Optimizing Outcomes in ALS: Best Practices in Screening, Diagnosis, and Treatment

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CASE DISCOVERY

Introduction and Overview

Amyotrophic lateral sclerosis, which I am going to abbreviate as ALS, is a neurodegenerative disease that most obviously affects both populations of motor neurons. We have upper and lower motor neurons. The job of these cells is to be like wires conveying the information from the front part of our brains, where we make decisions, through the brain, brain stem, spinal cord, and eventually, the muscles that carry out our actions. There can be a lot of variability in how this disease presents, especially regarding where it starts and the distribution of the different types of motor neurons that are involved.

ALS is said to be a rare disease. I think it depends on how you define rare. If you look at the incidence and prevalence numbers, incidence about 1 to 2 per 100,000 per year, prevalence about 4 to 8 per 100,000 people living with this right now, that does sound rare. But there are certain places in the world where it is much more common, for example, the island of Guam. In fact, the prevalence is projected to increase by almost 70% by 2040. The other thing that makes it seem not so rare to me is the lifetime risk. The lifetime risk for an individual developing ALS is about 1 in 400. Who gets it? Men are affected a little bit more commonly than women, about 1.5 times as commonly. The peak age at which this disease presents is in the 50s and 60s, but there is such a wide range. The youngest patient I have seen was 15 and the oldest was 90.

Signs, Symptoms, and Presentation

ALS is a disease of motor neurons, and its hallmark is weakness. Typically, that weakness starts gradually, without any pain. Unfortunately, once it starts, it progresses relentlessly, both in the place where it started and across the body. The weakness is accompanied by muscle atrophy, also known as shrinkage, fasciculations, also known as twitching, and cramping. Usually, it is not accompanied by any pain or sensory loss. Cognitive impairment, which is of the frontal temporal variety, happens in about half of patients. Usually, this is subtle, but that does not mean it is not important.

This is why we screen for it in our clinics. People with ALS who have any degree of cognitive impairment survive far shorter times than people without it, and I think it is because we have so many complicated things to offer now. These are things that would be tough even for a person who is cognitively normal to decide on and to be compliant with. If you have some cognitive impairment, I think you are much more likely to either make bad decisions or not be compliant with some of the things that we know help.

Also, as mentioned, there can be a lot of variability between patients with this disease. What do I mean by this variability? First, it can start in different places. Most commonly, it starts in an arm or a leg. We call that limb onset ALS. About one-third of the time, it starts in the bulbar region, that is, the part of the body that is comprised of the face, pharynx, and tongue. Rarely, this disease can start in other places, such as the trunk or diaphragm. That is about 1% of cases. It can also start with either primarily lower or upper motor neuron involvement.

Let us discuss some of the specific things that you might see in a patient with ALS. Somebody who starts with predominantly bulbar lower motor neuron signs might have weakness in their face, tongue atrophy, and tongue fasciculations. They would have a flaccid dysarthria, meaning it would kind of sound like their tongue was lazy. Someone who has it start in the bulbar region, but in the upper motor neurons, might present with a spastic dysarthria. This sounds like the muscles in the back of the throat are really tight. You could also have it start in this region with what is called pseudobulbar affect. This is interesting. It is when a person loses the ability to control their laughing or crying.

If it is cervical onset and it is primarily lower motor neuron, you could see atrophy and fasciculations in the arms and hands. If it is cervical onset and it is primarily upper motor neurons, you could see stiff upper extremities and pathologically brisk biceps, triceps, and brachioradialis reflexes. You could see Hofmann's signs.

If it is a lower motor neuron problem that starts in the lumbar region, you could see atrophy and fasciculation in the legs. If it starts in the upper motor neurons in the lumbar region, you

would see spastic tone in the legs with very brisk, sometimes crossed adduction, knee reflexes, and sometimes, you would see what are called Babinski signs.

Then, I talked about those very rare presentations. These are hard to diagnose until they spread to other areas, but if it started in the thoracic region in the lower motor neurons, you might see a problem with axial instability or a bended posture, and when you took the patient's shirt off and you looked carefully at the muscles alongside the spine, you might see the atrophy and fasciculation there. If it started in the upper motor neurons in the thoracic region, you would see absent superficial abdominal reflexes.

