Care for ALS patients and ALS patients with cognitive difficulties

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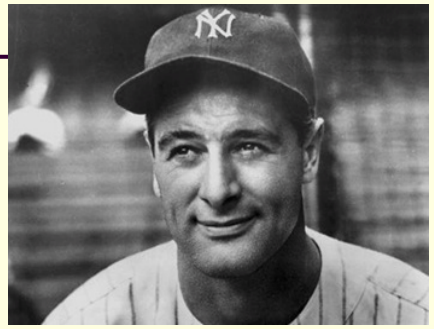
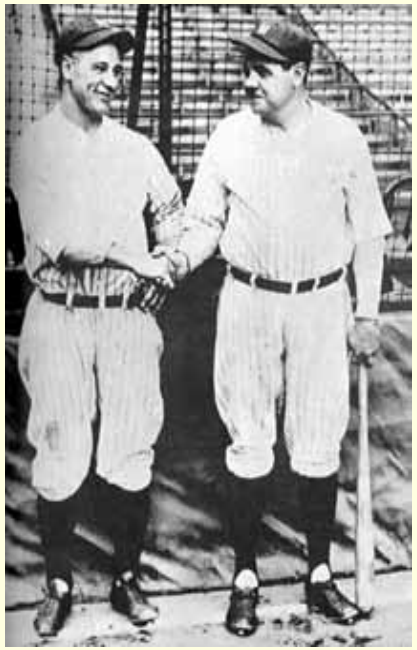
What do we know about ALS today?

- Progressive
  - Universally fatal
  - Mean survival after first symptom: **3-5 years**
- Most common adult-onset motor neuron disease
- Pathogenesis is complex and incompletely understood
- Heterogeneous
  - Every patient with ALS is unique



Lou Gehrig

- Poor 1938 season
- Leg> arm weakness
- Winter 38-39, many falls when skating, dropped things
- Played 2,130 games for 14 years straight
- Played 8 games 1939
- Stopped May 2, 1939
- Diagnosed June 1939
- 1940, Hoarse speech
- Died June 1941 38y/o



- 'But even from the midst of it, he saw himself "not a mere victim of a form of paralysis but a symbol of hope for thousand of suffers of the same disorder."

Kasarskis, EJ, Neurology1989;39:1243-1245

ALS is Heterogeneous

- The diagnosis is clinical and a process of exclusion
- Patients vary in:
  - Rate of progression
  - Regions affected during the disease course
  - Family history of degenerative disease
- Accurate categorization of patients into clinical categories is of utmost importance in facilitating research into targeted therapies
- A key aspect of disease heterogeneity is cognitive-behavioral involvement including frontotemporal dementia

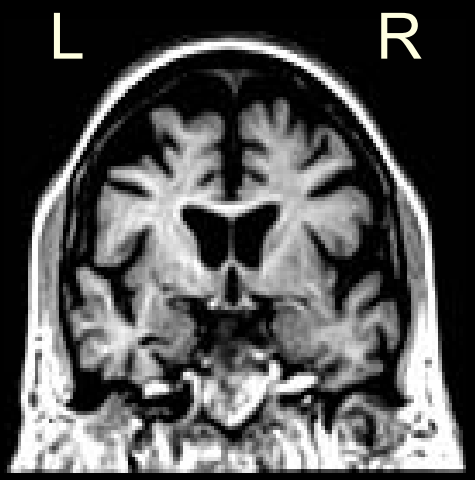
What is Frontotemporal Dementia?

- FTD
  - Selective degeneration and atrophy of frontal and anterior temporal lobes of brain
  - Presents with personality changes, language difficulty, or behavioral disturbance
  - Progressive, irreversible
  - Not a higher risk in pseudobulbar patients
  - Clear criteria established (Neary, 1998)
  - Clearly distinguished from Alzheimer's disease

Major FTD variants

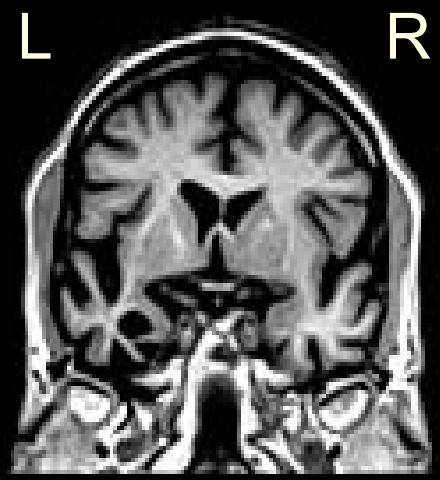
Three prototypical presentations

Behavioral-variant (bvFTD) 'Frontal'



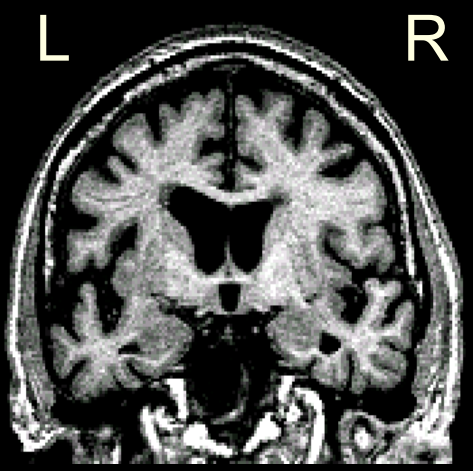
Apathy, disinhibition
Decreased speech output,
Disorganization,
Poor insight

Semantic-variant (svPPA) 'Temporal'



Loss of semantic knowledge,
Poor word comprehension,
Word finding problems,
Good insight

Non-fluent variant (nfvPPA) Left perisylvian



Non-fluent,
effortful speech,
agrammatism, good
comprehension

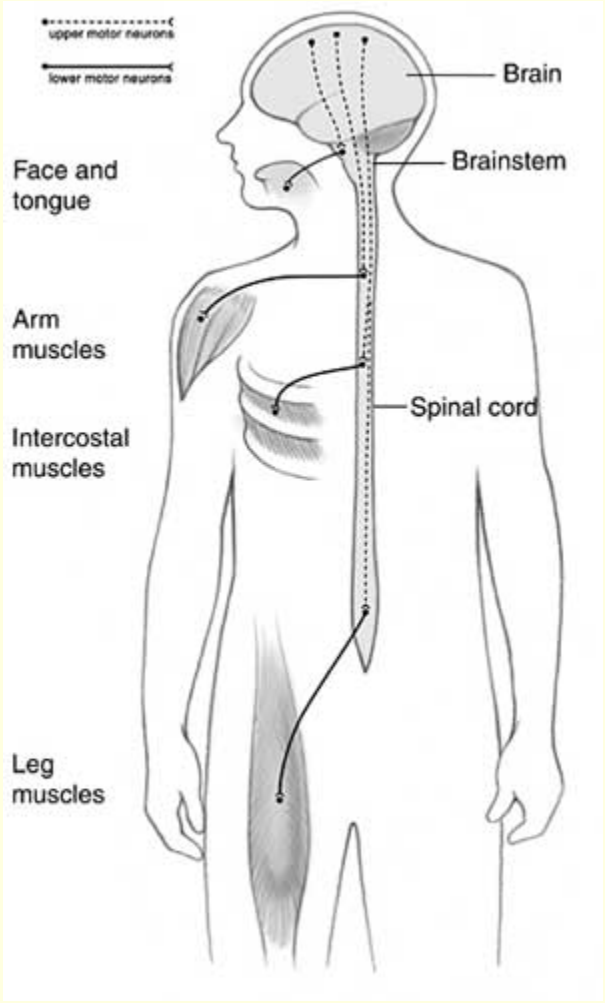
Genetic overlap of ALS and FTD

- Familial: 10% of ALS, 40% of FTD
- Affected family members may have only ALS, only FTD, or both in familial cases
- Suggests a relationship in the pathogenesis of these 2 disorders
- Do ALS and FTD overlap in sporadic cases?
- Is there a spectrum between ALS and cognitively normal and dementia?

