Diagnosis, Treatment and Research for ALS: Old and New Ideas

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Learning Objectives

- Recognize phenotypes of ALS and common variants
- Learn minimum work-up to diagnose ALS
- Understand principles of management of ALS patients
- Be aware of current research
Disclosure

- Consultant – NuFactor, Regeneron
- Speaker’s Bureau – Grifols, Sanofi, Walgreen’s
- Grant Agencies – NIH, FDA OPD, PCORI, ALSA, MDA
- Industry Studies – Cytokinetics, TEVA, Synapse, Questcor, CSL Behring, Alexion, Catalyst, BioMarin, Sanofi, Novartis, Eli Lilly
ALS Case #1

- 1st eval by KU neuro Jan ‘07
- 63 female
- Right leg weak July 2006
- Gradually worse -> RT foot drop
- Cramps RT calf
- No numbness, tingling, pain
ALS Case #1 (cont.)

- Exam
  - Arm strength normal
  - Legs – RT leg grade 4/5 prox & distal
    - Left ankle grade 4+
  - Reflexes – brisk grade 3 knees/ankles (0 to 4 scale)
    » Babinski signs bilateral (extensor plantar responses)
    » Sensory – normal
- EMG – active denervation RT leg, arm and thoracic paraspinous muscles
- Dx: ALS
- Rx – Rilutek 50 mg bid; CoQ10 trial (NIH)
- Course – progression in legs bilat & slurred speech & dysphagia
- Lithium trial (MDA) x 12 months
- Progression – weakness to arms
- BiPap Rx for shortness of breath
- Death July 2009
Amyotrophic Lateral Sclerosis

[Image of a brain diagram with labels and arrows]

[Image of a portrait of a person with a signature]
Motor Neuron Disease

**Terminology:**
- Amyotrophic Lateral Sclerosis
  - Lou Gehrig’s Disease
  - Charcot’s Disease
- Spinal Muscular Atrophy
- Progressive Muscular Atrophy
  - Aran-Duchenne Syndrome
  - Brachial Amyotrophic Diplegia (BAD)
  - Leg Amyotrophic Diplegia (LAD)
- Primary Lateral Sclerosis
- Progressive Bulbar Palsy
  - Isolated Bulbar ALS (IBALS)
Spectrum of Motor Neuron Disorders

- amyotrophic lateral sclerosis
- primary lateral sclerosis
- IBALS
- progressive muscular atrophy
- hereditary spastic paraplegia
- spinal muscular atrophy

UMN - HEREDITARY - LMN

BAD - LAD
ALS

Demographics:

- Incidence U.S.: 2 to 3 per 100,000
- Prevalence U.S.: 35,000
- Male slightly > Female
- Peak age onset - 6th decade
  - But range < 20 to > 80
- 95% sporadic
  - 5-10% aut dom (FALS)
  - 20% of these secondary SOD mutation
  - TDP-43, VCP, FUS, ubiquilin sentaxin mutations
  - New 25-50% hexanucleotide expansion in chrom 9p21-c9ORF/4% sporadic
ALS

**Symptoms/Signs:**

- Lower motor neuron:
  - Weakness/asymmetric
  - Atrophy
  - Cramps
  - Fasciculations

- Upper motor neuron:
  - Weakness and stiffness
  - Spasticity/clonus
  - Pathologic hyperreflexia

- Dysphagia/dysarthria/shortness of breath

- Pseudobulbar affect

- Cognitive changes – frontotemporal dementia

**Site of Onset:**

- Approximately 1/3 Arm
- Approximately 1/3 Leg
- Approximately 1/3 Bulbar
ALS

**ALS: Lab Work-Up:**

- Minimal Labs Needed:
  
  - ? CBC/Chem 20
  
  - Creatinine kinase (CK)
  
  - ? Serum protein electrophoresis (SPEP)
  
  - ? Thyroid tests T4/TSH
  
  - ? Parathyroid tests (PTH, calcium, phosphate)
  
  - Electromyography (EMG) for denervation potentials and R/O myopathies, neuropathies
    
    - Fibs in 2 muscles in 2 ext or 1 ext + 1 bulbar muscle
    
    
  - Cervical MRI if no bulbar symptoms/signs
I have generally been checking paraneoplastic antibodies (through Mayo Clinic) in my patients with suspected ALS which I know is also standard practice at some major ALS Centers (like Mayo and Cleveland Clinic). In the last year or so, I have identified at least four subjects with either moderately elevated GAD65 or nicotinic ganglionic acetylcholine receptor antibodies from blood, none of whom were found ultimately to have a neoplasm. The GAD65 positive patient was treated aggressively with IVIG and IV methylprednisolone without any response and ultimately died.

