Neuromuscular Disorders:
Update on Treatment Guidelines and Emerging Therapies

Marat Reyzelman, MD
Board-certified, American Board of Psychiatry and Neurology
Board Certified, Clinical Neurophysiology

WellStar Neurology and Headache Center
WellStar Neuroscience Network
Disclosures

- No conflicts of interest
- Off-label use of pharmaceuticals for neuromuscular disease
Outline

• Diseases:
  • Myasthenia gravis
  • Myopathies
  • Polyneuropathy
  • ALS

• Current treatment paradigms
  • Emphasis on drug therapies

• Emerging treatments

• Future directions and experimental therapies
Myasthenia Gravis

- Post-synaptic neuromuscular junction disorder
- Antibodies bind to acetylcholine receptor or related molecules in the post-synaptic membrane
- Antibodies induce weakness of skeletal muscles
  - Only manifestation of disease
- Generalized or focal weakness, proximal > distal
- 8-10/1,000,000
- Most common disorder of the neuromuscular junction
Myasthenia Gravis

Myasthenia gravis. Gilhus, NE. *NEJM* 2016;375:2570-81
Myasthenia Gravis

• Treatment considerations
  • Age of onset
    • Juvenile
    • Young adult
    • Late onset
  • Symptom distribution
    • Ocular
    • Generalized
Myasthenia Gravis

- Treatment considerations (Con’t)
  - Antibody status
    - AChR
    - MuSK
    - Seronegative
  - Thymic status
    - Hyperplasia
    - Atrophy
    - Thymoma
- Goals of Treatment
  - Symptom relief
  - Disease control -- normal physical function and quality of life
  - Early recognition and treatment of myasthenic crisis
Myasthenia Gravis

- Symptom relief
  - Acetylcholinesterase inhibitors
    - All types of myasthenia usually respond (caution with MuSK)
  - Pyridostigmine (Mestinon, Mestinon TimeSpan)
  - Neostigmine
  - 3,4 diaminopyridine (pre-synaptic)
Myasthenia Gravis

- Pyridostigmine (Mestinon, Mestinon TimeSpan)
  - Inhibition of acetylcholinesterase in the post-synaptic neuromuscular membrane
  - Directly increase amount of acetylcholine available to bind to receptor in the post-synaptic membrane
  - Half-life of about 3 hours
  - Preferred form of cholinesterase inhibition in MG
Myasthenia Gravis

- Pyridostigmine (Mestinon, Mestinon TimeSpan)
  - Starting dose: 30 mg TID
  - Titration goal: 60 mg 3-6 times daily
  - May titrate higher if tolerated, allow patient to manage dosing
  - Max 1500 mg/day
  - ER forms: 180 mg BID-TID, space at least 6H apart
Myasthenia Gravis

• **Neostigmine**
  - Used only when cannot reliably get PO access
  - ICU (limited role to treat myasthenic crisis)
  - Intubated patients (help wean ventilator)
  - Half-life 1-1.5 hours
  - 0.5-1mg IM/IV, may repeat q3H, or follow with continuous infusion 0.15-0.5 mg IV/hr, up to several days
  - Max 12 mg-20 mg/day
Myasthenia Gravis

• Benefits of cholinesterase inhibitors
  • Symptom improvement
    • Improved fatigue
    • Improved diplopia
    • Improved limb strength
  • Nearly full remission of symptoms in mild disease
    • Immune suppression sparing
    • Monitor for progression/spread of disease
Myasthenia Gravis

• Adverse effects of cholinesterase inhibitors
  • Increased peripheral cholinergic activity
    • Abdominal cramps
    • Diarrhea
    • Urinary retention
    • Sweating
    • Sialorrhea/Increased bronchial secretions
    • Erectile dysfunction
    • Cholinergic crisis (rare)
  • Can be mitigated by co-administration of peripheral anti-cholinergic medication
    • Hyoscymine 0.125 mg with each dose of pyridostigmine
Myasthenia Gravis

• Disease Control
  • Immune suppression
    • Glucocorticoids
    • Steroid sparing agents
    • Biologics
    • IVIG
    • Plasmapheresis
  • Thymectomy
Myasthenia Gravis

• Glucocorticoids
  • First line therapy
    • Prednisone or prednisolone equally effective
    • **Reduce risk of generalization in ocular MG**
    • Quickly stabilize symptomatic patients
    • Combine with steroid-sparing agent long term
    • May use during pregnancy
  • Induction doses:
    • 10-20 mg for ocular MG
    • 40-60 mg for generalized disease
    • Titrate up gradually
  • Maintenance doses:
    • Alternate day dosing, titrate to lowest effective dose
    • 5-20 mg every other day for most patients
    • Combine with steroid-sparing agents for improved functional outcome
Myasthenia Gravis

• Steroid-sparing agents
  • Azathioprine
    • First line therapy
    • Affects purine synthesis, reduced B and T cell proliferation
    • 2-3 mg/kg body weight; 100-250 mg daily doses for most patients
    • Check TPMT (thiopurine methyltransferase) activity prior to initiation
    • Can be used during pregnancy
    • Monitor LFTs, WBC, skin
Myasthenia Gravis

- Steroid-sparing agents
  - Second line
    - Methotrexate
      - 15-30 mg/week
      - Monitor WBC, LFTs, rare pulmonary fibrosis (PFTs)
      - Not during pregnancy
    - Cellcept
      - 1000-2000 mg/day
      - Likely similar to MTX and AZA despite negative trials
      - Not during pregnancy
      - Monitor WBC, LFTs, ? PML
    - Cyclosporine
    - Tacrolimus
    - Cyclophosphamide

- Not during pregnancy
Myasthenia Gravis

• Steroid-sparing agents
  • Set expectations with patients
    • Significant time to full effect
    • 9-14 months for AZA
    • 6-9 months for MTX, Cellcept
    • Regular follow up for monitoring
  • Most patients will respond to one of these and may achieve long term disease control
Myasthenia Gravis

