AMCP MARKET INSIGHTS

Exploring Opportunities to Improve the Quality of Life for Those with Amyotrophic Lateral Sclerosis (ALS)

FINDINGS FROM THE AMCP MARKET INSIGHTS PROGRAM

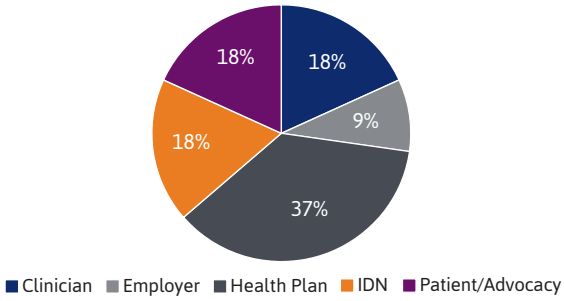
Meeting Objectives

- Review the current and evolving treatment landscape for ALS
- Discuss the differences between the clinical trial environment and real-life experience and the potential difficulty in developing formulary management strategies that consider the individual nature of the disease
- Identify the points within the patient's healthcare journey that increase the mental, physical, and financial burden they experience and the resulting impact on the patient's overall health and cost of care
- Review the decision-making process and discuss how health plans can collaborate across internal departments and with providers to minimize access to care barriers to ensure optimal patient outcomes and lower overall cost of care

Introduction

Amyotrophic lateral sclerosis (ALS) is a rare, rapidly progressive, and fatal neurodegenerative disease characterized by loss of motor neurons in the brain and spinal cord.[1] The etiology of ALS is unknown, however it is thought to be due to a combination of genetic predisposition, environmental exposures, and aging-related dysfunction. The clinical presentation of ALS varies depending on which motor neurons are affected. ALS commonly presents with localized weakness that progresses to muscle paralysis, respiratory failure, and death. Additionally, approximately 30% of patients develop some form of behavioral impairment.[3] In the United States, it is estimated that up to 32,000 people are living with ALS.[2] The greatest risk factor for developing ALS is age, with the highest prevalence of symptom onset occurring between 55 and 75 years of age.[4] The average life expectancy is two to five years after symptom onset and as the disease progresses there is significant caregiver burden.[1,2] Current treatments for ALS are largely focused on supportive care. Typically, treatment includes a combination of therapies along with durable medical equipment (DME) to help preserve quality of life as long as possible.

Figure 1. Expert Panel Representatives



AMCP convened an expert panel of clinical and managed care stakeholders to increase understanding on how payers can inform strategies to improve the care and treatment of those impacted by ALS. Panelists included representatives from national and regional health plans, integrated delivery systems, employers, clinical experts, and a patient and patient advocacy organization. (Figure 1). Participants discussed the heterogeneity of the disease, changing treatment landscape, coordination of insurance benefits, and opportunities to improve outcomes for patients with ALS.

The Patient Journey

AMCP engaged a patient with ALS to share the lived experience of ALS, challenges, unmet needs, and to identify outcomes of importance to patients and the ALS community. There was an emphasis on the diverse range of disease experiences, the profound caregiver burden and costs, and concerns about timely access to treatments and DME.

Panelists heard how during the early stages of ALS it can be difficult to diagnose, as the symptoms may be subtle and mimic other conditions. Patients may experience muscle weakness, twitching, cramps, and difficulty with fine motor tasks. As the disease progresses, the weakness and atrophy spread to other muscles, including those responsible for talking, breathing, and swallowing.

Delivering the diagnosis of ALS can be challenging for clinicians and patients.[5] But there is hope that the development of more biomarkers in ALS will speed up time to diagnosis. Once a diagnosis is confirmed patients will benefit from multidisciplinary care, including a neurologist, respiratory therapist, speech therapist, and occupational therapist, to manage their symptoms and optimize their quality of life. Patients frequently require DME like wheelchairs, respiratory support, and feeding tubes to manage their symptoms.

> **"Through this disease, you become a prisoner in your own body."**
> ***– Patient with ALS***

Obtaining access to recommended treatments and support for ALS may require navigating the health plan formulary and medical policies for obtaining necessary DME. The primary burden patient representatives identified around prior authorization (PA) is the delay in timely access to medications and adaptive support devices. However, even with insurance coverage, copays and deductibles can be high, making it difficult for some patients to afford recommended care. This is especially true for patients with slow progressing ALS because of concerns about long-term financial security.

