Updates in the Management of Amyotrophic Lateral Sclerosis

Managed Care and Specialty Pharmacy Perspectives

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Disclosures

Dr. Dehoney has disclosed that she has no actual or potential conflict of interest in relation to this program.

The clinical reviewer, **Deanna Kelly**, **PharmD, BCPP**, has disclosed that she has served as a consultant for HLS Therapeutics and Alkermes.

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Type of Activity: Application

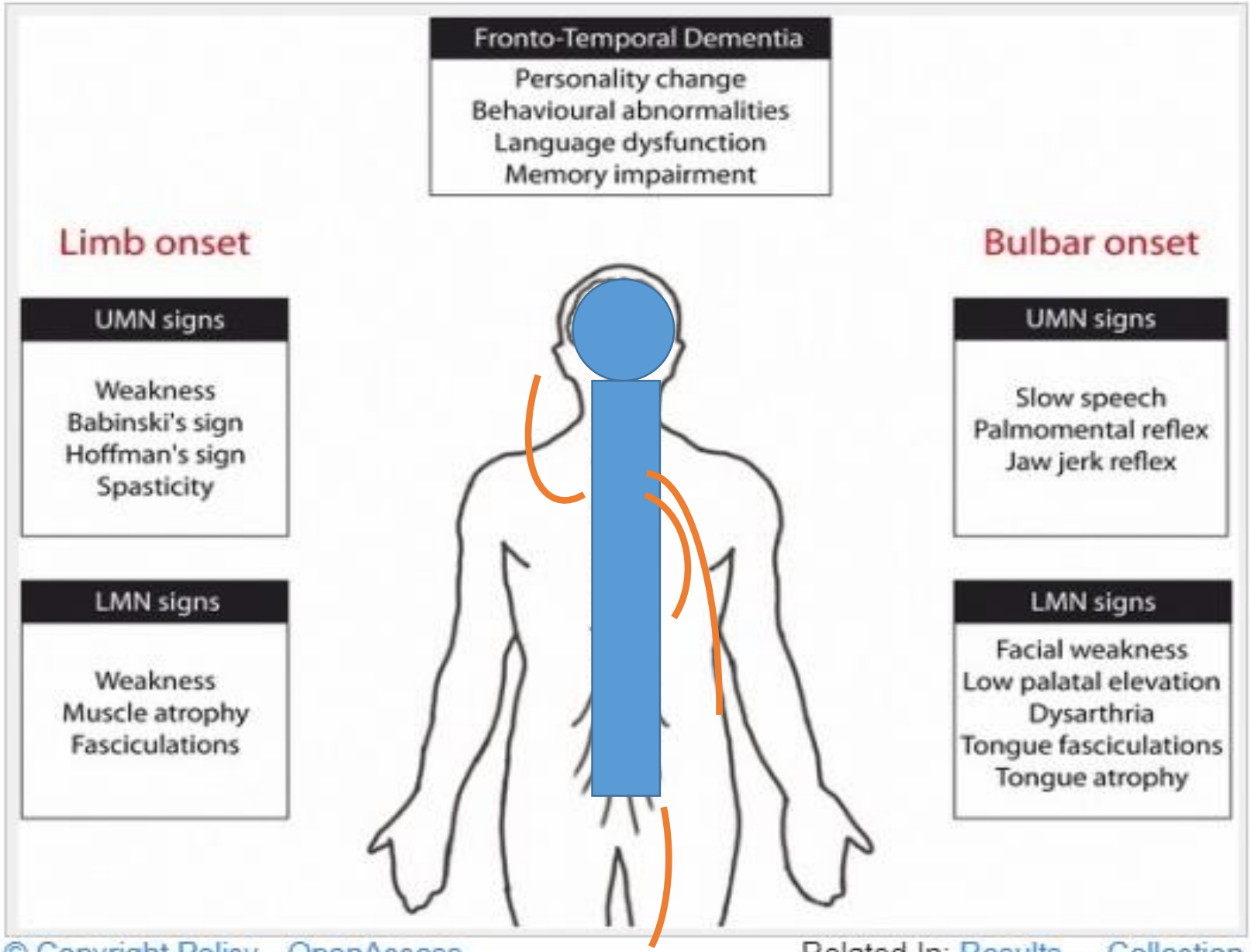
Learning Objectives

- **Describe** the efficacy of available treatment options for amyotrophic lateral sclerosis (ALS), including disease-specific and symptomatic therapies
- **Assess** the safety of disease-modifying ALS treatments
- **Implement** a treatment plan for a patient with newly diagnosed ALS

What is ALS?

- A progressive neurological disorder that affects motor neurons
- Loss of motor neurons in the brain and spinal cord leads to focal weakness
- Muscle weakness spreads over time
- Respiratory muscle weakness leads to respiratory failure and death

Brown RH, Al-Chalabi A. *N Engl J Med.* 2017;377(2):162-72.;
Rowland LP, Schneider NA. *N Engl J Med.* 2001;344(22):1688-700.



