

The Voice of the Patient

Summary report resulting from an externally conducted
Patient-Focused Drug Development survey, a parallel effort to the
U.S. Food and Drug Administration's Patient-Focused Drug Development Initiative

Amyotrophic Lateral Sclerosis (ALS)

ALS Patient-Focused Drug Development Survey
October – November 2017

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Center for Drug Evaluation and Research (CDER) &
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Title of Resource:
The Voice of the Patient Report for Amyotrophic Lateral Sclerosis (ALS)

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Version Date:

This voice of the Patient report has not been revised or modified since October 24, 2019.

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Table of Contents

Executive Summary	
I.	Introduction.....
A.	Overview of Amyotrophic Lateral Sclerosis (ALS).....
B.	Survey Overview
C.	Report Overview
II.	Amyotrophic Lateral Sclerosis (ALS).....
A.	Key Themes in ALS
B.	Living with ALS
i.	Most Significant Symptoms of ALS
ii.	Impact of ALS on Daily Life
iii.	Change to Symptoms Over Time
C.	Current Approaches to Living with ALS
i.	Current Treatments and Other Approaches for ALS
ii.	Management of ALS with Current Treatments.....
D.	Preferences for Future Therapies for ALS.....
III.	Benefit-Risk Framework
IV.	Conclusion

Executive Summary

The ALS Association developed a patient and caregiver-driven initiative, ALS Focus, to help facilitate robust patient experience and preference studies in ALS. This first survey initiative within this program, IMPACT ALS, is a United States-focused patient experience survey, designed to expand the data available from the experiences of individuals with ALS and their caregivers in order to guide drug development and inform U.S. Food and Drug Administration (FDA) regulatory decision-making. This survey gathered information about the functional burden of ALS and unmet needs related to treating those burdens. The results of this survey should be viewed with the overlay that ALS swiftly progresses to death, with individuals typically surviving just three to five years after diagnosis.

Overall, 1,534 people participated. A full summary of the survey can be found in this Voice of the Patient report. Key findings about the experiences of individuals living with ALS and their caregivers include:

Topic 1: Living with ALS

- ALS is characterized by a progressive deterioration in the ability to perform everyday tasks.

"ALS is like death by a thousand paper cuts - it takes bits of your independence slowly and consistently. Two months ago I could pick up a coffee mug easily. Today, I have to be careful doing it because I feel some weakness while doing it."

"I feel like I'm reverting to childhood. I have been a very active and independent adult, and I'm losing both."

- ALS most frequently results in weakness in hands, arms, feet, and/or legs.

"At this point, my ALS has primarily affected my legs. Skiing was extremely important to me, but I can accept not be able to do this. I would have to say being mobile is the greatest loss since it affects my ability to do the everyday task of yard work, assisting around the house, and shopping. These are now burdens placed on my wife."

- Individuals with ALS and caregivers of individuals with ALS reported significant symptoms of fatigue and weakness, followed by speech problems, shortness of breath, difficulty sleeping, and pain.

"I have gone from working full time to completely dependent, no use of extremities at all and dependent on a BiPAP to breathe. My husband and I had our own business. Now the business is run out of our house by my husband with no help from me. Obviously our income has gone down dramatically."

- These progressive symptoms result in a loss of independence and led to less time spent at work or school, socializing, or traveling.

"My husband and I both worked full-time jobs until he retired and I had to quit my job as a banker due to not being able to speak clearly. I had always taken pride in being independent. I cannot drive, prepare our food, bathe myself, dress myself nor go to bathroom on my own. I can't walk. I sleep in a recliner which my husband has to put me into and get me out. My independence is gone."

"He can no longer do anything for himself and it is devastating to his self esteem. As someone who was very involved and active, it is almost unimaginable that he is so imprisoned by his own body."

"I have 12 grandchildren very active in their lives. Volunteered at church, helped family..... now it all upside down. Being forced to be still and have others help me do everything, is not my idea of living"

Topic 2: Current & Future Treatments for ALS

- While people with ALS use a range of prescription drugs (e.g., riluzole, anti-depressants), vitamins and supplements, peg tube, physical therapy, and assistive devices for motility and breathing support, individuals with ALS do not report high satisfaction with these current treatments, both with respect to disease progression and symptomatic relief. Treatments were reported to only "somewhat help" with managing ALS and the everyday impacts of the disease. Breathing assistance devices were reported to be very inconvenient and burdensome, but necessary.
- When asked what is one thing they wished they could still do, individuals with ALS most often reported that they wish they could walk. Caregivers indicated that they wished the person for whom they cared could still talk. However, individuals with ALS and their caregivers provided a range of activities they wish they could still do.

"Drive. Go any place, outside of my home, and not have to worry about where to park, how high the curb is to the sidewalk, can I be easily seated in a restaurant without getting in someone's way or someone getting in mine. Not being able to go anywhere without someone with me to open doors, get something off the top shelf at the grocery store. The list is long."

- With current treatments mainly focused on supportive care, individuals with ALS would like treatment options that stop disease progression and assist with breathing or respiratory function.

"ALS has practically taken everything; I have no wish to just get "one" thing back. It's been a slow progression, going on 8 years. At year 2, when I was told I had ALS to long and wouldn't be selected for any clinical trials, that's when I wished the ALS would finish its job."

I. Introduction

The ALS Association developed a patient and caregiver-driven initiative, ALS Focus, as a cross-sector collaboration intended to help facilitate robust patient experience and preference studies in ALS. IMPACT ALS is a United States-focused effort within the ALS Focus platform and is the first survey initiative within ALS Focus intended to expand on the data available from the experiences of individuals with ALS and their caregivers in order to guide drug development.

The results from the survey, as summarized in this report, are submitted to the U.S. Food and Drug Administration (FDA) in accordance with the Agency's Patient-Focused Drug Development Initiative, an FDA commitment under the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA V) to more systematically gather the perspectives of patients, such as those with ALS, on their condition and available therapies to their condition.

Furthermore, this report is submitted to FDA to serve as patient experience data or related information for the Agency's consideration in the review of applications for new drugs to treat or prevent ALS that are submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) or section 351(a) of the Public Health Service Act, pursuant to section 569C of the FD&C Act.

A. Overview of Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that affects motor neurons. It has no known cause and affects at least 16,000 people in the United States at any one time, with approximately 6,000 new diagnoses made per year.^{1, 2} As the disease progresses, motor neurons that control voluntary and involuntary muscles deteriorate. People with ALS progressively lose the ability to perform everyday activities like walking, speaking, and eating. Eventually, the nerves that control muscles used for breathing are affected and individuals with ALS require a ventilator to live. Respiratory failure is the leading cause of death in individuals with ALS.

After diagnosis, individuals with ALS typically survive three to five years,³ with only about a 10 to 20 percent chance of surviving for more than 10 years.⁴ Current treatment options are limited and focus mostly on supportive care through assistive devices. In part due to the heterogeneity of the ALS population, which complicates clinical trials,⁵ and due to the lack of a clear pathogenesis, only three treatments are available that have a modest impact on the disease course. For example, Riluzole, through either survival or function, does not significantly increase survival beyond a few months. Lack of a cure is a major unmet need in ALS.⁶

¹ Mehta, P., Kaye, W., Bryan, L. et al. 2016. Prevalence of Amyotrophic Lateral Sclerosis - United States, 2012-2013. *MMWR Surveill Summ.* 65:1-12.

² Beghi, E., Logroscino, G., Chio, A. et al. 2006. The epidemiology of ALS and the role of population-based registries. *Biochim. Biophys. Acta* 1762:1150-1157.

³ Brown, R.H., and Al-Chalabi, A. 2017. Amyotrophic Lateral Sclerosis. *N. Engl. J. Med.* 377:162-172.

⁴ Beghi, E., A.Chio, P.Couratier, et al. 2011. The epidemiology and treatment of ALS: focus on the heterogeneity of the disease and critical appraisal of therapeutic trials. *Amyotroph. Lateral. Scler.* 12:1-10.

⁵ Beghi et al. 2011..

⁶ Brown and Al-Chalabi. 2017.

Existing information regarding the burden of ALS in daily life is limited and gleaned only from small or geographically restricted studies.^{7, 8, 9, 10, 11, 12} There is an opportunity to collect input from individuals with ALS and their caregivers to guide drug development and regulatory decision-making. This Voice of the Patient Report is one way to use the survey data to improve development and review.

B. Survey Overview

This survey gathered information about the functional burden of ALS from people with ALS and their caregivers. These data will help ensure that the voices of individuals with ALS and their caregivers are included in the development and evaluation of new therapies. This survey was developed using input from The ALS Association and an advisory committee of regulatory and methodology experts, ALS clinical thought leaders, a person with ALS, a caregiver for a person with ALS, and representatives from industry partners. In addition, input on the draft survey was provided by a group of individuals living with ALS and caregivers, as well as officials from FDA, including from the Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health, and Office of Orphan Products Development.¹³

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⁷ Foley, G., O'Mahony, P., and Hardiman, O. 2007. Perceptions of quality of life in people with ALS: effects of coping and health care. *Amyotroph. Lateral. Scler.* 8:164-169.

⁸ Raheja, D., Stephens, H.E., Lehman, E. et al. 2016. Patient-reported problematic symptoms in an ALS treatment trial. *Amyotroph. Lateral. Scler. Frontotemporal. Degener.* 17:198-205.

⁹ Pagnini, F., Phillips, D., Bosma, C.M. et al. 2015. Mindfulness, physical impairment and psychological well-being in people with amyotrophic lateral sclerosis. *Psychol. Health* 30:503-517.

¹⁰ Rabkin, J.G., Goetz, R., Factor-Litvak, P. et al. 2015. Depression and wish to die in a multicenter cohort of ALS patients. *Amyotroph. Lateral. Scler. Frontotemporal. Degener.* 16:265-273.

¹¹ Pagnini, F., Lunetta, C., Rossi, G. et al. 2011. Existential well-being and spirituality of individuals with amyotrophic lateral sclerosis is related to psychological well-being of their caregivers. *Amyotroph. Lateral. Scler.* 12:105-108.

¹² O'Brien, M.R., Whitehead, B., Jack, B.A. et al. 2011. From symptom onset to a diagnosis of amyotrophic lateral sclerosis/motor neuron disease (ALS/MND): experiences of people with ALS/MND and family carers - a qualitative study. *Amyotroph. Lateral. Scler.* 12:97-104.

¹³ The ALS Association and its partners thank the FDA Patient Affairs Staff for working with the IMPACT ALS study team to facilitating meetings with the Agency to get input during the design of the survey and to present topline results.

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Two versions of the survey were developed: a survey of the perspective of individuals with ALS (patient-centric), and a survey of the experiences of individuals with ALS from the view of the caregiver (patient-centric via caregiver). Both versions of the survey had the following four modules: (1) disease background, (2) living with ALS, (3) approaches to treating ALS, and (4) demographics. Caregivers responded to the survey with information about the individual with ALS for whom they care.¹⁴ If a caregiver responded to the survey with information about an individual with ALS who had passed away, the caregiver was instructed to provide information about the last two weeks of the individual's life.

The survey was approved via a central institutional review board (Western IRB), and recruitment was conducted through the following channels: The ALS Association Chapters, the Northeast ALS (NEALS) Consortium, the Clinical Research in ALS and related disorders for Therapeutic Development (CReATE) Consortium, the ALS Therapy Development Institute (TDI), and the Centers for Disease Control and Prevention (CDC) National ALS Registry.

The survey was conducted anonymously online through SurveyGizmo between October 11, 2017, and November 2, 2017 and took approximately 30 minutes to complete. All survey participants self-reported as one of the following: person with ALS, person assisting person with ALS to answer the survey, current caregiver of person with ALS, or past caregiver of person with ALS.

The survey was made available to approximately 10,000 people living with ALS and caregivers, providing the opportunity for survey engagement. Overall, 1,534 people participated, but not all participants responded to all modules. The data from the survey respondents was grouped and analyzed as follows:

¹⁴ Caregivers also responded to the survey with information about his or her own experiences as a caregiver, but this caregiver-centric data is outside the scope of this Voice of the Patient Report.

- **Three-way grouping of all respondents [hereinafter referred to as “Primary Analysis”]:**
 - **Individual with ALS (n=887):** This data showed the perspective of an individual with ALS at the time of the survey. This individual could have been at any point in their disease progression.
 - **Caregiver of living individual with ALS (n=448):** This data showed the perspective of the caregiver of an individual with ALS at the time of the survey. The individual with ALS could have been at any point in their disease progression.
 - **Caregiver of individual with ALS who has passed away (n=193):** This data was the perspective of a caregiver from the last two weeks of the life of the individual with ALS for whom they cared. Unlike the individual with ALS data and caregiver of living individuals with ALS data, listed above, this data represented a retrospective point of view of the last stages of the disease progression of an individual with ALS.
- **Individual with ALS who has passed away (n=193) vs. living individual with ALS (n=1,335):** This analysis compared data from the caregivers of individuals with ALS who have passed away, from the last two weeks of that individual’s life, compared to data from living individuals with ALS and the caregivers of living individuals with ALS.
- **Paired individuals with ALS and their caregivers (n=86; 43 pairs):** For this analysis, data from individuals with ALS and their caregivers were viewed together. This analysis looked at the same individual’s experience with ALS from both their own perspective and the perspective of their caregiver.

When the term “survey respondents” is used in this report to describe the responses to a survey question, that term refers to all individuals with ALS and caregivers who responded to that survey question. The results presented in this report reflect only a subset of the full results collected in the survey; the complete dataset will be made available to the public for independent review and analysis through The ALS Association’s website.

Demographics

The demographics of our survey participants were similar to those in the US CDC National ALS Registry suggesting that the respondents are broadly representative of the PALS population in the USA shown in **Figure 1** below, the survey respondents closely match the portion of the US population in each state.

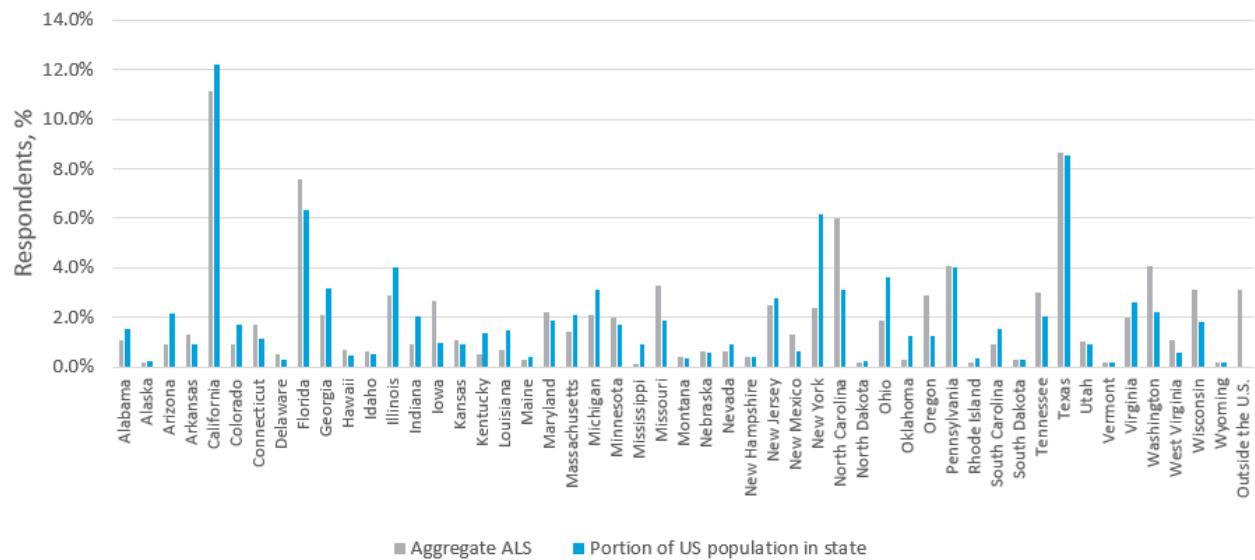


Figure 1. Portion of Survey Respondents in Each State (n=1005) vs. Portion of U.S. Population in Each State¹⁵

The majority of individuals with ALS represented by the survey data were between 55 and 74 years old (37 percent were 55-64 years old and 30 percent were 65-74 years old) (**Figures 2a-2b**). Ninety-one percent (91 percent) of individuals with ALS represented were white. African American individuals with ALS were underrepresented in the survey data (3 percent). Such underrepresentation is typical in ALS and other health-related research without investing heavily in targeted, community-based recruitment methods, which this study did not employ.