ALS Treatment Landscape

There is no curative treatment for ALS. There are several drugs approved by the U.S. Food and Drug Administration (FDA) to treat ALS and its symptoms (Table 1): riluzole, edaravone, and sodium phenylbutyrate/taurursodiol are disease modifying treatments that may modestly slow progression.[6] Riluzole, which is believed to target glutamate activity, slows the progression of disease and is the only approved drug that prolonged survival in clinical trials (average of two to three months). Edaravone is thought to reduce oxidative stress and can slow functional impairment in a subset of early-onset ALS patients. Sodium phenylbutyrate/taurursodiol therapy targets two different potential mechanisms of neurodegeneration, endoplasmic

Table 1. Medications for Use in ALS

Drug	Use in ALS
Dextromethorphan Hbr/quinidine sulfate	Treatment of pseudobulbar affect (PBA)
Edaravone, IV and oral	Reduce oxidative stress
Riluzole	Inhibit glutamate release and prolongs life approximately three months
Riluzole, oral film	Developed for patients with severe swallowing difficulties
Riluzole, thickened	Designed to avoid potential problems of crushing riluzole tablets
Sodium phenylbutyrate/taurursodiol	Prevent nerve cell death by blocking stress signals in cells
Tofersen	ALS associated with a mutation in the superoxide dismutase 1 (SOD1) gene*

**Approved under the accelerated approval pathway and must still show confirmatory evidence of clinical benefit.*

reticulum stress and mitochondrial dysfunction. In post hoc analyses, an overall survival benefit was observed for those patients who were originally randomized to sodium phenylbutyrate/taurursodiol compared to those originally randomized to placebo.[7] The FDA recently granted accelerated approval of tofersen based on a reduction of neurofilament, a marker of neurodegeneration, for patients with superoxide dismutase 1 (SOD1) ALS.[8] Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s), but tofersen is the first treatment to target a genetic cause of ALS. The clinical experts described how using a combination of therapies has the potential to ameliorate several pathophysiological mechanisms contributing to motor neuron injury in ALS.

Challenges with Current Payer Policies

It is well established that payers build coverage policies on the available clinical evidence for populations of patients. Overall, payers consider efficacy, effectiveness, safety, FDA approval status, availability of alternative treatments, and acquisition cost of drugs to be important factors in formulary decision-making. Payers are grounded in using the FDA label as a guide to coverage policy development in ALS but can also benefit from engaging ALS clinical experts and patient representatives in considering how to address coverage issues when there is limited or no evidence.[6] While health plans typically cover drugs for ALS, they also apply coverage criteria beyond the FDA label.[9]

These variations can have important consequences for access to care, as patients with different insurers will have different access to the same therapies. For physicians, differences in coverage criteria means that treatment decisions must be tailored not only to the patient's clinical presentation but also the patient's insurance coverage. Particularly for diseases with a high burden of illness, like ALS, delays in access to therapy due to lengthy appeals processes negatively impact both patients and caregivers.[9]

Additionally, payers look to national professional societies, such as the American Academy of Neurology (AAN), for guidance around developing coverage criteria. The AAN released updated guidelines in 2009 and reaffirmed these guidelines February 25, 2023.[5] The guidelines include a level A recommendation for riluzole, but no mention of edaravone, sodium phenylbutyrate/taurursodiol, or tofersen. Payers commented that while treatment guidelines may not be referenced in payer coverage policies, the guidelines are a resource for determining appropriate coverage criteria. A consensus guideline could be helpful to reduce treatment variation and barriers to timely treatment by supporting more consistent coverage across different payer organizations. In the absence of up-to-date guidelines, real world evidence (RWE), medical cost offsets, and improvements in patient quality of life are important data payers consider when developing coverage criteria.

Payer representatives maintain that PA criteria reflect evidence-based medicine, but physician experiences with lack of timely review of coverage requests significantly impacts the time to treatment. Time to treatment is important for patients with ALS because it is a rapidly progressive disease leading to worsening disability and death over a short period of time. The earlier the treatment is started, the better the opportunity of slowing disease progression and preserving quality of life. In addition, early treatment can help patients better manage their symptoms and maintain their independence for longer.