Environmental Risk Factors

- Chronic traumatic encephalopathy
  - For decades dementia was known to be associated with boxing
  - Trauma is associated with AD, FTD, ALS, and Parkinsonism
  - TDP43 and tau pathology found predominantly
- Increased frequency of degenerative disease in trauma causing professions
  - Soccer players at greater risk for ALS
  - NFL players 4 times more likely to get ALS
  - Military veterans 2 times more likely to get ALS
    - Higher in deployed versus non-deployed veterans

Clinical Features of ALS



- Upper motor neuron findings
  - Slow speech
  - Brisk gag and jaw jerk, brisk limb reflexes
  - Spasticity
- Lower motor neuron findings
  - Atrophy
  - Fasciculations
  - weakness

Steps in the Management

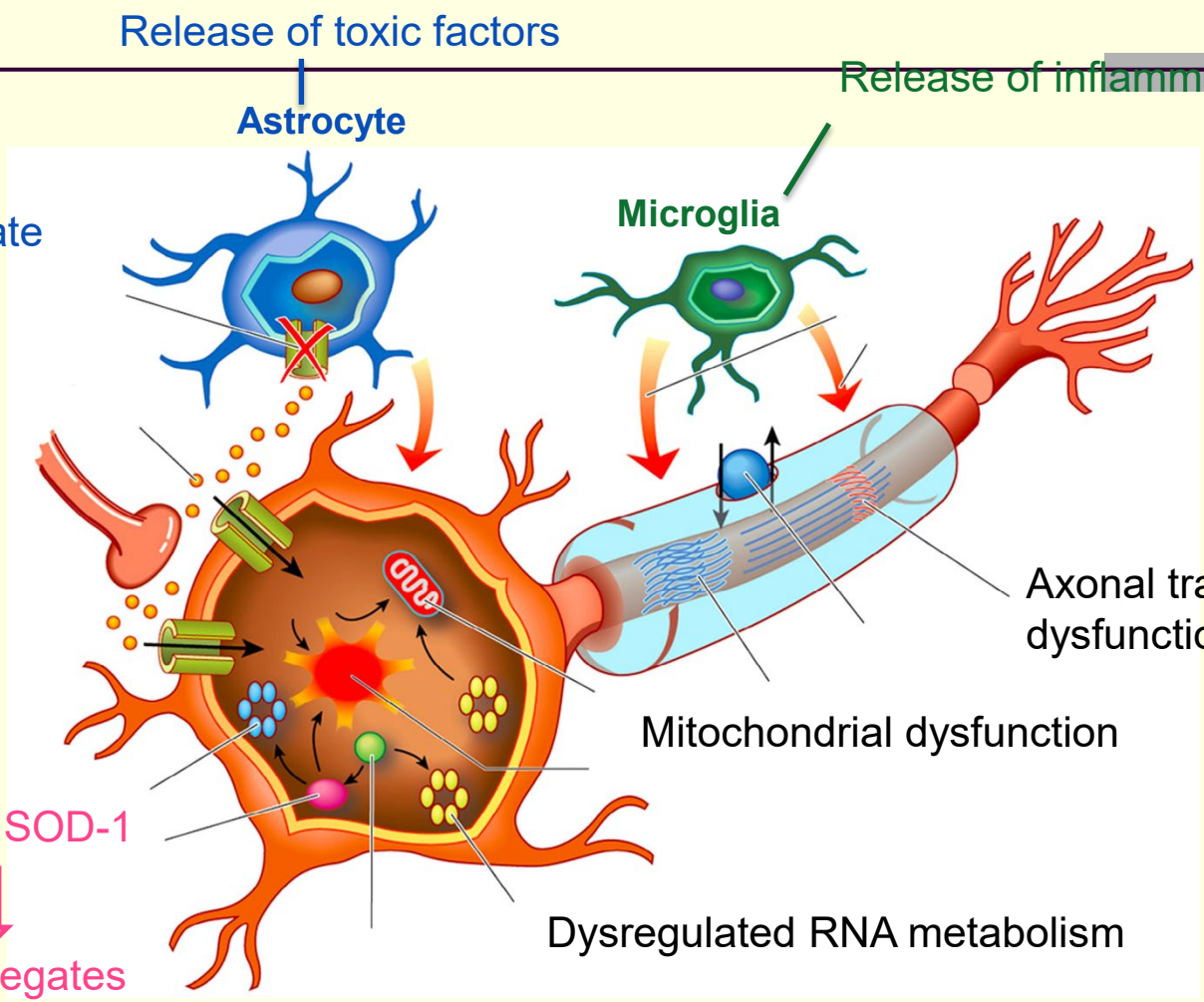
- Making the diagnosis and breaking the news
- Starting treatments that slow the disease process
- Managing respiratory insufficiency
- Managing dysphagia / preventing malnutrition
- Treating symptoms that reduce quality of life
  - Sialorrhea, pseudobulbar affect, spasticity, cramps
  - Maintaining mobility
  - Multidisciplinary care
  - Palliative care

AAN Practice Guidelines Neurology 1999;52:1311; 2009; 73: 1227-1239

ALS-Mimic Syndromes

- Radiculopathies
- CNS disorders (Stroke, Brain tumor, Parkinson's disease, MS)
- Post-poliomyelitis syndrome
- Multifocal motor neuropathy
- Endocrinopathies
  - hyperparathyroidism and hyperthyroidism
- Lead intoxication
- Infections
  - Lyme disease and HIV/AIDS
- Paraneoplastic syndromes - lymphoma, MGUS

How do we treat ALS?