• Acute exacerbations and myasthenic crisis
  • MG-related weakness severe enough for intubation
  • May affect 1 in 5 patients at some point in their disease
• Goals of treatment
  • Recognize and treat quickly
  • Myasthenic crisis: one of few true neurologic emergencies
  • FVC<1L or NIF< -20 to -30 may require ventilator support
  • Precipitating factors: upper respiratory or systemic infection, surgical procedure, rapid tapering of immune modulating drugs, corticosteroid-induced worsening or exposure to other drugs that can exacerbate myasthenia, cholinergic crisis
  • Prevent long term disability
  • Reduce artificial ventilation time and/or need for tracheostomy
  • Be aggressive!
Myasthenia Gravis

- Acute exacerbations and myasthenic crisis
  - Intensive care setting
  - Mechanical ventilation for FVC <1L, NIF <20-30
  - Non-invasive ventilation using BiPAP may be sufficient for some patients without hypercapnia
  - Stop cholinesterase inhibitors after intubation
  - PLEX 4-6 treatments QOD
  - IVIG (some reports less effective in crisis)
  - Concomitant steroids and/or long term immune suppressants
  - Wean ventilator when VC > 15ml/kg
  - Rituxan for refractory cases
Myasthenia Gravis

**FIGURE 2-5**

Diagrammatic representation of approach to the immune-directed therapy of myasthenia gravis.

Pred = prednisone; PE/IVlg = plasma exchange/IV immunoglobulin; IDT = immune-directed therapy; Inc = Increase.

Modified with permission from Richman DP, Agius MA. Treatment of autoimmune myasthenia gravis. Neurology 2003;61(12):1652-1661. Copyright © 2003, AAN Enterprises, Inc. All rights reserved.
Randomized Trial of Thymectomy in Myasthenia Gravis

Myasthenia Gravis

- Thymectomy Trial
  - 126 patients
  - Age 18-65
  - Generalized disease, less than 5 years duration
  - Antibody positive
  - On steroid agents
  - 2 groups:
    - Thymectomy plus alternate day prednisone
    - Alternate day prednisone alone
  - 3 year follow up
Myasthenia Gravis

- **Thymectomy Trial**
  - Thymectomy group
    - Lower 3 year QMG scores
    - Lower prednisone doses
    - Fewer patients required azathioprine
    - Fewer patients hospitalized with exacerbation
    - Treatment complications did not differ between groups
    - Fewer side effects due to immune suppressants
    - Lower distress levels related to symptoms

*Figure 1. Quantitative Myasthenia Gravis Score and Prednisone Dose, According to Treatment Group.*

Quantitative Myasthenia Gravis scores range from 0 to 19, with higher scores on each of 11 items indicating more severe disease; a reduction of 2.3 points correlates with improved clinical status. Bars indicate standard errors.
Myasthenia Gravis

• Thymectomy
  • Always recommend for thymoma
  • Antibody-positive patients, generalized disease:
    • Recommend early for patients of juvenile or young onset, without thymoma (likely to have hyperplasia)
    • Consider in patients less than 60-65 years of age with drug resistant disease, less than 3-5 years since onset
    • Do not recommend for MuSK or LRP4 positive patients
  • Do not recommend for ocular MG unless drug-resistant and high risk for generalization (i.e. antibody positive, abnormal neurophysiological testing)
  • Usually do not recommend for antibody-negative patients
Myasthenia Gravis

• Thymectomy
  • Reduction in symptom burden
  • Reduction in number and/or dose of immune suppressive drugs
  • Reduction in exacerbations
  • All thymic tissue must be removed, including any tissue within the mediastinal fat
• Minimally invasive methods now available
  • Video-assist
  • Robotic-assist
  • Similar to traditional methods as long as all tissue removed
Myasthenia Gravis

Figure 3. Proposed Treatment Algorithms for Generalized Myasthenia Gravis and for Severe Exacerbations of Generalized Disease.
Panel A shows treatments for generalized myasthenia gravis, and Panel B shows treatments for severe exacerbations. Both algorithms are from Gilhus and Verschuuren. IV denotes intravenous.
Myasthenia Gravis

International consensus guidance for management of myasthenia gravis

Executive summary

ABSTRACT

Objective: To develop formal consensus-based guidance for the management of myasthenia gravis (MG).

Methods: In October 2013, the Myasthenia Gravis Foundation of America appointed a Task Force to develop treatment guidance for MG, and a panel of 15 international experts was convened. The RAND/UCLA appropriateness methodology was used to develop consensus guidance statements. Definitions were developed for goals of treatment, minimal manifestations, remission, ocular MG, impending crisis, crisis, and refractory MG. An in-person panel meeting then determined 7 treatment topics to be addressed. Initial guidance statements were developed from literature summaries. Three rounds of anonymous e-mail votes were used to attain consensus on guidance statements modified on the basis of panel input.

Results: Guidance statements were developed for symptomatic and immunosuppressive treatments, IV immunoglobulin and plasma exchange, management of impending and manifest myasthenic crisis, thymectomy, juvenile MG, MG associated with antibodies to muscle-specific tyrosine kinase, and MG in pregnancy.

Conclusion: This is an international formal consensus of MG experts intended to be a guide for clinicians caring for patients with MG worldwide. *Neurology* 2016;87:1-7
Myopathy

• Toxic
  • Statins
  • Fibrates
  • Chloroquine
  • ARVs
  • Steroids
  • Colchicine
  • Chloroquine/Hydroxychloroquine
  • Amiodarone
  • Many others
Myopathy

• Endocrine
  • Thyroid
  • Parathyroid
  • Adrenal
  • Diabetic

• Metabolic
  • Glycogen storage
  • Fatty acid oxidation
  • Mitochondrial

• Autoimmune
  • Dermatomyositis
  • Polymyositis
  • Immune–mediated necrotizing myopathy
  • Anti-synthetase syndrome