The payers expressed that they would like to initiate the processes to develop coverage policies for new ALS treatments well in advance of FDA approval. Payer representatives encourage manufacturers to the use pre-approval information exchange (PIE), as its purpose is to provide payers with relevant and timely information about a new product, allowing them to make more informed decisions about coverage and reimbursement.

"As the drugs get more costly, the PAs get more complex, and the payers will need more data and information to support broad access."
– Regional Health Plan

Several payers acknowledged the PA process is the same across all disease states, which may not adequately address when timely treatment is critical. Since timeliness of care and administrative burdens are the main considerations, modifying the PA approval process for ALS medications warrants consideration. Payer representatives thought through the development of an expedited authorization process – akin to the FDA expedited review programs. This kind of program could align coverage review speed to the FDA's inclusion in expedited approval programs. While the FDA's inclusion of a drug in an expedited review program signals that the agency considers the drug to be an important therapeutic advance, payer coverage policy speed and coverage restrictiveness appears to be more influenced by factors such as indication or orphan disease status.[9] Clinical expert representatives expressed that in ALS, streamlining authorization and coverage processes will likely not result in additional patients being treated but would remove the administrative barrier for providers and patients.

"In ALS time is motor neurons, we call it the ALS Clock. Delays in care can be the same as denial of care."
– ALS Nurse

Patient representatives raised a question to payers to understand if drugs approved under the Accelerated Approval pathway would have more restrictive coverage criteria and therefore be harder for patients to access. Drugs approved through the FDA Accelerated Approval program are based on outcomes from surrogate markers; some payer decision makers may prefer clinical outcomes.[10,11] However, payer representatives expressed that they do not consider the approval pathway in coverage policies, nor create restrictive criteria based on the approval pathway. However, there is support for the FDA to create a well-defined pathway for conditional approvals under the Accelerated Approval pathway that is structured and requires timely completion of a confirmatory trial.[5]

Clinical Trials and Real-Life Experience

Real-life experiences refer to the experiences of patients who are receiving treatment outside of a clinical trial setting. These patients likely have different or more advanced disease than patients enrolled in clinical trials. While most payer coverage criteria are based on the clinical trial data, both clinical trials and real-life experiences are important for advancing the care of ALS. Clinical trials provide valuable information about the safety and efficacy of treatments under controlled conditions, while real-life experiences provide insights into the effectiveness of treatments in diverse patient populations and in routine clinical practice. Disease

rarity and heterogeneity, rapid course, knowledge of pathogenesis, and absence of biomarkers are challenges for developing ALS clinical trials. Given the limited supporting evidence and relatively high cost of ALS therapies, it is understandable that payer decision makers would look to the products' pivotal trial inclusion criteria when formulating their coverage decisions.[9] However, the clinical expert representatives stressed that coverage for ALS treatments should not be limited to clinical trial inclusion or exclusion criteria as it results in patients' circumstances and preferences not being considered.

"It is important to understand that when we design clinical trials, it is not the only group we think will benefit from the drug and it doesn't mean that it should only be used in that group as we would expect the benefit to translate to all patients with ALS."
– Neurologist

An example of how a health plan may use clinical study criteria in medication coverage criteria was discussed and included criteria such as: (1) functionality defined by scores on the ALS Functional Rating Scale—Revised (ALSFRS); (2) normal respiratory function; (3) diagnosis/management/consultation by a neurologist; and (4) disease duration of 2 years or less. Clinical expert representatives expressed that clinical measures and scales administered in a controlled clinical trial setting may not be practical for use in an outpatient setting. When a health plan incorporates these measures and scales in approval or recertification criteria it can place undue burdens on the provider and the patient, adding to the complexity of patient management. Moreover, the provider may not correctly administer these scales, which can be complex and time-consuming. Finally, it is important to remember that disease stabilization beyond 2 years is valuable, as the natural course of ALS is rapidly progressive and fatal.