	Patient-paired n = 43	Caregiver-paired n = 43	All ALS Patients n=620	All Caregiver (Not Passed) n=280	All Caregiver (Passed) n=105	Passed Away (n = 105)	Did Not Pass Away (n = 900)
Age groups, n (%)							
18-24	0 (0)	0 (0)	2 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	3 (0.3)
25-34	1 (2.3)	1 (2.3)	9 (1.5)	4 (1.4)	2 (1.9)	2 (1.9)	13 (1.4)
35-44	3 (7.0)	3 (7.0)	27 (4.4)	17 (6.1)	2 (1.9)	2 (1.9)	44 (4.9)
45-54	6 (14.0)	6 (14.0)	105 (16.9)	38 (13.6)	17 (16.2)	17 (16.2)	143 (15.9)
55-64	15 (34.9)	16 (37.2)	247 (39.8)	93 (33.2)	28 (26.7)	28 (26.7)	340 (37.8)
65-74	15 (34.9)	14 (32.6)	174 (28.1)	92 (32.9)	39 (37.1)	39 (37.1)	266 (29.6)
75+	3 (7.0)	3 (7.0)	56 (9.0)	35 (12.5)	17 (16.2)	17 (16.2)	91 (10.1)
Male, n (%)							
Male	26 (60.5)	26 (60.5)					
Race, n (%)							
American Indian /Alaska Native	0 (0)	0 (0)	5 (0.8)	0 (0.0)	0 (0.0)	2 (1.9)	8 (0.9)
Asian	0 (0)	0 (0)	7 (1.1)	6 (2.1)	0 (0.0)	3 (2.9)	13 (1.4)
Black/African American	1 (2.3)	1 (2.3)	15 (2.4)	9 (3.2)	2 (1.9)	2 (1.9)	24 (2.7)
Native Hawaiian /Other Pacific Islander	0 (0)	0 (0)	1 (0.2)	3 (1.1)	1 (1.0)	1 (1.0)	4 (0.4)
Other	0 (0)	0 (0)	567 (91.5)	253 (90.4)	92 (87.6)	92 (87.6)	820 (91.1)
Prefer not to answer	0 (0)	0 (0)	14 (2.3)	4 (1.4)	2 (1.9)	2 (1.9)	18 (2.0)
White	42 (97.7)	42 (97.7)	15 (2.4)	9 (3.2)	5 (4.8)	5 (4.8)	24 (2.7)
Ethnicity, n (%)							
Not Hispanic or Latino	43 (100)	43 (100)	598 (96.5)	267 (95.4)	98 (93.3)	98 (93.3)	865 (96.1)

Figure 2a. Demographics by Subgroups

¹⁵ “Aggregate ALS” in the chart legend refers to the portion of survey respondents in each U.S. state.

	Fast Progression (n = 65)	Non-Fast Progression (n = 940)	<5 years since 1st symptom (n = 714)	5+ years since 1st symptom (n = 291)
Age groups, n (%)				
18-24	0 (0.0)	3 (0.3)	3 (0.4)	0 (0.0)
25-34	1 (1.5)	14 (1.5)	12 (1.7)	3 (1.0)
35-44	0 (0.0)	46 (4.9)	39 (5.5)	7 (2.4)
45-54	10 (15.4)	150 (16.0)	113 (15.8)	47 (16.2)
55-64	12 (18.5)	356 (37.9)	246 (34.5)	122 (41.9)
65-74	27 (41.5)	278 (29.6)	224 (31.4)	81 (27.8)
75+	15 (23.1)	93 (9.9)	77 (10.8)	31 (10.7)
Male, n (%)				
Race, n (%)				
American Indian				
/Alaska Native	1 (1.5)	9 (1.0)	9 (1.3)	1 (0.3)
Asian	3 (4.6)	13 (1.4)	15 (2.1)	1 (0.3)
Black/African American	2 (3.1)	24 (2.6)	18 (2.5)	8 (2.7)
Native Hawaiian				
/Other Pacific Islander	1 (1.5)	4 (0.4)	5 (0.7)	0 (0.0)
Other	54 (83.1)	858 (91.3)	641 (89.8)	271 (93.1)
Prefer not to answer	2 (3.1)	18 (1.9)	16 (2.2)	4 (1.4)
White	3 (4.6)	26 (2.8)	9 (1.3)	5 (1.7)
Ethnicity, n (%)				
Not Hispanic or Latino	61 (93.8)	902 (96.0)	685 (95.9)	278 (95.5)

Figure 2b. Demographics by Subgroup

Of the individuals with ALS represented by the survey data, 8 percent had familial ALS, 71 percent had sporadic ALS, and 21 percent did not know their type of ALS. The mean ALS Functional Rating Scale-Revised (ALSFRS-R) score of individuals with ALS represented by the survey data was 32. For 28 percent of the individuals with ALS represented by the survey data, greater than five years had elapsed since their first symptom (**Figure 3**). The survey data included the smallest representation of individuals with ALS who recently experienced their first symptom, which may be due to the typical length of time until diagnosis, which has been reported previously to range from eight to 15 months in ALS (i.e., individuals who have only recently experienced their first symptom may not have received a definitive diagnosis).¹⁶ For 4 percent, less than six months had elapsed since their first symptom.

¹⁶ Paganoni, S., Macklin E.A., Lee A. et al. 2014. Diagnostic timelines and delays in diagnosing amyotrophic lateral sclerosis (ALS). *Amyotroph. Lateral. Scler. Frontotemporal Degener.* 2015 15(5-6):453-456.

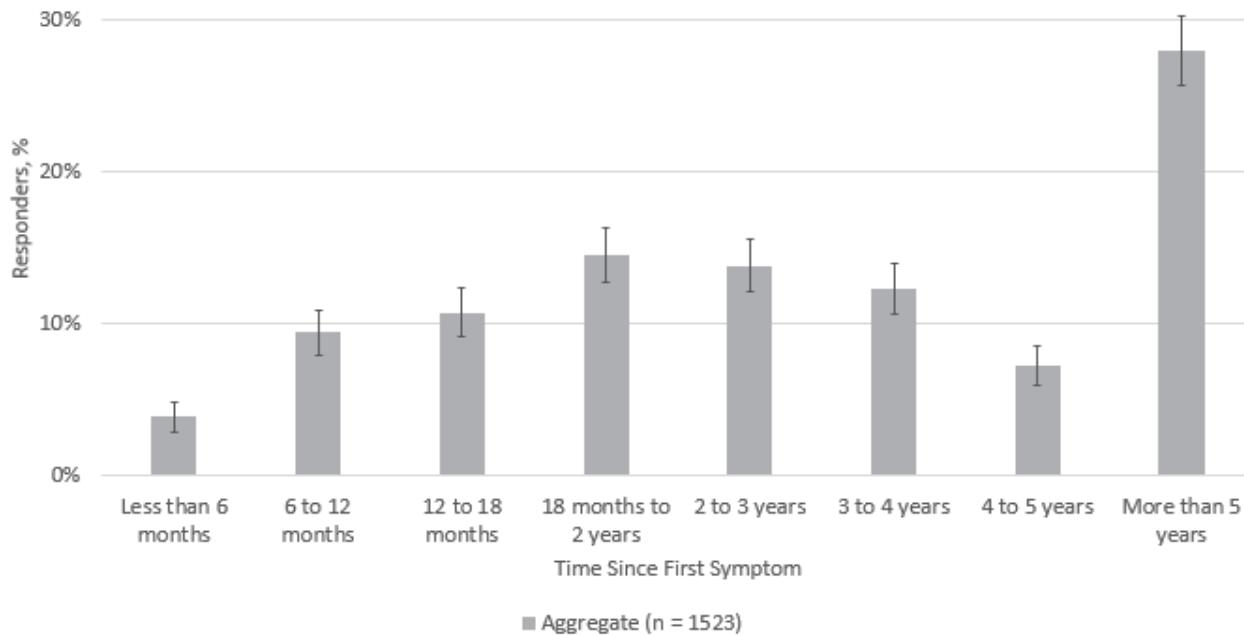


Figure 3. Time Since First Symptom^{17,18}

C. Report Overview

This report summarizes the input provided by individuals with ALS and their caregivers in response to the IMPACT ALS survey. To the extent possible, the terms used in this report to describe the specific symptoms and treatment experiences reflected and the words used by survey respondents.

II. Amyotrophic Lateral Sclerosis (ALS)

A. Key Themes in ALS

ALS is characterized by a progressive deterioration in ability to perform everyday tasks, including communication, walking, swallowing, and breathing. Individuals with ALS and caregivers of individuals with ALS reported significant symptoms of fatigue and weakness, leading to less time spent at work or school, socializing, or traveling. Overall, survey respondents reported that current treatments only somewhat help with managing ALS and the everyday impacts of the disease, and that breathing assistance devices are very inconvenient. The highest proportion of survey respondents want a treatment to stop the progression of ALS and assist with breathing and respiratory function.

¹⁷ “Aggregate” in the chart legend refers to the aggregate of all survey respondents, both individuals with ALS and caregivers.

¹⁸ Error bars represent 95 percent confidence intervals.

B. Living with ALS

i. Most Significant Symptoms of ALS

Survey respondents were asked to select all symptoms experienced by the individual with ALS within the last 2 weeks, or in the last 2 weeks before passing. Symptom response options were based off the ALSFRS-R self-report questionnaire.

Question for Individuals with ALS:

Which symptoms of ALS have you experienced within the last 2 weeks (Please select all that apply)

- Fatigue
- Pain
- Weakness in hands, arms, feet, and/or legs
- Shortness of breath
- Difficulty sleeping
- Speech problems
- Depression or other mood changes including despair or hopelessness
- Disturbances in thinking or concentration

Question for Caregivers:

Which symptoms of ALS has the individual experienced within the last 2 weeks, or in the 2 weeks before passing? (Please select all that apply)

[Same options as for individuals with ALS]

Survey respondents most frequently reported weakness in hands, arms, feet, and/or legs (89 percent). Fatigue was the next most commonly reported symptom (79 percent), followed by speech problems (57 percent), shortness of breath (52 percent), difficulty sleeping (43 percent), and pain (41 percent) (**Figure 4**). Depression and other mood changes and disturbances in thinking or concentration were reported by 30 percent of survey respondents.

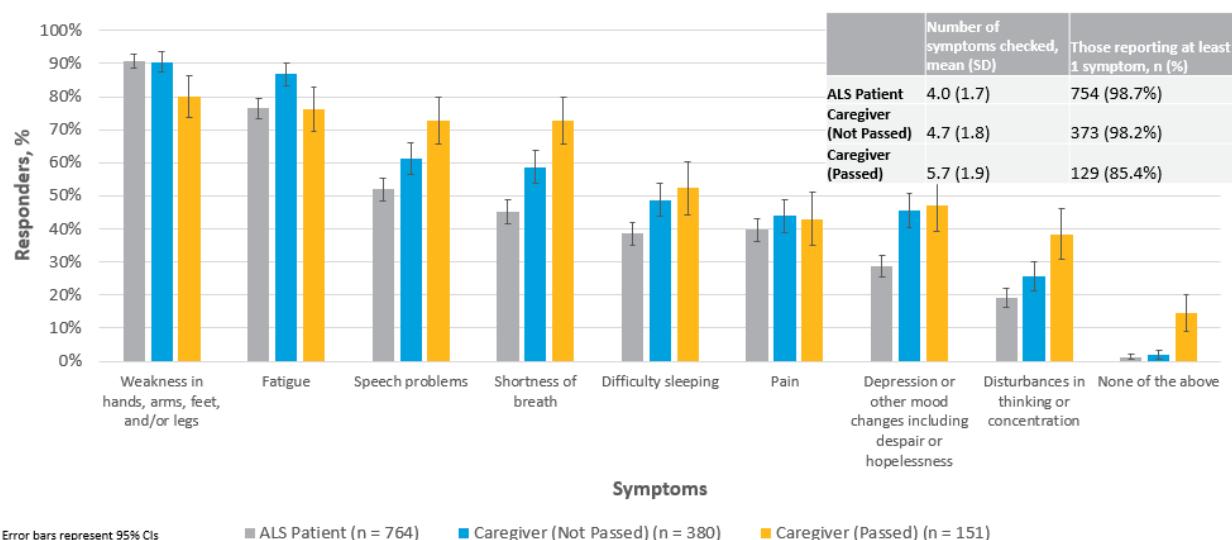


Figure 4. Symptoms of ALS in the Past 2 Weeks: Primary Analysis¹⁹

Overall, individuals with ALS and their caregivers had very similar responses for symptoms in the past two weeks (**Figure 5**). Individuals with ALS reported higher rates of shortness of breath than reported by caregivers of the same individuals.

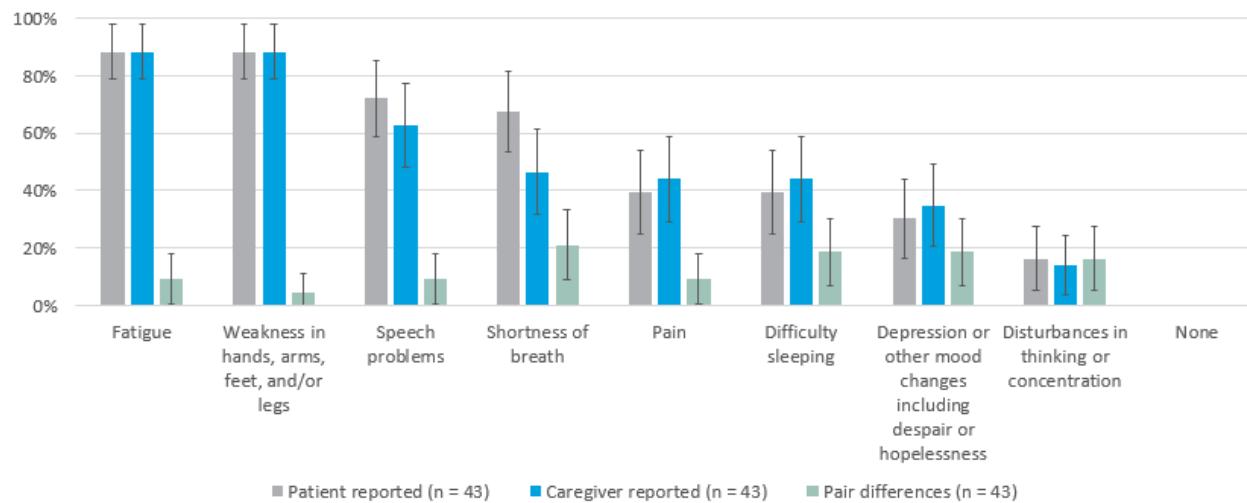


Figure 5. Symptoms of ALS in the Past 2 Weeks: Paired Patient-Caregiver Analysis²⁰

Caregivers who responded on behalf of individuals with ALS who had passed away reported the symptoms of speech problems, shortness of breath, difficulty sleeping, depression, and disturbances in thinking or concentration more frequently than individuals living with ALS and caregivers of individuals living with ALS (**Figure 6**). This analysis suggests that these symptoms may become more pronounced or more prevalent in the end stages of disease, because caregivers who responded on behalf of individuals who had passed away reported observations pertaining to the last two weeks of that individual's life.

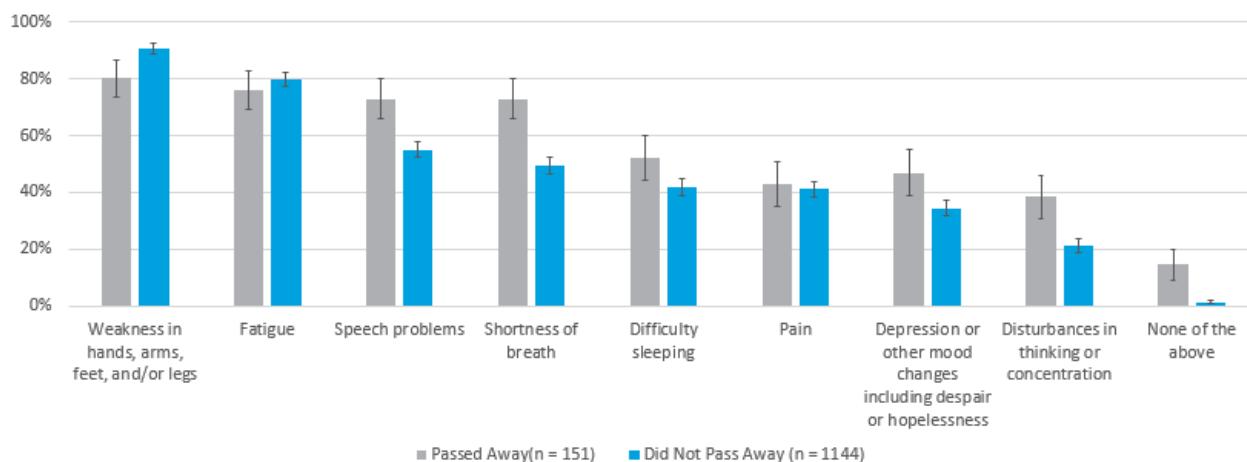


Figure 6. Symptoms of ALS in the Past 2 Weeks: Living vs. Passed Away²¹

¹⁹ Error bars represent 95 percent confidence intervals.

²⁰ Error bars represent 95 percent confidence intervals.

²¹ Error bars represent 95 percent confidence intervals.

The 79 percent of survey respondents who selected “fatigue” were asked to rate the severity of the fatigue (**Figure 7**).

Question for Individuals with ALS: <i>How fatigued have you been over the last 2 weeks?</i>
<ul style="list-style-type: none"><input type="checkbox"/> <i>Very fatigued</i><input type="checkbox"/> <i>Moderately fatigued</i><input type="checkbox"/> <i>Mildly fatigued</i><input type="checkbox"/> <i>Not fatigued</i>
Question for Caregivers: <i>How fatigued was the individual over the last 2 weeks?</i> [Same options as for individuals with ALS]

About half (46 percent) indicated that they were moderately fatigued, 30 percent indicated that they were very fatigued, and 24 percent indicated that they were mildly fatigued. One caregiver stated the following about the fatigue experienced by the person for whom he/she cares: “Fortunately he is not paralyzed, but he is getting weaker all over. He needs more help with getting his medication ready as he is too fatigued to do it himself. He feels more tired and it is harder to get out and do things as you have to have your machines ready and wheel chair which makes everything a more difficult challenge.”