• Inclusion Body Myositis
Statin-induced Myopathy

- HMG-CoA reductase inhibitors
  - Most common medication class associated with myopathic disorders
  - Asymptomatic hyperCKemia
  - Myalgia
  - Toxic necrotizing myopathy
  - Immune-mediated necrotizing myopathy (with or without HMG-CoA reductase antibodies)
  - Rhabdomyolysis

Statin-induced Myopathy

- Most muscle-related adverse effects of statin use improve following discontinuation
  - Mild musculoskeletal problems occur with same frequency in patients taking statins and placebo
  - Serious muscle problems such as elevated CK and weakness only in 1 per 10,000 patients treated
- Immune-mediated necrotizing myopathy does not improve and should be treated with immune suppressant medications
  - Rare disorder, 1 in 10,000 patients treated

Statin-induced Autoimmune Myopathy

• Soon after treatment, or at any time while on statin
• Weakness persists or worsens after stopping statin
• May have HMG-CoA reductase antibodies or not
• Mild to moderate proximal weakness
• CK >10 upper limit of normal (>2000) in 90% of cases
• Confirm with antibody testing, EMG, biopsy

Statin-induced Autoimmune Myopathy

- **Treatment**
  - Stop statin
  - If CK mildly elevated and weakness is mild, observe
  - Most patients with symptoms will require treatment and few improve spontaneously
  - Prednisone 1 mg/kg
  - Methotrexate, Cellcept, Imuran usually added at the same time as steroids
  - **IVIG** or Rituxan if no improvement after 8-12 weeks
  - May try tapering therapies slowly after CK is lowered and strength returns close to normal levels
  - Varied reports of relapse rates, some may need long term treatment

Statin-induced Autoimmune Myopathy

Patients with proximal muscle weakness, muscle pain, or both

Check creatine kinase

Creatine kinase <10 times the upper limit of normal

Consider other causes of weakness and muscle pain; if cause unclear, consider referral for neurologic evaluation (especially for patients with weakness or those with higher-than-normal creatine kinase)

Negative for autoantibody

Creatine kinase ≥10 times the upper limit of normal

Discontinue statin and reassess creatine kinase in 8 wk (or sooner if symptoms progress); consider initiating referral for neurologic evaluation

Check for anti-HMG-CoA reductase autoantibody

Positive for autoantibody

Presumptive diagnosis of statin-associated autoimmune myopathy

Refer to neurologist or rheumatologist for further evaluation (e.g., consideration of muscle biopsy and immunosuppressive treatment)

Creatine kinase <10 times the upper limit of normal

Consider referral to specialists (e.g., neurologist, endocrinologist, cardiologist) to assess patient and weigh risks and benefits of restarting lipid-lowering therapy
Other Toxic Myopathies

• **Treatment**
  • Quick recognition and withdrawal of possible toxic agent
  • Supportive care
    • Low intensity exercise
    • CoQ 10 supplementation
    • Treatment of myalgia with medication if necessary
    • Treatment of rhabdomyolysis in rare cases
Endocrine Myopathies

• Thyroid disease
  • Multiple neurologic manifestations, including myopathy
  • Neuromuscular symptoms in up to 80% of patients
    • Weakness
    • Fatigue
    • Cramps
    • Myoedema or muscle enlargement
    • Rhabdomyolysis
    • Thyroid ophthalmopathy
    • Thyrotoxic periodic paralysis

• Treatment varies
  • Achievement of euthyroid state is key
  • Corticosteroids for ophthalmopathy
  • K supplementation for thyrotoxic periodic paralysis
Metabolic Myopathies

- Genetic disorders affecting metabolism of glucose or fatty acids
  - Glycogen storage disease
    - McArdle
    - Muscle cramps usually triggered at onset or soon after starting exercise
  - Fatty acid oxidation
    - CPT II deficiency
    - Exercise induced myalgia
    - Delayed rhabdomyolysis following exercise
    - Prolonged fasting exercise or superimposed illness
  - Mitochondrial myopathy
    - MELAS/MERRF/CPEO
    - Extremely varied in time of onset and symptoms
    - Stroke, seizures, cardiomyopathy, ophthalmoplegia, limitations in exercise capacity
    - Dyspnea, premature fatigue during exercise
    - “last in sports”; “worst athlete”
## Metabolic Myopathy Treatments

<table>
<thead>
<tr>
<th>Disease</th>
<th>Treatment*</th>
</tr>
</thead>
</table>
| Glycogen-storage disease        | Careful and progressive exercise training  
Pre-exercise sucrose/glucose in glycolytic defects (e.g., McArdle disease)  
Overnight fasting for glycolytic defects (e.g., phosphofructokinase deficiency or Tarui disease)  
Creatine monohydrate (0.1 g/kg/d), NOT higher dose  
Consider pyridoxine 50 mg/d in patients with null phosphorylase mutations (e.g., R49X mutations) |
| Fatty acid oxidation defects    | Careful and progressive exercise training; no exercise during illness  
Avoid fasting  
L-carnitine (only if low or in SLC22A5 mutation transporter defect); start at 330 mg 2 times per day  
High-carbohydrate diet  
Carbohydrate before and during exercise  
Consider triheptanoin |
| Mitochondrial myopathy          | Careful and progressive exercise training; no exercise during illness  
Avoid fasting  
Cocktail treatment consists of coenzyme Q10 or idebenone (5–15 mg/kg/d) plus α-lipoic acid (5–15 mg/kg/d) plus vitamin E (5–15 IU/kg/d) plus creatine monohydrate (0.1 g/kg/d)  
L-carnitine, only if levels are low; start at 330 mg 2 times per day and retest |

* Start medications at the lower dose range and titrate to tolerance/clinical effect using twice daily dosing and taken with meals.
Other Immune-mediated Myopathies

- Dermatomyositis
- Necrotizing myopathy
- Antisynthetase (Jo-1) syndrome
- Overlap syndrome
- Polymyositis
Other Immune-mediated Myopathies

- Incidence 4/100,000
- Women affected twice as often as men
- Symmetric, proximal muscle weakness
- Various systemic symptoms
  - Rash or other skin disorders
  - Joint pain
  - Respiratory symptoms
Other Immune-mediated Myopathies