"Failure to improve is not failed therapy, the goal is to slow progression of disease."
– ALS Nurse

The panelists discussed the opportunity for RWE to fill in evidence gaps from ALS clinical trials. RWE obtained from an analysis of real-world data (RWD) from observational studies can bridge gaps in evidence not addressed by randomized controlled trials and is thus valuable to payers for decision-making.[12] Patient registries, such as the National ALS Registry, are now a common source of RWE. RWE could help to determine broader patient populations that could benefit from treatments, outside of those who meet clinical trial inclusion criteria. A RWD aggregator for ALS was an appealing solution to the payer representatives as they estimated each plan would only have a small number of patients with ALS. One challenge the clinical experts raised around creating RWE is the lack of biomarkers and that the progressive nature of the disease means patients don't have a lot of time for evidence to accumulate.

Coordination of Care and Benefits

Payer representatives acknowledged the importance of care coordination for patients with ALS. Care navigators/case managers play a vital role in supporting patients with ALS by providing them with the information, resources, and support. Some of the key responsibilities of a care navigator may include coordinating care, coordinating coverage across benefits, addressing psychosocial needs, and advocating for patients.

Unfortunately, payer and patient representatives stated that patients often initially decline care navigator support for various reasons (Table 2).[13] To overcome these barriers, payers and providers can educate patients and their families about the role of care navigators in supporting patients with ALS.

Care coordination is of high value for patients with ALS and can also help address barriers to

Table 2. Possible Factors Influencing Patient Acceptance of Care Navigator Support

Lack of awareness	Patients and their families may not be aware that care navigator support is available to them.
Independence	Patients may want to maintain their independence and may feel that accepting care navigator support is a sign of weakness or dependence.
Trust	Patients may be hesitant to work with a care navigator. It may take time for patients to build a rapport and feel comfortable working with them.
Fear of stigma	Some patients may be hesitant to accept support due to the stigma.
Cost	Patients may be concerned about the cost of care navigator support and may not want to incur additional healthcare expenses.

care between pharmacy and medical benefits. Clinical expert, patient, and payer representatives uniformly stressed the need for timely coverage of DME for patients with ALS, and noted that delays in covering these services negatively impacts the quality of care and quality of life for patients. Payer and patient representatives expressed that coverage is highly variable, and while DME can be essential for the treatment and management of ALS, there are several challenges patients have with accessing recommended medical equipment, including:

- Coverage restrictions: Health plans often have coverage restrictions on DME. This can result in patients being unable to access the equipment they need to manage their ALS effectively.
- Complex documentation requirements: The process of obtaining DME can be complicated, with complex documentation requirements that vary across payers.
- Lack of communication and coordination: There can be a lack of communication and coordination between prescribing providers, DME, and payers, which can result in delays and misunderstandings in the DME ordering and delivery process.
- Cost: DME can be expensive, and patients may have significant out-of-pocket costs, particularly if their DME benefit is limited. Financial assistance may not adequately address the needs of a patient.

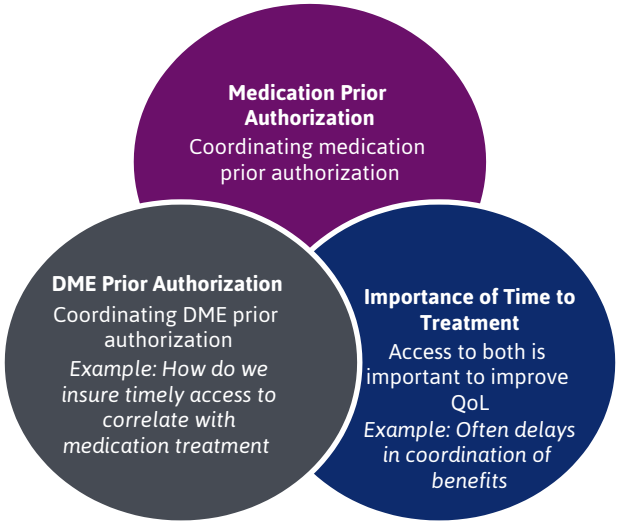
"It is not uncommon for patients to die before they get approval for their power wheelchair."
– ALS Nurse

Addressing these challenges requires collaboration among providers and payers to ensure that patients receive the DME they need in a timely manner to manage their ALS and to benefit from the effects of disease modifying treatments. A framework for quality improvement from an integrated delivery system was presented around coordination across pharmacy and medical benefits (Figure 2). This program focused on creating an integrated PA and medical policy to support streamlined requests and more timely access to ALS treatments and DME (Figure 3). Key steps in improving the coordination between pharmacy and medical benefits are to create consensus on preferred treatment(s) with internal and network providers, use of order sets in the electronic medical record (EMR) bundling the ordering of medications and equipment at the same time, and to use the ICD-10 diagnosis code to trigger handoffs and care coordination within health plans and systems. Planned measurement of the quality improvement program includes a metric around time to DME approval.