My questions to the group:
1. Are many people checking these antibodies routinely?
2. For those who do, has anybody had these specific autoantibodies come back positive and if so, have any of the patients been found to have a neoplasm or responded to immunomodulatory therapy?
3. Given that no specific autoantibody has ever been identified in ALS and any association between ALS and any neoplasm is quite tenuous, should paraneoplastic antibody testing be routinely deferred and NOT considered standard of care in the diagnosis of ALS?

this is new to me… i have never heard of getting these panels on ALS pts… ever!
i am sure we have never done it at KU and i also dont ever recall an ALS pt having
“paraneoplastic” als in 25 years…..can anyone in RRNMF give an example of a case they think is paraneoplastic ALS? or an example where these Mayo antibodies gave a result that was related to the clinical presentation of ALS?
Tomorrow i am giving the annual ALS talk at U colorado… i have one slide on the wu of als…. i argue there is no blood work at all to get on a typical patient and essentially no tests to run except a limited EMG to confirm the clinical suspicion. we ultra specialists should be able to dx ALS with no lab tests… and we usually do. Katz and i have been talking about this for years…. the health care system would save a lot of money if they paid us ultra specialists to just make a dx

ALS

Prognosis:

- Rochester, Minn.
  - 50% survival at 3 years
  - 20% live 5 years
  - 10% live 10 years

- Worse prognosis if:
  - Bulbar onset
  - FALS
  - Simultaneous arm/leg onset
  - Older age at diagnosis
    - Onset < 40: 8.2 years duration
    - Onset 61-70: 2.6 years duration
Brachial amyotrophic diplegia
A slowly progressive motor neuron disorder

J. S. Katz, MD, G. I. Wolfe, MD, P. B. Andersson, MD, D. S. Saperstein, MD, J. L. Elliott, MD, S. P. Nations, MD, W. W. Bryan, MD and R. J. Barohn, MD

**Article abstract - Objective:** To describe a sporadic motor neuron disorder that remains largely restricted to the upper limbs over time. **Background:** Progressive amyotrophy that is isolated to the upper limbs in an adult often suggests ALS. The fact that weakness can remain largely confined to the arms for long periods of time in individuals presenting with this phenotype has not been emphasized. **Methods:** We reviewed the records of patients who had a neurogenic "man-in-the-barrel" phenotype documented by examination at least 18 months after onset. These patients had severe bilateral upper-extremity neurogenic atrophy that spared lower-extremity, respiratory, and bulbar musculature. **Results:** Nine of 10 patients meeting these criteria had a purely lower motor neuron disorder. During follow-up periods ranging from 3 to 11 years from onset, only three patients developed lower-extremity weakness, and none developed respiratory or bulbar dysfunction or lost the ability to ambulate. **Conclusion:** Patients presenting with severe weakness that is fully isolated to the upper limbs, without pyramidal signs, may have a relatively stable variant of motor neuron disease. **Key words:** Man-in-the-barrel syndrome—Amyotrophic lateral sclerosis—Focal amyotrophy—Motor neuron disease—Brachial amyotrophic diplegia.
Brachial Amyotrophic Diplegia
“Flail Arm Syndrome”

Katz et al 1999

Gowers 1885
Leg Amyotrophic Diplegia
KUMC Results

- 318 patients at KUMC with MND:
  - ALS 260 (82%)
  - FALS 6 (1.9%)
  - PLS 21 (6.6%)
  - LMN 29 (9.2%)
- 29 LMN patients:
  - PMA 16
  - BAD 5
  - LAD 8
- At mean follow up of 8 yrs from symptom onset, mean survival of LAD 87 months