- Treatment centered on immune suppression
  - Corticosteroids, high dose
  - Methotrexate, Cellcept, Azathioprine often started with steroids
  - IVIG or Rituxan for refractory disease
  - Evaluation and treatment of co-existing systemic disorders and cancer screenings where appropriate
  - IVIG may be effective in HMG-CoA reductase myopathy, even as monotherapy
  - Rituxan may work well for anti-SRP myopathy
  - When muscle strength improves or is close to normal, wean steroids to avoid systemic complications
Other Immune-mediated Myopathies

| TABLE 5-2 | Immunosuppressive/Immunomodulating Therapy for Inflammatory Myopathies | a,b |
| --- | --- | --- | --- |
| **Therapy** | **Route** | **Dose** | **Side Effects** | **Monitor** |
| Prednisone | Oral | 0.75-1.5 mg/kg | Hypertension, fluid and weight gain, hyperglycemia, hypokalemia, cataracts, glaucoma, gastric irritation, osteoporosis, infection, avascular femoral necrosis, steroid myopathy, mood alteration, psychosis | Weight, blood pressure, serum glucose/potassium, cataract formation |
| Methylprednisolone | IV | 1 g in 100 ml normal saline over 1-2 h, daily or every other day for three to six doses | Arthritis, flushing, dyspepsia, anxiety, insomnia, fluid and weight gain, hyperglycemia, hypokalemia, infection | Heart rate, blood pressure, serum glucose/potassium |
| Azathioprine | Oral | 2-3 mg/kg, divided into two daily doses | Fluki amines, hepatotoxicity, pancreatitis, leukopenia, leukopenia, infection | Complete blood cell count, liver enzymes |
| Methotrexate | Oral | 7.5-20 mg weekly, single or divided doses, 1 day/week dosing | Hepatotoxicity, pulmonary fibrosis, infection, neoplasia, infertility, leukopenia, thrombocytopenia, alopecia, gastric irritation, stomatitis, teratogenicity | Liver enzymes, complete blood cell count, creatinine, blood urea nitrogen |
| IVIM | 20-50 mg weekly; 1 day/week dosing | Same as oral route | Same as oral route |
| Cyclophosphamide | Oral | 1.5-2 mg/kg, single morning dose | Bone marrow suppression, infection, fever, alopecia, infection, neoplasia | Complete blood cell count, urinalysis |
| IV | 0.5-1 g/m²/mo for 6 to 12 months | Same as oral route | Same as oral route |
| Cydosporine | Oral | 4-6 mg/kg, divided into two daily doses | Neuphototoxicity, hypertension, infection, hepatitis, infection, neoplasia, teratogenicity | Complete blood cell count, bone marrow suppression, infection |
| Tacrolimus | Oral | 1-2 mg 2 times a day for a total of 2-4 mg/d | Neuphototoxicity, hypertension, infection, hepatitis, infection, neoplasia | Complete blood cell count, bone marrow suppression, infection, neoplasia |
| Myophosphonate mofetil | Oral | Adults: (1-1.5 g 2 times a day) Note: No more than 1 g/d in patients with renal failure | Bone marrow suppression, infection, leukopenia, thrombocytopenia, infection, neoplasia | Complete blood cell count |
| Children: 600 mg/m² per dose 2 times a day (not to exceed 2 g/d) | | |

* TABLE 5-2 | Immunosuppressive/Immunomodulating Therapy for Inflammatory Myopathies | a,b |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Therapy</strong></td>
<td><strong>Route</strong></td>
<td><strong>Dose</strong></td>
<td><strong>Side Effects</strong></td>
</tr>
<tr>
<td>M = Methotrexate, N = IVIM</td>
<td>IVIM</td>
<td>2 g/kg total dose over 2-5 days, then 1 g every 4-8 weeks as needed</td>
<td>Hypertension, arthralgia, flushing, myalgias, headache, fatigue, myasthenia gravis, skin rashes, leukopenia, thrombocytopenia, anorexia, fever</td>
</tr>
<tr>
<td>Rituximab</td>
<td>IV</td>
<td>750 mg/m² (up to 1 g) and repeated in 2 weeks; course is then repeated every 2-6 months</td>
<td>Infusion reactions (as per IVIM), infection, progressive multifocal leukoencephalopathy, skin rashes, fatigue, myasthenia gravis, skin rashes, fever</td>
</tr>
</tbody>
</table>

---

Continuum 2016;22(6):1852-70
Peripheral Neuropathy

- Hereditary
- Acquired
  - Toxic
  - Metabolic
  - Immune
  - Infectious
Peripheral Neuropathy

• Hereditary
  • Charcot-Marie-Tooth disease (CMT)
    • Demyelinating and axonal forms
    • Involve sensory and motor nerves
    • Heterogeneous phenotypes and age of onset
    • Very slowly progressive
    • Extensive number of genetic mutations identified
Peripheral Neuropathy

• **Hereditary (Con’t)**
  • **Treatment approach**
    • No medications to treat any form of CMT
    • Symptom-based supportive treatment
      • PT for ROM of joints, prevention of contractures and deformity
      • Gait and strengthening activity/exercise
      • OT for hand function and tools to aid with ADLs
      • AFOs
      • Orthopedic surgery for correction of hammer toes and tendon release/transfer
    • Pain management: NSAIDs, neuropathic pain medications
Peripheral Neuropathy

- Toxic

**TABLE 7-1** Modified Bradford Hill Criteria to Establish Causation in the Case of Peripheral Nerve Toxins

- Dose-response relationship
- Consistent manifestations related to biological activity of toxin if known
- Proximity of symptoms to exposure
- Stabilization or improvement following drug cessation
- Reproduction of pathology in animal models
- Epidemiologic studies or case reports
- Exclusion of other causes