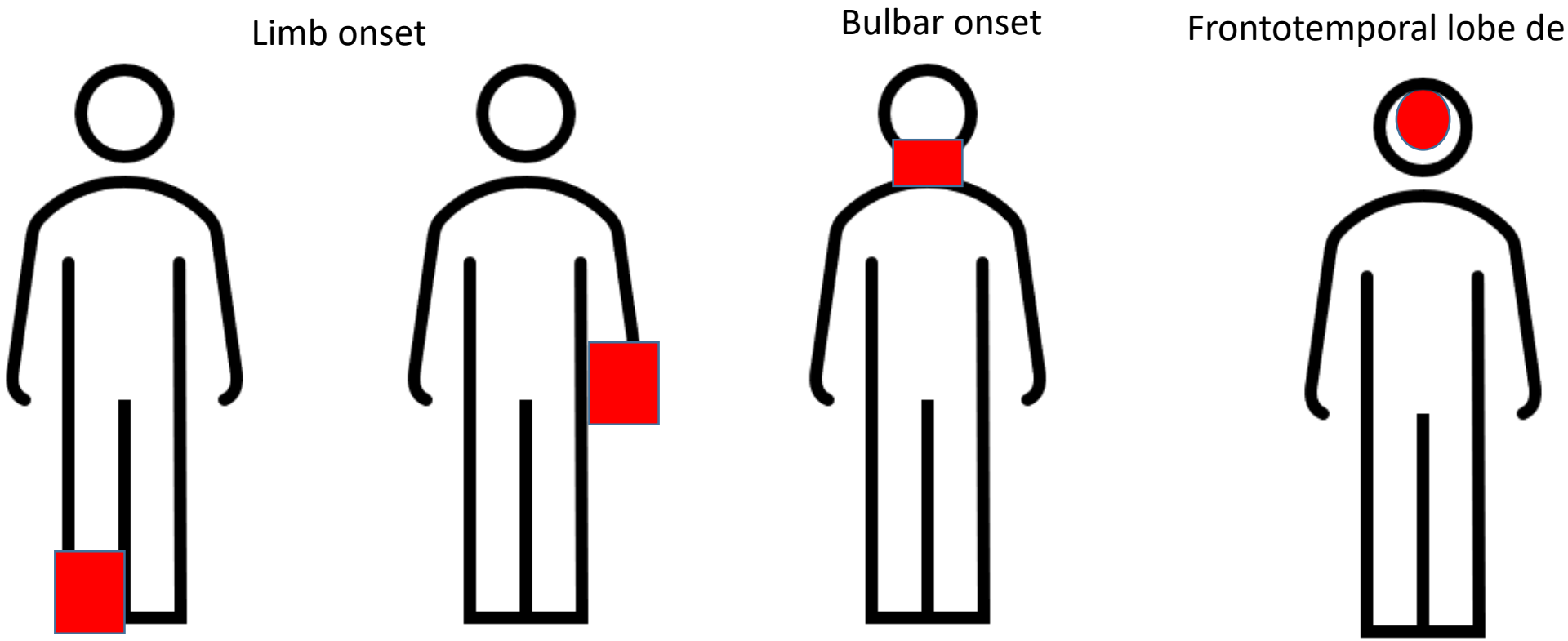
LMN, lower motor neuron;
UMN, upper motor neuron.

Who is affected by ALS?

- It is considered a rare disease
- 5,000 Americans are diagnosed with ALS yearly
- It is estimated that 16,000 Americans have ALS at any given time
- 90% of patients have no family history of ALS (sporadic ALS)
  - Remaining 10% of patients have a family history (familial ALS)
- Average age of diagnosis is 55 but may affect patients from 20 to 80 years old

ALS Association. http://www.alsa.org/about-als/facts-you-should-know.html. Updated May 2019. Accessed June 1, 2020.;
Brown RH, Al-Chalabi A. *N Engl J Med.* 2017;377(2):162-72.

Clinical Presentation



- Denotes focal weakness or area affected

Pathogenesis of ALS

- Cause of motor neuron death is unknown
- Neuron death in other parts of the brain can occur
    - Frontal and temporal lobe in cortex
    - Bulbar area in brainstem
- Critical mass of neurons must be lost for symptoms to occur
- Theories include genetic, environmental, and a combination of both factors
    - Genetic mutations have been associated with both familial and sporadic ALS
- Genetic mutations have downstream effects on cellular processes leading to neuronal death

Brown RH, Al-Chalabi A. *N Engl J Med.* 2017;377(2):162-72.;
Rowland LP, Schneider NA. *N Engl J Med.* 2001;344(22):1688-700.

Diagnosing ALS

- Based on neurological examination, symptoms, electrodiagnostic criteria (e.g., EMG), and time
- It is a diagnosis of exclusion to be done by an experienced clinician
- El Escorial criteria originated as inclusion criteria for clinical trials
  - Diagnosis ranges from suspected to definite
  - Symptoms should be present in both UMN and LMN in more than 1 body region
- Average time from onset to diagnosis is 12 months
- Early diagnosis can be difficult because symptoms may not be present in enough body regions

Brown RH, Al-Chalabi A. *N Engl J Med.* 2017;377(2):162-72.;
Ludolph A, et al. *Amyotroph Lateral Scler Frontotemporal Degener.* 2015;16(5-6):291-2.