432 cases
- 238 (55.1%) classic limb onset arm
- 159 (36.8%) bulbar onset arm
- 22 (5.1%) flail arm
- 13 (3.0%) flail leg
ISOLATED BULBAR ALS (IBALS)
Dumitru, 2007

- 543 ALS pts over 5 years
- 150 bulbar deficits
- 28 No extremity weakness
- 14/28 Remain confined to bulbar for >2 years (up to 8 years)
- 4/14 IBALS cognitive impairment.
- 5/14 IBALS impaired smooth pursuit eye movements.
- 4/14 IBALS pseudobulbar affect.
ALS Pathogenesis

- Glutamate excitotoxicity
- Free radical/oxidative stress
- Mitochondrial dysfunction
- Neurofilament accumulation
- Protein misfolding
- Auto-immune disease
ALS:
Treatment & Clinical Trials

- Slow disease process
- Symptomatic Rx
Multiple Potential Targets

- **Anti-glutamate**
  - Riluzole
  - Gabapentin
  - Topiramate
  - Dextromethorphan
  - Talampanel
  - Ceftriaxone
  - Memantine*

- **Growth Factors**
  - BDNF-IT and SC
  - CNTF
  - IGF-1
  - Xaliproden
  - VEGF

- **Protein Aggregation**
  - Arimoclomol

* = active

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**Antioxidant/Bioenergetics**

- Creatine (5 and 10 g)
- Vitamin E
- Selegiline
- Acetylcysteine
- Coenzyme Q
- R-pramipexole
- Cytokinetics*
- Rasagiline*
- Mexiletine*
- NGOS*

**Anti-inflammatory**

- Celebrex
- Minocycline
- Neuraltus
- Tocilizumab
- Acthar*

**Anti-apoptotic**

- TCH386
- Pentoxyfilline
- Glatiramer acetate
- Lithium
- Stem cell*
- Anti-sense oligos*
ALS Treatment Trials at
University of Kansas Medical Center

Most preceded by beneficial results in laboratory models
All multicenter with other ALS centers

No Benefit
COX-2 inhibitor (glutamate inhibitor) (MDA)
  Celebrex trial
Creatine – ? improves strength in athletes (NIH)
Minocycline – oral (cell death inhibitor) (NIH)
CoQ10 (antioxidant) (NIH)
Celebrex/creatinne vs mino/creatinne (ALSA)
THC (Novartis)
Lithium (MDA/WALS)
Talampanel (TEVA)
Arimoclomol (increases heat shock protein)
  Neuraltus
  Tamoxifen/creatinne
  R-Pramipexole analogue (Knopp/Biogen)
Ceftriaxone – intravenous (cell death inhibitor) (NIH)
Vascular endothelial growth factor (VEGF) (Sangamo)

Benefit
Myobloc
Dextromethorphan/Quinidine (Nuedexta)

Active
Rasagiline
Cytokinetics
ACTHAR
Diaphragm stim
Riluzole (Rilutek)

- Mechanism Act:
  - Inhibits release of glutamate (presynaptic)
- Phase II and Phase III Multicenter Trials organized by French
- Placebo controlled
- Avg. increased survival – 3 months
- Side effects in 10 – 20%: nausea, dizziness, asthenia
ALSFRS-R

1. Speech
   4 – Normal
   3 – Detectable speech with disturbances
   2 – Intelligible with repeating
   1 – Speech combined with nonvocal communication
   0 – Loss of useful speech

2. Salivation
   4 – Normal
   3 – Slight but definite excess of saliva in mouth; may have nighttime drooling
   2 – Moderately excessive saliva; may have minimal drooling
   1 – Marked excess of saliva with some drooling
   0 – Marked drooling; requires constant tissue or handkerchief

3. Swallowing

4. Handwriting

5a. Cutting Food and Handling Utensils (patients without gastrostomy)

5b. Cutting Food and Handling Utensils (alternate scale for patients with gastrostomy)