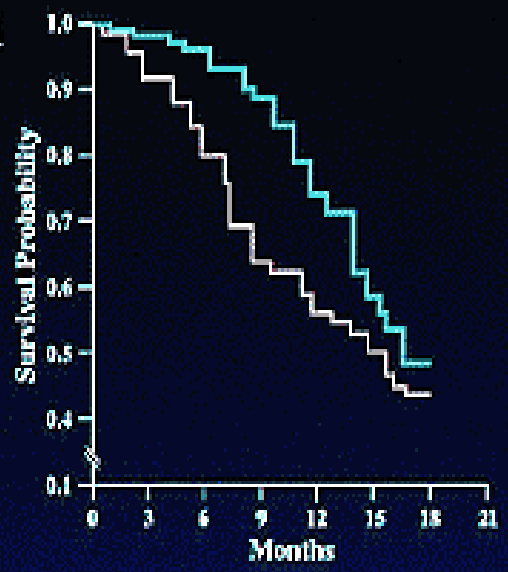
Four FDA approved drugs for ALS

- The precise mechanisms are still unknown
- There may be convergence of multiple pathways
- There are many potential targets for drug intervention and innovative delivery methods
- Current experimental trials are targeting these pathways
- Riluzole, a glutamate antagonist, was FDA approved in 1993 to treat ALS
- Nuedexta, an NMDA agonist, was FDA approved in 2011 for pseudobulbar affect (easy laughing and crying) and may help speaking and swallowing
- Edaravone, a free radical scavenger, was FDA approved in 2017 to treat ALS
- Relyvrio (sodium phenylbutyrate plus TUDCA) targets cell death, was FDA approved in 2022 to treat ALS

THE GLUTAMATE HYPOTHESIS

RILUTEK® (riluzole) Tablets Significantly Extend Tracheostomy-free Survival in ALS Patients

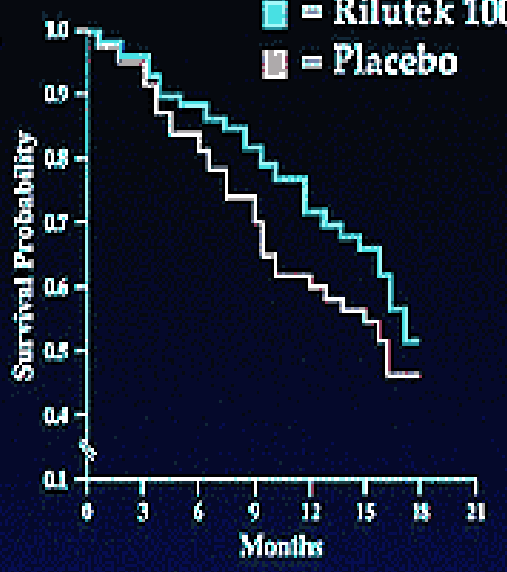
Study 1



P=0.05 Wilcoxon test, P=0.12 Logrank test.
Rilutek (N=77), Placebo (N=78)

Adapted from Bensimon G et al. A controlled trial of riluzole in amyotrophic lateral sclerosis. *NEJM*. 1994;330:585-591.

Study 2



P=0.05 Wilcoxon test, P=0.076 Logrank test.
Rilutek (N=236), Placebo (N=242)

Adapted from Lacomblez L et al. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. *Lancet*. 1996;347:1425-1431.

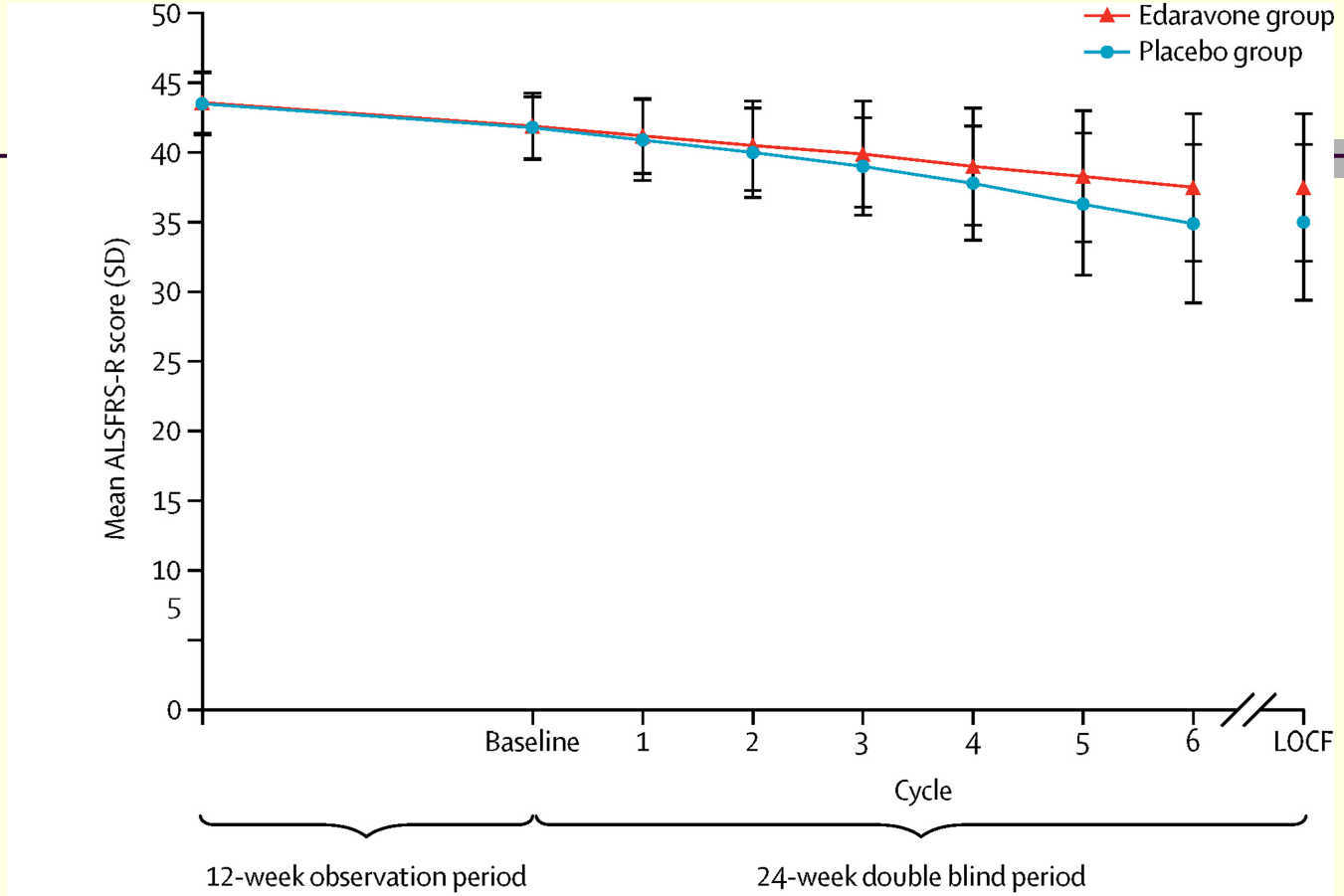
ALS Functional Rating Scale-R

- Speech
- Salivation
- Swallowing
- Handwriting
- Cutting Food and Handling Utensils
- Dressing and Hygiene
- Turning in bed and adjusting clothes
- Walking
- Climbing Stairs
- Dyspnea
- Orthopnea
- Respiratory Insufficiency