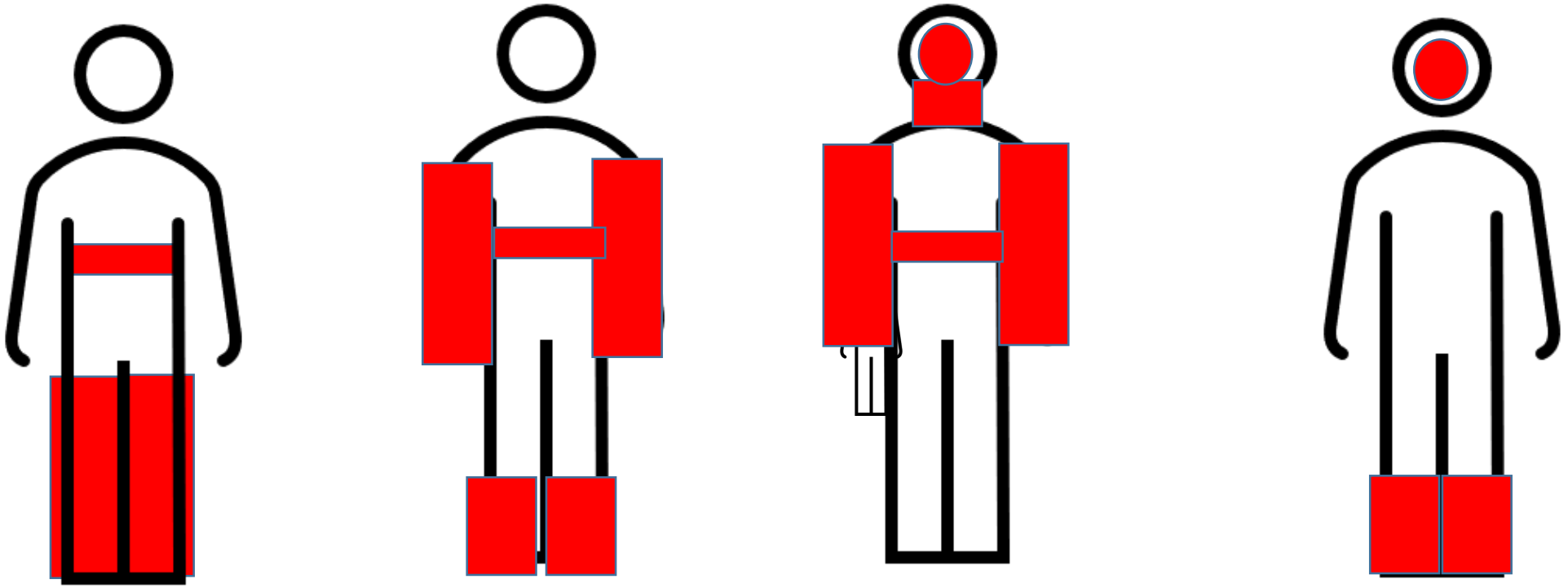
EMG, electromyography.

Implications of an ALS Diagnosis

- Early, but accurate, is key
- Personal
  - Terminal illness
  - Unknown life expectancy
- Economic
  - Ability to continue working
  - Loss or change of health insurance
  - Significant medical equipment and bedside care costs

Bromberg M, et al. *Amyotroph Lateral Scler*. 2010;11(1-2):110-5.

Disease Progression



- Denotes focal weakness or area affected

ALSFRS-R Score

- ALS Functional Rating Scale – Revised (ALSFRS-R) is used to measure disease progression in clinical trials
- Score of up to 4 on each of 12 items

Salivation	**Speech**
Handwriting	**Swallowing**
Cutting food	**Walking**
Turning in bed	**Dyspnea**
Dressing and hygiene	**Climbing stairs**
Orthopnea	**Respiratory insufficiency**

The ALS C.A.R.E. Program. Center for Outcomes Research, University of Massachusetts Medical School. http://www.outcomes-umassmed.org/ALS/alsscale.aspx. Accessed May 27, 2020.

Disease Progression

- There is no cure
- Functional decline will occur
- Respiratory function declines leading to death
  - Respiratory function measured by FVC and NIF
- Patient survival is an average of 3 years but varies

Miller RG, et al. *Neurology.* 2009;73(15):1218-26.

FVC, forced vital capacity;
NIF, negative inspiratory force.

Realities in Disease Progression

- Slowing loss of function is the goal
- Sustained improvement is not realistic
- Heterogenous disease progression
  - Presents challenges for clinical trials

- This should all be considered when re-evaluating insurance approval of disease-modifying therapy

Bedlack R, et al. *Neurology*. 2016;86(9):808-12.

Patient Case

- KP is a 65 year-old female diagnosed with probable ALS and location of onset was bulbar region

Current ALSFRS-R Score	Forced Vital Capacity (FVC)	Onset of symptoms	El Escorial Criteria
34	75% predicted	11 months ago	Probable ALS

- What are appropriate next steps for medication therapy?

Goals of Therapy

- Slow disease progression
- Manage symptoms to improve or maintain the patient's quality of life

Andersen PM, et al. *Eur J Neurol*. 2012;19(3):360-75.;
Miller RG, et al. *Neurology*. 2009;73(15):1218-26.