6. Dressing and Hygiene

7. Turning in bed and adjusting bed clothes

8. Walking

9. Climbing Stairs

10. Dyspnea

11. Orthopnea

12. Respiratory Insufficiency

Maximum score: 48
Phase III Minocycline for ALS
P. Gordon & WALS Study Group
Lancet Neuro 2007

- 412 pts
- Plac vs. mino 400 mg/d
- 9 months
- Primary – ALSFRS
- Secondary – FVC, MMT, QoL, survival, safety
- Results:
  - ALSFRS 25% faster deterioration in mino group
  - Other secondary endpoints also worse in mino
- ? why
Lithium Rx for ALS
Fornai et al PNAS; 105:2052-2057

SOD Mice – Li inc survival
  – Inc. spinal cord neurons Lamina VII
  – Dec. deaths in spinal cord cultures

Clinical Trial – 16 pts Li + riluzole
  – 28 pts riluzole
  – Slower progression ALSFRS in Li and
    no deaths

3 Follow-up Studies
  - WALS – open-label
    – compare to natural history treatments
  - NEALS – placebo-controlled
  - European study
  - All negative!
Phase II Screening Trial of Lithium Carbonate in Amyotrophic Lateral Sclerosis: Examining a More Efficient Trial Design

Miller, Moore, Forshew, Katz, Barohn, & WALS, Neurology 2011;77:973-979

- Open label
- 107 pts
- 249 “controls” from Mino trial
- ALSFRS slope/month
  - Lithium – 1.20 (decrease)
  - Controls – 1.01 (decrease)
- Conc: Lithium pts worse!
  - Those not on riluzole worse (-1.54)
  - Screening trial design useful
Ceftriaxone in ALS

- In large NINDS sponsored drug screen for neurodegenerative disease, beta lactams were active in 4 separate assays, including excitotoxic stress, glutamate toxicity
- Most oral cephalosporins have poor CNS penetration
- Ceftriaxone has good CNS penetration
- Phase II study positive
- Phase 2 study: 450 pts
- IV Cef vs. placebo daily
- Side effects – gallstones!
- Results – negative! Study halted by DSMB 2012
Ceftriaxone, upregulates mRNA for glutamate transporter on astrocytes

Positive phase II

Negative phase III

ALSFRS-R

0 10 20 30 40 50

Week

0 10 20 30 40 50 60 70 80 90

RX

Placebo 2 gm/day 4 gm/day

Phase II, 38% slowing, p 0.04 Phase III, 8.2%, p 0.20

NINDS supported
Possible explanations for why positive pre-clinical studies have not led to positive human trials in ALS

1. SOD animal model does not translate to sporadic ALS.
2. Different trial designs in animal models could bias to positive results.
3. Other in vivo and in vitro studies do not translate.
4. Drugs not based on pathophysiologic cause.
5. Inadequate outcome measures.
6. Underpowered studies.
7. Heterogeneous human ALS study population.
8. Lack of funding.
9. Starting Rx too late.

Other challenges:

- “Positive” phase II and negative phase III trials
- Lack of biomarkers
- Drug delivery issues
Why Rasagiline

- Rasagiline has broad neuroprotective activity in neuronal cell culture system that may occur at a mitochondrial level
- Rasagiline may have a neuroprotective effect in Parkinson’s disease (ADAGIO)
- Mitochondrial dysfunction occurs in ALS patients
- Another drug that is closely related to a compound that is effective in PD, R-pramipexole, is believed to modulate at mitochondrial level, & had a “positive” Phase 2 trial

But…. Phase 3 ALS results are negative

- Rasagiline prolongs survival in the SOD1 mouse model of ALS
- Small Israeli ALS clinic experience (Drory)
- European study starting - Ludolph
Rasagiline-Open Label Study Design

- Phase II, open label; 2 mg/day for 12 months
- No IND #: exempt
- TEVA investigator initiated grant –PI: Yunxia Wang, MD, University of Kansas Medical Center
- Sites:
  - University of Kansas Medical Center
  - University of Nebraska
  - McGill University
  - California Pacific Medical Center
  - University of Pennsylvania
  - Phoenix Neurological Institute
  - University of Iowa
  - University of Minnesota
  - The Methodist Hospital System
### Six Month ALSFRS-R Rasagiline versus Historical Control