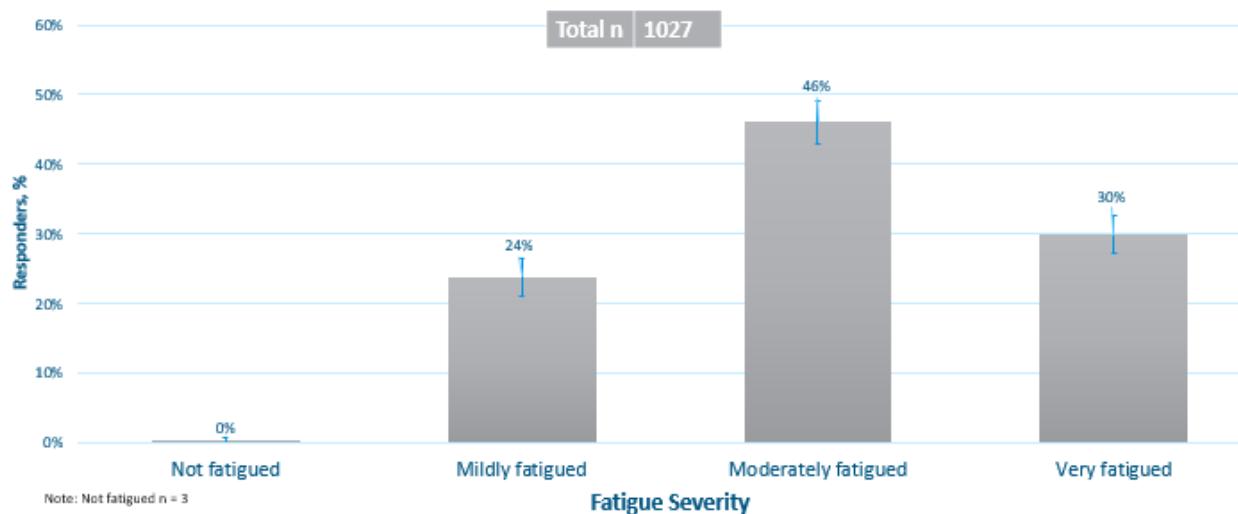


Figure 7. Severity of Fatigue for Those Who Checked “Fatigue”²²

The 41 percent of survey respondents who checked “pain” were asked to rate the pain on a scale of 0 (no pain) to 10 (worst pain imaginable) (**Figure 8**).

²² Error bars represent 95 percent confidence intervals.

Question for Individuals with ALS:

On a scale of 0-10, please rank your pain level over the last 2 weeks from no pain (0) to worst pain imaginable (10)

Question for Caregivers:

On a scale of 0-10, please rank the individual's pain level over the last 2 weeks from no pain (0) to worst pain imaginable (10)

Most of the respondents to this question (about 60 percent) ranked the pain between 3 and 6. Eighty-five percent of respondents to this question ranked the pain from 3-10, and 26 percent ranked the pain from 7-10. One individual with ALS stated, "Pain keeps me from being as active as I want or could be." Another individual with ALS stated that they wished they could "simply be comfortable," because they have "ongoing chronic discomfort and intermittent pain."

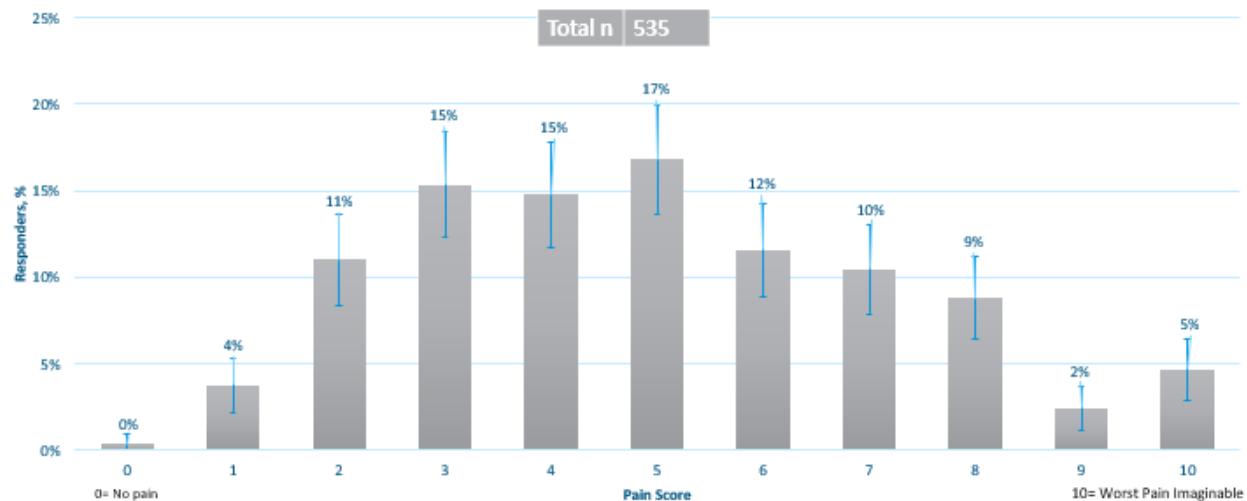


Figure 8. Severity of Pain for Those Who Checked "Pain"²³

The 89 percent survey respondents who selected "weakness in hands, arms, feet, and/or legs" were asked to indicate the specific limitation caused by this symptom (**Figure 9**).

Question for Individuals with ALS:

Which activities do you have trouble doing? (select all that apply)

- Washing my hair*
- Getting up from a chair without using my arms*
- Lifting my head off the bed when lying flat*
- I have no functional use of my extremities*

Question for Caregivers:

Which activities does the individual have trouble doing? (select all that apply)

- Washing his/her hair*

²³ Error bars represent 95 percent confidence intervals.

- Getting up from a chair without using his/her arms
- Lifting his/her head off the bed when lying flat
- He/she has no functional use of his/her extremities

Seventy-seven percent responded that this caused limitations with getting up from a chair, 59 percent responded that this caused limitations with washing hair, and 39 percent identified limitations with lifting their head off of the bed. About one-quarter of respondents (24 percent) responded that they had no functional use of their extremities.

One individual with ALS stated that they were “no longer able to work” because “weakness in fingers and hands makes programming too slow.” Another individual with ALS stated, “gardening and craft activity is limited due to weakness in right hand and drop foot/muscle weakness in right leg.”

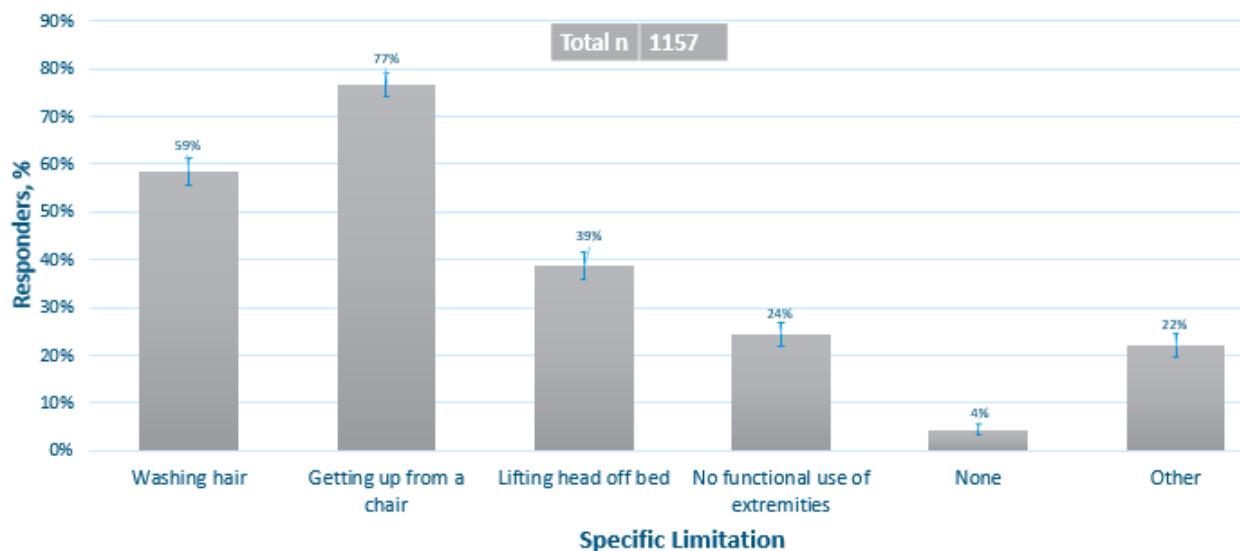


Figure 9. Degree of Weakness in Hands, Arms, Feet, and/or Legs for Those Who Checked This Symptom²⁴

The 52 percent of survey respondents who checked “shortness of breath” were asked to indicate the severity of this symptom (**Figure 10**).

Question for Individuals with ALS:

When do you feel short of breath?

- When performing moderate activities such as walking
- While performing light activities such as eating or dressing
- While at rest, such as sitting or lying down

Question for Caregivers:

When does the individual feel short of breath?

[Same options as for individuals with ALS]

²⁴ Error bars represent 95 percent confidence intervals.

Forty-eight percent indicated that shortness of breath occurred when performing moderate activities such as walking, 48 percent indicated that this occurred while performing light activities such as eating or dressing, and 46 percent indicated that this occurred while at rest such as sitting or lying down. One individual with ALS stated, “I have shortness of breath when I do the least little things.” Another survey respondent stated, “Shortness of breath prohibits more than just a few words in response.”

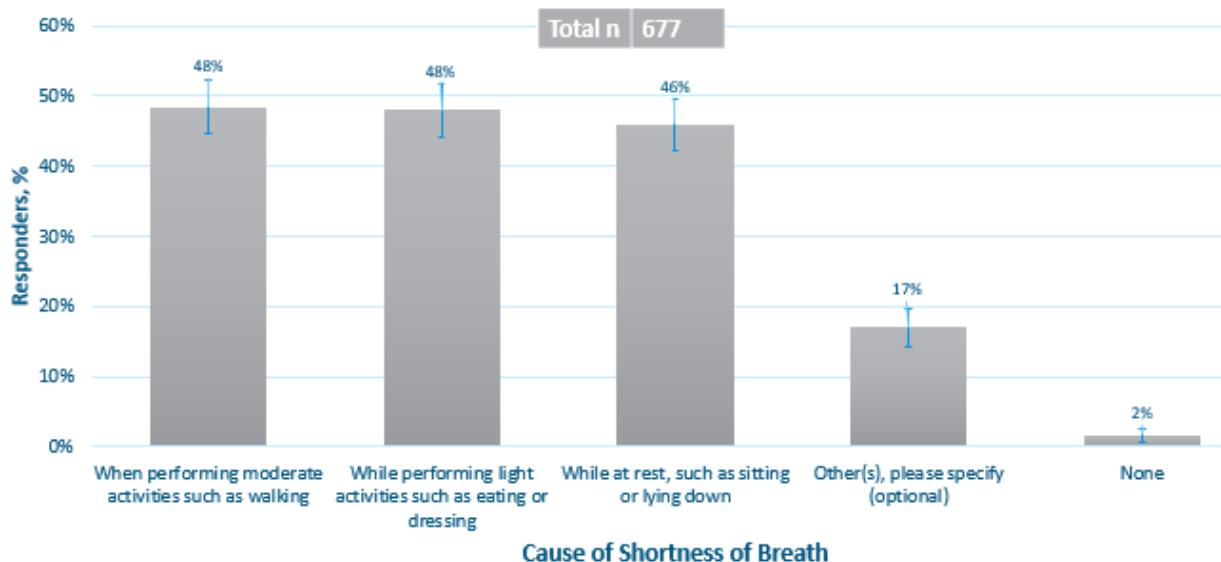


Figure 10. Severity of Shortness of Breath for Those Who Checked This Symptom²⁵

The 43 percent of survey respondents who checked “difficulty sleeping” were asked to identify the frequency of sleep disturbance (**Figure 11**).

Question for Individuals with ALS:

How often is your sleep disturbed?

- Less than 1 night a week
- 1 night a week
- 2-3 times a week
- 4-6 times a week
- Every night is disturbed

Question for Caregivers:

How often is the individual’s sleep disturbed?

[Same options as for individuals with ALS]

The majority of respondents (58 percent) indicated that every night of sleep is disturbed. One individual with ALS stated, “I have much more back pain, my hip bothers me and I can't sleep well, so I am fatigued.” One caregiver stated the following about the disrupted sleep of the individual with ALS for whom they care, “Waking up in the middle of the night multiple times to take him to the beach. The

²⁵ Error bars represent 95 percent confidence intervals.

night is always the worst - he can't sleep and can't breathe so he felt the need to go to an open space. Also, seeing him wake up blue from not getting enough oxygen when he did sleep."

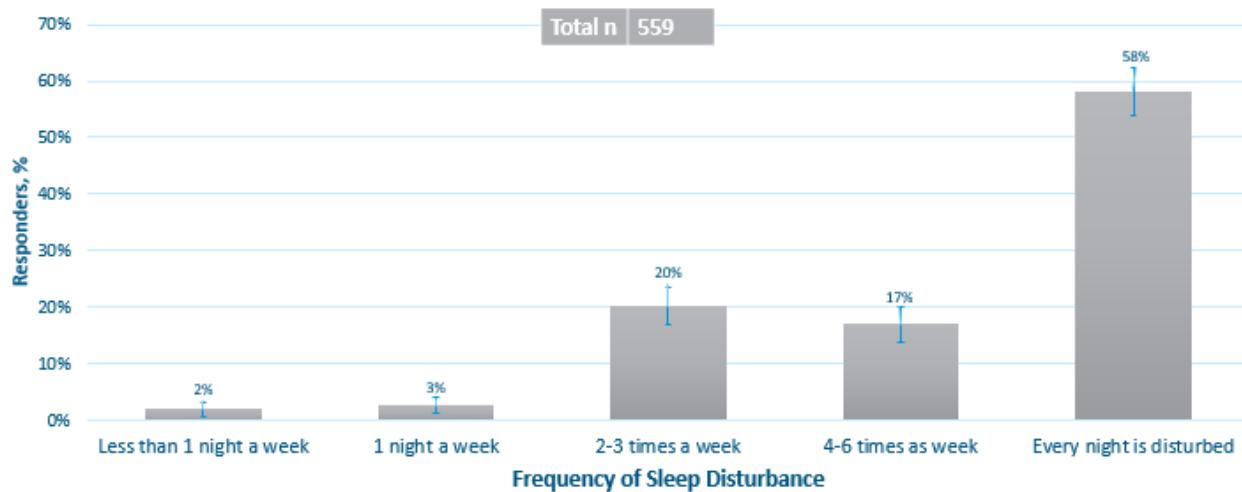


Figure 11. Degree of Difficulty Sleeping for Those Who Checked “Difficulty Sleeping”²⁶

The 57 percent of survey respondents who checked “speech problems” were asked to identify the type of speech problems (**Figure 12**). This question and the response options were based off the ALSFRS-R self-report questionnaire.

Question for Individuals with ALS:

Have you noticed any changes in your speech?

- no change*
- noticeable but minor speech difference*
- speech has changed; asked often to repeat words or phrases*
- speech has changed a lot; sometimes need the use of alternative communication methods (i.e. computer, writing pad, letter board or eye chart)*
- unable to communicate verbally anymore*
- Other(s)*

Question for Caregivers:

Have you noticed any changes in the individual’s speech?

[Same options as for individuals with ALS]

About one-third of respondents (31 percent) indicated that their speech had changed, 20 percent indicated that their speech had changed a lot, and 30 percent indicated that they were unable to communicate verbally.

²⁶ Error bars represent 95 percent confidence intervals.

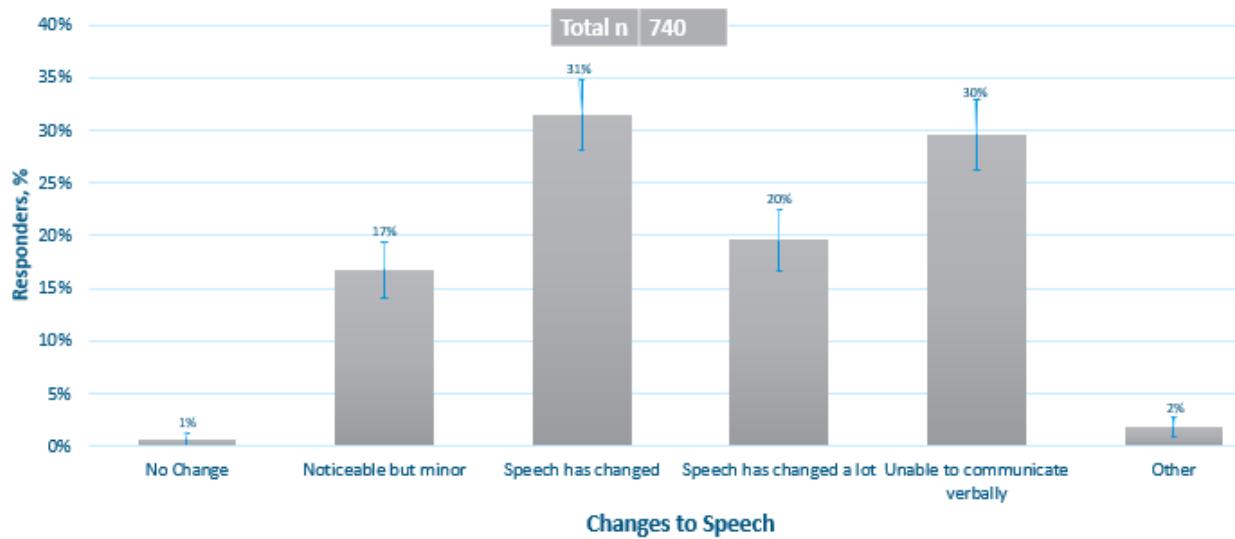


Figure 12. Type of Speech Problem for Those Who Checked “Speech Problems”²⁷

One individual with ALS stated, “I don’t talk on the phone anymore because of my speech. I have to get someone else to make my calls. I can’t communicate well with my family without typing or writing.” Individuals with ALS reported that speech problems can limit their work and other activities. One individual with ALS stated that they “volunteer less due to my speech issues.” Another individual with ALS stated, “I can no longer work or hold a job due to my fatigue and limited speech.”