Interventions Shown to Modify Progression

- Non-invasive ventilation
- Gastronomy tube
- Multidisciplinary ALS care
- Riluzole
- Edaravone

Abe K, et al. *Lancet Neurol.* 2017;16(7):505-12.;
Bensimon G, et al; ALS/Riluzole Study Group. *N Engl J Med*. 1994;330(9):585-91.;
Bourke SC, et al. *Lancet Neurol.* 2006;5(2):140-7.;
Chiò A, et al. *J Neurol Neurosurg Psychiatry.* 2006;77(8):948-50.;
Cui F, et al. *PLoS One.* 2018;13(2):e0192243.

Riluzole

- General mechanisms
  - Inhibits glutamate release, inactivates voltage-dependent Na channels
- Mechanism in ALS
  - Unknown
- FDA approved for ALS in 1995
  - Dosing: Riluzole 50 mg PO BID
- Generic tablets became available in 2003
- Brand oral solution and oral film recently FDA approved

Rilutek tablets [prescribing information].; 2012.;
Riluzole in Lexicomp database. Accessed June 2, 2020.;
Wang SJ, et al. *Neuroscience*. 2004;125(1):191-201.

FDA, United States Food and Drug Administration.

The ALS/Riluzole Study Group Findings

1994 study	1995 study

• 155 patients with probable or definite ALS were randomized to placebo or riluzole 100 mg daily for 12 months
  • Primary endpoints were tracheostomy-free survival and rates of change in functional status at 12 months
 	
  • Tracheostomy-free survival (many subgroup analyses performed)
  • No significant difference at 12 months due to exclusion of 24 patients
  • Significant difference at 18 months
• Primary endpoint was the slope of the rate of deterioration in muscle strength and was slower in the riluzole group than in the placebo group (34.4 vs. 22.9; *P*=0.028)
	• 959 patients with probable or definite ALS were randomized to placebo or riluzole 50 mg, 100 mg, or 200 mg daily for 18 months
	  • Primary endpoints were tracheostomy-free survival and rates of change in functional status at 18 months
	
	  • Tracheostomy-free survival
	  • Unadjusted relative risk at 18 months was 0.95 (0.91-0.99, p=0.04)
	  • Adjusted risk at 12 months was 0.57 (p=0.001) and 18 months was 0.65 (p=0.002) of 100 mg/day
	• Rate of change in functional status (limb and bulbar function, muscle strength)
	  • No discernable effect

Bensimon G, et al; ALS/Riluzole Study Group. *N Engl J Med*. 1994;330(9):585-91.;
Lacomblez L, et al; ALS/Riluzole Study Group II. *Lancet*. 1996;347(9013):1425-31.

Select Other Results

- ALS/Riluzole Study group
  - Risk of death or tracheostomy was reduced by 35% at 18 months compared with placebo
  - Median survival was 83 days longer when compared with placebo (449 days for placebo vs. 532 days for riluzole)
- 2012 Cochrane Review
  - “Riluzole 100 mg daily is reasonably safe and probably prolongs median survival by about 2 to 3 months in patients with ALS”
- Hinchcliffe 2017
  - Number needed to treat is between 6 and 11 to delay 1 death until after 12 months

Bensimon G, et al; ALS/Riluzole Study Group. *N Engl J Med*. 1994;330(9):585-91.; Hinchcliffe M, Smith A. *Degener Neurol Neuromuscul Dis.* 2017;7:61-70.; Lacomblez L, et al; ALS/Riluzole Study Group II. *Lancet*. 1996;347(9013):1425-31.; Miller R, et al. *Cochrane Database of Syst Rev*. 2012;2012(3):001447.

Safety Profile

- Riluzole adverse effects
  - From the package insert
    - ≥ 1 ALT level above normal will occur in approximately half of patients treated with riluzole
    - Elevations greater than 3 to 5 times the ULN occur in < 10% of patients
    - Monitor for signs and symptoms of liver dysfunction for the first 3 months of riluzole treatment and periodically thereafter
    - Neutropenia: monitor for febrile illness
    - Interstitial lung disease: monitor for dry cough or dyspnea, perform chest x-ray
  - From clinical experience
    - Nausea, vomiting, diarrhea, dizziness, circumoral paresthesia

Rilutek tablets [prescribing information].; 2012.

ALT, alanine aminotransferase;
ULN, upper limit of normal.

Riluzole Recommendations

National and European guidelines recommend riluzole should be offered to all patients (Level A recommendation)

Andersen PM, et al. *Eur J Neurol*. 2012;19(3):360-75.;
Hinchcliffe M, Smith A. *Degener Neurol Neuromuscul Dis.* 2017;7:61-70.;
Miller RG, et al. *Neurology.* 2009;73(15):1218-26.