Peripheral Neuropathy

- **Toxic**

### TABLE 7-3 Toxic Neuropathies Summary: Pharmaceuticals

<table>
<thead>
<tr>
<th>Medication</th>
<th>Nerve Fiber Type or Affected Nerves</th>
<th>Site of Injury</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimicrobials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleoside analogs (azidovine, didanosine, stavudine, lamivudine)</td>
<td>Small fiber sensory, large fiber, sensory, motor</td>
<td>Axonal</td>
<td>Subacute, chronic</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Pansensory, motor</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Pansensory, motor</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Motor, pansensory, autonomic</td>
<td>Axonal</td>
<td>Subacute, chronic</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Pansensory</td>
<td>Axonal</td>
<td>Subacute</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Pansensory, motor</td>
<td>Axonal</td>
<td>Subacute</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Pansensory, motor</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Pansensory, motor</td>
<td>Axonal</td>
<td>Subacute</td>
</tr>
<tr>
<td><strong>Cardiovascular drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Pansensory, motor</td>
<td>Demyelinating</td>
<td>Chronic</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Pansensory, motor</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
<tr>
<td>Procaniamide</td>
<td>Pansensory, motor</td>
<td>Demyelinating</td>
<td>Chronic</td>
</tr>
<tr>
<td>Perhexiline</td>
<td>Pansensory, motor, autonomic</td>
<td>Demyelinating</td>
<td>Chronic</td>
</tr>
<tr>
<td>Statins</td>
<td>Pansensory, motor</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitotic spindle drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td>Pansensory, motor, autonomic</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
<tr>
<td>Taxanes</td>
<td>Pansensory, motor</td>
<td>Axonal (neuronal)</td>
<td>Chronic</td>
</tr>
<tr>
<td><strong>DNA-binding drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin/Carboplatin</td>
<td>Large fiber, small fiber sensory</td>
<td>Neuronal</td>
<td>Chronic</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Large fiber, small fiber sensory</td>
<td>Neuronal</td>
<td>Chronic, acute</td>
</tr>
<tr>
<td>Proteasome inhibitors (bortezomib)</td>
<td>Pansensory, motor</td>
<td>Axonal (demyelinating)</td>
<td>Chronic</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Pansensory, motor</td>
<td>Axonal (neuronal)</td>
<td>Chronic</td>
</tr>
<tr>
<td>Suramin</td>
<td>Pansensory, motor</td>
<td>Axonal (demyelinating)</td>
<td>Chronic</td>
</tr>
<tr>
<td>Mitoindazole</td>
<td>Pansensory</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
</tbody>
</table>

**Continued**

<table>
<thead>
<tr>
<th>Immunosuppressives</th>
<th>Nerve Fiber Type or Affected Nerves</th>
<th>Site of Injury</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold</td>
<td>Pansensory &gt; motor</td>
<td>Demyelinating (axonal)</td>
<td>Acute or subacute</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Pansensory &gt; motor</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Pansensory &gt; motor</td>
<td>Demyelinating (axonal)</td>
<td>Chronic</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Pansensory, motor</td>
<td>Demyelinating</td>
<td>Acute</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Small fiber &gt; large fiber &gt; motor</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
</tbody>
</table>

**Other**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Nerve Fiber Type or Affected Nerves</th>
<th>Site of Injury</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aptirine</td>
<td>Small fiber, large fiber &gt; motor</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Pansensory, motor</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
<tr>
<td>Pyridoxine (vitamin B6)</td>
<td>Small fiber sensory, large fiber sensory, autonomic</td>
<td>Neuronal</td>
<td>Chronic</td>
</tr>
</tbody>
</table>
Peripheral Neuropathy

- Toxic

**TABLE 7.4** Toxic Neuropathies Summary: Occupational, Biological, and Environmental Agents

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Nerve Fiber Type or Affected Nerves</th>
<th>Site of Injury</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heavy metals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lead</td>
<td>Motor &gt; sensory</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Sensory, motor</td>
<td>Axonal, demyelinating</td>
<td>Acute or chronic</td>
</tr>
<tr>
<td>Thallium</td>
<td>Small fiber &gt; large sensory, motor</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
<tr>
<td>Mercury</td>
<td>Sensory, motor</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
<tr>
<td><strong>Seafood toxins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciguatera</td>
<td>Sensory, autonomic</td>
<td>Demyelinating</td>
<td>Acute</td>
</tr>
<tr>
<td>Red Tide</td>
<td>Sensory, motor</td>
<td>Demyelinating</td>
<td>Acute</td>
</tr>
<tr>
<td>Saxitoxin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brevetoxin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetrodotoxin</td>
<td>Sensory, motor, autonomic</td>
<td>Demyelinating</td>
<td>Acute</td>
</tr>
<tr>
<td><strong>Environmental/occupational</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organophosphates</td>
<td>Sensory, motor</td>
<td>Axonal</td>
<td>Subacute</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>Sensory, motor</td>
<td>Axonal</td>
<td>Acute</td>
</tr>
<tr>
<td>Hexacarbons</td>
<td>Sensory, motor</td>
<td>Axonal, demyelinating</td>
<td>Subacute</td>
</tr>
<tr>
<td>Acrylamide</td>
<td>Sensory, motor, autonomic</td>
<td>Axonal</td>
<td>Subacute</td>
</tr>
<tr>
<td>Vioxor</td>
<td>Sensory, motor, autonomic</td>
<td>Axonal</td>
<td>Acute</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Sensory, motor</td>
<td>Axonal</td>
<td>Subacute</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>Sensory, motor</td>
<td>Demyelinating</td>
<td>Subacute</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>Large fiber sensory</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buckthorn</td>
<td>Motor &gt; sensory</td>
<td>Demyelinating</td>
<td>Acute</td>
</tr>
<tr>
<td>Tick</td>
<td>Motor, autonomic</td>
<td>Axonal</td>
<td>Acute</td>
</tr>
<tr>
<td>Diphtheria toxin</td>
<td>Motor &gt; sensory</td>
<td>Demyelinating</td>
<td>Acute</td>
</tr>
</tbody>
</table>
Peripheral Neuropathy