#### Graph
- **Placebo**
- **Rasagiline**

#### Table

<table>
<thead>
<tr>
<th></th>
<th>Rasagiline Treatment at 6 Months (N = 31)</th>
<th>Historical Controls at 6 Months (N = 349*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope Deterioration</td>
<td>0.96/month (95% CI -0.19 - 0.44)</td>
<td>1.08/month (95% CI 0.99-1.17)</td>
</tr>
<tr>
<td>of ALSFRS-R per Month</td>
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</tbody>
</table>

* Western ALS Study Group 1997-2007; Baseline FVC >75%, Symptom duration < 3 years for Treatment & Control Groups

\[ p-value = 0.44 \]
Twelve Month ALSFRS-R Rasagiline versus Historical Control

Rasagiline ALSFRS-R slope = 1.18/month
Mitochondrial Biomarker Assays

- Mito membrane potential on lymphocyte mitos
  o JC1 ratio flow cytometry
  o Lymphocyte mitotracker flow cytometry

- Apoptosis markers in lymphocytes
  o Phosphatidylserine-annexin assay

- Oxidative stress markers in blood
  o Oxygen Radical Antioxidant Capacity (ORAC) assay

- Bcl2/Bax ratios on blood protein lysates
  o Rationale: Bcl2/Bax RNA ratio changes in cell culture
Serum Biomarkers: Mito Membrane Potentials

Both evaluate mitochondria polarization. An increase in the ratio indicates hyperpolarization which is thought to be protective for cells by preventing cell death. After 12 months of treatment, mitochondria were relatively hyperpolarized.
Lymphocyte Annexin Levels Flow Cytometry

Evaluates the display of specific proteins on mitochondria that occurs when a cell is undergoing apoptosis.
Bcl is thought to be anti-apoptotic and Bax is pro-apoptotic. When we see an increase in this ratio (Bcl/Bax), it indicates the cell is moving away from apoptosis and is being protected from cell death.
Oxygen Radical Antioxidant Capacity (ORAC) Assay

Measures the antioxidant effect on cells and protection from damaging free radicals. Another protective mechanism of rasagiline
Conclusion

- There is scientific rational to study rasagiline in ALS
- Rasagiline is safe in this population
- We may be demonstrating mitochondrial target engagement
- We may be demonstrating a biomarker measure of disease progression
- CTSA Ethics Consultation –
  - OK to proceed if pts informed of Ras 36 benefits
- Next steps:
  - Publish data
  - Begin 80 patient placebo controlled study
Rasagiline 80 – Randomized Placebo Controlled Trial

- IND# 104,360
- Funded by FDAOPD RO1-003739, September 2012
- PI is Richard J. Barohn; Co-PI’s: Yunxia Wang, Russell Swerdlow (KUMC), Jonathan Katz (CPMC)
  - 12 month placebo-controlled study
- 3:1 randomization (60 on rasagiline 2 mg/day, 20 on placebo)
  - Using WALS Historical Controls bleed-in
- Biomarkers
  - Swerdlow mito markers
  - Urine oxid stress marks (Columbia)
    - Isoprostane levels
    - Urinary 8-oxodG levels
  - Brain Glutathione MRS
  - TDP 43 in platelets
Two Regulatory Approved Phase I/II stem cells studies active in ALS. Neuralstem and BrainStorm

Neural stem cells engrafted into the spinal cord (J. Glass, E. Feldman)  

NurOwn™ bone marrow-derived Mesenchymal Stromal Cells (MSCs) D. Karussis
Lumbar Intraspinal Injection of Neural Stem Cells in Patients with ALS: Results of a Phase I Trial in 12 Patients