Riluzole: Clinical Considerations

- Riluzole is offered to all patients without preference for type of onset or genetic factors
- Riluzole tablets are generic and cost ~$60 per month on goodrx.com
- Tablets can be crushed and administered via feeding tube
- Best practice is to obtain baseline liver function and monitor for signs of liver toxicity (e.g., labs, patient interview, etc.)
- There are no data on discontinuing riluzole due to disease progression or any other factor except safety

Patient Case

- KP is a 65 year-old female diagnosed with probable ALS and location of onset was bulbar region

Current ALSFRS-R Score	Forced Vital Capacity (FVC)	Onset of symptoms	El Escorial Criteria	Liver function
34	75% predicted	11 months ago	Probable ALS	Normal

- What are appropriate next steps for medication therapy?
  - Discuss benefits:risks and offer riluzole

Edaravone

- General mechanisms
  - Free radical scavenger
- Mechanism in ALS
  - Unknown
- FDA approved for ALS in 2017
  - Dosing:
    - **Cycle 1:** 60 mg edaravone IV daily for 14 days, followed by 14 days drug free
    - **Cycles 2-6:** 60 mg edaravone IV daily for 10 of 14 days, followed by 14 days drug free
- Intravenous infusion

Radicava [prescribing information].; 2018.

Edaravone Study Group Findings: Background

- The first study population was narrowed to those with expected efficacy according to post-hoc analysis
  - Studies involved Japanese patients only
- Subsequent study results in select subset of ALS population met primary outcome of slowing ALS progression
  - This has generated both interest and criticism
  - Supports the theory of ALS population heterogeneity

Abe K, et al. *Lancet Neurol.* 2017;16:505-12.;
Maragakis NJ. *Amyotroph Lateral Scler Frontotemporal Degener.* 2017;18(suppl 1):98-103.

Edaravone Study Group Findings

Edaravone in Well Defined Patients with ALS 2017 study

137 patients receiving 6 courses of edaravone over 6 months

Cycle 1: 60 mg edaravone IV daily for 14 days, followed by 14 days drug free

Then

Cycles 2-6: 60 mg edaravone administered 10 of 14 days, followed by 14 days drug free

Inclusion criteria:

- Age 20 to 75 years
- "Definite" or "probable" ALS with < 2-year duration from first ALS symptom
- ALS grade 1 or 2 in the Japan ALS Severity Classification
- Scores of ≥ 2 points on all 12 items of ALSFRS-R
- FVC ≥ 80%
- Patients were allowed to continue riluzole

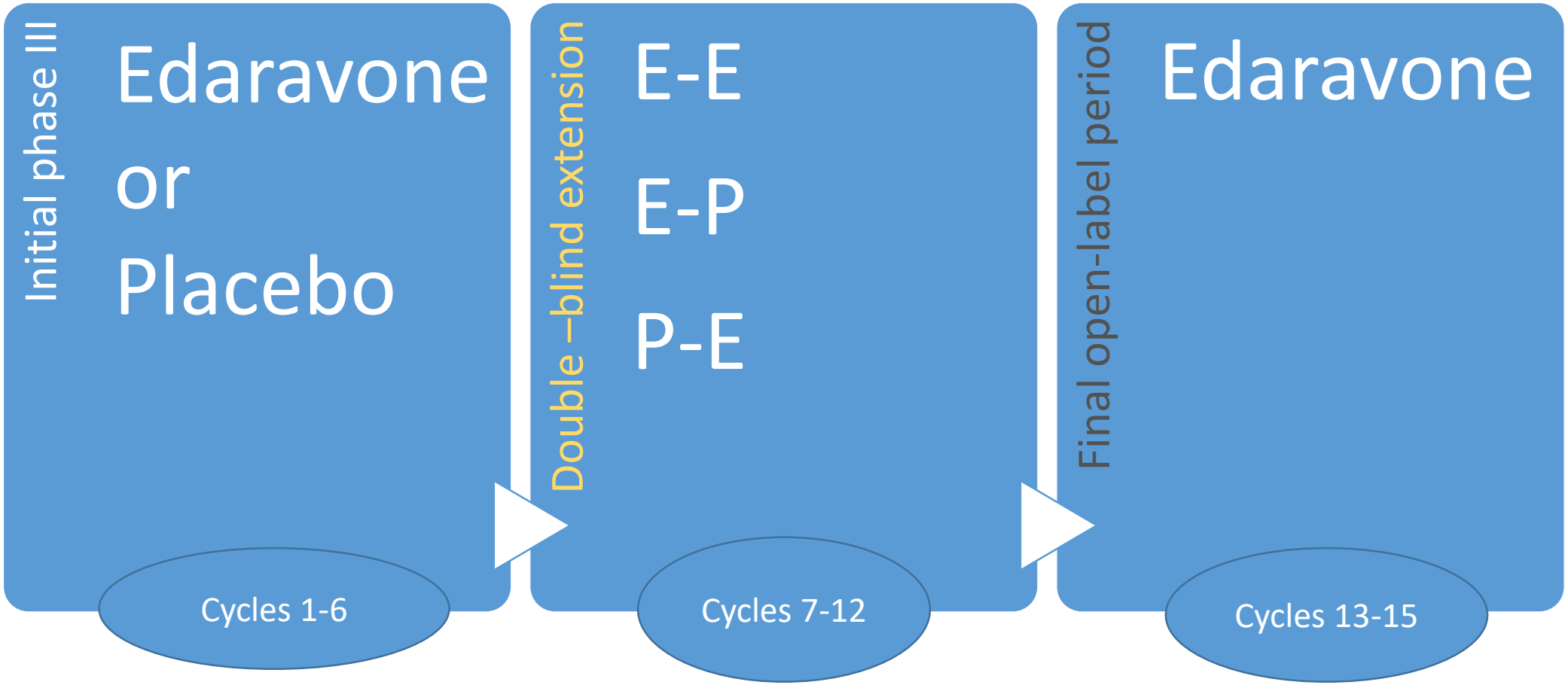
Primary endpoint: change from baseline in ALSFRS-R score at 24 weeks