Edaravone (Radicava)

- Edaravone is a free radical scavenger
- Edaravone initially not proven to be effective in treating ALS
- Subgroup analysis showed a benefit in slowing of ALSFRS-R in patients with greater baseline functionality, confirmed by a larger study in Japanese patients
- August 2016 FDA accepted a new drug application for Edaravone for consideration of approval in the US by June 2017 and it was released on the US market in August 2017
- May 12, 2022 FDA approved an oral liquid form based on global safety study

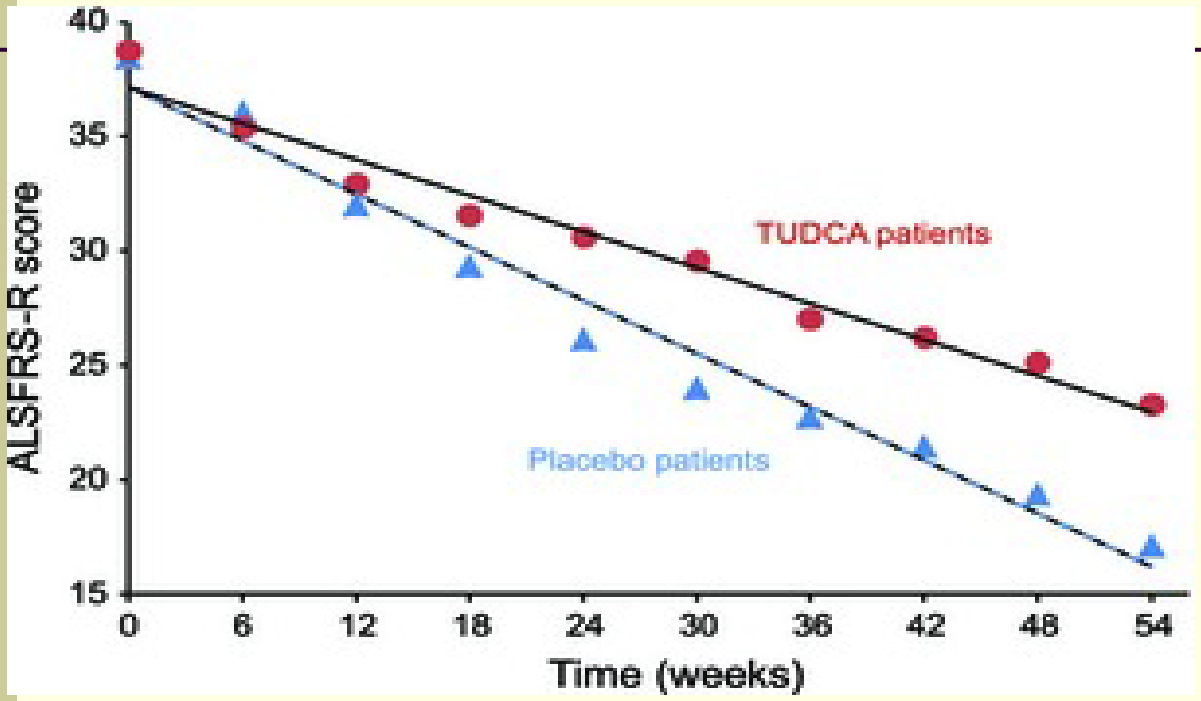
Figure 2



Number of participants									
Edaravone	69	69	69	67	68	68	68	68	68
Placebo	68	68	67	66	65	63	63	61	66

The Lancet Neurology 2017 16, 505-512DOI: (10.1016/S1474-4422(17)30115-1)

TUDCA alone may have benefit

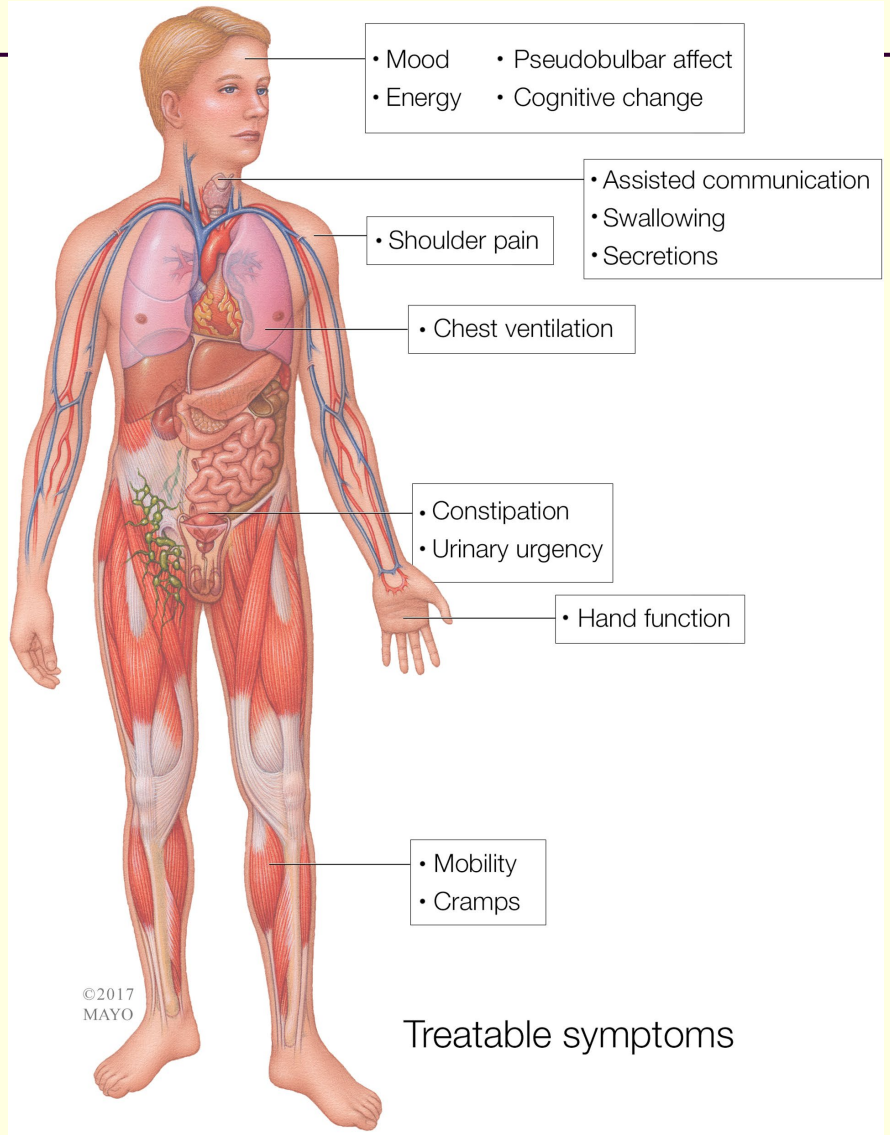


Eur J Neurol. 2016 Jan;23(1):45-52.

How to find a clinical trial?