Not only is ALS variable in terms of where it starts and what it looks like in the very beginning, it is also variable in how it progresses. Most commonly, it progresses relentlessly and fast along anatomical pathways. What do I mean by that? If it starts with a foot drop, typically it progresses up that same leg and then over to a foot drop on the other side and up that leg and then over to the arm on the side where the foot drop was, starting distally and progressing more proximally. It does not skip around from foot drop to slurred speech. Eventually, this progresses to a point where all voluntary muscle control is typically lost.

Now, there are a couple of exceptions. Usually, eye movements, bowel, and bladder sphincter are spared. We do not fully understand why these motor neuron pools seem to be more resistant to this disease. Sensory functions are also usually spared. As a result of this rapidly progressive loss of motor control, death or a difficult decision to be attached to a ventilator usually occurs within 2 to 5 years of symptom onset. But again, there can be tremendous variation. Twenty percent of people who get ALS live more than 5 years from their first symptoms, 10% live more than 10 years, and 5% live more than 20 years. There are examples of people living 50 years with ALS. You can think of Stephen Hawking, the famous physicist, who was diagnosed around age 20 and lived to be in his 70s. There are even examples of people where the disease seems to plateau or stop progressing and even a handful of people where it seems to reverse, where people progress for awhile and then recover some of their lost motor function.

Burden of Disease

If it is not already obvious, this disease creates tremendous physical and mental strain on both the patient and caregiver. Most, but not all, studies show a decline in quality of life with loss of motor function, especially early on and in older patients. To appreciate the true horror of this disease, I think about this description that a patient gave me. She said, "You know, doc? Ever since you told me this is what I had, it is like you put me in a box, and that box gets a little smaller on all sides, further restricting what I can do every day. And I know one day that box is going to get so tight that it's going to suffocate me to death." I still get the goose bumps, even though I have repeated that description a hundred times. I cannot think of anything worse.

ALS is also a tremendous financial burden to families. It depends on what kind of insurance you have and what options you choose, but it can range anywhere from $10,000 to $100,000 in out-of-pocket costs over the course of the disease. There are studies showing that this disease can cost hundreds of millions, even billions, of dollars, per year to specific societies. How could it cost that much when it is so rare? Because of the devastation and the fact that this occurs usually in the prime earning years of a patient.

Unfortunately, ALS is not like a stroke where it starts and is either stable or improves. Unfortunately, as people progress, they keep losing function and that keeps creating more burdens, such as physical burdens. Patients lose the ability to walk, dress themselves, feed themselves, and use the toilet. Economic burdens? Eventually people are put out of work by this disease, and they have to go on disability. It causes a decreased quality of life, as mentioned, because of all these burdens happening, especially in that first year when people are not sure what is going on. And, there are a lot of complications that can arise from this disease. We know that people can fall. We know that they can aspirate and get an aspiration pneumonia. We know that they can have respiratory failure. In fact, that is usually how the disease ends. We also know that they can have cognitive decline.

Best Practices for Screening, Assessment, and Referral

It is said that ALS is under-recognized and under-diagnosed. I would say that is almost certainly true for the first year. People with this disease typically go a few months before they even see their primary care doctor because of how gradually this starts and the fact that there is no pain. Then, they typically see their primary care doctor. I know how these folks think because I am married to one. They think about common things. Common reasons why a person would have hand weakness or foot drop would not be ALS. It would be a pinched nerve. They might treat the patient conservatively with anti-inflammatories or physical therapy, have them