"For example, we may reach out to our colleagues on the medical side and say, 'Hey we received a request for an ALS medication through pharmacy, did you receive a request for DME?'"
– Integrated Delivery System

Payer representatives discussed opportunities and limitations around implementing this kind of quality improvement program in a non-integrated system. It was recommended to look at the learnings from other

Figure 2. Considerations for Improved Coordination of Care for Patients of ALS



programs such as the Oncology Care Model. Other key considerations include greater efforts to coordinate and be proactive with providers around medication and DME ordering, and to build a checklist or use the order set approach to connect medication and DME orders into the care navigator work.

Panelists reiterated that early diagnosis, care coordination, and timely access to DME can reduce healthcare costs by avoiding unnecessary hospitalizations, emergency department visits, and delaying costly interventions such as tracheostomy.[14]

Multidisciplinary Care

Efforts around collaborative, multidisciplinary approaches to deliver health care are important for a patient with ALS. Certified Treatment Centers of Excellence for ALS are the standard of care delivery.[15] By providing comprehensive care across a range of clinical disciplines, the multidisciplinary care approach in ALS increases the use of evidence-based therapies, improves quality of life, and may extend survival.[5] However, access to these centers of excellence can be a challenge. To expand access and reduce health inequities, several payer representatives recommended the use of telehealth to deliver high-quality multidisciplinary care from specialized ALS clinics. Payers can support the use of telehealth services by ensuring adequate payment for telehealth is included in provider contracts.

Summary

Patient representatives emphasized the diverse range of ALS experiences and challenges with timely access to ALS medications and DME. Actions encouraged by panelists included rethinking payer authorization processes, increasing collaboration across internal departments and with providers, and utilizing PIE for drugs under investigation for progressive and fatal diseases. It is also important for the AAN to update their practice guidelines for ALS to include best practices for diagnosis and recommendations for new drug therapies as payers consider clinical guidelines in their coverage decisions and utilization tools. The differences between the clinical trial environment and real-life patient experience also deserve consideration when developing formulary management strategies and should consider provider burden and the progressive and varied nature of ALS. Finally, care and benefit coordination for patients with ALS is vital in making progress toward ensuring optimal patient outcomes and lowering overall cost of care. Payers can look to the example framework to improve appropriate access to ALS treatments and other quality improvement programs to identify simple steps to improve benefit coordination and the quality of care for patients with ALS.

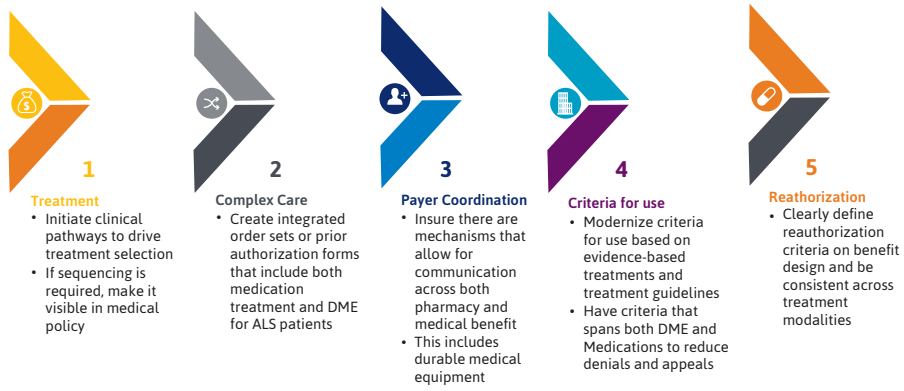
Disclosures

This Market Insights Summit was independently conducted by AMCP with funding from Amylyx.

Acknowledgements

This summit was moderated by Michelle Rice, Michelle Rice and Associates, LLC. This proceedings document was developed by Impact Education, LLC.

Figure 3. Framework to Improve Appropriate Access to ALS Treatments



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