- **The change in ALSFRS-R score defined as least-squares mean difference was –5.01 (SE 0.64) in the edaravone group and –7.50 (SE 0.66) in the placebo group (p=0.0013)**
- **This translated to 33% less worsening of function over 6 months**

> 90% patients were taking riluzole

Abe K, et al. *Lancet Neurol.* 2017;16(7):505-12.

Subsequent Edaravone Study Group Findings



Abe K, et al. *Amyotroph Lateral Scler Frontotemporal Degener*. 2017;18(sup1):20-31.

Edaravone Study Group Findings

Exploratory Double-Blind, Parallel-Group, Placebo-Controlled Extension Study of Edaravone in ALS	
Patients receiving edaravone in initial trial: Randomized to edaravone or placebo for additional 6 months Patients receiving placebo in initial trial: Received edaravone for additional 6 months Additional open-label period of 12 weeks: All patients received edaravone	181 patients enrolled Adjusted mean change in ALSFRS-R score (SE): E-E: -4.01 ± 0.86 E-P: -5.86 ± 0.98 Resulting inter-group difference: 1.85 (-0.45, 4.15), p=0.1127 No significant differences in %FVC or other measures of function No statistically significant difference in death or specified state of disease progression during the double-blind period (i.e., cycles 7-12) No comparison group that received only placebo and tracheostomy-free survival was not a singular endpoint

Abe K, et al. *Amyotroph Lateral Scler Frontotemporal Degener*. 2017;18(sup1):20-31.

Other Results

- Post-hoc analysis of the open-label study
  - Time period: baseline to 48 weeks
  - Mean change in ALSFRS-R comparison between groups using projections
    - Projections used for placebo-only group and edaravone group
    - Assumes linear progression of ALS loss of function
  - Actual edaravone results: -8.0 mean change in ALSFRS-R score
  - Projected edaravone results: -8.6
  - Projected placebo results: -13.0 ($p<0.001$ for comparison with each edaravone group)

Shefner J, et al. *Muscle Nerve*. 2020;61(2):218-42.

Other Results

- 2018 meta-analysis
  - “Intravenous edaravone is efficacious in ALS patients, with no severe adverse effects. Additional reliable randomized controlled trials with larger sample sizes will further assess the efficacy and safety of edaravone in ALS.”
- 2019 retrospective cohort study
  - 22 patients in edaravone group and 71 patients in no-edaravone group
    - No patients met all phase III trial inclusion criteria
  - 7-month follow-up period
  - No difference in rate of ALSFRS-R decline, muscle strength, %FVC, or rate of death

Abraham A, et al. *Amytroph Lateral Scler Frontotemporal Degener*. 2019;20(3-4):260-3.; Luo L, et al. *Neurol Sci*. 2019;40(2):235-41.

Other Results

- 2018 survey of 75 U.S. physicians caring for ALS patients 1 year after edaravone product launch
  - Administration
    - 43% - home infusion
    - 32% - physician's office
    - 26% - referred site (e.g., infusion center)
    - *> 50% patients receive edaravone via port access*
  - Adverse effects
    - Similar to clinical trials
    - Death or respiratory failure but difficult to delineate true cause
    - 1 case of hypersensitivity that resolved with steroids
  - Average duration of therapy
    - 6.5 months (range, 3 days to 12 months)
  - Concomitant riluzole
    - 67% patients

Jackson C, et al. *Amyotroph Lateral Scler Frontotemporal Degener.* 2019;20(7-8):605-10.

Safety Profile

- Edaravone adverse effects
  From the package insert
  - Most common, with incidence of 10%-15%
    - Contusion, gait disturbances, and headaches
  - Use caution
    - Hypersensitivity reactions: spontaneous reports
    - Sulfite allergic reactions
      - Contains sodium bisulfite
      - Special considerations for patients with asthma
      - Prevalence of sulfite sensitivity in the general population is unknown
  - From clinical experience
    - Weakness, breathing difficulty, fatigue, and disease progression also reported

Radicava [prescribing information].; 2018.

Edaravone Recommendations

- Edaravone was not available at the time guidelines were written
- Approved by the FDA for all patients with ALS
- 2017 European Network for the Cure of ALS Statement
  - “Weighing up the pros and cons of edaravone treatment should be made on an individual basis, taking into account how closely the patient matches the trial clinical criteria, the therapeutic goals of the affected person, and their personal resources.”
  - The neurologist group requested a longer, European trial that looked at efficacy and survival and the 2nd edaravone trial results were published almost simultaneously

Al-Chalabi A, et al. Am*yotroph Lateral Scler Frontotemporal Degener.* 2017;18(7-8):471-4.
ENCALS Statement on edaravone July 2017. Available at: https://www.encals.eu/wp-content/uploads/2017/08/ENCALS-statement-on-edaravone-FINAL.pdf. Accessed on 7/8/20.