come back in a few months, and now the patient is worse. Then, they might get some pictures of the spine, and inevitably, we see things. We see bone spurs or discs that are slightly out of place. That might prompt a referral to a surgeon. If the surgeon is good, they will recognize this does not make sense for a pinched nerve because there is no pain or sensory loss. If the surgeon is not careful , they might just operate. Fifteen percent to 20% of all the patients I have seen have had unnecessary surgeries on their way to an ALS diagnosis. It could be carpal tunnel releases, neck surgery or back surgery, but eventually, they get in to see their first neurologist and those neurologists, those community neurologists, are great at doing a history and an exam and localizing a problem. They usually do write in their notes, "Looks like a motor neuron disease, worried about ALS." But rarely do they sit down and have the conversation or get treatment started. I think there are probably several reasons. One is there is no single test that makes this diagnosis. Since a general neurologist might not see that many cases, they might not be that confident that they have it right, and it is a terrible thing to tell someone. The other is a practical issue. It takes time. I have about two hours to spend with my new patients. Most private practice docs would not get even half of that. Rolling this diagnosis out and not doing it right with an opportunity for the patient and family to ask questions would not be good. Typically, that general neurologist refers to somebody like me who runs a specialty clinic, and as a result, this whole process, from symptom onset to the time that I see them and make the definitive diagnosis, is more than a year. By the time the patient sees me, the disease has evolved. It has gotten much worse. It has spread across the body, and I can clearly see those upper and lower motor neuron signs,. I can clearly get the history that this has spread, and by the time they get to see me, there are usually quite a few tests that have been done that can rule out ALS mimics: imaging, blood work, EMG, sometimes even muscle or nerve biopsies.

This diagnostic delay has a lot of consequences. One is for that whole first year. I think part of why the quality of life decreases so dramatically is that patients and families recognize that there is something going on, but no one can figure it out. Then, they are accumulating all these burdens that I talked about before. They are having symptoms, and they are having complications, like falls. They are missing days of work. The other real issue is that we have so many treatments now, including medications, that can slow the progression of the disease. We think that these medications work better when they are started earlier in the course of the disease. Finally, we have so many clinical trials now that are exciting, but they all want patients who are early in the course of their disease who have a lot of preserved function. It is especially heartbreaking when I see a new patient who has already progressed beyond where they could participate in any clinical trials. We have got to find a way for non-ALS specialists to help us decrease this time to diagnosis.

Here is a nice thing that the ALS Association put together. It seems complicated, but it can be boiled down to this. If you have a patient that comes to see you—as a primary care physician or a surgeon—early in the course of all this, and they have progressive, asymmetric muscle weakness without any significant pain or sensory loss, something weird is going on. That patient probably needs to be referred directly to the neuromuscular expert, and you could even put in there the term "clinical suspicion for ALS." If you shop around, you can usually find one of the ALS clinics in the United States that will be able to get your patient in within a few weeks.

Summary

ALS is a somewhat rare neurodegenerative disease that most obviously affects motor neurons. Affected patients will usually have gradual onset, painless weakness that rapidly spreads across their body and disables them. One of the frustrating things about what is going on now is that we have a lot to offer, but we are seeing these people too late for a lot of this stuff to work as well as it could. We have got to find a way to get primary care docs, surgeons, and general neurologists to refer these patients to us much sooner.

EVIDENCE-BASED TREATMENT PLANNING

Breaking The News

I saw my first person with ALS more than 25 years ago. Now, back when I was still a resident, I remember thinking, "Wow, this is the most incredible story, the most amazing collection of exam findings I have ever seen in one person." Then, I remember my attending coming in and saying, "This is called ALS. We do not know why it happens. There is nothing we can do. You have got limited time. Go home, and get your affairs in order." Then, they walked out. I remember how bad I felt. I thought to myself, "If I felt that bad, imagine how that patient and family must feel." That is when I decided I would try to stay at my institution and do something different. I have learned that there is a better way to make a diagnosis, a more honest way.

First, you explain to people what this is, what part of the body is being affected, some of the theories we have on why it is happening. Then, I think it is important to stress two things. One, stress the variability between patients and even within a patient at different times. People probably have read something when they come in. They are going to see on the internet that it could be as little as 2 years from symptom onset, and they have been waiting a year or a year-and-a-half to see me. They are thinking that their time is quite limited, and I say no. There are a wide range of things, and there are examples of people that have lived amazing lives for many years. This does not have to define you. Think about the life that Stephen Hawking lived with ALS, one of the most extraordinary lives ever documented. The second thing is that there is a lot we can do for people with this disease that will make their lives longer, slow the rate of their disability accumulation, and empower them to live a more normal, safer, and better life. I think it is important to say those things because people need hope. The last thing you want someone to do is walk away from your clinic with this diagnosis and no hope.