The 57 percent of survey respondents who checked “speech problems” were also asked to identify the methods used to aid speech (Figure 13).

Question for Individuals with ALS:

What types of speech therapies, assistance, and devices are you using? (select all that apply)

- Nothing
- Regular visits to a speech therapist
- Voice amplification device
- Paper/dry erase board
- Communication board using letters, pictures and/or phrases
- Electronic devices with voice and/or text output from typing
- Electronic devices with voice and/or text output from eye-gaze input
- Gestures or eye blinks
- Other(s)

Question for Caregivers:

What types of speech therapies, assistance, and devices is the individual using? (select all that apply)
[Same options as for individuals with ALS]

About one-third of respondents (34 percent) indicated that they use electronic devices with voice and/or text output from text typing, 22 percent indicated that they use electronic devices with voice

²⁷ Error bars represent 95 percent confidence intervals.

and/or text output from eye-gaze input, 28 percent indicated that they use nothing, 23 percent indicated that they use paper or a dry erase board.

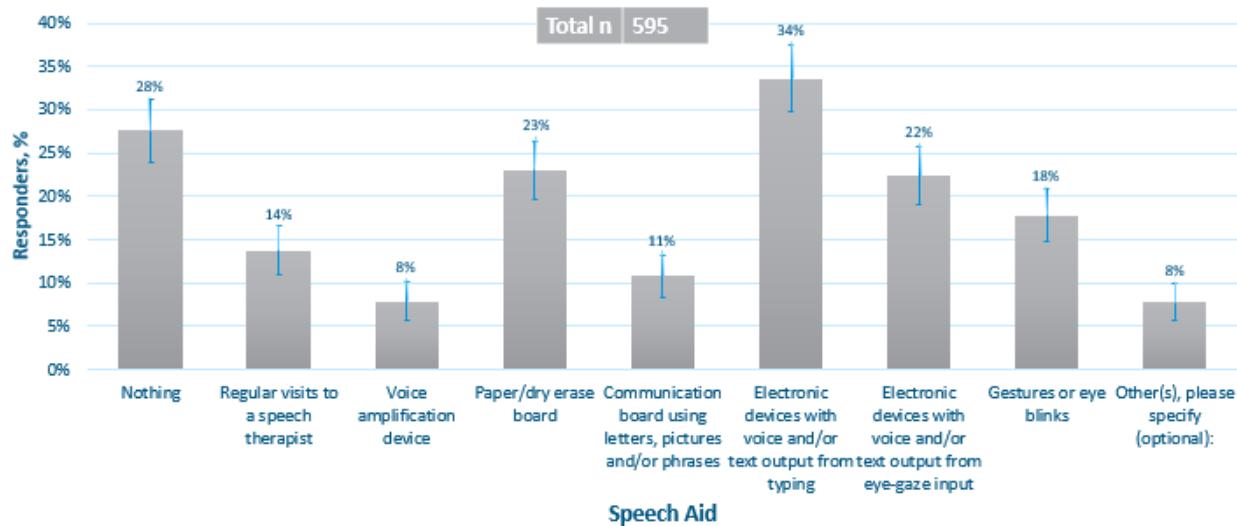


Figure 13. Methods Used to Aid Speech for Those Who Checked “Speech Problems”²⁸

Depression or Mood Changes

The 36 percent of survey respondents who checked “depression or mood changes” were asked to respond to PHQ-9 depression score questions (Figures 14-15).

Question for Individuals with ALS:				
Over the last two weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
<i>Little interest or pleasure in doing things?</i>				
<i>Feeling down, depressed, or hopeless?</i>				
<i>Trouble falling or staying asleep, or sleeping too much?</i>				
<i>Feeling tired or having little energy?</i>				
<i>Poor appetite or overeating?</i>				
<i>Feeling bad about yourself - or that you are a failure or have let yourself or your family down?</i>				
<i>Trouble concentrating on things, such as reading the newspaper or watching television?</i>				
<i>Moving or speaking so slowly that other people could have noticed?</i>				
<i>Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual?</i>				

²⁸ Error bars represent 95 percent confidence intervals.

<i>Thoughts that you would be better off dead, or of hurting yourself in some way?</i>				
Question for Caregivers: <i>[Same as for individuals with ALS]</i>				

Most of the respondents indicated that nearly every day they think about how they are moving or speaking so slowly that others could have noticed. One individual with ALS stated, "I don't enjoy going out in public because I'm afraid [I'll] do something to embarrass myself. It gets very scary and depressing at times." Most of the respondents also indicated that they feel tired and have little energy nearly every day.

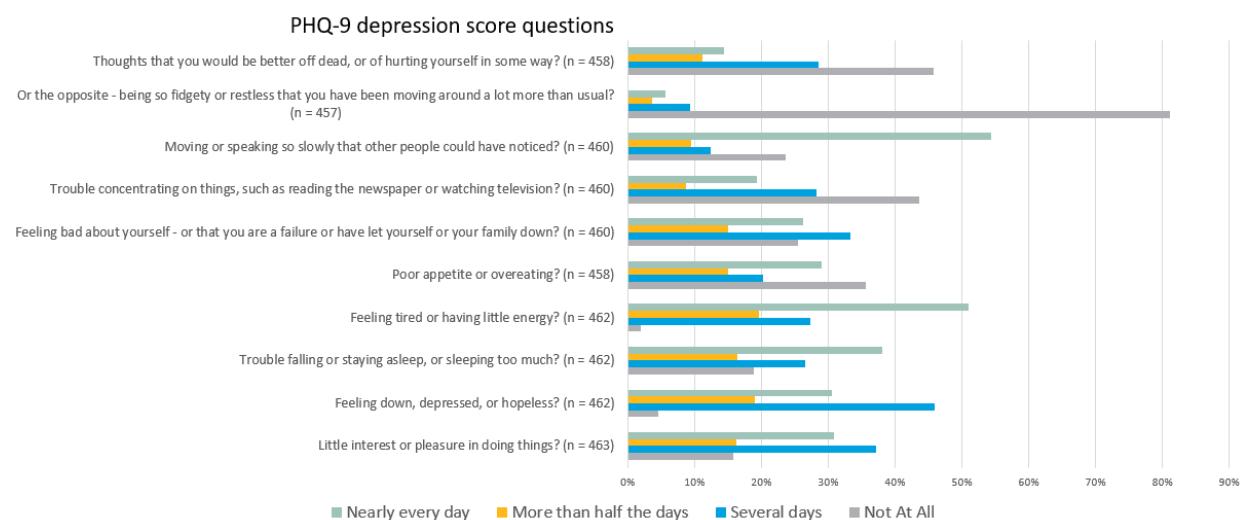


Figure 14. Depression or Mood Changes for Those Who Checked This Symptom

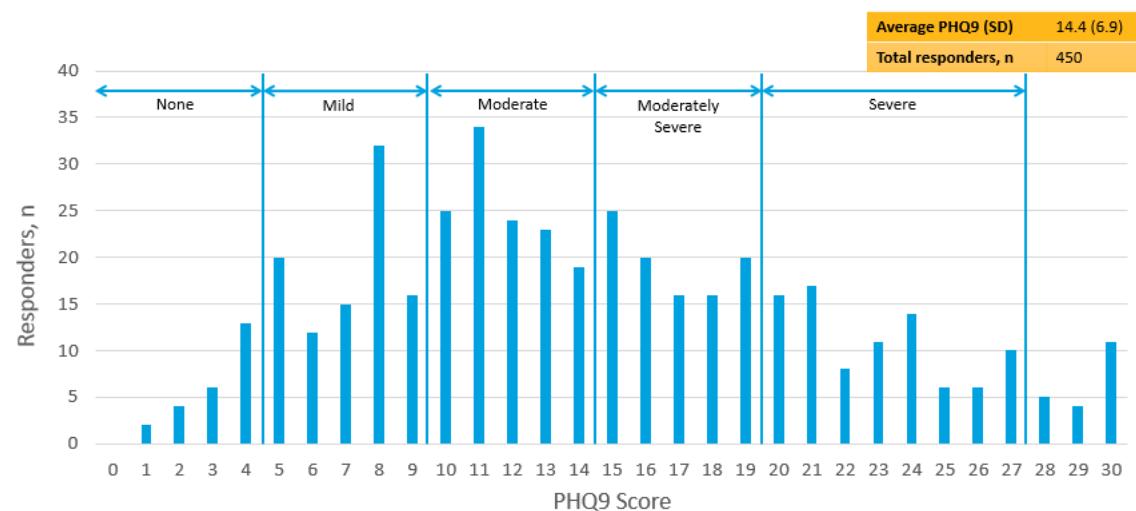


Figure 15. PHQ9 Depression Score Distribution

The 23 percent of survey respondents who indicated that they had disturbances in thinking were asked to identify the types of disturbances (**Figure 16**).

Question for Individuals with ALS:

What kind of thinking disturbances have you experienced over the past 2 weeks?

Question for Caregivers:

What kind of thinking disturbances has the individual experienced over the past 2 weeks?

The majority of respondents (58 percent) indicated that they experienced difficulty with word finding, and 47 percent indicated that they had difficulty completing simple tasks.

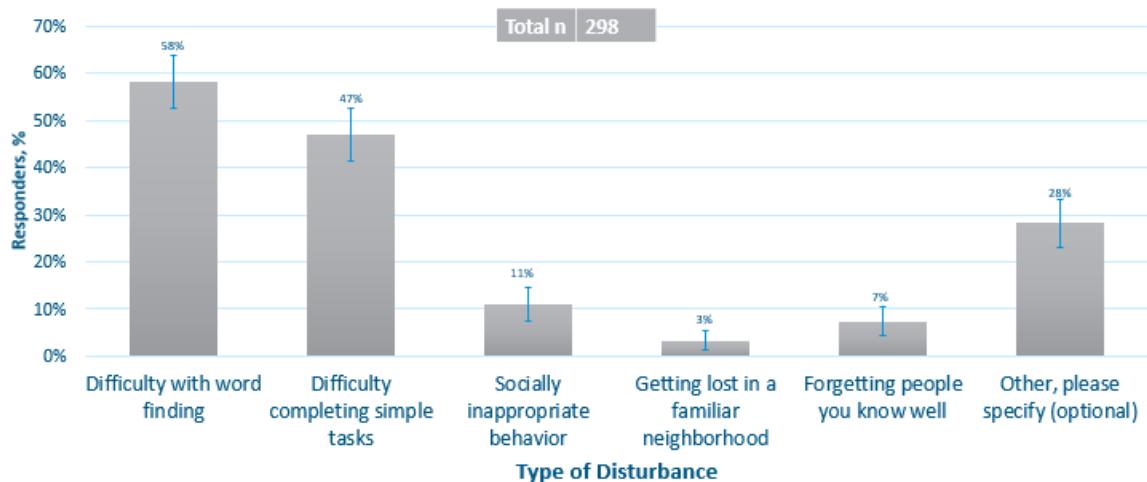


Figure 16. Types of Disturbances in Thinking for Those Who Checked This Symptom²⁹

Additional Symptoms Experienced by Individuals with ALS

Survey respondents were asked to select any additional symptoms experienced by the individuals with ALS in the last two weeks.

Question for Individuals with ALS:

Of the following additional symptoms, which have you experienced in the last 2 weeks? (Please select all that apply)

- Anxiety
- Balance issues while walking or standing
- Constipation
- Daytime sleepiness
- Decreased self-esteem
- Difficulty swallowing
- Increased saliva
- Morning headache
- Muscle cramps and twitches
- Muscle stiffness

²⁹ Error bars represent 95 percent confidence intervals.

- Muscle strength loss
- Poor appetite
- Poor concentration
- Poor night sleep
- Uncontrollable periods of laughing or crying
- Weight loss
- Other (please specify) _____
- Other (please specify) _____
- Other (please specify) _____

Question for Caregivers:

*Of the following additional symptoms, which have the individual experienced in the last 2 weeks?
(Please select all that apply)*
[Same options as for individuals with ALS]

The most frequently reported additional symptoms were muscle strength loss (76 percent), muscle cramps and twitches (63 percent), and balance issues while walking or standing (58 percent) (Figure 17). In response to the “Other” options in this question, 12 percent indicated psychological/emotional/neurologic symptoms and 11 percent indicated swallowing and choking symptoms.

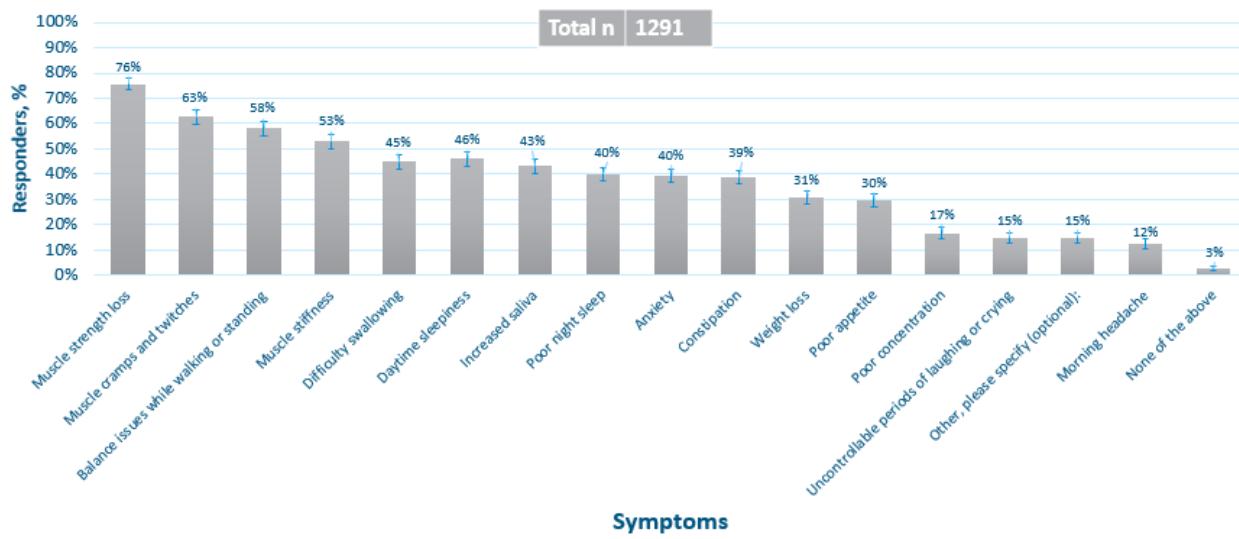


Figure 17. Additional Symptoms in the Past 2 Weeks³⁰

Survey respondents stated that they “cry from depression,” experience “extreme boredom,” “impatience with loss of function,” and “disbelief and anger at the slowness of the process of getting help.” Other respondents noted “muscles hurt a lot,” “balance issues later in the day,” “unable to move or communicate difficulty,” “feeling like she was always choking,” and “tired most of the time.” Several

³⁰ Error bars represent 95 percent confidence intervals.

respondents noted “difficulty breathing,” “incontinence,” “increased secretions,” and pain in abdomen, legs, back, hips, knees, and neck.

Other Additional Symptoms in Past Two Weeks

“wish death would come fast”

“Could not use her legs or arms”

“Horrible [unbelievable] PAIN”

“Everything was gone in her spirit. She gave up”

“He could not communicate”

“Difficulty holding up head”

“feels like a bother to others”

“Began to lose his voice”

“Choking on saliva”

ii. Impact of ALS on Daily Life

Lifestyle Changes Since Diagnosis

Survey respondents were asked to select any lifestyle changes that have been made since being diagnosed with ALS.

Question for Individuals with ALS:

How have you changed your lifestyle since being diagnosed with ALS? (Please select all that apply)

- I have not changed anything
- I work less
- I stopped working
- I travel more
- I travel less
- I socialize more
- I socialize less
- I spend more time with family
- I spend less time with family
- I gave up my favorite activity (input box: What was your favorite activity?)
- I joined an ALS support group
- I spend more time online
- I spend less time online
- I spend more time reading
- I spend less time reading
- Other

Question for Caregivers:

How has the individual's lifestyle changed since being diagnosed with ALS? (Please select all that apply)

[Same options as for individuals with ALS; presented as "He/she..."]

Nearly all of the survey respondents (97 percent) reported that their lifestyle had changed (**Figure 18**). The largest impacts to lifestyle reported were less time doing household chores (87 percent) and less time traveling (82 percent). One respondent stated, “Used to travel all the time. Now it is way too difficult/scary for her, even with help. Bathroom/shower accommodations & wheelchair access is limited in places where she'd want to stay. So travel has ceased.”

About three-quarters of all survey respondents reported less time working or at school (79 percent), socializing (77 percent), and doing one’s favorite activity (77 percent).

The survey respondents who reported an impact on work or school indicated that they retired (37 percent) or stopped working or attending school (36 percent). Respondents provided the following explanations: “she retired once she had difficulty walking,” “unable to work due to slurred speech,” “by noon I’ve burn[ed] all my energy and have to nap,” and “no use of hands.”

