patient perceptions on potential adverse side effects or barriers arising from insurance coverage, which is province-dependent (Figure 5). Inconsistent riluzole coverage by province may only partially explain the observed differences in its usage; for example, riluzole usage was the lowest in British Columbia (18%) despite its coverage through the provincial formulary and the Fair Pharmacare Program. There may be multiple possible contributors to this discrepancy: deductible payments may be unaffordable, alternative pharmaceutical or non-pharmaceutical symptom management, a more widely-held patient perspective on not prolonging a diminishing quality of life or the prescribing physician’s perspectives on riluzole benefits. Interestingly, a recent study evaluating cost-sharing models across provinces of Canada found variation in out-of-pocket expenses for medications due to province of residence, along with income and age. (56) Saskatchewan’s limited drug coverage for riluzole during the time of analysis may have contributed to its below average usage (52%), however as the sample size in this province is limited, caution in interpretation is warranted. Further investigations into the motivations and barriers to riluzole usage by province are required.
Similarly, feeding tube use among provinces was statistically significant, with the lowest percent usage in British Columbia (16%) and highest in Nova Scotia (53%). A recent study evaluated factors correlated with feeding tube usage in 635 ALS patients in the Canadian population (37), and found associations with dysphagia and respiratory status. While there were no differences in, overall ALSFRS-R progression rates, or in the percentage of patients with bulbar onset, or ventilation usage by province in our study (data not shown), variation in patient characteristics may contribute to these findings. It will be important to evaluate factors affecting differences in feeding tube usage in Canada in our patient population. Additionally, given the variability in the referral process for feeding tubes across Canada (57), it will be essential to review guidelines and recommendations for feeding tube insertion to standardize care and outcomes across Canada.

The data in this study demonstrate that neither varying times to diagnosis nor differences in use of riluzole or feeding tubes results in significant differences in survival rates among provinces. The patients reported here are all seen at multi-disciplinary clinics which is known to confer some survival advantage for ALS patients. (2,3) This may account for the lack of significant difference in survival among provinces. Similarly, as data included patients newly diagnosed to 2017, it is expected that median survival will change over time, as the incident cases progress through to death. As the CNDR continues to register participants and the Canadian ALS Research Network (CALS) publishes the Canadian ALS best practice guidelines (which are currently under development), time to diagnosis, riluzole, feeding tube usage, and survival by province will be important metrics to monitor.

These results should be interpreted in consideration of the limitations of the methodology employed. There is the possibility of selection bias in the process of obtaining informed consent for recruitment into the CNDR compared as some participants may not provide consent excluding them from the data. As well, selection bias may occur as some individuals are not followed by ALS clinics. One aim of the CNDR is to improve recruitment of ALS patients and prospectively re-evaluate.

Conclusion

In addition to the recent study of feeding tube usage and nutritional recommendations (37) in Canada, this study contributes another ‘first look’ at the Canadian ALS population. It demonstrates the need for further investigation of barriers to riluzole usage and time to diagnosis across Canada to equalize ALS patient access to more timely care and improve clinical outcomes in this terminal disease. Similarly, studies investigating standard interventions including ventilation usage and access to experimental therapies across provinces are needed.

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**Table 1: Descriptive statistics for ALS patient population in CNDR**

|  |  |  |
| --- | --- | --- |
|  | **CNDR** | **United States** |
| Total number of cases | 1085 |  |
| Number of cases (complete data) | 1006 |  |
| Mean age at onset (years) ± S.D. | 60.1 ± 12.0 |  |
| Mean age at diagnosis (years) ± S.D. | 61.8 ± 11.9 | 63.5 |
| % Male | 60.3 | 62.5 |
| Median survival (months from onset) | 36.5 | 36 |

S.D.= standard deviation

AB= Alberta; BC= British Columbia; NB= New Brunswick; NS= Nova Scotia; ON= Ontario; QC= Quebec; SK= Saskatchewan

**Table 2: Means comparison between provinces for time between symptom onset and diagnosis. P values are represented in provincial comparisons.**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Number of cases** | **Mean (m)** | **S.D. (m)** | **AB** | **BC** | **NB** | **NS** | **ON** | **QC** | **SK** |
| **AB** | **173** | **18.1** | **15.5** |  | **p=0.766** | **p=0.764** | **p=0.998** | **p=0.116** | **p=0.939** | **p=0.580** |
| **BC** | **84** | **22.6** | **32.2** | **p=0.766** |  | **p=1.000** | **p=0.827** | **p=1.000** | **p=0.260** | **p=0.984** |
| **NB** | **51** | **23.5** | **26.5** | **p=0.764** | **p=1.000** |  | **p=0.790** | **p=1.000** | **p=0.318** | **p=0.997** |
| **NS** | **22** | **15.1** | **13.1** | **p=0.998** | **p=0.827** | **p=0.790** |  | **p=0.646** | **p=1.000** | **p=0.595** |
| **ON** | **524** | **23.5** | **24.9** | **p=0.116** | **p=1.000** | **p=1.000** | **p=0.646** |  | **\*\* p=0.006** | **p=0.991** |
| **QC** | **128** | **15.2** | **16.4** | **p=0.939** | **p=0.260** | **p=0.318** | **p=1.000** | **\*\* p=0.006** |  | **p=0.258** |
| **SK** | **24** | **27.0** | **24.4** | **p=0.580** | **p=0.984** | **p=0.997** | **p=0.595** | **p=0.991** | **p=0.258** |  |

m= months

S.D.= standard deviation

AB= Alberta; BC= British Columbia; NB= New Brunswick; NS= Nova Scotia; ON= Ontario; QC= Quebec; SK= Saskatchewan

\*\*p<0.01 by Tukey’s HSD test; (F=3.395, p=0.006)