- Connect with an MDA/ALS Center
  - https://www.mda.org/care/care-center-list
- MDA clinical trial finder
  - https://www.mda.org/research/clinical-trials
- NIH clinical trial site
  - https://clinicaltrials.gov/

Treatable symptoms in ALS

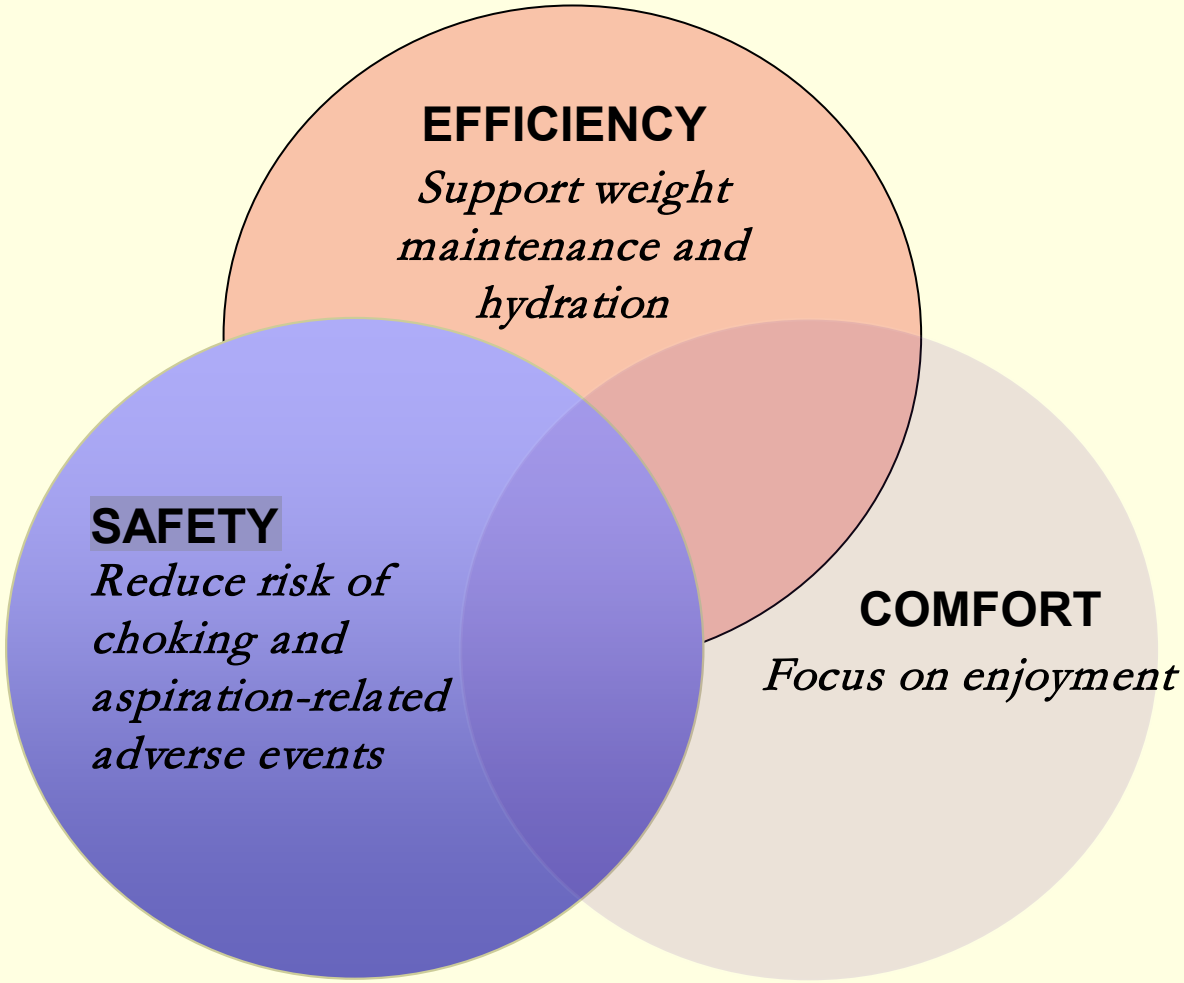


Mayo Clin Proc. 2018 Nov;93(11):1617-1628.

Poor Nutrition

- Causes
  - swallowing trouble
  - arm weakness
  - shortness of breath
  - Increased energy expenditure
- Solutions
  - Breathing support
  - Eating aids
  - High Calorie High Protein Diet
  - Food consistency modifications
  - Feeding tube

Balancing Needs



Pattee, G. L., Plowman, E. K., et al. 2019; Muscle & Nerve, 59(5), 531-536.

Poor Breathing

- Causes
  - Diaphragm weakness
  - Chest muscle weakness
  - Increased energy expenditure
- Solutions
  - Breathstacking/Cough Assist Machine
  - Non-invasive positive pressure ventilation
  - Diaphragm stimulation
  - Invasive ventilation

Breathing equipment helps

- DAYTIME FATIGUE
- SHORTNESS OF BREATH
- COGNITION
- MORNING HEADACHES
- SPEECH AUGMENTATION

Cramps

- Massage, hot baths, stretching
- Tegretol and Baclofen
- Mexiletine
- Quinine Sulfate
  - Prescribe qualaquin if patients have prescription coverage
  - Order quinine sulfate from Canada if no prescription coverage
  - Drink tonic water which contains low doses of quinine

Spasticity

- Balance between too stiff and too loose
- Use baclofen, diazapam, dantrolene, mementine, and tizanidine
- Consider a baclofen pump
- Botox for focal spasticity

Excess Saliva

- Amitriptyline
- Glycopyrrolate
- Atropine pills/drops
- Scopolamine patch
- Radiation therapy
- Botox A or B to parotid and submandibular salivary glands

Thick Saliva

- Guiafenesin (Robitussin)
- Papaya enzyme and Pineapple
- Increase fluids
- Hypertonic saline and mucomyst nebulized
- Cough assist machine