One of the other things that is brought up in that first conversation is the different reasons why this happens. We talk about genetic vs sporadic ALS. About 10 to 12% of everybody with this disease has it because they are born with a disease-causing genetic mutation. The other 90% or so do not understand why they have it. We think there may be things in the environment, but we do not know for sure what they are. Because of that 10 to 12%, I think it is important for people with ALS to consider genetic testing at the time of diagnosis. Now, some people have said, " Why? What are the benefits?" First, in my experience, almost every patient wants to know why they have this. This is the only test we can do that sheds some light on that. Second, every family that I have ever met wants to know their risk of getting this disease. Again, this is the only test I can do that sheds some light on that.

Also, we are coming into an era now where there are many clinical trials and possibly an FDA-approved medication for people with certain specific genetic mutations that are causing their disease. Most of my patients want some guidance from me on what is the most promising trial for them. If you have a genetic mutation, let us try to find a trial that targets that mutation. Then last, but not least, for the first time ever, there are trials opening up for people that are asymptomatic but have ALS-causing mutations. Even if I cannot find a way to stop or reverse a patient's disease, by knowing that this particular gene runs in the family, their children might someday be able to find a clinical trial that stops them from ever getting ALS, which is amazing.

Goals, Strategies and Considerations

The treatment of ALS has to be comprehensive, multifaceted, and holistic. That means that we need a team of people involved, a multidisciplinary team. In many patients, this disease changes too fast and affects too many body functions for one clinician to keep up. At my clinic, for example, beyond neurologists, we have respiratory therapists. The respiratory therapist's job is to measure pulmonary function testing. If they see that the disease is trying to take away from that, then we have a pulmonologist who comes in and talks about breathing exercises and equipment that can be used. We have speech therapists that help evaluate communication and swallowing. If they see that those things are being taken away, there are communication devices. There are ways to modify the liquids and the solids to make them easier to swallow. At some point in the course of the disease, there is a discussion about a feeding tube. We have physical therapists that help people get from one place to the next more safely. At some point, that might involve bracing, a cane, a walker, or a wheelchair. We have occupational therapists who help us evaluate activities of daily living, such as the ability to brush our teeth, take a shower, get dressed, use the toilet, and drive a car. There is a way to modify these activities to keep people doing them as long as possible, and when they cannot do them, to teach families how to do them in the most efficient way. We have a nutritionist because many people with ALS struggle to keep their weight up, and we must make recommendations for them to maintain their weight, based on what they can swallow and whether they have a feeding tube. We have a social worker who helps with disease education, disability, coping strategies, and community resources. We have a variety of different nurses that help me manage symptoms and, help with paperwork, such as disability paperwork, prior authorizations, things like that. And we have a research team.

As the director of the clinic and one of the neurologists there, I see my goal as being the one to explain the disease to patients, determine whether we have gotten any worse from last time, present disease-modifying therapies to patients, and present the research. Then finally, I haveto be the go-between between clinic visits. I ask my patients to reach out directly to me if they have clinical questions. If I do not know the answer, then I forward it to the appropriate member of my team.

This model of ALS care is incredibly resource intensive.. We have about twenty clinicians that work every Tuesday, and we see about twenty total patients. That i not a money-maker. In fact, it is a huge money-loser for the institution.To make this work, two things must be true. One, it needs to have benefits, and there is no doubt that it does. Study after study shows that attendance in these multidisciplinary clinics is associated with better quality of life, fewer hospitalizations, and better survival. Also, there hasgot to be a way to bring in money to offset those losses. Thankfully, there is a lot of philanthropy out there, for example, patient advocacy groups and individual patients who are willing to donate to keep these teams together.

Let us discuss things that we can do to maximize quality of life. You must understand what some of the factors are that decrease either overall or health-related quality of life. Some of the more common ones include anxiety, depression, fatigue, hopelessness, impaired breathing, pain, dysphagia, and pseudobulbar affect. As our teams identify these specific things, then we can offer options. For people who are having anxiety or depression, sometimes they just need to talk to the social worker for awhile. Sometimes, they need a medication. Sometimes, they need professional help, like a therapist. For people who are having pain, that is something that we can easily treat. For people that are having trouble with their swallowing or pseudobulbar affect, there are interventions that we can use. Some of them might be medications, some of them might be activity modification, and some of them might be equipment or exercises. There are so many things we can do if we can just identify the specific factors.