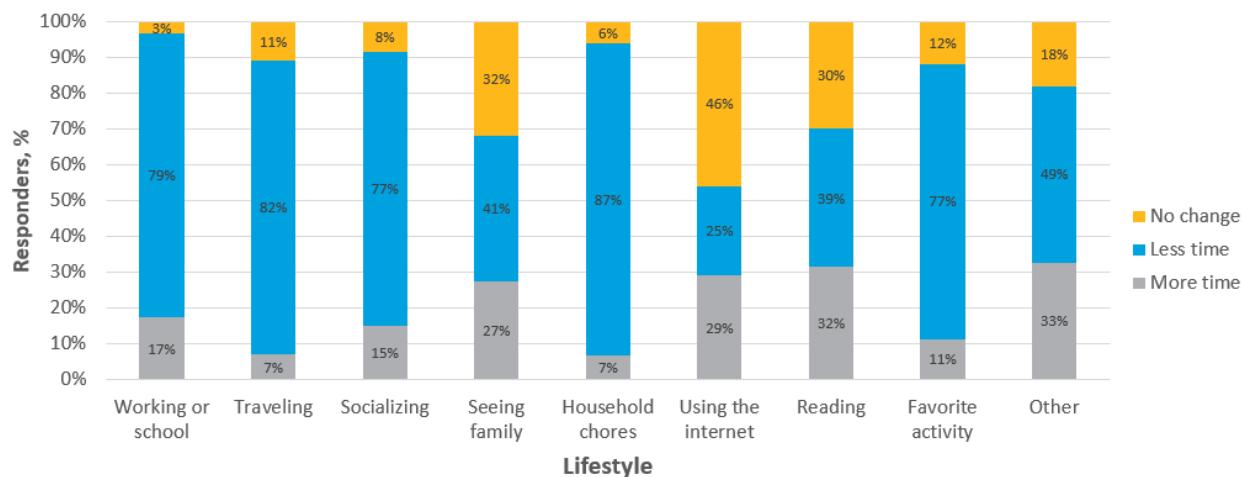


Figure 18. Lifestyle Changes Since Diagnosis

Other Lifestyle Changes Since Diagnosis

“Hard to socialize with when [you] can’t eat or talk”

“Used to get out for lots of events/activities. Now can only go where parking/bathroom facilities are adequate for wheel chairs.”

“I enjoy playing piano, but it is not easy getting into that room and rising from the piano bench, so I need to do this when someone is available to help me get up.”

“used to LOVE square dancing and has been unable to dance for a year now...used to several times a week”

“Any physical activity, walking, gardening, piano, art, work, stairs, going places alone”

“Can no longer participate in daily activities outside of the home”

“Can’t work at home on any type of project due to shortness of breath and muscle weakness”

“He used to love his part time bar tending jobs and had to give them up.”

Survey respondents were asked what is the one thing the individual with ALS wishes they could still do, or what is the one thing the caregiver of an individual with ALS wishes the individual could still do.

Question for Individuals with ALS:

What is one thing you wish you could still do?

Question for Caregivers:

What is one thing you as the caregiver wish the person could still do but can no longer do because of ALS?

The highest proportion of individuals with ALS who responded to this question indicated that they wished they could walk (**Figure 19a**), whereas the highest proportion of caregivers indicated that they wished the person for whom they cared could still talk (**Figure 19b**).

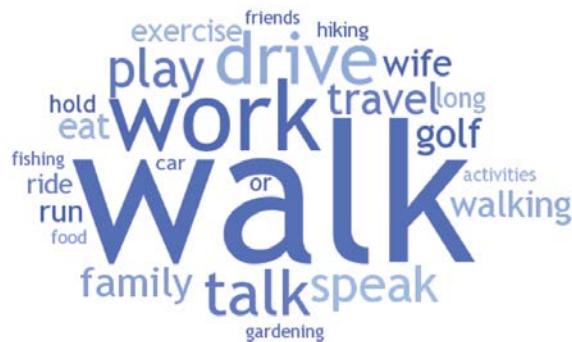


Figure 19a. Responses from Individuals with ALS to “What is one thing you wish you could still do?”



Figure 19b. Caregiver Responses to “What is one thing you as the caregiver wish the person could still do but can no longer do because of ALS?”

One Thing Individuals with ALS Wish They Could Still Do or the One Thing the Caregiver Wishes the Individual With ALS Could Still Do

"At this point, my ALS has primarily affected my legs. Skiing was extremely important to me, but I can accept not be able to do this. I would have to say being mobile is the greatest loss since it affects my ability to do the everyday task of yard work, assisting around the house, and shopping. These are now burdens placed on my wife."

"ALS has practically taken everything; I have no wish to just get "one" thing back. It's been a slow progression, going on 8 years. At year 2, when I was told I had ALS to long and wouldn't be selected for any clinical trials, that's when I wished the ALS would finish [its] job."

"Be independent, was out on my own since I was 14. Helped raise my brother and sister, raised my own children. I have 12 grandchildren very active in their lives. Volunteered at church, helped family..... now it all upside down. Being forced to be still and have others help me do everything, is not my idea of living"

"Communication at the end, unable to adequately use the eye gaze or verbally communicate. Could see he was getting frustrated with the inability to communicate."

"Continue to work; drive a car; walk up and down stairs; cook a meal; walk out the dog; tender the garden; walk with confidence; bathe and get dressed without help."

"**DRIVE A CAR!** I really miss that independence."

"Drive a car, truck, push a lawn mower, write a letter, hug my wife, hold her hand! And anything else that you have to have muscles!!"

"Drive. Go any place, outside of my home, and not have to worry about where to park, how high the curb is to the sidewalk, can I be easily seated in a restaurant without getting in someone's way or someone getting in mine. Not being able to go anywhere without someone with me to open doors, get something off the top shelf at the grocery store. The list is long."

Effects on Level of Independence

Survey respondents were asked to provide information about how ALS has affected individuals' level of independence. This question and response options was based off the ALS Assessment Questionnaire 40 (ALSAQ-40) ADL/Independence items.

Question for Individuals with ALS:

How has ALS affected your level of independence? Select any of the below that you have.

- Difficulty using arms and hands*
- Difficulty turning and moving in bed*
- Difficulty picking things up*
- Difficulty holding books and turning pages*
- Difficulty writing clearly*
- Difficulty doing jobs around the house*
- Difficulty feeding myself*

- Difficulty combing hair*
- Difficulty getting dressed*
- Difficulty washing at hand basin*

Question for Caregivers:

*How has ALS affected the individual's level of independence? Select any of the below that you have.
[Same options as for individuals with ALS]*

Survey respondents most frequently reported having difficulty doing jobs around the house, picking things up, getting dressed, and using arms and hands (**Figure 20**).

Individuals with ALS and their caregivers reported similar effects of level of independence. Eighty-eight percent of individuals with ALS and 84 percent of caregivers reported that the person with ALS had at least one difficulty with daily living. Approximately 40 percent of survey respondents selected all ten difficulties.

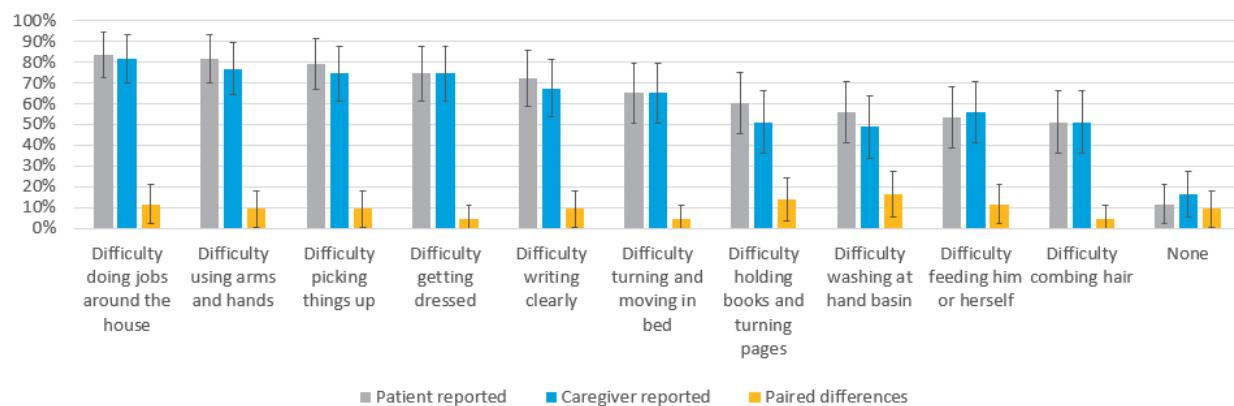


Figure 20. Difficulties with Everyday Tasks: Primary Analysis³¹

One caregiver provided the following description of how an individual's ALS symptoms progressed over time, "At diagnosis in October 2008 she had experienced atrophy of the muscles in her palms below her thumbs, which resulted in difficulty squeezing the gas pump handle. Within a year, she couldn't hold a full gallon of milk. In 2010, she could barely write her name, she sold her car and stopped trying to paint. By Summer 2011 she had lost her fine motor skills and started slurring her speech. When she was admitted to a Nursing Home in November 2011, she could still talk somewhat & feed herself with a spoon (but messy, like she would drop the spoon or not hit her mouth with the food). She died in February 2012."

The survey data reflected a trend in greater effect on independence amongst those with a longer disease progression (five or more years since first symptom) (**Figure 21**). Though, even early in the disease, there is a high symptom burden that only continues to grow with disease progression over time. Of the respondents for whom less than five years had elapsed since first symptom, 34 percent checked all 10 difficulties and 95 percent checked at least one difficulty. Of the respondents for whom

³¹ Error bars represent 95 percent confidence intervals.

five or greater years had elapsed since first symptom, 52 percent checked all 10 difficulties and 97 percent checked at least one difficulty.

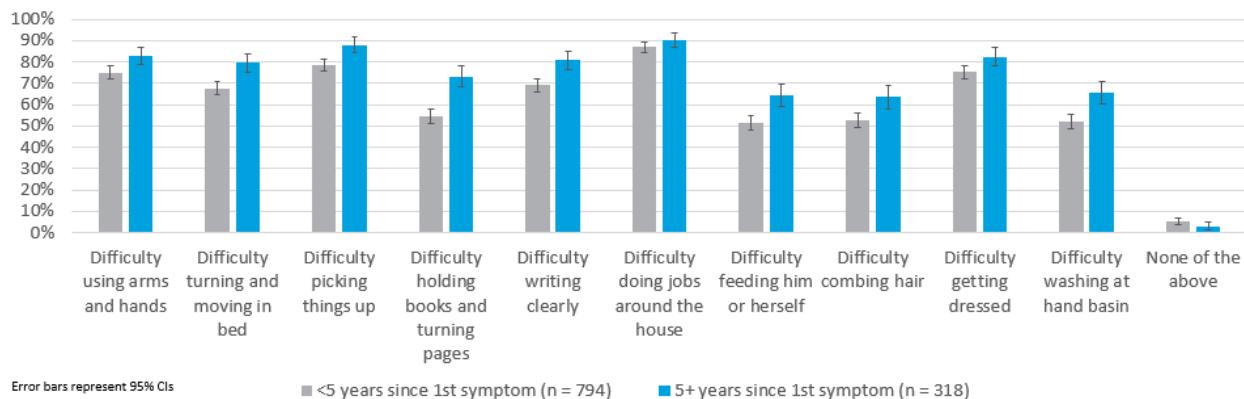


Figure 21. Difficulties with Everyday Tasks: Time Since First Symptom³²

Survey respondents were asked to elaborate on how the person's independence has been affected by ALS.

Question for Individuals with ALS:

If desired, please elaborate on how your independence has been affected by ALS.

Question for Caregivers:

If desired, please elaborate on how the individual independence has been affected by ALS.

Nearly half of the respondents (46 percent) indicated that they have substantial loss of independence or no independence. Respondents reported difficulty with walking, mobility, driving, dexterity, and everyday tasks.

Stress Levels

Survey respondents were asked to rank stress level of the individual with ALS over the last two weeks.

Question for Individuals with ALS:

Please rank your stress level over the last 2 weeks.

- Maximum
- High
- Medium
- Low
- None

Question for Caregivers:

Please rank the individual's stress level over the past two weeks.

[Same options as for individuals with ALS]

³² Error bars represent 95 percent confidence intervals.

Overall, individuals with ALS and their caregivers mostly reported low and medium stress levels on a scale of 1-5, with an overall average stress level of 2.7 (**Figure 22**). The highest stress level (5; Maximum) was reported primarily by caregivers of individuals with ALS who have passed away, which may be because caregivers of individuals with ALS who have passed away were reporting stress levels for the last two weeks of the life of the individual who passed away.

How Independence Has Been Affected by ALS

“He can no longer do anything for himself and it is devastating to his self esteem. As someone who was very involved and active, it is almost unimaginable that he is so imprisoned by his own body.”

“Slowly took everything from him starting with the legs then his arms to become fully dependent for all aspects of life-eating, dressing, bathing, communication, etc.”

“ALS is like death by a thousand paper cuts - it takes bits of your independence slowly and consistently. Two months ago I could pick up a coffee mug easily. Today, I have to be careful doing it because I feel some weakness while doing it.”

“All my life I've been a diy guy and now to [lose] the ability to use my hands to fix things has made me feel useless.”

“‘Difficulty’ is too mild. I am essentially quadriplegic with minimal arm movement that allows me to press the communicator control button.”

“I feel like I'm reverting to childhood. I have been a very active and independent adult, and I'm losing both.”

“I can function alone, however, simple tasks take forever to complete. Things like pulling up pants, putting on socks/shoes.”

“I have gone from working full time to completely dependent, no use of extremities at all and dependent on a BiPAP to breathe. My husband and I had our own business. Now the business is run out of our house by my husband with no help from me. Obviously, our income has gone down dramatically.”

“I have to be careful not to fall which limits my freedom to do so many chores and picking up things. Because of bathroom issues, I don't freely do things like going out to shop or attend events like I used to. It is not easy to get into public bathrooms without assistance.”

“Loading and unloading store purchases in store and at home is difficult. Use of anything demanding a handle to be gripped, pulled or pushed, or a button to be pushed with any effort is a potential limit. Raising from the ground to a standing position is impossible without a stair or series of handrails. Balance with any product in hand is challenging.”

“My husband and I both worked full-time jobs until he retired and I had to quit my job as a banker due to not being able to speak clearly. I had always taken pride in being independent. I cannot drive, prepare . . . our food, bathe myself, dress myself nor go to bathroom on my own. I can't

walk. I sleep in a recliner which my husband has to put me into and get me out. My independence is gone."

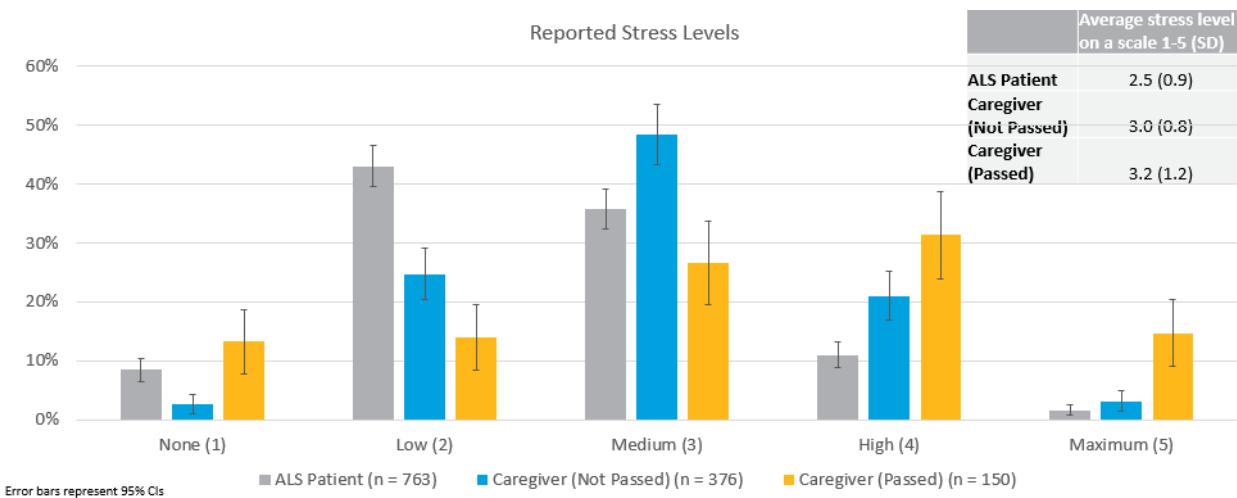


Figure 22. Stress Levels: Primary Analysis³³

On a scale of 1-5, caregivers reported only slightly higher stress (0.2 points) for the person with ALS for whom they care than individuals with ALS reported (**Figure 23**).

One individual with ALS described one source of stress, "My greatest need is finding quality caregivers and finding the money to pay them. This creates a lot of stress and diminished quality of life." One caregiver stated, "He used running and activity to manage stress at work and now no longer has that as an outlet."

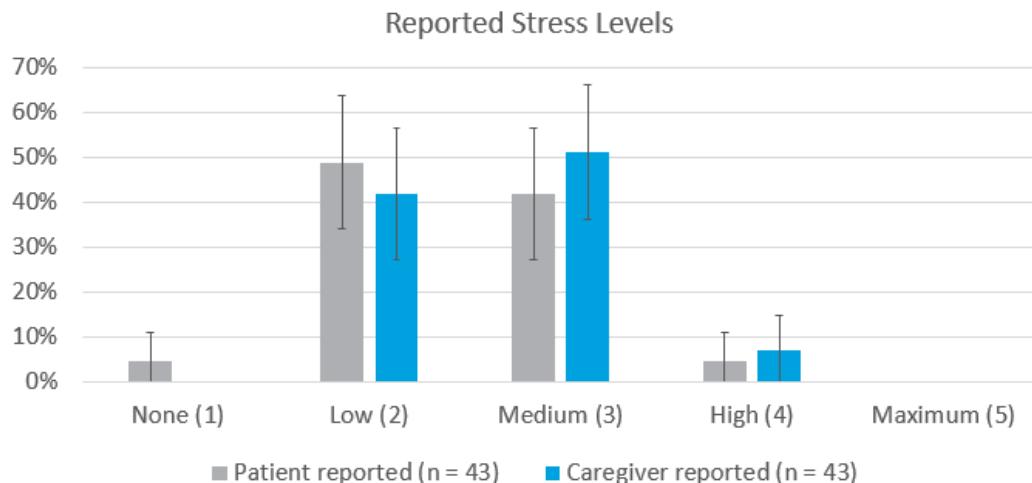


Figure 23. Stress Levels: Patient Reported vs. Caregiver Reported³⁴

³³ Error bars represent 95 percent confidence intervals.