Jonathan D. Glass, MD\textsuperscript{1,}*, Nicholas M. Boulis, MD, PhD\textsuperscript{2}, Karl Johe, PhD\textsuperscript{3}, Seward B. Rutkove, MD\textsuperscript{4}, Thais Federici, PhD\textsuperscript{2}, Meraida Polak, RN\textsuperscript{1}, Crystal Kelly, MA\textsuperscript{1}, Eva L. Feldman, MD, PhD\textsuperscript{5}
- Single 11.5-hr intrathecal infusion
  - 4 sequential cohorts, doses of 0.15, 0.5, 1.5 and 3 mg
- 8 patients per cohort: 3 active:1 placebo
- Primary endpoints:
  - safety/tolerability and
  - pharmacokinetics (plasma and CSF drug levels)
- 4 sites in the US
- Subject participated in multiple dosage cohorts
Mexiletine as a Proposed Therapy in SALS

- Increased persistent sodium current and hyperexcitability of spinal and cortical motor neurons from SOD1\textsuperscript{G93A} mice
- Cortical hyperexcitability in SALS/FALS patients
- Effects similar to riluzole in a rat model for cerebral ischemia in preventing neuronal death
- Significantly extends survival in SOD\textsuperscript{G93A} mice comparable to riluzole
- Could potentially reduce neurogenic cramps in addition to conferring neuroprotection
### Symptomatic Rx for ALS

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Rx</th>
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<tbody>
<tr>
<td>Pseudobulbar affect</td>
<td>Dextromethorphan/quinidine (Nuedexta)</td>
</tr>
<tr>
<td>Sialorrhea</td>
<td>Anti-cholinergics</td>
</tr>
<tr>
<td></td>
<td>Botulinum toxin</td>
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<tr>
<td>Spasticity</td>
<td>Botox or baclofen</td>
</tr>
<tr>
<td>Respiratory insufficiency</td>
<td>BiPAP</td>
</tr>
<tr>
<td></td>
<td>? Diaphragm stim</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>PEG</td>
</tr>
</tbody>
</table>

AAN ALS Practice Parameters. Miller et al, Neurology 2009;1218 and 1227. Miller et al Neurology 2013;2136
ALS Case #2

- 73 y/o WM with ALS presents with complaints of episodes of uncontrolled crying.
- Denies symptoms of depression.
- Trials of several SSRIs and amitriptyline have been unsuccessful.

“Doctor - Is there anything else that can be done?”
Dextromethorphan plus ultra low dose quinidine reduces Pseudobulbar Affect
Pioro et al, *Ann Neurol* 2010

- Large phase III trial 197 ALS/ 129 MS
- Dextromethorphan  20-30 mg/quinidine sulfate 10 mg bid
- PBA daily episode rate lower compared to placebo
- Nudexta FDA approved (20 mg/ DM/10 mg PS)
Figure 1: Mean PBA Episode Rates by Visit

Mean Change from Baseline in Laughing and Crying Episodes

- NUEDEXTA 20/10
- Placebo

* Statistically significant at $p < 0.05$
ALS Case #3

- 70 y/o WF with 3 year history of bulbar-onset ALS presents with c/o drooling.
- Pt chokes constantly on saliva.
- Unable to tolerate prior trials of scopolamine, hyoscyamine, and amitriptyline.
- Currently requiring use of suction machine multiple times per hour.

“Doctor - I’m too embarrassed to leave my home… Is there anything you can do?”
Target: Sialorrhea
Common Treatments

- Amitriptyline (Elavil) 25-100 mg qhs
- Nortriptyline (Pamelor) 20-100 mg qhs
- Diphenhydramine (Benadryl) 25-50 mg TID
- Glycopyrrolate (Robinul) 1-2 mg q 4h
- Hyoscyamine sulfate (Levsin) 0.125-0.25 mg q 4-6h (available as oral tabs, elixir, or SL tabs)
- Transdermal scopolamine 0.5mg behind ear q 3 days
- Atropine tabs 0.4 mg q 4-6h or ophthalmic drops SL q 4-6h
Randomized Double-Blind Study of Botulinum Toxin Type B for Sialorrhea in ALS Patients