- Toxic

**TABLE 7-5** Vitamin and Other Deficiencies Summary

<table>
<thead>
<tr>
<th>Vitamin or Mineral</th>
<th>Nerve Fiber Type or Affected Nerves</th>
<th>Site of Injury</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobalamin (vitamin B&lt;sub&gt;12&lt;/sub&gt;)</td>
<td>Large fiber sensory</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
<tr>
<td>Thiamine (vitamin B&lt;sub&gt;1&lt;/sub&gt;)</td>
<td>Small fiber &gt; large fiber sensory, motor</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
<tr>
<td>Pyridoxine (vitamin B&lt;sub&gt;6&lt;/sub&gt;)</td>
<td>Small fiber &gt; large fiber &gt; motor</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
<tr>
<td>Niacin (vitamin B&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>Small fiber &gt; large fiber, motor</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
<tr>
<td>Alpha tocopherol (vitamin E)</td>
<td>Large fiber sensory</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
<tr>
<td>Copper</td>
<td>Pansensory, motor</td>
<td>Axonal</td>
<td>Chronic</td>
</tr>
</tbody>
</table>
Peripheral Neuropathy

- Toxic
  - Treatment
    - Supportive
    - Recognition/withdrawal of offending agent where possible
    - Change of chemotherapeutic agent if neuropathy is severe
    - Treat underlying vitamin deficiencies
    - Alpha-lipoic acid, B complex, vitamin E, glutamine, acetyl-carnitine supplement tried
Peripheral Neuropathy

• Metabolic
  • Diabetic neuropathy
    • Distal symmetric polyneuropathy (DSP) is most common neurologic complication of DM
    • DSP is most common form of peripheral neuropathy worldwide
    • Multiple other manifestations
      • Diabetic autonomic neuropathy
      • Diabetic amyotrophy
      • Insulin “neuritis”
      • Diabetic neuropathic cachexia
      • Cranial neuropathies (oculomotor or abducens nerve palsies)
      • CIDP
Peripheral Neuropathy

- Metabolic
  - Diabetic neuropathy
    - DSP
      - 50% of patients with DM will develop DSP
      - 20% have DSP at time of DM diagnosis
      - Pre-diabetic levels of hyperglycemia and impaired glucose tolerance contribute to risk (HA1C only mildly elevated or borderline)
        - Use OGTT for screening patients at risk
      - Other factors (obesity, hyperlipemia) also contribute
      - Major cause of disability
        - Ulcers and amputations; falls

Continuum 2012;18(1):60-84
Peripheral Neuropathy

- **Metabolic**
  - **Diabetic neuropathy**
  - **Treatment**
    - Glucose control, glucose control, glucose control...
    - Intensive glucose control reduced development of DSP by 65% after 5 years
      - More effective in type I patients (HA1C <7.0)
      - Other risk factors (obesity, hyperlipemia) important in type II patients
  - **Antioxidant therapy**
    - Alpha-lipoic acid
      - 600-1200 mg/day
    - B complex

Peripheral Neuropathy

- **Metabolic**
  
  - Neuropathy associated with impaired glucose tolerance and metabolic syndrome (IGT neuropathy)
  
  - Nerve injury precedes diagnosis of DM
    - (NCSs abnormal in 20% of patients at time of DM diagnosis)
  
  - Impaired glucose tolerance (IGT) are at increased risk of neuropathy
    - 30-50% of patients with “idiopathic neuropathy” have IGT
      - 3 times background rate
    - Patients with idiopathic neuropathy more likely to be obese, hypertensive, hyperlipemic
      - HTN, serum lipids and triglycerides, BMI, smoking independent risk factors for neuropathy in Eurodiab study

---

**TABLE 3-1** Diagnostic Criteria for Diabetes and Prediabetes

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Fasting Plasma Glucose</th>
<th>2-Hour Oral Glucose Tolerance Test</th>
<th>Hemoglobin A1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 100 mg/dL (5.6 mmol/L)</td>
<td>&lt; 140 mg/dL (7.8 mmol/L)</td>
<td>&lt; 5.7%</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>100 mg/dL to 125 mg/dL (5.6 mmol/L to 6.9 mmol/L)</td>
<td>140 mg/dL to 199 mg/dL (7.8 mmol/L to 11.0 mmol/L)</td>
<td>5.7% to 6.4%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>≥ 126 mg/dL (7.0 mmol/L)</td>
<td>≥ 200 mg/dL (11.1 mmol/L)</td>
<td>≥ 6.5%</td>
</tr>
</tbody>
</table>

---

*Continuum 2012;18(1):60-84*  
*Arch Intern Med 2004;164(9):1021-1025*  
*Diabetes Care 1998;21(4):518-524*  
Peripheral Neuropathy

- **Metabolic**
  - IGT neuropathy
  - Treatment
    - Diet/exercise program with goal of normalizing/reducing BMI
    - Moderate aerobic exercise 3 times weekly (150 min total)
      - Improvement in blood glucose
      - Improved lipid metabolism
      - Increased numbers of cutaneous nerve fibers
      - Improvement in neuropathic pain over 2 years
      - Treatment with metformin or insulin-sensitizing agent is warranted in patients not able to diet/exercise/reduce BMI, when neuropathy is present

J Neurol Sci 2008;273(1-2);25-28
Peripheral Neuropathy

- Immune-mediated
  - Guillain Barre (GBS)
  - Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
  - Multifocal motor neuropathy (MMN)
  - Neuropathy associated with monoclonal protein disorders
  - Vasculitic neuropathies
  - Paraneoplastic neuropathies
Peripheral Neuropathy

• Immune-mediated
  • Complex groups of disorders
  • Varied clinical presentation
  • Targets are peripheral nerves or supporting blood vessels
  • Quick recognition is very important
    • Can lead to severe neurologic disability
    • Many are treatable
Peripheral Neuropathy