Edaravone

- Time counts!
  - Patients self-select by opting out of edaravone
  - Delays in ordering to administration process have a detrimental effect on patients' and caregivers' stress and outlook
- Clinical considerations
  - Home infusion is often preferred by patients and families
  - First infusion in a medical facility is advisable
  - Implanted port access is common
  - Watch for blood clots
  - There are no data on discontinuing edaravone due to disease progression or any other factor except safety

Patient Case

- KP is a 65 year-old female diagnosed with probable ALS and location of onset was bulbar region

Current ALSFRS-R Score	Forced Vital Capacity (FVC)	Onset of symptoms	El Escorial Criteria	Liver function
34	75% predicted	11 months ago	Probable ALS	Normal

- What are appropriate next steps for medication therapy?
  - Discuss benefits:risks and offer riluzole
  - Discuss trial criteria, expected benefit, side effects, cost, logistics (and offer edaravone)?

Medications for Symptom Management

- Cochrane Review 2017
  - Botulinum toxin for sialorrhea is the only medication with moderate evidence
- Challenges to randomized controlled trials (RCTs)
  - Ethical
  - Cost

Andersen PM, et al. *Eur J Neurol*. 2012;19(3):360-75.;
Miller RG, et al. *Neurology.* 2009;73(15):1218-26.;
Ng L, et al. *Cochrane Database Syst Review*. 2017;1(1):CD011776.

Medications for Symptom Management

Symptom	Best evidence	Weaker evidence	Clinical practice
Sialorrhea	Botulinum toxin type B	Radiation therapy	Amitriptyline, atropine eye drops, glycopyrrolate, scopolamine patch
Pseudobulbar affect	Dextromethorphan-quinidine	Amitriptyline, SSRI	
Muscle cramps	Quinine	Mexiletine	
Spasticity		Nabiximols	Baclofen, tizanidine
Bronchial secretions			N-acetylcysteine, guaifenesin, beta-blockers, nebulized medications
Insomnia			Amitriptyline, trazodone, mirtazapine

Andersen PM, et al. *Eur J Neurol*. 2012;19(3):360-75.;
Miller RG, et al. *Neurology*. 2009;73(15):1218-26.;
Ng L, et al. *Cochrane Database Syst Review*. 2017;1(1):CD011776.

SSRI, selective serotonin reuptake inhibitor.

Medications for Symptom Management

- Pseudobulbar affect
  - FDA-approved product dextromethorphan-quinidine based on 2 RCT
    - For patients with CNS-LS score ≥ 13
  - Clinically, this can be incredibly effective and vital for quality of life
    - Evaluate prior authorization process to ensure therapy availability and prompt reauthorization
- Cramps
  - Mexiletine has 1 small RCT
- Spasticity
  - Nabiximols (THC:CBD) oral spray available in Europe
  - 1 phase II/III trial completed

Brooks B, et al. *Neurology*. 2004;63(8):1364-70.; Oskarsson B, et al. *Muscle Nerve*. 2018;10.1002/mus.26117.; Pioro E, et al. *Ann Neurol*. 2010;68(5):693-702.; Riva N, et al. *Lancet Neurol.* 2019;18(2):155-64.

CBD, cannabidiol; CNS-LS, Center for Neurologic Study Lability Scale.; THC, tetrahydrocannabinol.

Mood Management

- Depression
  - Occurs in up to 56% of people with ALS
  - Consider tricyclic antidepressants, SSRIs, mirtazapine
    - Choice based on comorbid symptoms (e.g., sialorrhea, dry mouth, weight, insomnia)
- Anxiety
  - Occurs in up to 30% of people with ALS
  - Cognitive behavioral therapy addressing coping skills, enjoyable activities
  - Consider SSRIs or as-needed lorazepam
    - Choice based on comorbidities and severity of symptoms

Andersen PM, et al. *Eur J Neurol*. 2012;19(3):360-75.;
Atassi N, et al. *Amyotroph Lateral Scler*. 2011;12(2):109-12.;
Kurt A, et al. *CNS Drugs*. 2007;21(4):279-91.

Patient Case

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- What are appropriate next steps for medication therapy?
  - Discuss benefits:risks and offer riluzole
  - Discuss trial criteria, expected benefit, side effects, cost, logistics (and offer edaravone)?

- She complains of excessive salivation and some uncontrollable laughing
  - Consider amitriptyline and educate on side effects

Medication Administration

- Pharmacists play a key role in guiding families on proper administration of medication via a feeding tube

- Review medication list often
  - Watch for pellets (duloxetine, omeprazole capsules)
  - Note long-acting formulations (oxybutynin ER)
  - Assess true benefit or necessity of each medication

- Helpful resources
  - Lexicomp database
  - Handbook of Drug Administration via Enteral Feeding Tubes

Future Directions

- Oral edaravone
  - Phase III open-label safety study in ALS
    - Expected completion June 2021
  - 2 small phase I pharmacology evaluations in ALS patients with gastronomy
    - Expected completion September 2020
- Gene therapy
  - Phase I study of BIIB078, an antisense oligonucleotide for C9ORF mutation-associated ALS
  - Phase III study of tofersen, an antisense oligonucleotide for SOD1 mutation-associated ALS
- Intrathecal stem cell therapy
  - Phase III for “rapid progressors”