The mainstay of treating this disease is multidisciplinary team care because it allows us a comprehensive assessment of what the disease is doing to this patient. That is the best way to be able to offer a long list of options. We focus on what we can do about this disease in our clinics, not what we cannot.

There are now entire books written about all the options that can be offered to a person with ALS. I do not expect primary care docs, surgeons, or general neurologists to read those books, but the nice thing is the American Academy of Neurology has distilled everything down into a short list. This is a few years old now. It is all the way back to 2013 when they published this. They are about to update it, but as of today, these are the most important things to offer people with ALS: multidisciplinary team care; disease-modifying pharmacotherapy; cognitive and behavioral screening; symptomatic treatment; respiratory insufficiency querying, which is pulmonary function testing; use of noninvasive ventilation, if respiratory insufficiency is discovered; screening for dysphagia, weight loss, and impaired nutrition, offering support from a dietician if those things are found; screening for communication problems and offering support if those are happening; talking about end-of-life decision-making; and querying for falls and offering options if that is happening.

Disease-Modifying Therapies: An Overview and Summary

We now have 4 FDA-approved medications which can be used to treat ALS: riluzole, also known as Rilutek; edaravone, also known as Radicava; sodium phenylbuterate/taurursodiol, also known as Relyvrio. Those three are indicated for the treatment of ALS. Then, there is also dextromethorphan/quinidine, also known as Nuedexta, which has an FDA approval for pseudobulbar affect. We will talk more about that one in a minute.

Riluzole is the oldest of these. It is a benzothiazole, s given orally. It blocks the release of glutamate and modulates sodium channels. It was approved for ALS way back in 1995 because multiple randomized, double-blind, placebo-controlled trials showed that it increased tracheostomy-free survival by a few months. It i now available in multiple forms: pills, films, liquids. The biggest reason why I see people reluctant to take this is because they look back at those trials and say, “Well, it is only a few months that this gives me, right? Do I really want to take a pill every day for a few extra months?” What I have to explain to them is that just because a trial showed a difference of a few months between several hundred people on a medication and several hundred people on a placebo does not mean that every other patient will get those exact same few months. In fact, there are real-world studies that show survival benefits all the way up to nineteen months, so it is possible that some patients get a lot more out of it. We do know that it can work at every stage, even very late in the course of the disease. For all these reasons, most people in this country are taking it all the way through their disease.

The trials were prospective, double-blind, placebo-controlled trials of riluzole. One of the key ones was this. One hundred fifty- five patients got riluzole, and the rest got placebo. Participants were stratified based on the site of their disease, bulbar vs limb. What you can see here is the one-year survival. It is clear that, overall, more patients survived for a year on riluzole than on placebo. Again, I would say that is

the most minimal evidence that this works. There is much more now than that. This is also a safe and well-tolerated medication. The main thing that we must watch out for, is elevation in liver transaminases. On placebo, those were seen in 8% of patients. On riluzole, they were seen in about 17%. This means that when people are started on this, we must do a liver function test. We do it monthly for the first 3 months and then every 3 months after that.

The next medication that got FDA-approved for the treatment of ALS was edaravone, also known as Radicava. Initially, this was only available in an intravenous formulation. Last year, there was an oral formulation that was approved. This agent is an antioxidant. It is interesting. There have only been 2 clinical trials of this. The first one was a negative study. It did not show any benefit in people taking this vs placebo. But, after it was published, the company that owns this went back, looked at the data, and got a hint that maybe a certain type of patient was benefiting. Based on that, they did a second trial,focusing on people in the first couple of years of their symptoms who had a lot of function who were progressing quickly. What they were able to show in that trial was about a 30% slowing in the rate of decline on a disability measure called the ALS Functional Rating Scale, ALSFRS-R, vs placebo. Both trials suggest good tolerability and safety. Ten to 15% of participants had minor side effects, for example, bruisingwith the IV, headaches, or gait disturbance. Occasionally, we see a hypersensitivity reaction. You must avoid this with people who have a sulfite allergy.