- Immune-mediated
  - Guillain-Barre Syndrome
    - Admission for monitoring of respiratory status
    - Respiratory support/mechanical ventilation
      - Symptoms may worsen for several weeks prior to reaching nadir
    - Management of autonomic dysfunction, hypotension, urinary retention
  - Plasmapharesis and IVIG
    - Equally efficacious when used within the first 2 weeks (more sick patients in the PLEX trial)
    - Combination treatment not more effective
    - High dose steroids do not seem to be effective
    - Repeat course of IVIG may be reasonable for the 10% of patients that may have an immediate relapse
  - Long term prognosis is generally good even for severely ill patients
Peripheral Neuropathy

• Immune-mediated
  • CIDP
    • Oral glucocorticoids
      • Response rates 65-95%
      • 1 mg/kg for 1-2 months, then taper gradually to every other day dosing
      • Omeprazole, vitamin D/calcium; BP and BG monitoring, diet and exercise
    • Pulsed IV or PO steroids
      • Dexamethasone 40 mg daily for 4 days, every 4 weeks
      • Better tolerated, less weight gain
    • IVIG or plasmapheresis
      • Both are effective, relatively quick response, but up to 3 months in some
    • Chronic immune suppression with steroid-sparing agents
      • Azathioprine, Methotrexate, Cyclophosphamide
# Peripheral Neuropathy

## TABLE 4-5 Commonly Used Immunotherapies: Dosages and Side Effects

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>1 mg/kg/d orally until improvement appears, then taper slowly.</td>
<td>Mood swings, fluid retention, weight gain, impaired wound healing, gastrointestinal ulcers, cushingoid faces, osteoporosis, hyperglycemia, cataracts, adrenal suppression, infection.</td>
<td>Ulcer and osteoporosis prophylaxis. Monitor bone density if adrenal-suppressed, consider hydrocortisone during periods of stress or infections.</td>
</tr>
<tr>
<td>Pulsed corticosteroids</td>
<td>IV methylprednisolone 1 g/d for 3 to 5 days; repeat monthly or Oral dexamethasone 40 g/d for 4 days; repeat monthly</td>
<td>Similar to daily oral prednisone, especially if daily prednisone is used between pulsed dosing.</td>
<td>Similar to oral prednisone.</td>
</tr>
<tr>
<td>IV immunoglobulin</td>
<td>2 g/kg divided over 3 to 5 days, then half dose monthly as needed</td>
<td>Headache, aseptic meningitis, nephrotoxicity, hypersensitivity reaction, thrombotic complications</td>
<td>Relative contraindication in patients with renal or vascular diseases. Aspirin prophylaxis. Home infusion possible for some patients.</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>50 mL/kg per exchange, four to five exchanges over 7 to 10 days</td>
<td>Hypertension, hypotension, coagulopathy, electrolyte disturbances</td>
<td>Monitor vital signs, prothrombin time, partial thromboplastin time, fibrinogen.</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>50 mg/d orally to start, increase to 2 mg/kg to 3 mg/kg/d</td>
<td>Bone marrow suppression, hepatotoxicity, teratogenicity, oncogenicity, infection. 10% have flulike hypersensitivity reaction.</td>
<td>Monitor blood count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT).</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>5 mg/m² orally to start, increase to 10 mg to 20 mg/m²; may be given subcutaneously; reduce dosing in renal insufficiency</td>
<td>Toxicity to bone marrow, liver or kidney, infection, alopecia, stomatitis, teratogenicity, oncogenicity, pulmonary fibrosis.</td>
<td>Monitor complete blood count, blood urea nitrogen, creatinine, AST, ALT, GGT.</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1 mg/kg to 2 mg/kg/d orally or 500 mg/m² to 1000 mg/m²/ivo IV</td>
<td>Hemorrhagic cystitis, leukopenia, alopecia, infection, nausea, stomatitis, pneumonitis, teratogenicity, oncogenicity.</td>
<td>Liberal intake of fluids before and after treatment. Administer antiemetics as needed. Monitor complete blood count, urinalysis. Monthly pulsed dosing may be better tolerated.</td>
</tr>
</tbody>
</table>
Peripheral Neuropathy

• Immune-mediated
  • MMN
    • Subacute asymmetric weakness, often upper extremity
    • ~50% have antibodies against GM1
    • NCSs can be helpful, especially when conduction block is present
    • Slow progression when untreated
    • Mainstay of treatment is regular IVIG infusions
      • 2 g/kg initial induction, then 1g/kg every 3-6 weeks
    • Plasmapharesis and steroids usually not effective
    • Rituxan may be useful
    • Azathioprine, cellcept not effective
Peripheral Neuropathy

• Immune-mediated
  • Neuropathy associated with monoclonal protein disorders
    • Heterogeneous group of disorders
    • Influenced by paraprotein subtype
    • Antibodies: MAG, anti-sulfatide, GM1
    • Varied clinical course, response to treatment
    • IVIG, steroids, plasmapheresis have all been tried
    • MAG responds to rituxan, usually does not respond to others
    • Treatment of systemic disease
Peripheral Neuropathy

• Immune-mediated
  • Vasculitic Neuropathy
    • Due to systemic disease
    • Isolated vasculitic neuropathy
    • Nerve biopsy is critical for diagnosis
    • Treatment often challenging
      • Immunosuppression
      • Collaborate with rheumatology/IM
      • Prednisone 1 mg/kg/day
        • Consider IV induction for 3-5 days
      • Cytotoxic agents for aggressive disease
        • Cyclophosphomide 500-1000 mg/m2
        • Monthly doses
        • Bladder and bone marrow toxicity
        • May transition to Imuran or MTX
Amyotrophic Lateral Sclerosis (ALS)

• Disorder of the motor neurons
  • Widespread degeneration of upper and lower motor neurons
  • Not a single disease: groups of sporadic and hereditary disorders
    • Multiple familial subtypes and susceptible genes recognized
      • SOD1; TDP-43
    • Interaction with environmental triggers
  • Association with other neurodegenerative disorders
    • Dementia (FTD); Parkinsonism
  • Not just a disease of the motor neurons
    • Sensory dysfunction
    • Autonomic dysfunction
    • Behavioral dysfunction
Amyotrophic Lateral Sclerosis (ALS)

