SYMPTOM MANAGEMENT IN AMYOTROPHIC LATERAL SCLEROSIS: WE CAN DO BETTER

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Patients with amyotrophic lateral sclerosis (ALS) may receive the erroneous message, either from their physicians or through the lay press, that their disease is untreatable. The error lies in the misinterpretation of *treatment* as *cure*. There are many diseases we cannot cure. Treatment in the form of symptom management has long been a key role of physicians, nurses, and other health care providers, as noted by Hippocrates more than 2,000 years ago: "Cure sometimes, treat often, comfort always."[1] A cure for ALS remains elusive. Disease modifying therapies can slow progression or prolong survival but cannot improve strength or function.[2,3] Thus, as they have since ALS was initially described by Charcot in 1869,[4] clinicians have directed their efforts toward optimizing quality of life (QOL) for persons with ALS and their families through symptom management.[5–7] In doing so, a multidisciplinary approach to ALS care prolongs survival and provides improved QOL compared with conventional care.[8,9]

The study presented by Nicholson and colleagues[10] in this issue provides insight into the current state of symptom management of a cohort of ALS patients. Data on the presence and severity of these symptoms, the degree to which symptoms were bothersome, and the efficacy of symptom management were collected. About 31% of those who were contacted responded. The mean disease duration was 5 years. In order of decreasing prevalence, patients cited fatigue (90%), muscle stiffness (84%), muscle cramps (74%), shortness of breath (66%), sleep difficulty (60%), pain (59%), anxiety (55%), depression (52%), increased saliva (52%), constipation (51%), pseudobulbar affect (38%), loss of appetite (37%), and weight loss (29%). Fatigue was not only the most frequently reported symptom but also the least frequently treated one. It is striking that so many other symptoms commonly encountered in ALS were found to have low treatment prevalence: weight loss 22%, pseudobulbar affect 29%, sialorrhea 32%, muscle stiffness 39%, pain 44%, and dyspnea 49%. If symptom management is the best care we have to offer our patients, then it is concerning that these percentages are so low. Are we missing opportunities to improve the quality of the lives of our patients and, if so, why? Mental health care fares no better. Specifically, this study also calls attention to the relatively high prevalence of anxiety and depression, consistent with the overall significant psychological morbidity noted in patients with ALS.[11] Several years ago, a call was issued for further research into psychological intervention.[12] However, treatment prevalence of anxiety and depression in this recent large survey was only about 50%, suggesting that the need for effective psychological intervention remains, to a great degree, unmet. Why does this continue to be true?

Can some of the blame be attributed to a lack of awareness of these symptoms on the part of physicians? This seems unlikely. Attention to the need for symptomatic treatment of patients with ALS is not new. The American Academy of Neurology issued practice parameters in 2009,[5,13] identifying a number of areas in which symptomatic treatment is important. Many of the symptoms cited at that time appear prominently in the article by Nicholson and colleagues. It is notable that the high prevalence of fatigue in ALS patients is not a new finding. It can worsen over the course of the disease[14,15] and has been shown to improve with modafinil therapy.[16]

Is the gap in providing adequate symptom management due to lack of evidence for the efficacy of such treatments? Most likely, this is at least partially the case. The 2009 American Academy of Neurology guidelines note varying degrees of evidence for symptomatic treatments. Then and now, double-blind, placebo-controlled studies were available for only a few such treatments, such as dextromethorphan plus quinidine for pseudobulbar affect[17] and botulinum toxin for sialorrhea.[18] The lack of high-quality clinical trials for the treatment

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Published online 6 July 2017 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/mus.25740

of many other symptoms likely leads to the use of ineffective therapies or to the inconsistent use of potentially effective ones. Unfortunately, the development of more effective symptomatic treatments will be challenging. Many of the drugs now used to treat pain, spasticity, and other bothersome symptoms of ALS are off-label, and there is little incentive for pharmaceutical companies to sponsor trials for the treatment of a small population of individuals with a rare disease if these drugs are already FDA-approved for other more common disorders. Even if drugs for symptom management are shown to be effective for those with ALS, payers may decline to pay for off-label uses.

Could the fault lie with the physician's training and self-perception? These may play a role. In the United States, most physicians who provide ongoing ALS care in large centers are neurologists, few of whom have received formal training in palliative care. Effective management of pain or of depression and anxiety are often learned "on the job." Perhaps it is time for us to rethink the training we provide to those who will be directing such clinics in the future. It is essential that ALS physicians avoid misleading generalities or false statements, such as the lack of treatments for ALS. Evaluating a long list of possible symptoms that are of potential concern *to the patient* at each visit is essential for good care.

As with all studies, this one has limitations, and the authors accurately describe some of these. The study population was limited to those registered with the Muscular Dystrophy Association, a group that may not be representative of the ALS population as a whole, and about 70% of those to whom the survey was sent did not return it. Although the patient population in some ways appears to be representative of those with ALS (mean age 60 years, 61% men, 77.8% limb onset), we do not know whether the 70% of those who chose not to return their surveys had a different set or frequency of treated or untreated symptoms. Certainly those who responded had a longer average duration of disease than most ALS patients, and the authors acknowledge this. They may also have differed from the other 70% or from the ALS population as a whole with regard to resources such as insurance or access to health care providers and medications. The authors do not describe how the survey was developed. Were patients and their caregivers involved in determining the list of symptoms about which patients were questioned? Although respondents could free text responses that were not on the list of symptoms, they may have been less likely to do so than to choose from the existing list, as the authors indicate. This survey could not address the fact that many symptoms are moving targets, controlled with therapies one month but uncontrolled the next or absent entirely early in the disease and then severe and bothersome as the disease progresses. Adequate symptom management requires frequent reassessment of symptom presence and severity. The survey by Nicholson and colleagues is a snapshot in time, and longitudinal studies would be useful. One smaller study looked at evolution of symptoms and found, not surprisingly, that patients perceived most symptoms to worsen over time.[14] ALS care providers must be constantly vigilant for new or worsening symptoms.

The bottom line is that ALS is a terrible disease. It produces a large number of symptoms that are bothersome at best and debilitating at worst, each of which may require active management.[6] For those who are treating patients with ALS, cure is not yet within reach, but treatment with the goal of providing comfort should remain a guiding principle. Nicholson and colleagues remind us that management of symptoms can be overlooked in ALS but remains a critical component of treatment and comfort. Their study provides us with an important roadmap drawn by our patients, leading to a better understanding of those symptoms that are most frequent and bothersome to them, providing guidance regarding the extent to which patients are receiving adequate symptomatic relief. Our job is to use our patients' insights and their collective wisdom not only to identify the most effective symptom management strategies but also to implement them aggressively in a process of shared decision making with our patients. It is essential that ALS specialist physicians as a group shift our emphasis from *identifying* to *addressing* gaps in treatment and shortcomings in care. If trained in the modern era, Hippocrates likely would have understood and approved of this approach.

Dr Goutman has received research support from the NIH/NIEHS (K23ES027221), Agency for Toxic Substances and Disease Registry/Centers for Disease Control, the ALS Association, Cytokinetics, and Neuralstem, Inc; has received honorarium from Continuum; has consulted for Cytokinetics; and has participated in market research. Dr Simmons has received research support from Neuralstem, Cytokinetics, and GlaxoSmithKline and has served as a consultant for Neuralstem and Cytokinetics.

Ethical Publication Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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