Biogen Pipeline. https://www.biogen.com/en_us/pipeline.html. Accessed June 9, 2020.; Identifier NCT03280056. https://clinicaltrials.gov/show/NCT03280056. Accessed June 9, 2020.; Identifier NCT04165824. https://clinicaltrials.gov/show/NCT04165824. Accessed June 9, 2020.; Identifier NCT04176224. https://clinicaltrials.gov/show/NCT04176224. Accessed June 9, 2020.; Identifier NCT04254913. https://clinicaltrials.gov/show/NCT04254913. Accessed June 9, 2020.

Current State of Affairs

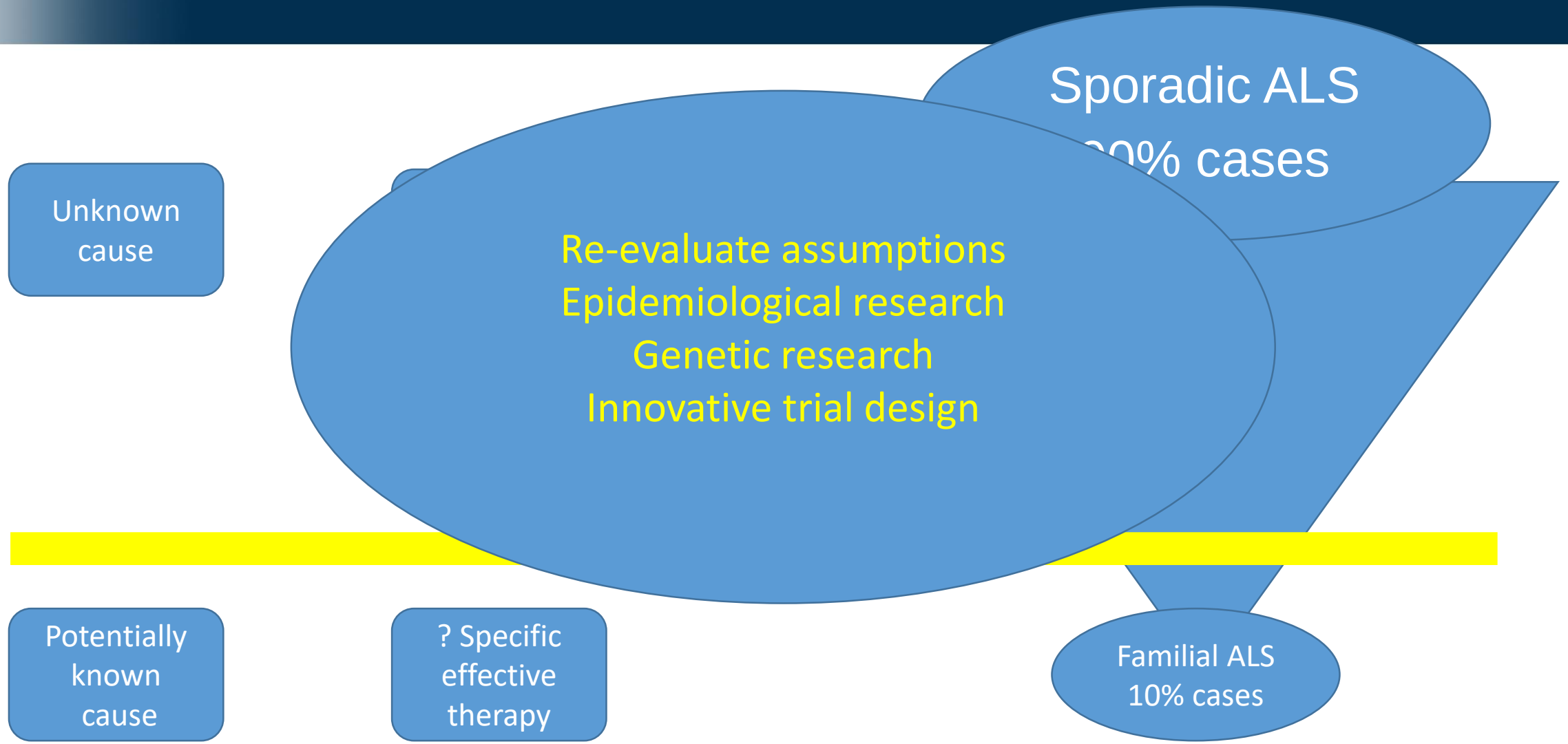
Sporadic ALS

- Riluzole
- Edaravone

Familial ALS

- C90RF-targeted therapy
- SOD1-targeted therapy

Current State of Affairs



Conclusion

- ALS is a terminal diagnosis
- 2 FDA-approved therapies to slow disease progression
- Weigh evidence vs. broader FDA indication for payer approval and re-authorization criteria
- Ensure patient-centered, rapid process for initial and continued approval of therapy

Helpful Resources

- AAN Practice Parameter
- EFNS Guidelines
- ALSuntangled.com
- Clinicaltrials.gov
- ALS Association website