Here is the data from the positive phase 3 clinical trial. Of , 137 patients, half got the drug, and half got placebo. The participants had to be in the first 2 years of their symptoms. They had to be progressing. They had to have a reasonable amount of function at baseline on their ALS Functional Rating Scale and their breathing. There, you see the main outcome measure at the end of the trial. Patients on a placebo over 5 months lost 7.5 points on the ALS Functional Rating Scale, and patients on edaravone only lost 5 points. That is highly significant. Again, you saw similar adverse events in drug vs placebo, with the exception of things like contusion and contact dermatitis.

Then, we have one of the newer ones, taurursodiol and sodium phenylbuterate, TUDCA/NaPB, also known in this country as Relyvrio. This was just approved in September of 2022. It was approved based on only one clinical trial, and we will talk about that in a minute. There is a replication trial that is underway, results expected at the end of 2023. What does this combination of drugs do? We think it targets transcriptional dysregulation, stress in the endoplasmic reticulum, and mitochondrial dysfunction. Those are completely different events than what riluzole or edaravone target. We are starting to get an array of products that do different things, and we will talk more about that in a minute. But, with this drug in particular, in one 6-month trial, it showed the ability to slow the rate of decline on the ALS Functional Rating Scale by about 25% vs placebo. They continued to follow people in this trial in what is called an open-label extension. There, they saw that folks who initially got this drug right from the start of the trial were living as much as 6 months longer than people who initially got a placebo.

Here is a drill-down on the key phase 3 clinical trial that was used to approve Relyvrio. It was randomized, multicenter, double-blinded, and placebo-controlled. Of 137 patients, twice as many got Relyvrio than placebo. Over the course of 6 months, those are the slopes. The slope of decline for people on placebo was 1.66 points per month; the rate of decline for people on Relyvrio was 1.24 points per month. That is statistically significant.

Again, this was well-tolerated. There are some GI side effects. Up to 20% of people who take this can have nausea or diarrhea. There is also something noted here, salivary hypersecretion, that seemed to be more common in people on the drug.

Last, but not least, is dextromethorphan and quinidine, also known as Nuedexta. This was FDA-approved in 2010 for the symptom complex called pseudobulbar affect, where people lose their ability to control their laughing and crying. You had randomized, controlled trials that showed a reduction in frequency and severity. This is an oral medication. Since those trials came out, some of us have just noticed spontaneously that people that we put on this for pseudobulbar affect appear to have improvements in the clarity of their speech,their swallowing function, or their sialorrhea. The people that discovered this went back and did a clinical trial, and sure enough, on objective measures of bulbar function, people do better on this medication. Now, unfortunately, we cannot prescribe it just for that because it does not have an FDA indication. It will not get paid for by insurance. For folks who have both pseudobulbar affect and bulbar dysfunction, this can be a great option. One thing to watch out for is QT prolongation because of the tiny amount of quinidine. What I do in my clinic is I ask patients if they have any history of heart problems, specifically QT prolongation, and then I look at their medications to see if they are on anything that might

do that. If I have any doubts, I do an EKG, give them a dose of this medication in clinic, do another EKG 3 hours later, and look to see if the QT has been prolonged by this medication.

Here is a drill-down on the pivotal Nuedexta treatment trial. Again, this was multicenter, randomized, and double-blind. It was a crossover trial with 60 patients. They were randomized to about a month of active treatment vs placebo, got a washout, and then were switched to the opposite treatment arm. Primarily what they were looking at here was pseudobulbar affect, but again, there is another trial, shown in the table here, where they measured what is called a Central Nervous System Bulbar Function Score. You can see whether they look at the score overall or just specifically the parts of it that measure sialorrhea, speaking or swallowing. Everything seems to improve in these patients. It is generally a well-tolerated medicine. Dizziness, constipation, diarrhea, and nausea are a little more common in people who take this vs a placebo.

Disease-Modifying Therapies: The Role of Rational Polypharmacy

These medications have different mechanisms of action, so there is a rationale for combining them. Typically, I would start a person on the one that is the easiest to get that has the most data, that is, riluzole. I would see how they did for a month or two. If they were still progressing, which unfortunately most patients will, then I would try to get them the second medication, which would either be edaravone or Relyvrio. In reality, we can try to apply for both at the same time because we are finding thatit takes a long time to get insurance approvals. Sometimes, they go quickly, but usually, they take at least a few weeks to get approved. Most of my patients are on combination therapy. I call it rational polypharmacy, hitting the disease with multiple medications that target multiple downstream pathways. Until we can go after the cause of ALS, this is going to be the way to give people the optimum outcomes.

