The Canadian Journal of Neurological Sciences (2024), **51**, 606–607
doi:10.1017/cjn.2023.320

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Editorial

Rethinking Drug Reimbursement Criteria in Amyotrophic Lateral Sclerosis

Lorne Zinman[1,2], Emili Duni[2] and Agessandro Abrahao[1,2]

[1]Division of Neurology, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada and [2]Sunnybrook Research Institute, University of Toronto, Toronto, ON, Canada

Keywords: Amyotrophic lateral sclerosis; therapeutics

We would like to congratulate Dr. Andrew Darke for his thoughtful manuscript.[1] Patients provide a unique perspective in health-related matters, and it is essential for their voices to be heard to optimize care. It is of paramount importance to engage those individuals most directly impacted by the decisions of regulatory agencies, and we are thankful that Dr Darke shared his experience, thoughts, and frustrations that, unfortunately, are all too common in the amyotrophic lateral sclerosis (ALS) community.

The manuscript highlights a number of valid concerns regarding the use of strict trial inclusion criteria to determine drug reimbursement eligibility for patients with ALS. While we must continue to adhere to the tenets of evidence-based medicine, there should be some leeway in the eligibility criteria. Real-world practice differs greatly from the controlled setting of a clinical trial, and the rigid inclusion criteria employed to select candidates for studies should mainly be used as a guide in the care of an individual patient. As an example, the pivotal trial of edaravone in ALS included patients with predicted forced vital capacity (FVC) of at least 80% and demonstrated its efficacy.[2] As a reimbursement criterion, it seems illogical to conclude that a patient with an FVC of 81% would benefit, but a patient with an FVC of 79% would not and should be denied coverage. This is particularly relevant when such criterion is based on a measurement tool susceptible to intertrial variability.[3]

Along with FVC parameters, "time from symptom onset to diagnosis" is used to select a more homogenous cohort for trials and can be even more problematic as a drug reimbursement criterion. ALS symptoms onset time is often difficult to ascertain with confidence as it represents the best estimate founded on patient recall and clinical interpretation by the attending neurologist. In addition, delays in obtaining access to specialists and investigations like magnetic resonance imaging, nerve conduction studies/electromyography, and pulmonary function tests can inflate the time to ALS diagnosis,[4] particularly in our publicly funded healthcare system. These delays may result in patients "timing-out" for drug reimbursement due to system-level factors unrelated to disease biology, prognosis, or likelihood of responding to therapeutic. With a mean time from onset to diagnosis of 21 months in Canada,[5] the majority of patients with ALS, in fact, do not meet the criteria for reimbursement from public plans and are faced with the compounded cruelty of being diagnosed with a terminal disease and then subsequently denied access to disease-modifying therapies.

From the perspective of the regulatory agencies, they are impossibly tasked with determining funding eligibility for increasingly costly drugs and limited taxpayer funds. In addition to assessing drug efficacy and cost, they must also consider disease severity, incidence, prevalence, and matters of equity. To assist policy makers with decisions regarding allocation prioritization, the cost per quality-adjusted life year (QALY) can be calculated and compared across diseases. In this way, health economists can determine which interventions are most cost-effective, and policy makers can determine how broadly a drug should be covered. For example, in a rare disease like ALS, eligibility criteria for coverage could be loosened for an intervention with high efficacy and low cost, but the corollary would also be true. The high costs and marginal efficacy of the new ALS therapeutics (approximately $2 million/QALY gained for edaravone)[6] make it very challenging to argue for broader eligibility and the inclusion of patients who were not represented in the trials.

Advances in ALS will assist with many of these obstacles. The development of more sensitive diagnostic biomarkers such as transcranial magnetic stimulation[7] will shorten delays in diagnosing ALS in its most undifferentiated early phases when it is most likely to respond to a therapeutic. Disease-monitoring biomarkers, such as neurofilament[8] and motor unit estimation techniques,[9] will revolutionize how eligibility criteria are crafted for trials and may serve to broaden the generalizability of effective therapeutics in clinical practice. Real-world studies for approved drugs can determine if effectiveness is demonstrated in non-trial eligible patient populations and help to persuade regulatory agencies to broaden inclusion.

Ultimately, as the pathophysiological underpinnings of sporadic ALS are uncovered, we will be better able to determine which patients are most likely to respond to a therapeutic. This has

Corresponding author: L. Zinman; Email: lorne.zinman@sunnybrook.ca

Cite this article: Zinman L, Duni E, and Abrahao A. (2024) Rethinking Drug Reimbursement Criteria in Amyotrophic Lateral Sclerosis. *The Canadian Journal of Neurological Sciences* **51**: 606–607, https://doi.org/10.1017/cjn.2023.320

already occurred with genetic forms of ALS, and intrathecal gene therapy was recently approved in the United States for patients with *SOD1* mutations.[10] However, until then, the ALS community must work to minimize the large proportion of patients who are ineligible for approved therapeutics by increasing awareness. In this way, primary care physicians will consider the possibility of ALS earlier in the disease course, thereby expediting the time to diagnosis and the likelihood of eligibility for drug coverage.

Competing interests. Dr. Zinman has received consulting honoraria from Biogen, Mitsubishi Tanabe Pharma, and Amylyx.

References

1. Darke AC. Can I be honest with my neurologist? A problem of health technology assessment in Canada. Can J Neurol Sci. 2023.1–3. DOI: 10.1017/cjn.2023.307.
2. Abe K, Aoki M, Tsuji S, et al. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2017;16:505–512. DOI: 10.1016/S1474-4422(17)30115-1.
3. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of spirometry 2019 update. An official American thoracic society and european respiratory society technical statement. Am J Respir Crit Care Med. 2019;200:e70–e88. DOI: 10.1164/rccm.201908-1590ST,
4. Richards D, Morren JA, Pioro EP. Time to diagnosis and factors affecting diagnostic delay in amyotrophic lateral sclerosis. J Neurol Sci. 2020;417:117054. DOI: 10.1016/j.jns.2020.117054.
5. Hodgkinson VL, Lounsberry J, Mirian A, et al. Provincial differences in the diagnosis and care of amyotrophic lateral sclerosis. Can J Neurol Sci. 2018;45:652–659. DOI: 10.1017/cjn.2018.311.
6. CADTH Common Drug Reviews. Pharmacoeconomic review report: edaravone (radicava): (mitsubishi tanabe pharma corporation): indication: for the treatment of amyotrophic lateral sclerosis (ALS). Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2019.
7. Tankisi H, Nielsen CS-Z, Howells J, et al. Early diagnosis of amyotrophic lateral sclerosis by threshold tracking and conventional transcranial magnetic stimulation. Eur J Neurol. 2021;28:3030–3039. DOI: 10.1111/ene.15010.
8. Benatar M, Wuu J, Turner MR. Neurofilament light chain in drug development for amyotrophic lateral sclerosis: a critical appraisal. Brain. 2022;146:2711–2716. DOI: 10.1093/brain/awac394.
9. Escorcio Bezerra ML, Abrahão A, Nunes KF, et al. Motor unit number index and neurophysiological index as candidate biomarkers of presymptomatic motor neuron loss in amyotrophic lateral sclerosis. Muscle Nerve. 2018;58:204–212. DOI: 10.1002/mus.26087.
10. Blair HA. Tofersen: first approval. Drugs. 2023;83:1039–1043. DOI: 10.1007/s40265-023-01904-6.

https://doi.org/10.1017/cjn.2023.320 Published online by Cambridge University Press