³⁴ Error bars represent 95 percent confidence intervals.

Future Fears

Survey respondents were asked to provide information about future fears.

Question for Individuals with ALS:

Do you have fears about the future?

- Yes
- No

Question for Caregivers:

Does the individual have fears about the future?

[Same options as for individual]

The majority of survey respondents (69 percent) reported having fears about the future (**Figure 24**).

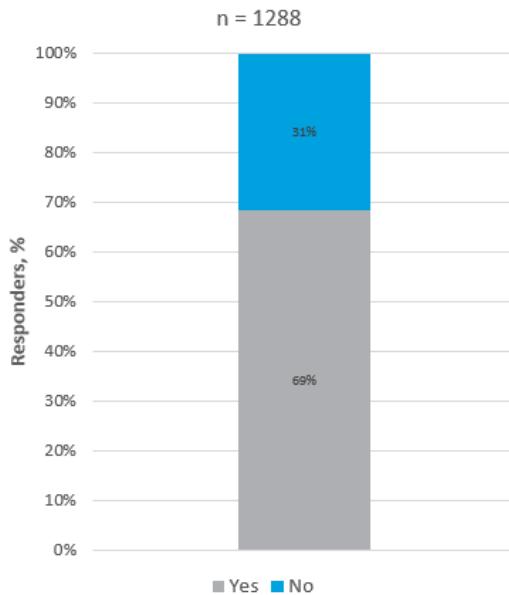


Figure 24. Portion of Survey Respondents Who Have Fears About the Future

The 69 percent of respondents who reported having fears about the future were asked to provide information about their most significant fears.

Question for Individuals with ALS:

What are your most significant fears? (Select your top 3)

- Spending the family's savings on my medical care
- Leaving my family too soon
- Dying from respiratory failure
- Choking to death on food or liquid
- Dying from an injury sustained by falling
- Being isolated from friends and family
- Being tracheotomized without my consent
- Other

Question for Caregivers:

*What are the individual's most significant fears? (Select the individual's top 3)
[Similar options as for individuals with ALS; stated as "his/her" where applicable]*

Of the 69 percent of survey respondents who reported having fears about the future, the fears most frequently reported were related to dying, "leaving family too soon," followed by "dying from respiratory failure" (**Figure 25**). The next most reported fear was "spending the family's savings on medical care." There was relative concordance in the responses to questions about the types of future fears between caregivers and individuals with ALS.

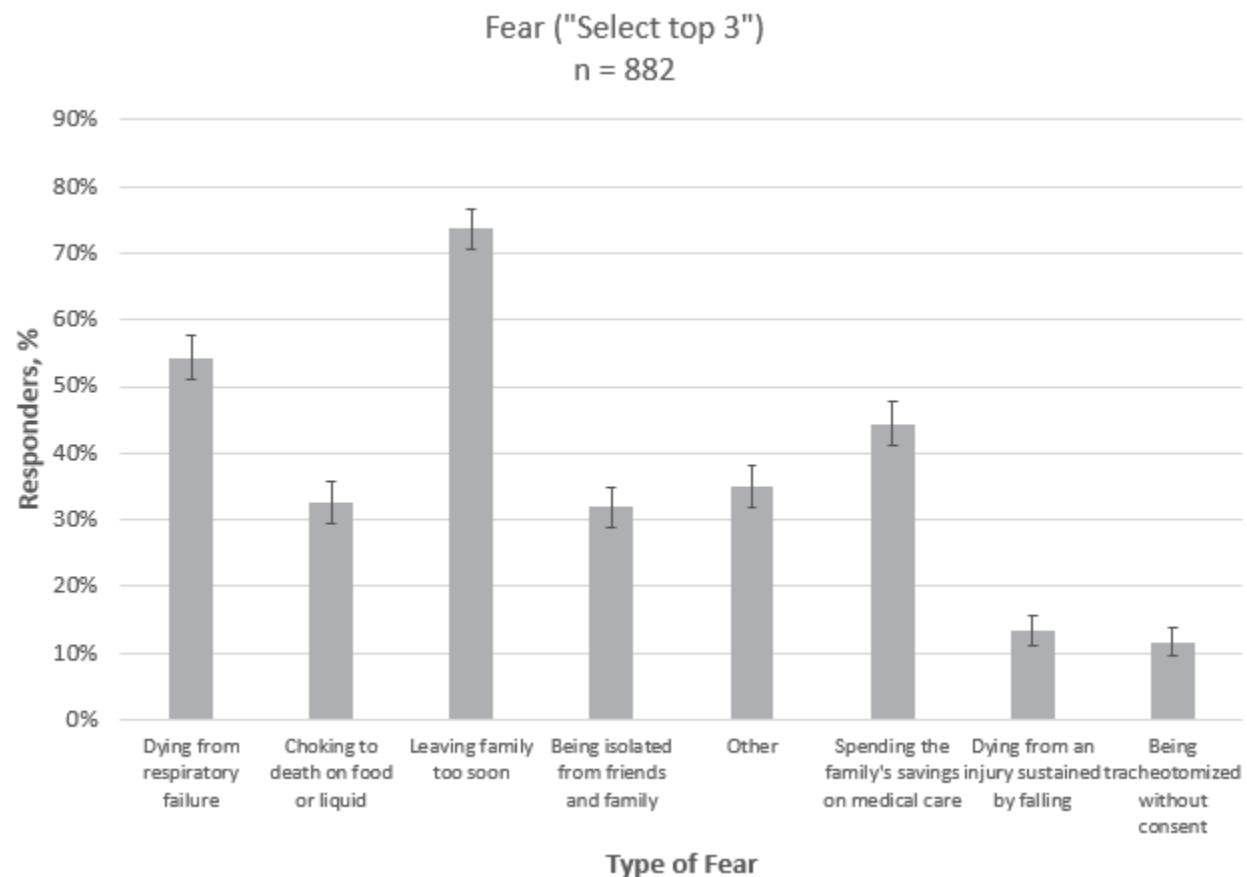


Figure 25. Types of Future Fears³⁵

The most frequently reported fears provided in response to the "Other" option, from the respondents who selected "Other," were "burden" and "independence loss" (**Figure 26**).

³⁵ Error bars represent 95 percent confidence intervals.

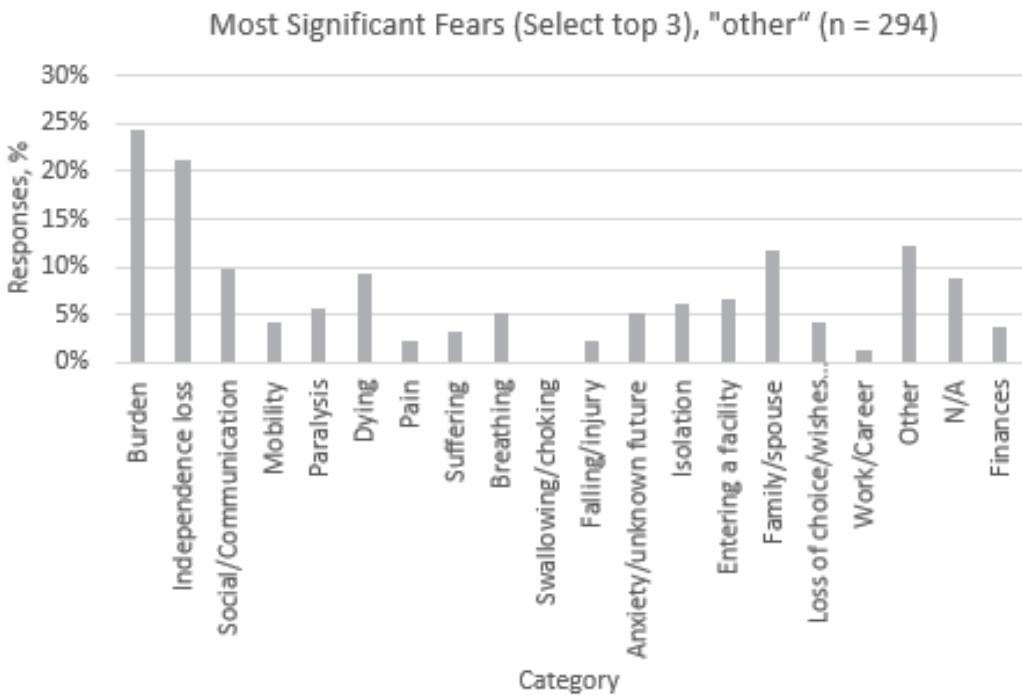


Figure 26. Other Future Fears

Survey respondents were given the opportunity to elaborate on their choices in narrative form.

Question for Individuals with ALS:

Please elaborate on your choices (not required)

Question for Caregivers:

Please elaborate on the individual's choices (not required)

Elaboration on Future Fears

“I don’t want to die in an institution”

“Not dying soon enough; don’t want to live when totally paralyzed”

“Since we are young (30’s) I worry about my wife being able to move on, find happiness, and feel ok about finding someone else.”

“Fear that when I am ready to die, my wishes will not be honored.”

“Feel guilty not able to contribute at home. Frustrated.”

“I have worked for the same company for 23 years, I’m dreading the day I am no longer able to drive myself to work.”

“Fear of the unknown. When and how will the fatal event occur?”

“Very fearful of a slow drowning death because of inability to breathe”

“We have three young children, my husband fears dying before they are adults and missing milestones like weddings and grandchildren.”

“It's scary being told that I'm going to die soon and nobody can help you get better.”

“I'm sad that I cannot fully participate in family activities. I worry that I won't live to see my son graduate from medical and get married.”

“I have a two-year old daughter and I fear I'm missing out on important childhood activities. Like I couldn't take her trick-or-treating.”

“I fear most being kept alive when my situation has become hopeless!”

“I am only 50, I have two young sons, I am fearing that I will die from ALS before seeing them grow up. Terrified at the thought of being paralyzed or unable to speak, and becoming a burden on my wife.”

iii. Change to Symptoms Over Time

Survey respondents reported a high impact of disease from early in disease onset (**Figure 27**). On average, 6 activities of daily living (ADLs) were affected in the first 6 months after onset of symptoms, compared to approximately 8 affected ADLs more than five years after onset of symptoms.

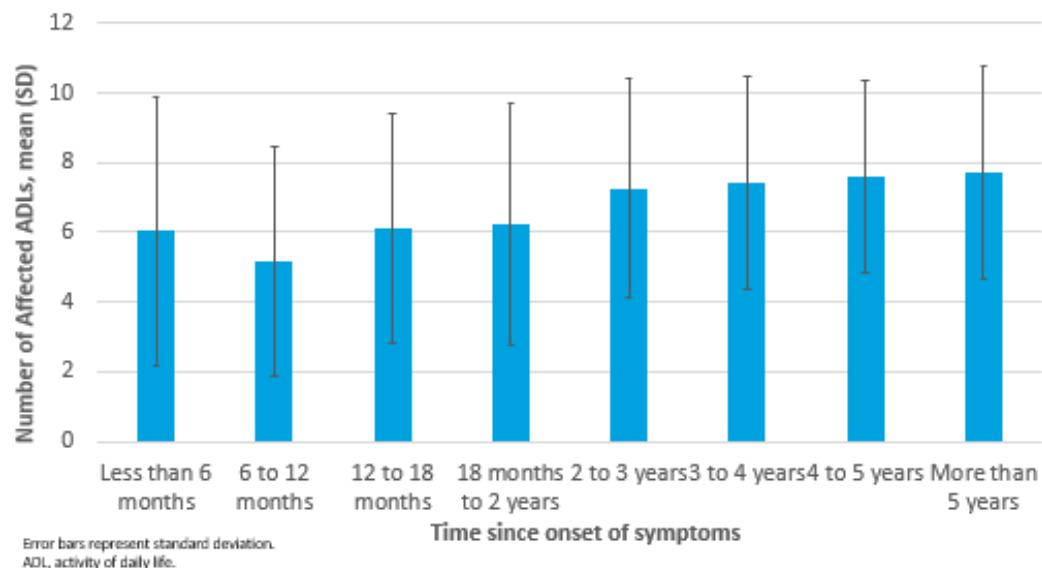


Figure 27. Average Number of ADLs Affected by Time Since First Symptoms (10 Maximum ADLs)³⁶

³⁶ Error bars represent 95 percent confidence intervals.

C. Current Approaches to Living with ALS

i. Current Treatments and Other Approaches for ALS

Survey respondents were asked to indicate the prescription drugs they have tried, are currently taking, or have tried in the past.

Question for Individuals with ALS:

What prescription drugs are you taking or have you tried? (Include medications that are prescribed off-label)

Drug	Tried	Taking Currently	Comment
RILUTEK (riluzole)			
RADICAVA (edaravone)			
Baclofen			
Tizanidine			
Amytryptaline			
Anti-depressant medication			
Anti-anxiety medication			
Other [enter]			
Other [enter]			
Other [enter]			

Question for Caregivers:

What prescription drugs is the individual taking or has the individual tried? (Include medications that are prescribed off-label)

[Same options as for individuals with ALS]

The prescription drugs that the highest proportion of individuals with ALS reported as currently taking were Rilutek (riluzole), anti-depressant medications, and other prescription drugs not listed in the survey question options (**Figure 28**). A very high proportion (more than 60 percent) of individuals with ALS tried, but are not currently taking, Radicava (edaravone), Neudexta (dextromethorphan/quinidine), Baclofen, Tizanidine, or Amytryptaline.

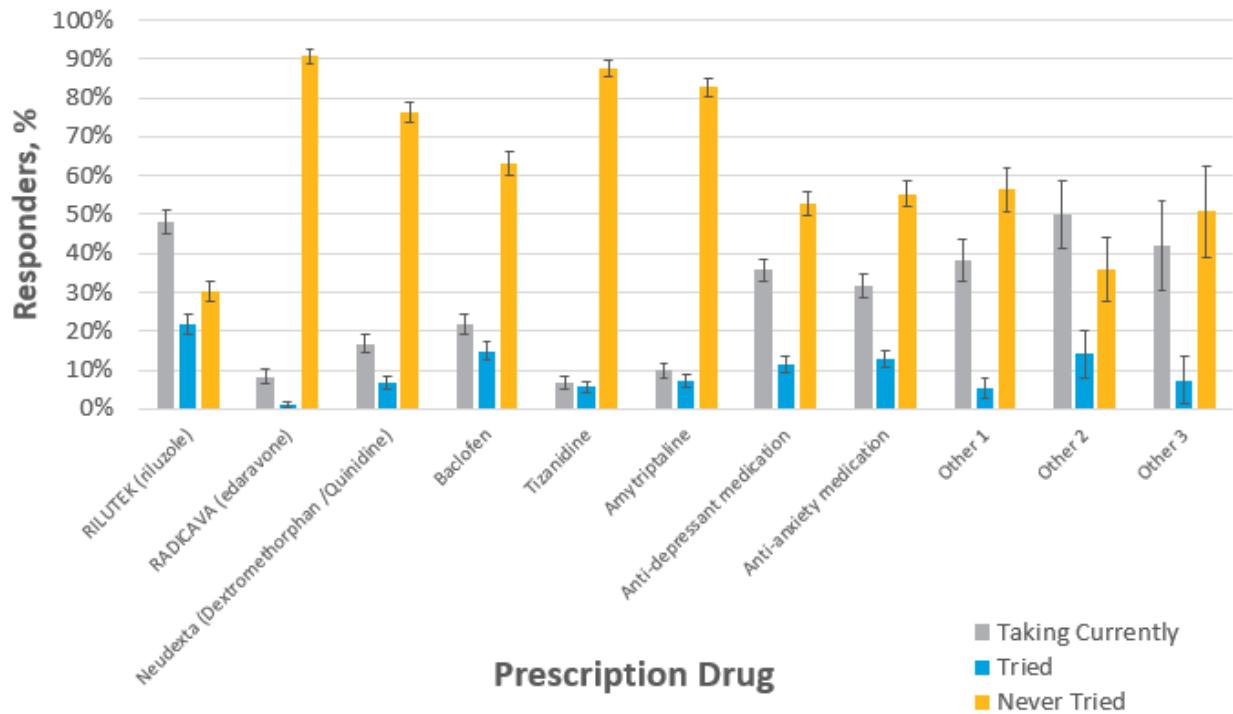


Figure 28. Prescription Drug Use³⁷

In response to the “Other” option, survey respondents reported using gabapentin, cannabis, glycopyrrolate, tirasemtiv, atropine, scopolamine, morphine, mexiletine, diazepam/Valium, vitamin B12, albuterol, and Ambien.

Survey respondents were asked to indicate whether they were taking any nutritional supplements or vitamins, or whether he/she has a PEG tube.

Question for Individuals with ALS:

Do you take nutritional supplements or vitamins, or do you have a PEG tube? Select from the list or enter

- Daily vitamins & minerals
- Lusasin/Lunarich
- Deanna Protocol
- PEG tube
- Others

Question for Caregivers:

Does the individual take nutritional supplements or vitamins, or does he/she have a PEG tube? Select from the list or enter

[Same options as for individuals with ALS]

³⁷ Error bars represent 95 percent confidence intervals.

The majority of individuals with ALS represented in the survey data (62 percent) take daily vitamins and minerals. About one-quarter (26 percent) of individuals with ALS represented have a PEG tube. Other non-prescription drug treatments listed include protein drinks, low-carb diets, essential oils, fish oil, CBD oil, and probiotics (**Figure 29**).