Symptomatic Treatments

The other part of treatment is symptomatic therapy. I want to appeal to primary care docs, surgeons, and general neurologists. You do not have to know for sure that a person has ALS to start treating them for symptomatic therapy or start trying to prevent complications. One of the saddest things I see is not just that diagnosis is delayed, but that patients were struggling with things that someone else could have managed a long time ago, but they were so focused on trying to find the diagnosis that they forgot to do it. For example, I often see people who have been struggling with drooling for six months before I see them, and nobody started them on any kind of agent to dry their secretions or cramps or falls. We have simple treatment for these things.

Here are some of the more common things we see. Fatigue. Pharmacological treatment is modafanil. For nonpharmacological treatment, we try to get people to practice energy conservation and sleep hygiene. That means making sure that you are getting a solid eight hours of sleep a night. Some people even need a nap in the middle of the day. Sometimes, that is enough to take care of the fatigue. Insomnia is common, and again, we have a variety of medications. We have nonpharmacological things. Sometimes, people cannot fall asleep because they are not comfortable in their bed. They are stuck in one place and that causes pressure pain. We have things called alternating pressure pads that we can put on top of the mattress that gently rock people so they can go to sleep that way. Sometimes, they cannot sleep because they cannot breathe, and we might need to start noninvasive ventilation for people at night.

Constipation is super common. There is nothing magical about the way that we manage it in ALS. We manage it the same way you would manage it in someone without ALS. We have pharmacological and nonpharmacological interventions, which you can see there. Erectile dysfunction does sometimes occur. It is more rare in this disease than other neurologic diseases. Urinary urgency is surprisingly common though, and there, we often use anticholinergics, like oxybutynin or tolterodine.

Cramps are very common. Many times, people do not have them bad enough to manage, but there are some people who want medication for it. There, we have things like mexiletine, vitamin E, phenytoin, and carbamazepine. I would add vitamin B complex to that list. that is my first pharmacological treatment for cramps. Vitamin B complex, one a day. Nonpharmacological interventions, like physical therapy for stretching and massage, can work well. Spasticity is related. Muscle relaxers, if you want to go pharmacologic and again, stretching, if you want to go nonpharmacologic.

Some people get laryngospasms, which are extremely disturbing, and there, I think the most important thing is reassurance. The larynx can suddenly close, and you cannot breathe or make a sound. But the good news is it usually only lasts seconds and just requires some relaxation and deep

breathing. It is not going to last so long that it ends someone's life. But if people want it treated, benzodiazepines can be helpful. Sialorrhea, or drooling, is incredibly common. There are a variety of different anticholinergics that we can try, if you want pharmacologic treatment. Other things that can be helpful include portable suction devices and radiation of the salivary glands for people who fail the anticholinergics.

Psychological symptoms, such as anxiety and depression, do happen. They are not as common as you would think, especially as the disease goes on. As I mentioned earlier, sometimes all people want is someone to talk to, and that is one of the functions of our social worker. She is terrific at just picking up the phone and talking to people about what is happening. Sometimes, they need more. The next thing we do, if that is not enough, is we have pharmacological treatments for anxiety and depression, some of which overlap, like the SSRIs. Then, we also have referrals to people, like psychologists or psychiatrists.

We already talked about pseudobulbar affect and how good Nuedexta is against that. For people that cannot get that paid for, or do not tolerate it, or people where you are trying to treat more than one thing with one drug, tricyclics and SSRIs can also work for pseudobulbar affect.

Expert Perspectives

The ALS Association has a quote that I like. They say, "By 2030, we need to make ALS a livable disease." What does this mean? We want people to have longer lives. We want life-extending treatments to be made accessible to all people with ALS. We want prevention of harms that are associated with ALS, like falls. We want to improve quality of life so that people can be empowered to live their lives as they want. We want to have partnerships with patients, so we want them more engaged. We want to make sure that we think about preventing this disease, which starts with genetic screening and directing people toward those prevention trials.