CNS-Lability Scale

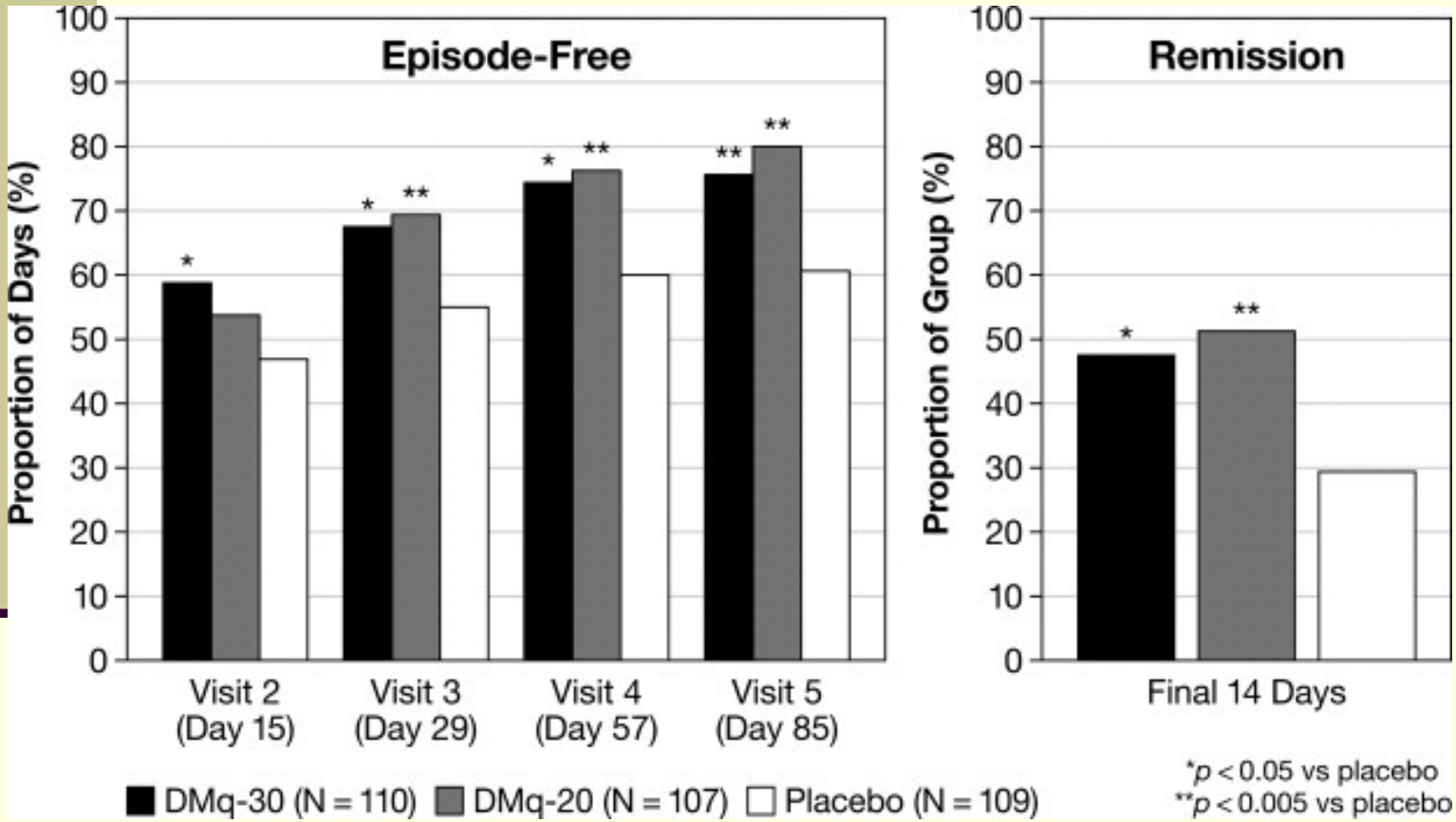
Applies never	Applies rarely	Applies occasionally	Applies frequently	Applies most of the time
1	2	3	4	5

1. There are times when I feel fine one minute, and then I'll become tearful the next over something small or for no reason at all.
2. Others have told me that I seem to become amused very easily or that I seem to become amused about things that really aren't funny.
3. I find myself crying very easily.
4. I find that even when I try to control my laughter, I am often unable to do so.
5. There are times when I won't be thinking of anything happy or funny at all, but then I'll suddenly be overcome by funny or happy thoughts.
6. I find that even when I try to control my crying, I am often unable to do so.
7. I find that I am easily overcome by laughter.

Pseudobulbar affect

- Hard to diagnose until CNS-LS scale
- Traditionally managed with amitriptyline
- SSRIs have a mild effect on symptoms
- Dextromethorphan hydrobromide and quinidine sulfate (Nuedexta)-also can improve speaking and swallowing ability
- Available from a compounding pharmacy if insurance issues covering Nuedexta

Nuedexta Effect



ANN NEUROL 2010;68:693–702

Urinary urgency

- Anticholinergics
  - Tolterodine tartate (Detrol)
  - Solifenacin (Vesicare)
- Condom catheters
- Suprapubic catheters
- Male and Female Urinals

Depression

- Exclude a respiratory problem
- Improve nutrition
- Make sure sleep is good
- Consider referral to a counselor
- Start antidepressants as needed

Sleep

- Most ALS sleep problems are mechanical
  - Lack of appropriate breathing support at night
  - Difficulty positioning during the night for comfort
- Start treatment with herbal or mild over the counter aids
- Consider sedating antidepressants
- Lastly, try the benzodiazepines

Constipation

- Increase fluids
- Increase fiber
- Consider stool softeners
- Consider lactulose

Weakness

- Optimization of home and work environments
- Anticipation of equipment needs
- Driving assessments for safety
- Exercise

Exercise Recommendations

Exercise DO's	Exercise DON'TS
✓ DO resistance training for unaffected/minimal weak muscles AND Stretching Exercises daily – active and passive if needed	✗ Don't exercise to the point of fatigue or overwork muscles
✓ DO light aerobic exercise in the form of walking, stationary bike/cycling, swimming.	✗ Don't push yourself until you are sore the next day
✓ DO take short rest breaks and save energy so you can continue doing self care activities	✗ Don't strengthen weak muscles

Optimization of home and work environments

- Work assessments with AT Network
- Home assessment with home safety evaluations
- Specialty contractors for home remodeling
- Hospice

Equipment Advances

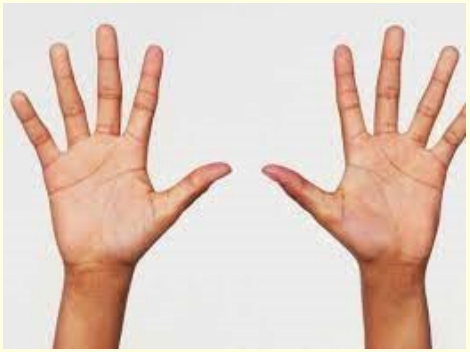
- Flexible Ankle Foot Orthodics
- Lighter, sturdier walkers, canes, and crutches
- Manual wheelchairs with tilt and recline features
- Electric wheelchairs weighing just 14 pounds
- Stair lifts and climbers
- Portable ramps and rail systems
- Specialized beds that turn patients

Exercise

- Prolongs survival
- Improves quality of life
- Reduces spasticity
- Strengthens stronger muscles
- Elevates mood