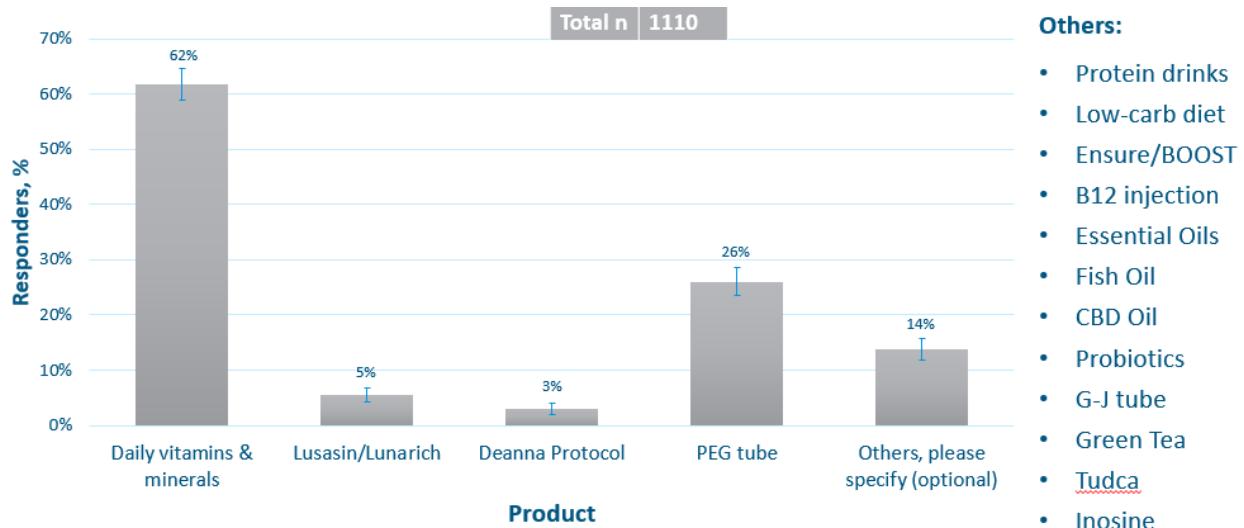


Figure 29. Supplements, Vitamins, Peg Tube Use³⁸

Survey respondents were asked to identify the types of assistive devices they use.

Question for Individuals with ALS:

What types of therapeutic strategies and mobility devices for mobility are you currently using, plan to use in the future as your needs change, or have you used in the past but are no longer using (and how long ago)? Please check all that apply.

	<i>Currently using</i>	<i>Plan to use in the future as my disease progresses and my needs change</i>	<i>Have used in the past but are no longer using</i>	<i>If checked used in the past, how long ago?</i>
<i>Nothing</i>				<u> </u> year(s) ago
<i>Regular Exercise</i>				<u> </u> year(s) ago
<i>Physical therapy</i>				<u> </u> year(s) ago
<i>Cane(s) or walking sticks</i>				<u> </u> year(s) ago
<i>Walker</i>				<u> </u> year(s) ago
<i>Manual wheelchair</i>				<u> </u> year(s) ago
<i>Motorized wheelchair</i>				<u> </u> year(s) ago
<i>Other [Enter]</i>				<u> </u> year(s) ago
<i>Other [Enter]</i>				<u> </u> year(s) ago
<i>Other [Enter]</i>				<u> </u> year(s) ago

³⁸ Error bars represent 95 percent confidence intervals.

Question for Caregivers:

What types of therapeutic strategies and mobility devices for mobility is the individual currently using, planning to use in the future as his/her needs change, or has the individual used in the past but is no longer using (and how long ago)? Please check all that apply.

[Same options as for individuals with ALS]

Over 70 percent of survey respondents indicated that they currently use an assistive device not listed in the survey answer options (“Other”). Of the respondents who indicated they were currently using each of the other listed assistive devices, the responses were fairly evenly divided among the various options (**Figure 30**).

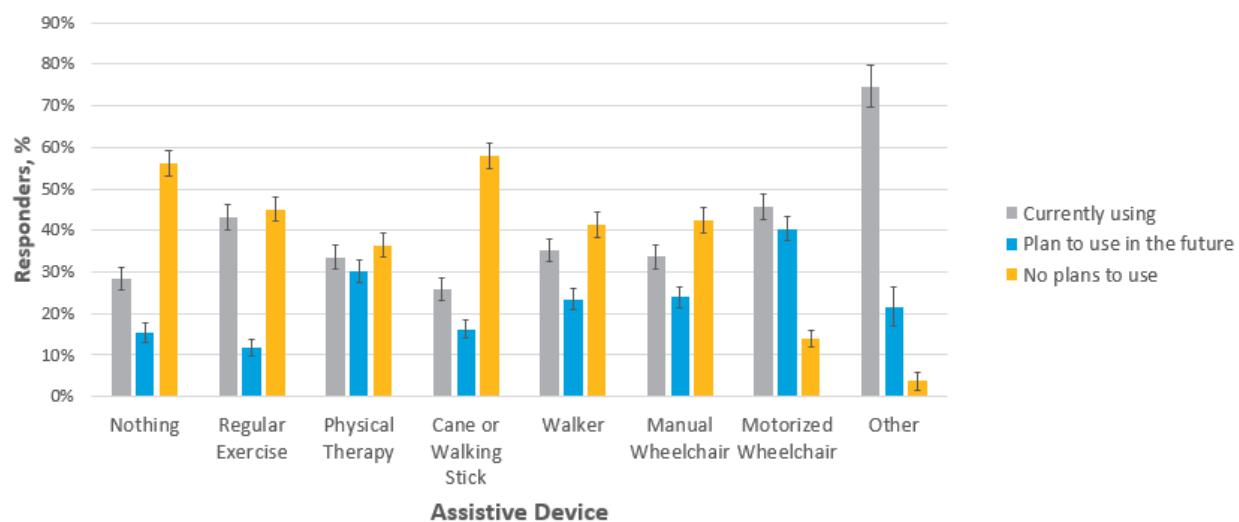


Figure 30. Assistive Devices: Strategies for Motility³⁹

Survey respondents were asked to indicate whether they use any breathing support, and if so, what type of breathing support is utilized.

Question for Individuals with ALS:

Do you require respiratory (breathing) support?

- No respiratory support*
- Non-invasive ventilation (Bi-Pap, C-PAP, trilogy) only at night*
- Occasional use of non-invasive ventilation (Bi-Pap, C-PAP, trilogy) during the day or night*
- Non-invasive ventilation (Bi-Pap, C-PAP, Trilogy) all night and occasional use during the day*
- Continuous use of BiPAP® at night and during the day (nearly 24 hours per day)*
- Mechanical ventilation by intubation or tracheostomy*
- Other(s)*

³⁹ Error bars represent 95 percent confidence intervals.

Question for Caregivers:
Does the individual require respiratory (breathing) support?
[Same options as for individuals with ALS]

The majority of individuals with ALS represented in the survey data (53 percent) reported use of some form of respiratory support (**Figure 31**).

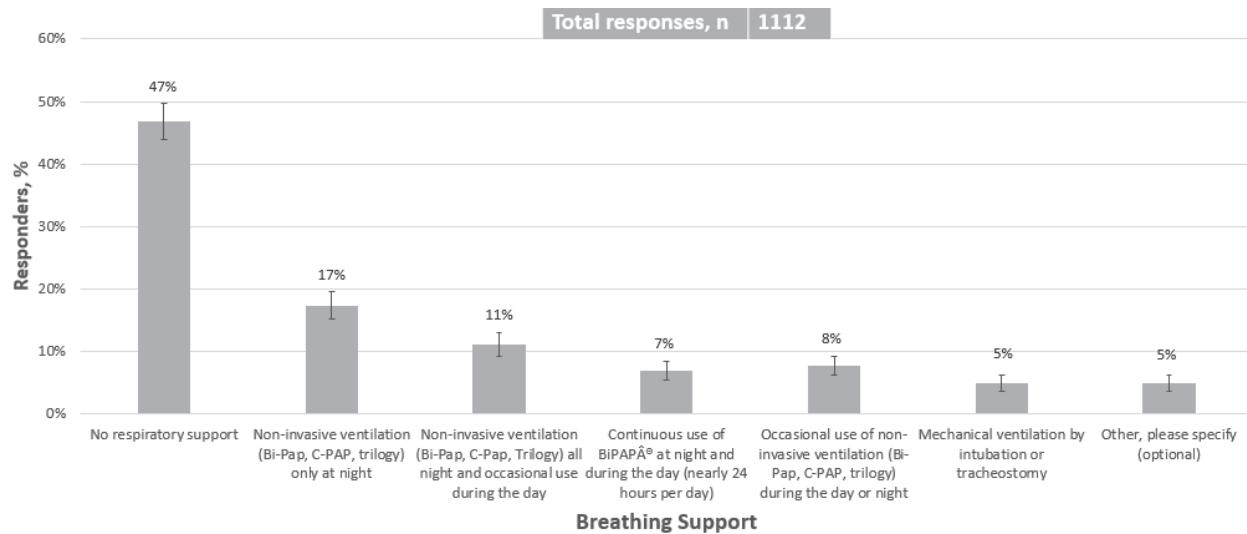


Figure 31. **Assistive Devices: Breathing Support⁴⁰**

Survey respondents were asked to elaborate, in narrative form, on how the individual's use of breathing support impacted his/her life.

Question for Individuals with ALS:
How does your usage of non-invasive ventilation impact your life right now?

Question for Caregivers:
How does the individual's usage of non-invasive ventilation impact his/her and your life right now?

The largest proportion of individuals with ALS and caregivers who responded to this question noted that ventilation is an inconvenience (22 percent), but allows for better sleep (15 percent). One respondent stated, it "helps me breath [sic] easier at night when lying down," and another respondent stated, "it limits my ability to be able to sleep all night and to do things I was once able to do." Other respondents noted that breathing support causes less sleep (6 percent). Ten percent of respondents stated that breathing support helps with breathing, and 9 percent stated that it helps generally.

Impact of Non-Invasive Ventilation

"We are only able to go as far as hoses and machines can travel. Trips outside receive stares and questions. My husband just shrugs this off but I know he is uncomfortable with the attention."

⁴⁰ Error bars represent 95 percent confidence intervals.

“It is in the only thing that kept him alive during the last month”

“I feel like it is actually making me more dependent on it, but there are times when I feel like it is essential to use.”

“I hate it. I can not communicate with it on. It is ncomfortable [sic].”

“It is the best thing that has happened for me. Sleep well 7 to 9 hours on the Bi Pap.”

“At the time the mask bothered his face, created an awful never-healing sore on bridge of nose. Hard to decipher what he was saying with mask on.”

“Don't like the daily maintenance required, so reluctant to use every night”

“He is having a hard time with the forced air machine they gave us. He gets panic attacks and feels smothered by masks since he can't raise his hands to remove it himself.”

“I have more energy during the daytime and do not require naps like I did before using the machine.”

“Makes it harder to do things as I'm tied to a machine, but a blessing as I know I can't breathe without”

Individuals with ALS and caregivers for individuals with ALS who did not plan to use assistive devices were asked to indicate their reason for not wanting to use such devices.

Question for Individuals with ALS:

If you do not plan to use these assistive devices, what is your rationale?

- I want the disease to run its natural course and I do not want to artificially extend my life.*
- The assistive device will compromise my quality of living beyond which I am willing to accept*
- I do not want to subject my family to the emotional burden required*
- I do not want to subject my family to the financial burden required*
- Other _____*

Question for Caregivers:

If the individual does not plan to use these assistive devices, what is this individual's rationale?

[Same options as for individuals with ALS]

The largest proportion of individuals with ALS represented by the survey data who did not plan to use assistive devices indicated that their reason was “ALS has not progressed that far yet” (46 percent) (**Figure 32**).

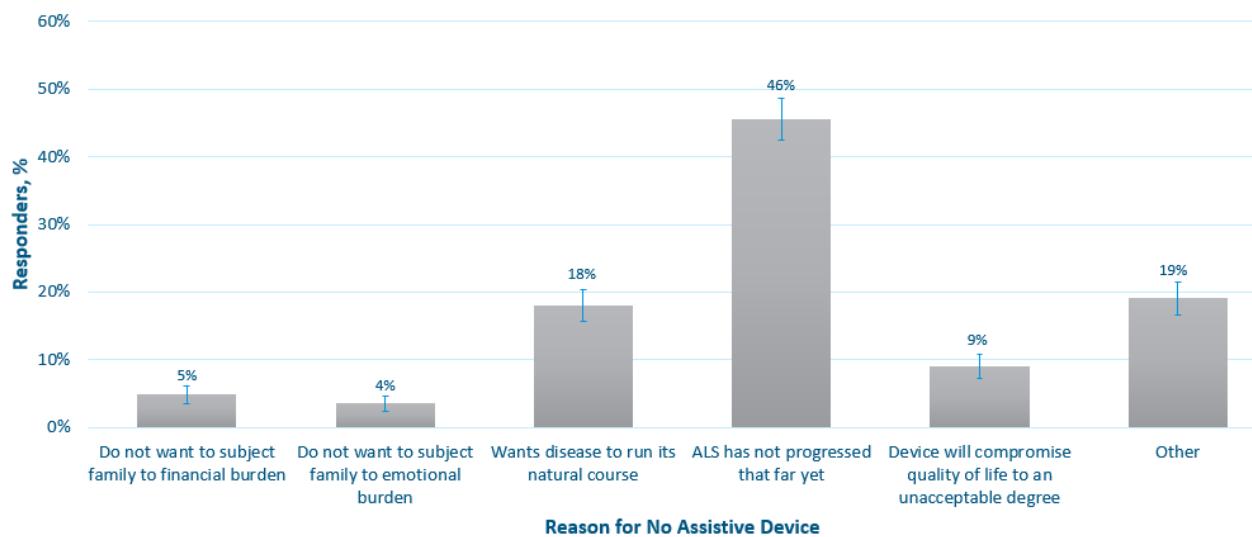


Figure 32. Assitive Devices: If None, Why Not⁴¹

Survey respondents also provided the following explanations for not using assistive devices: “too late for me,” “I do not want any invasive treatment because I do not want to artificially extend my life,” “difficulty getting used to it may cause him to discontinue,” “patient was not informed about choices,” “does not want to be frozen and only able to move eyes,” and “wants to die.”

Other Reasons for Not Using Assistive Devices

“He did not want to continue with that quality of life. Unable to move, speak, eat, hug his loved ones.”

“He has already used all these devices. ALS has progressed passed this level.”

“Mostly because he has progressed beyond a cane and exercise takes to[o] much out him.”

“She has frontotemporal dementia which makes using some of these devices difficult.”

“Progressed past the point of using earlier devices”

ii. Management of ALS with Current Treatments

Survey respondents were asked to indicate how well current treatment regimens and lifestyle changes managed ALS symptoms.

Question for Individuals with ALS:

How well do you feel your treatment regimen and lifestyle changes manage your condition?

- Significantly*
- A lot*
- Somewhat*
- Not at all*

⁴¹ Error bars represent 95 percent confidence intervals.

Unsure

Question for Caregivers:

*How well do you feel the individual's treatment regimen and lifestyle changes manage the condition?
[Same options as for individuals with ALS]*

The survey responses reflect the fact that there is still room for improvement in finding treatments for persons with ALS. The largest portion of survey respondents stated that their treatment only somewhat manages their disease (**Figure 33**).

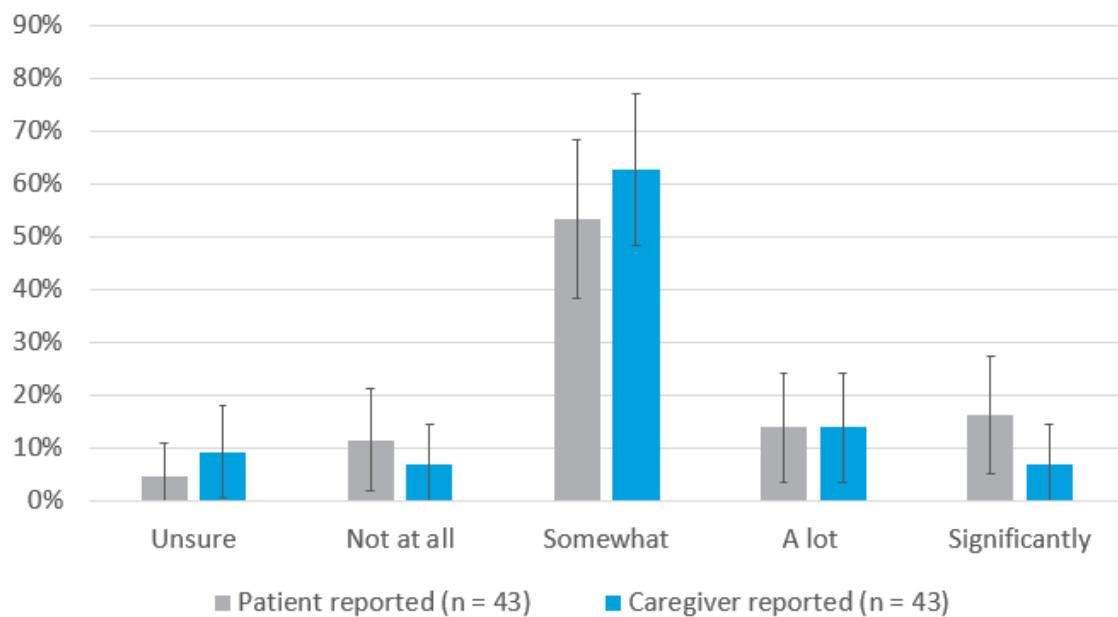


Figure 33. How Well Treatment Regimen or Lifestyle Manages ALS: Patient- vs. Caregiver-Reported⁴²

Those individuals with ALS for whom five or more years elapsed since first symptom reported that their treatment regimen was more effective than those who are earlier in their disease (**Figure 34**). This is reflected by the responses indicating that individuals' current treatment regimen or lifestyle significantly manages their disease. This difference is perhaps because the subgroup of those with fewer than five years since first symptom includes some individuals with more rapid early decline.