How do we get there? Well, clearly, we are on our way, but we want more treatments and eventually treatments that stop or reverse the disease. We have to get there by getting people into research. It is kind of amazing. There are only a very small fraction of people with ALS that participate. It is better today than it was 20 years ago, but we still need to improve upon that, and there are a lot of reasons for that. Trials tend to be very restrictive. Many times, people are swayed by something they read about on the internet, so we have to develop programs that educate people of these things that are advertised on Facebook and Twitter. We want to make sure that we are optimizing current treatments and care, so we have got to be able to get people to the multidisciplinary clinics and make sure that there is a certain standard that those clinics are practicing. Then, we want to try to identify risk factors for ALS and get people on treatment much faster than we are today.

Summary

I am excited that we have so many more treatments, pharmacological treatments even, that can slow the progression of ALS, and I think these can be used together. It is my opinion that that rational polypharmacy is going to work better than any one of these things alone. I also think there are many treatments for people that have symptoms in this disease that are robbing them of quality of life, and we have pharmacologic and nonpharmacologic ways to manage so many symptoms, and those are best rolled out, again, through multidisciplinary clinics.

TEAM-BASED CARE

Introduction and Overview

An ALS team is referred to as multidisciplinary because there are a whole bunch of people on the team that do different things. Usually there is an ALS neurologist, and then usually, there is an assortment of the following: respiratory therapists, pulmonologists, gastroenterologists, physiatrists, psychiatrists, social workers, dieticians, dentists, genetics counselors, palliative care experts, specialized nurses, physical and occupational therapists, and speech therapists.

These are very resource-intensive clinics, but there is clearly a benefit, such as improved quality of life, reduced hospitalizations, and improved survival for people who come to these kinds of clinics. Based on patient surveys, patients usually find favor with this multidisciplinary approach. It is a long day for them, but I cannot tell you how many people have left clinic and thanked us, saying "You know, I'm exhausted, but I have learned so much, and I feel so much more control over this horrible situation. I have more hope." I do think that is another thing that comes out of these clinics. Like I mentioned before, when you get face-to-face with people who understand the variability, understand all the options, and understand the research, you can get some hope, which is incredibly important.

Best Practices and Clinical Pearls

Interprofessional and multidisciplinary approaches to symptom management are huge. We have talked already about that, but some of the things that we have in these clinics are treatment options for breathing difficulty, like assisted ventilation. Those are best rolled out by respiratory therapists and pulmonologists. For caregiver support, such as counseling and mental health support, a key person who is involved in that is our social worker, as well as palliative care doctors, psychologists, and psychiatrists. Cognitive, behavior and mood issues. Regarding communication, we talked about the role of speech therapists in that. Regarding disease progression, we have riluzole, edaravone, Radicava, and Relyvrio that can slow the disease down. Regarding eating and drinking difficulties, we have speech therapists that help us figure out what kinds of things people can safely swallow and nutritionists who help us decide how many calories someone needs and how they are going to get that, for example, whether by mouth or through a gastrostomy. We have physical and occupational therapists that help with mobility and activities of daily living. We have treatments for saliva. We have people that can help with grief and loss and end-of-life planning assistance.

It is very clear that people need a lot of support when they go through this disease, both patients and caregivers. Sometimes people forget about the caregivers, but in my experiences, the disease was harder on a caregiver than it was on the patient. These folks have unbelievable physical, emotional, and financial burdens. It is clear when we study it that the caregiver quality of life declines when they care for people with this disease.

One of the issues that I struggle with is access to the type of care that I can provide at Duke and that so many of my colleagues are providing now. We know that 50% of people with ALS live more than 50 miles from the nearest multidisciplinary ALS clinic. How do we get this sort of team approach to them? One way that we are starting to do it is by telemedicine. We can connect with them, no matter where they live. Also, it is possible to get multiple members of the team to come in front of the video monitor and do at least some screening and some education about medications, exercises, nutrition and equipment. I have found this to be a very useful way to stay in touch with my patients, all the way through the disease.

Summary

I think it is important for every person with ALS to have a multidisciplinary team because when they do, they are going to get a comprehensive, evidence-based treatment plan. That is going to assure that they will have the best quality of life, the lowest risk of hospitalization, and the longest life possible. It is also going to ensure that they have some hope in this terrible disease.