CARLAYNE E. JACKSON, MD,1 GARY GRONSETH, MD1, JEFFREY ROSENFELD, PhD, MD,3 RICHARD J. BAROHN, MD,3 RICHARD DUBINSKY, MD, MPH,2. C. BLAKE SIMPSON, MD,1 APRIL MCVEY, MD,2 PAMELA P. KITTRELL, MSN,1 RUTH KING, MHA,3 LAURA HERBELIN, BS,2 and the MUSCLE STUDY GROUP

1 University of Texas Health Science Center,
2 University of Kansas Medical Center, Kansas City, Kansas, USA
3 Carolinas Medical Center, Charlotte, North Carolina, USA

Funded by ALSA
Protocol

- Parotid glands:
  - 500U per site - 2 sites per gland (1000U)
- Submandibular glands:
  - 750U per site - 2 sites per gland (1500U)
  - 22 patients

- Improvement 2 weeks 12 weeks
  myobloc 82% 50%
  placebo 38% 14%
Criteria for Implementing NPPV: HCFA/BiPAP

- FVC < 50% of predicted or
- MIP < -60 cm H2O or
- PCO2 > 45 mm Hg or
- Nocturnal SpO2 < 88% for 5 continuous minutes
Effect of PEG on Survival

- Compared survival
  - 31 with PEG
  - 35 refused PEG

- 24 month survival
  - 40% with PEG
  - <10% w/o PEG

Mazzini et al., J Neurol 1994;241:223-227
Diaphragm Pacing

- Intramuscular implantation of electrodes
- DPS has received FDA approval for a humanitarian use device exemption
- Forced Vital Capacity (FVC) < 50% predicted
- Maximum Inspiratory Pressure (MIP) < 60cm H2O (Water)
- Arterial Blood Gas (ABG) ≥ 45mm Hg (Mercury)
- Oxygen Saturation (SaO2), 88% for 5 consecutive minutes during sleep
NeuRx DPS

- 9 clinical centers (8 in the U.S. and 1 in France)
- In the study 86 patients with ALS met criteria for hypoventilation
- The patients who used the NeuRx DPS® plus NIV survived 9 months longer (on average) than patients who just used NIV. This is from the time they started using NIV.
- Survival time was measured until death or the need for a full time ventilator and tracheostomy.
- Ongoing
  - Randomized controlled trial
  - Open-label registry
ALS Therapy

Other Supportive Rx:

- Equipment
- Speech Rx
- Symptomatic Drug Rx
- Counseling
- Social work
- PT/OT
- Nutrition
Multispecialty ALS Clinic

- Providers:
  - Neurologist
  - PM & R
  - Physical therapist
  - Occupational therapist
  - Respiratory therapist
  - Pulmonologist
  - Speech therapist
  - Nutritionist
  - Psychologist
  - Social worker
  - Research nurses
  - ALSA support
  - MDA support
New Directions in ALS Symptomatic Research via PCORI

- PCORI – Patient-centered Outcomes Research Institute
- Greater Plains Consortium – one of 11 newly funded
  – R. Waitman, KUMC, PI
- Kansas/Wisconsin/Iowa/Nebraska/Texas
- Link Epic EMR to do comparative effectiveness research
Slate Overview – CDRN
What is the geographic coverage?
ALS is Rare Disease Demonstration Project for GPC

- All sites use same ALS data forms
- 1st question – what’s best drug for sialorhea?
- Plan – randomize to glycopyrrolate, amitriptyline, scopolamine patch, atropine drops
  - 3 months
  - Ask patients to grade response and side effects
  - Patient Reported Saliva Management Scale (PRSMS)
    Since beginning the medication, do you feel that the drooling is:
    1. Markedly worse;
    2. Slightly worse;
    3. Not at all different”
    4. Slightly better;
    5. Markedly better.

- QoL – Simmons
- ALS-FRS
Conclusion

1. We can diagnose ALS better: quicker, less tests, more confidence, recognize variants.
2. We have improved clinical management of ALS.
   - Multidisciplinary clinics
   - Symptomatic Rx
3. We have more clinical trials for ALS.
4. We have new clinical trial designs.
5. We have increased advocacy for ALS nationally/internationally.
6. Our goal: help pts/families
   provide hope
   search for better Rx