Speech-Language Pathology & ALS

Communication



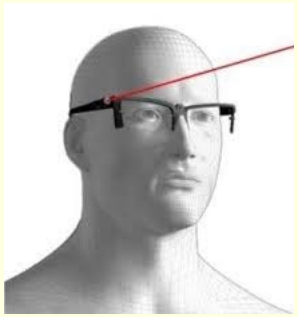
Speech-Language Pathology & ALS

Communication

High-Tech

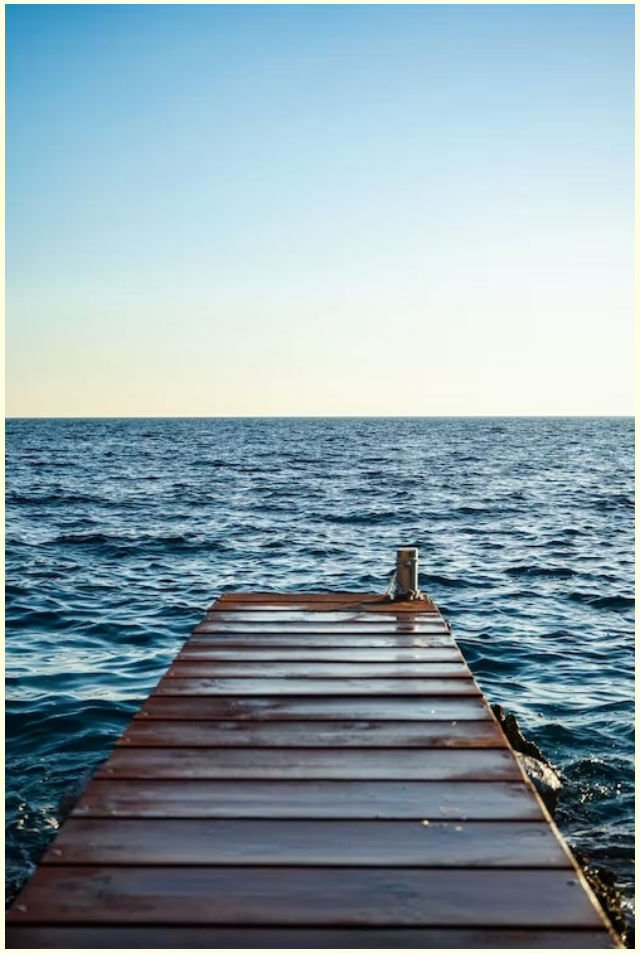
Mid-Tech

Low / No-tech



Very end of Life Issues

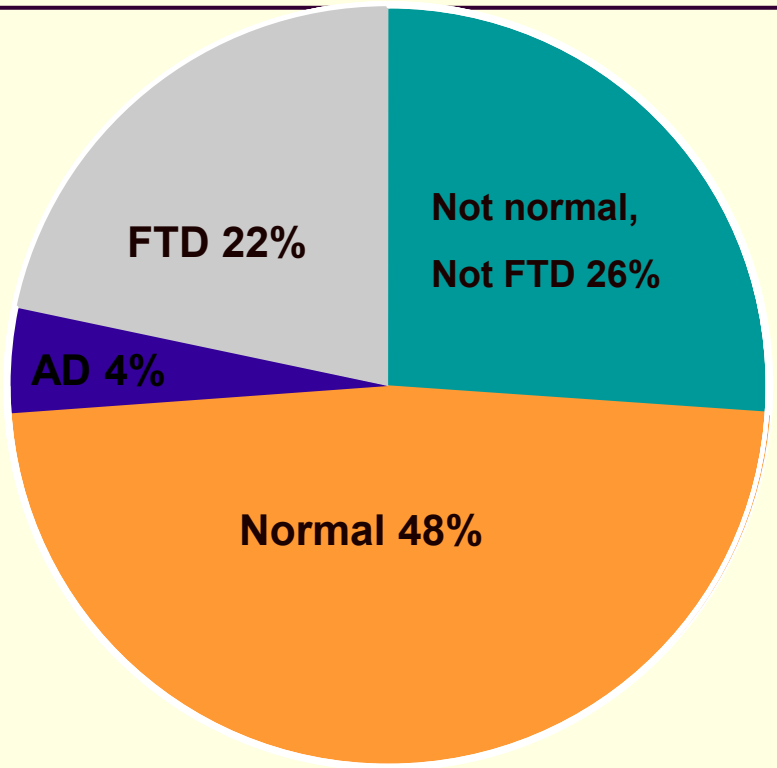
- Talk about end of life issues throughout the disease process
- Enroll in hospice as soon as eligible
- Utilize home care if not hospice eligible
- Continue to follow in an ALS multidisciplinary clinic while in hospice

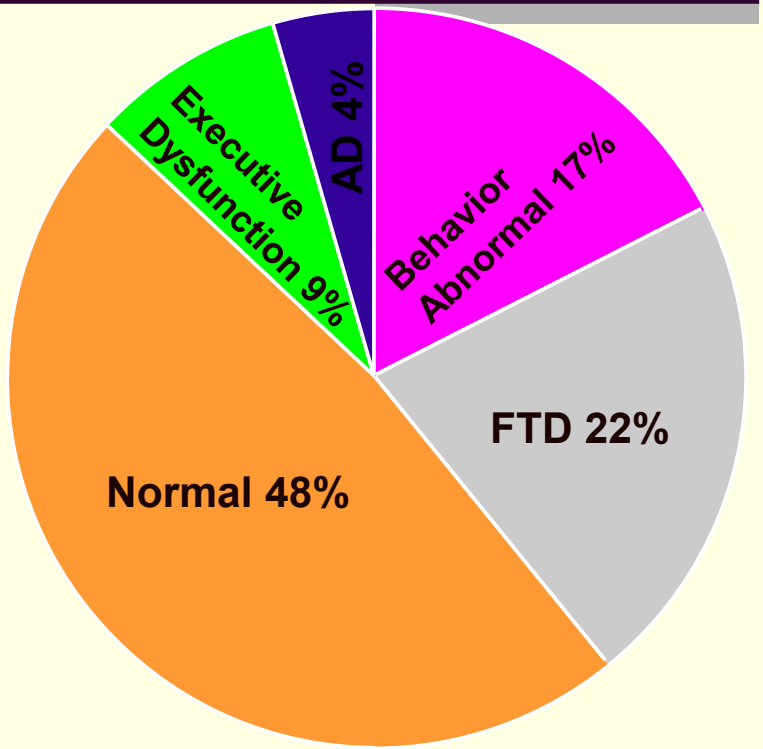


ALS, FTD, and in-between

- Frontotemporal impairment in ALS and vice versa
  - 30% FTD patients show signs of definitive or possible ALS
  - 50% of ALS patients show executive function deficits
- Four clinical subtypes (ALS FTD spectrum disorder)
  - ALS
  - ALS-cognitive impairment (ALSci)
  - ALS-behavioral impairment (ALSbi)
  - Frontotemporal dementia (FTD)