⁴² Error bars represent 95 percent confidence intervals.

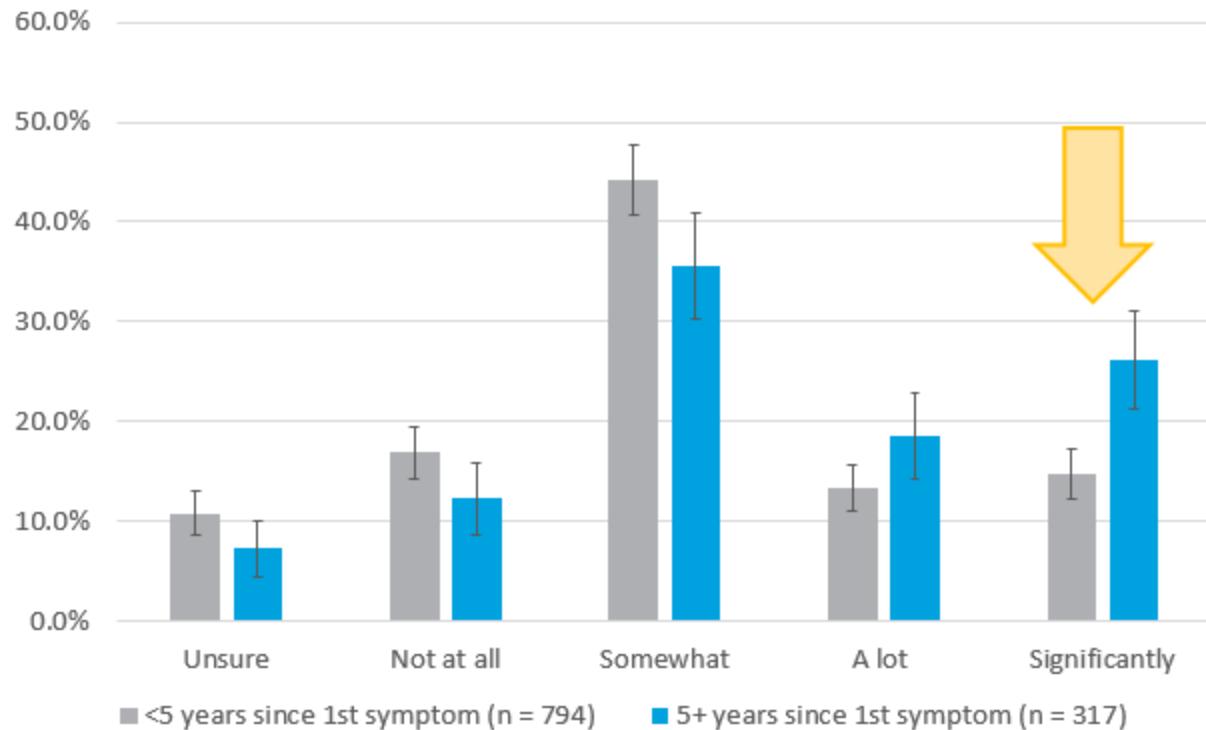


Figure 34. How Well Treatment Regimen or Lifestyle Manages ALS: Time Since First Symptoms⁴³

Survey respondents were asked to explain their selection in narrative form.

Question for Individuals with ALS:
Please explain your selection (optional)

Question for Caregivers:
Please explain your selection (optional)

Approximately 15 percent of respondents indicated that nothing helps their condition, while approximately 20 percent of respondents indicated that the current treatment and lifestyle changes help in general.

Explanation of How Well Treatment Manages ALS

“I feel like things I have done are helping, but I can also still feel myself going downhill”

“dont feel any change or improvement”

“Before I received braces, I was unable to walk and falling quite often. The braces have made me mobile again. I also was put on the drug neudexta which stopped the emotional lability I was having.”

“I believe my diet, exercise, outlook, and the clinical drug have helped significantly.”

⁴³ Error bars represent 95 percent confidence intervals.

“The options are non-existent, was thoroughly shocked at how little is known about the disease, who gets it and why. With all the money pouring in and for as long as the disease has been identified, treatment options are crap. The amount they extend a life is minimal, month or two MAYBE at best. Terribly frustrating, and it’s a HORRIBLE way to die!!”

“In the early stage if ALS the meds and assistive devices helped slow progression.”

“Any changes to manage is bittersweet, knowing the end is nearing is a heavy burden”

“Baclofen stopped the painful muscle cramping. Nortriptyline helps control the excessive laughing & crying. Antifungal cream & moisture barrier cream keeps skin in good condition.”

“Continual, gradual, and inevitable decline in health despite interventions”

“I am quite frustrated with the medical care regarding this diagnosis. There is little to offer and not much support or hope to get people involved with research or other options to make life easier. This has a huge impact on the immediate and extended family as it totally consumes their life. Treatments in the home, such as PT/OT have not been the greatest as they recommend many changes in the home for mobility, which is costly and involves getting contractors in the home but these changes only assist for a small amount of time.”

Survey respondents were asked to provide information about the downsides to their current treatments.

Question for Individuals with ALS:

What are the most significant downsides to the individual’s current treatments, and how do they affect his/her daily life? (Examples of downsides may include going to the hospital or clinic for treatment, time devoted to treatment, etc.) (Select the ones that best apply)

- None*
- Time it takes to receive treatment (e.g., infusion time)*
- Travel to go to the hospital/clinic for treatment*
- Common side effects of treatment regimen*
- Severe, rare side effects of treatment regimen*
- Cost, not covered by health insurance*
- Cost, after coverage by health insurance (e.g. co-payments/co-insurance, deductibles, etc)*
- Other [ENTER]*

Please explain your selections

Question for Caregivers:

What are the most significant downsides to the individual’s current treatments, and how do they affect his/her daily life? (Examples of downsides may include going to the hospital or clinic for treatment, time devoted to treatment, etc.) (Select the ones that best apply)
[Same options as for individuals with ALS]

Survey respondents indicated that there is little improvement from current treatments or that they are not on any treatment.

Explanation of Most Significant Downsides

“They only assist dying”

“Feel like I am just sitting here letting ALS slowly kill me. No treatments”

“Ineffective treatment. Since it was diagnosed there has been no hope to slow progression, there could be better communication to the patient and caregivers as to how the disease affects a person. As the disease progresses it would have been beneficial for the ‘experts’ to explain the ‘milestones’ and what can be expected next. Despite the bad news it allows a person with the disease to mentally prepare for the challenge as well as the caregiver.”

“With my motor wheelchair we now have to hire a handicap van and that is costing us almost \$200 for one trip to doctor.”

“Schedule of eating / not eating in concert with medicine guidelines”

“It is tiring waiting at the ALS clinics. Medicine side effects have been a big problem.”

“No treatment really, nothing to improve the condition, jus[t] kept him comfortable”

“The treatments I currently am involved in have little to no impact on my lifestyle or the disease.”

“Travel for a person with ALS to get a daily infusion is [unnecessarily] burdensome.”

“The worst thing is that nothing helps or makes any difference at all”

“We are currently not receiving any outside treatments -- haven't since 2015, other than then [breathing] machines.”

D. Preferences for Future Therapies for ALS

Survey respondents were asked to choose the top three ALS symptoms or functional impairments that they would like treatment to beneficially impact.

Question for Individuals with ALS:

Which ALS symptom or functional impairment do you want treatment to beneficially impact? Please rank your top 3 from least (1) to most (3) important.

- Breathing/respiratory function*
- Cognitive ability – focus and thinking*
- Daily self-care*
- Ease the overall burden of ALS*
- Mobility*
- Muscle weakness/spasticity*
- Overall mental health*
- Overall physical function*
- Pain*

- Relationships
- Sleeping
- Speaking/Communication
- Stop the progression of ALS
- Swallowing
- Other [ENTER]
- Other [ENTER]
- Other [ENTER]

Question for Caregivers:

*Which ALS symptom or functional impairment does the individual want treatment to beneficially impact? Please rank your top 3 from least (1) to most (3) important.
[Same options as for individuals with ALS]*

The highest proportion of survey respondents combined reported that they would like a treatment to stop the progression of ALS (**Figure 35**). The next highest proportion reported that they would like a treatment to impact breathing and respiratory function.

Caregivers of individuals currently living with ALS reported breathing and respiratory function and speaking and communication at a higher frequency than individuals with ALS (blue arrows). Meanwhile, individuals with ALS ranked muscle weakness and stopping disease progression higher than caregivers (grey arrows). Finally, caregivers for individuals with ALS who have passed away ranked swallowing much higher than living individuals with ALS and the caregivers of living individuals with ALS (yellow arrow).

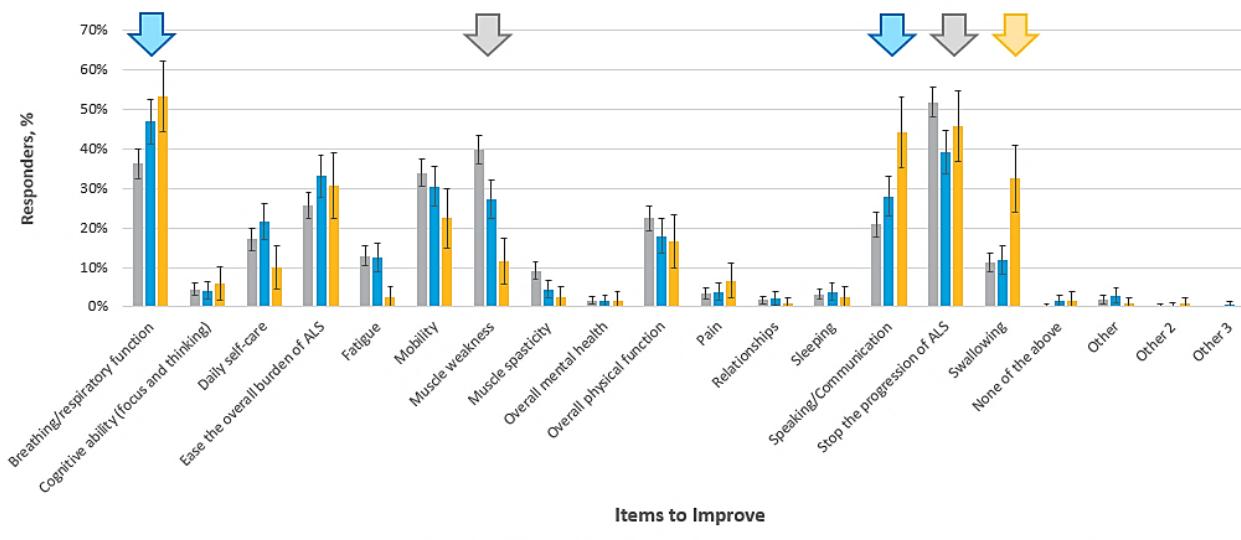


Figure 35. Preferred Items for Treatment to Improve⁴⁴

⁴⁴ Error bars represent 95 percent confidence intervals.

Other Preferred Items for Treatment to Improve

“Reverse the damage ALS has caused.”

“Reverse, not just stop, the ALS”

“Secretion management”

“reverse the progression, otherwise not worth it”

“length of life”

“the burden it places on my wife - physical, emotion and physical among other reasons.”

Survey respondents were asked to elaborate on their top three choices.

Question for Individuals with ALS:

Please describe why those are the top 3 (optional)

Question for Caregivers:

Please describe why those are the top 3 (optional)

The highest proportion of survey respondents indicated that the symptoms they chose were the top three because they are currently the most impactful (20 percent) or they affect daily functioning/self-care/independence (19 percent). One respondent, regarding speaking and communicating, stated, “they limit the most important aspects of her life, relating to family and friends.” Another respondent, regarding the most impactful symptoms stated, “to this point in the disease his mobility and his speech are his greatest deficits. I know these are the areas he would most like to see improve.”

Description of Top Three Items for Treatment to Improve

“She was a sociable person – losing her voice was hard”

“He just wants to be ‘normal’ as much as possible as long as possible”

“Inability to breathe meant patient felt as if she was drowning at all times”

“He wants to breathe so he can keep living. He wants mobility so he can keep his independence. ALS sucks, with how much pain he's in and that there's no cure, but he just wants to live longer, so if even ALS progression could be halted, that would be great. Our first grandchild is due in one week, and we still have a 13-year-old at home. He wants to be a part of their lives for much longer than a few more years.”

“Her breathing is our biggest concern. And swallowing food and drinks because she does not want a feeding tube.”

“To stop the progression of ALS should be everyone's # 1 answer. To aid with both mental health & physical functions would be a miracle!”

III. Benefit-Risk Framework

In 2013, the FDA developed a plan for a structured approach to benefit-risk assessment in regulatory decision making. This framework calls for assessing certain factors for each potential therapeutic under consideration for approval in the following categories: Analysis of Condition; Current Treatment Options; Benefit; Risk; and Risk Management. The first two categories are non-product-specific, but instead provide the therapeutic, or clinical, context for interpreting the product-specific information in the remaining categories. In each specific use case, this framework summarizes each decision factor and explains how it influences the FDA's rationale for its regulatory decision.

The input from the ALS community in response to this survey, as compiled in this report, can inform such a framework. Here we offer the therapeutic context for ALS, which is derived from the information gathered from this survey. The information from the framework below should be incorporated into a benefit-risk assessment framework for a drug under review. This framework may evolve over time as new therapies become available, the standard of care of ALS changes, and, as a result, the unmet needs of people living with ALS shift.

Dimensions	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> - Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disease that affects motor neurons. - It has no known cause and affects 20,000 to 30,000 people in the United States at any one time, with approximately 6,000 new diagnoses made per year. - As the disease progresses, motor neurons that control voluntary and involuntary muscles deteriorate. People with ALS progressively lose the ability to perform everyday activities like walking, speaking, and eating. - Individuals with ALS report significant symptoms of fatigue and weakness, leading to less time spent at work or school, socializing, doing favorite activities, or traveling. - The symptoms of ALS have a significant impact on activities of daily living and quality of life from early in disease onset. - Eventually, the nerves that control muscles used for breathing are affected and individuals with ALS require a ventilator to live. Respiratory failure is the leading cause of death in individuals with ALS. - The symptoms of ALS can cause depression and fears about the future, particularly the fear of leaving family too soon and dying from respiratory failure. - After diagnosis, individuals with ALS typically survive three to five years, with only about a 10 percent chance of surviving for more than 10 years. 	<p>ALS is a debilitating degenerative disease that causes significant burden for individuals with ALS and their caregivers. The loss of mobility and difficulty speaking and breathing can make it very challenging to perform everyday activities. Individuals with ALS report depression and fear about the future.</p>
Current Treatment Options	<ul style="list-style-type: none"> - Current treatment options are limited and focus mostly on supportive care through assistive devices, though some individuals with ALS choose not to utilize assistive devices because they feel it prolongs suffering. - In part due to the heterogeneity of the patient population, which complicates clinical trials, and due to the lack of a clear pathogenesis, only three approved therapies are available that have a modest impact on the 	<p>Overall, individuals with ALS do not report high satisfaction with their current treatment options, both with respect to disease progression and</p>

	<p>disease course. For example, Riluzole does not significantly increase survival beyond a few months.</p> <ul style="list-style-type: none"> - While current treatments and therapies only partially manage the effects of ALS, there is significant unmet need for new treatment options. - Individuals with ALS find breathing assistance devices very burdensome and inconvenient, but necessary. - Individuals with ALS reported that the one thing they wished they could do is walk, whereas caregivers of individuals with ALS reported that the one thing they wished the individual for whom they care could do is talk. - Individuals with ALS want a treatment to stop the progression of ALS, improve muscle weakness, and to assist with breathing and respiratory function. 	<p>symptomatic relief. Treatments only somewhat help with managing ALS, and current treatments are mainly focused on supportive care through assistive devices. Individuals with ALS would like a treatment option that stops disease progression, improve muscle weakness, and assists with breathing or respiratory function.</p>
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IV. Conclusion

The responses to the IMPACT ALS survey highlighted the significant unmet medical need for effective treatments for ALS, particularly treatments that slow or stop the progression of ALS and assist with respiratory function and muscle function. The current treatments for ALS are mainly focused on supportive care through assistive devices and can be inconvenient and burdensome. These treatments provide modest benefit but are not disease modifying. While a curative treatment would be ideal, a treatment that would stop disease progression or assist with respiratory and muscle function would be of great benefit to those living with ALS.

The survey provided an opportunity to learn more about the experiences of the functional burden of living with ALS from individuals who have ALS and their caregivers. The survey showed that caregiver answers about individuals living with ALS symptoms were remarkably similar to those individuals' answers about their own symptoms. This survey helped illustrate how patient experiences diverge from the standard scientific perspectives on ALS where the focus is mainly on degeneration of motor neurons. Muscle weakness is ubiquitous in ALS, but fatigue, speech problems, dyspnea, difficulty sleeping, and pain are common problems perceived by both patients and caregivers as impactful on quality of life. These symptoms should be considered when designing future research trials, quality of life scales, and other disease impact measurements for people with ALS. The survey results will also guide clinicians and researchers to focus on these symptoms in an effort to better understand and alleviate them.

The survey highlighted some of the fears of people living with ALS and may have implications for future palliative care. Most respondents identified dying an early death and choking or having respiratory difficulties as being primary fears for the future. These fears should prompt the need for improved planning and education around palliative care specific to ALS patients.

We are grateful to all individuals with ALS and caregivers who took the time to respond to the survey and shared their experiences of living with ALS.