Incidence of FTD in ALS

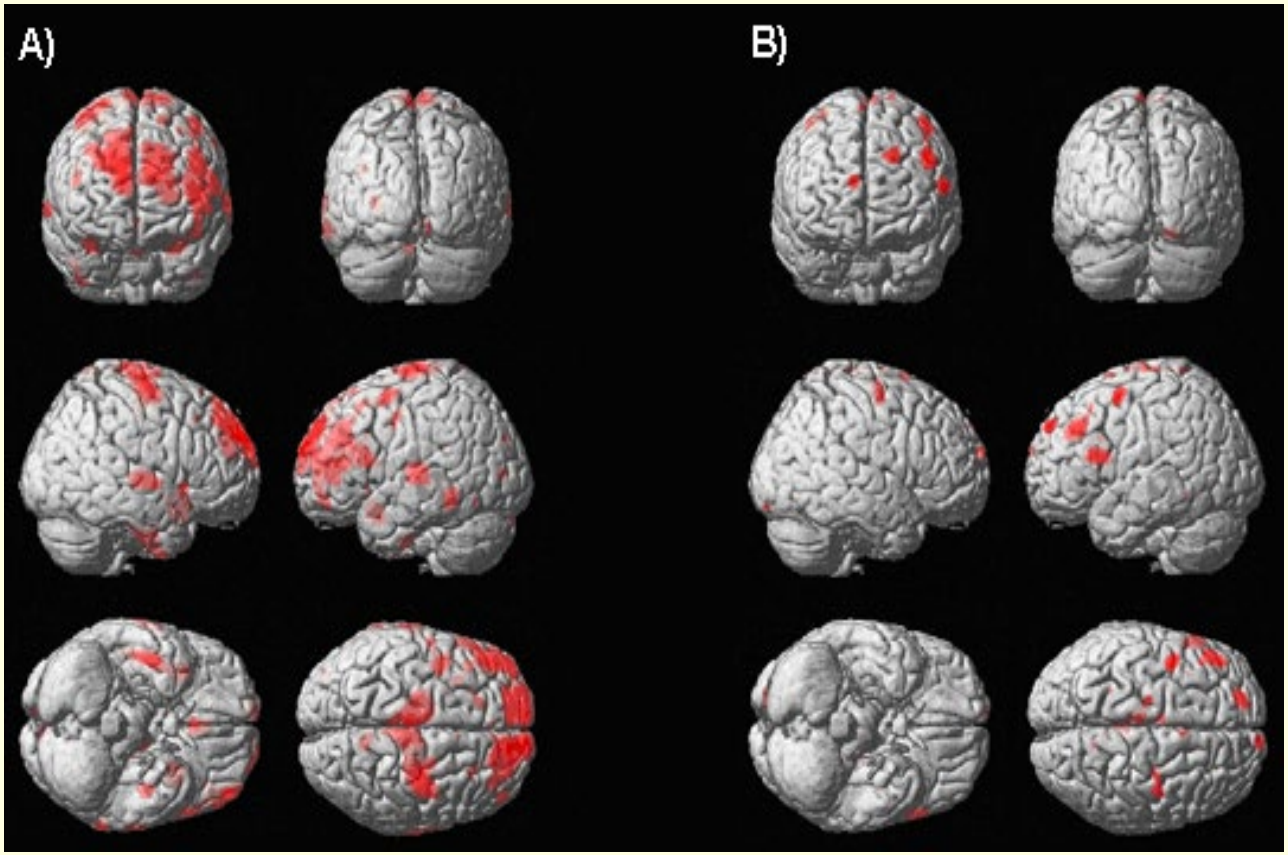




The 26% that is not normal but also not FTD is being redefined as Executive Dysfunction (9%), Behavior Abnormalities (17%)

Continuum of Abnormalities

Chang et al, Neurology 2005



Pathology of ALS-FTD

- Inclusions in spinal cord and frontal and temporal lobes
- TDP-43 was discovered to be the major disease protein in both ALS and the most common form of FTD. Mutations in TDP-43 cause ALS and FTD.
- The protein was recovered only from affected central nervous system regions, including hippocampus, neocortex, and spinal cord and represents the common pathologic substrate linking these neurodegenerative disorders.

Major Genetic Link Identified 2011

- 10% of ALS case are familial
- Families may have FTD, ALS, or both
- Mutations in TDP-43 found in FTD and ALS cases
- *C9ORF72* is responsible for 20-40% of all familial ALS cases and 12% of FTD cases
- 4% of sporadic ALS cases and 3% of sporadic FTD cases have mutations in C90RF72

Is it FTD behavior or is it a coping mechanism?

- Coping mechanisms
  - Withdrawn due to depression
  - Stubborn
  - Seeking control in some area of life
  - Anger outbursts due to frustration of ALS
  - Denial
  - Language problems due to dysarthria
- FTD behaviors
  - Apathetic
  - Dis-inhibited
  - Poor judgement
  - Easily frustrated
  - Quick to anger
  - Lack of insight
  - Language difficulty
    - Word finding
    - Spelling
    - Aphasia

Mimics of cognitive and behavioral impairment in ALS

- Depression or other underlying psych disorder
- Pseudobulbar affect
- Hypoxia or hypercapnea
- Educational level/baseline intellectual functioning
- Presence of bulbar palsy or paralysis limiting testing
- Advanced disease

Does this milder form of FTD have clinical significance?

- Two hypothesis:
- Survival is shorter in patients with ALS-FTD than ALS alone
- Compliance with treatment recommendations is significantly less in patients with ALS-FTD than ALS alone

Olney R, Murphy J, Forshew D, Garwood E, Miller B, Langmore S, Kohn M, Lomen-Hoerth C, “The effects of executive and behavioral dysfunction on the course of ALS” Neurology 2005; 65: 1774-1777.

Survival in ALS with co-morbid FTD

- Olney et al 2005 showed a survival difference of more than a year between patients with co-morbid disease versus ALS alone.
- Since the Olney publication, subsequent authors have demonstrated similar findings with a shortened survival in ALS patients with co-morbid disease for both mildly impaired and moderately impaired patients, Gordon et al 2010

NPPV and PEG Compliance

	NPPV	PEG
ALS-FTLD	25%	28%
ALS only	62%	69%
z	2.22	2.01
p (one-tail)	< 0.02	< 0.03

Important Clinical Issues for ALS Patients with Cognitive/Behavioral Impairments

- Reduced survival rate
- Poor compliance (poor use of PEG, BiPAP)
- Caregiver distress
- Poor safety awareness (falls, choking)
- Inability to manage important decisions
- Implications for stem cell therapy
- Impacts communication options for patients

Summary

- Medications are available to treat many of the symptoms of ALS
- Equipment advances enable patients to be more independent than ever
- Multidisciplinary clinics improve the quality of life for ALS patients and prolong survival
- It is important to be aware of cognitive and behavioral impairments that impact survival and management

Multidisciplinary ALS Team

Core Members

- Neurologist
- Nurse
- Speech pathologist
- Dietitian
- Respiratory therapist
- Physical therapist
- Occupational therapist
- Social worker
- Rehabilitation technologist
- Psychologist

Consultants

- Rehabilitation physician
- Pulmonologist
- Gastroenterologist

Associates

- Research scientists
- ALSA and MDA

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David Besio
(Nutritionist)

Christoph Karch
(Fellow)

Jennifer Coggiola
(Speech therapist)

Carrie Grouse
(Fellow)

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Mira Kleytman
(Respiratory therapist)

Mercedes Paredes
(Physician)

Colleen Meier
(Respiratory therapist)

Deborah Ha
(Speech therapist)

Virginia Santos
(Clinic Coordinator)

Miriam Crennan
(Occupational therapist)