- **Treatment**
  - Specialty multidisciplinary approach
    - ALS center or specialty clinic
    - Improved survival and quality of life for both patient and caregivers
    - ~8 month increase in survival time
    - 30% reduced 1 year mortality rates
    - Fewer unplanned hospitalizations
    - Independent positive prognostic factor

J Neurol Neurosurg Psychiatry 2003;74(9):1258-1261
Amyotrophic Lateral Sclerosis (ALS)

- **Treatment**
  - Multi-disciplinary team
    - ALS neurologist
    - Nurse clinician
    - SLP
    - PT and OT
    - Nutrition
    - Respiratory therapy
    - Neuropsychology
    - Research coordinator
    - Palliative care
  - Visits on average every 3 months
Amyotrophic Lateral Sclerosis (ALS)

• Treatment
  • Disease-modifying therapy
    • Riluzole
      • Neuroprotective for motor neurons
        • Inhibits excitatory amino acid release
        • Inhibits events after stimulation of excitatory amino acids
        • Stabilizes inactivated state of voltage-dependent sodium channels
      • Extends survival time and delays time to tracheostomy
        • 6 mo and 2-3 mo respectively
      • GI effects, monitor LFTs
      • Limited effect in late stages of disease
Amyotrophic Lateral Sclerosis (ALS)

• Treatment
  • Disease-modifying therapy
    • Non-invasive ventilation (NIPPV)
      • Improved median survival
      • Improved quality of life
      • Consider if symptomatic or VC<50% predicted
        • DOE
        • Supine dyspnea
        • Marked fatigue
        • Frequent nocturnal awakening
        • Morning headache
      • If SNIFF <40 in patients with bulbar disease (FVC not sensitive)
      • Preferred modality is BiPAP

Neurology 2006;67(5):736-737
Neurology 1999;52(7):1311-1323
Amyotrophic Lateral Sclerosis (ALS)

- **Treatment**
  - Disease-modifying therapy
    - Optimizing nutritional status
      - Avoid weight loss or BMI<18
        - Poor survival
      - PEG
        - Before VC <50%
        - Modest increase in survival
    - Symptom based therapies
      - Treatment of cramps, spasticity, emotional lability, bronchial secretions, depression, fatigue
## Amyotrophic Lateral Sclerosis (ALS)

### Table 4-5: Management of Common Symptoms in ALS

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Possible Etiology</th>
<th>Drug Therapy</th>
<th>Non-drug Therapies</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cramps</td>
<td>Anterior horn cell degeneration</td>
<td>Levetiracetam, Quinine</td>
<td>Massage, Phenytoin, Hydrotherapy in heated pools</td>
<td>Carbamazepine, Phenytoin, Gabapentin, Verapamil, Magnesium.</td>
</tr>
<tr>
<td>Spasticity</td>
<td>Upper motor neuron disease</td>
<td>Baclofen, Tizanidine,</td>
<td>Physical therapy, Hydrotherapy in heated pools</td>
<td>Dantrolene, Diazepam, Botulinum toxin type A.</td>
</tr>
<tr>
<td>Sialorrhea</td>
<td>Impaired handling of saliva</td>
<td>Amantadine, Transdermal</td>
<td>Mechanical suction device, Radiation 7 Gy to 8 Gy to parotid glands</td>
<td>Atropine drops, Glycopyrrolate, Benztpine.</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>Corticobulbar degeneration</td>
<td>Amantadine, Fluvaxamine</td>
<td>Psychosocial support to family</td>
<td>Combination of donepezil and quinidine (under trial).</td>
</tr>
<tr>
<td>Bronchial secretions</td>
<td>Impaired clearing</td>
<td>Gadolin, Macrolide,</td>
<td>Nebulizer, Mechanical cough-assisting devices (insufflator-exsufflator)</td>
<td>Ipratropium, Chlorpheniramine, mycophenolate.</td>
</tr>
<tr>
<td>Constipation</td>
<td>Immobility, poor fluid and fiber intake or secondary to medications such as opioids No studies in ALS</td>
<td>Senna, Colace</td>
<td>Hydration, Increase fiber intake</td>
<td>Dulcolax suppository, Lactose, Milk of magnesia.</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Hypercapnia, Muscle weakness Medication side effect</td>
<td>Modafinil</td>
<td>Evaluate respiratory function</td>
<td>Methylphenidate, Dextroamphetamine.</td>
</tr>
<tr>
<td>Depression</td>
<td>Job loss, Loss of independence and ability to communicate</td>
<td>Amantadine, Selective serotonin reuptake inhibitor</td>
<td>Counselling, Psychosocial support</td>
<td>Lisdexamfetamine, Mirtazapine.</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Fear of future Pain, New-dress dyspraxia, Need to be tolerated by others</td>
<td>Diazepam, Lorazepam, Buspan</td>
<td>Psychosocial support, Selective serotonin reuptake inhibitor</td>
<td></td>
</tr>
</tbody>
</table>
Amyotrophic Lateral Sclerosis (ALS)

• Treatment
  • Stem cell therapy
  • Animal studies
    • Transplantation of human spinal cord-derived neural stem cells (HSSCs) into ventral horn of spinal cord delays onset of ALS and improves survival in rodents
  • Human phase I and II trials completed
    • Test safety and tolerability of different concentrations and number of injections into the spinal cord
    • Multi-center and multi-surgeon
    • Determine outcome measures that would measure efficacy
    • No efficacy trials yet, but hopefully in the near future
Transplantation of spinal cord–derived neural stem cells for ALS
Analysis of phase 1 and 2 trials

ABSTRACT

Objective: To test the safety of spinal cord transplantation of human stem cells in patients with amyotrophic lateral sclerosis (ALS) with escalating doses and expansion of the trial to multiple clinical centers.

Methods: This open-label trial included 15 participants at 3 academic centers divided into 5 treatment groups receiving increasing doses of stem cells by increasing numbers of cells/injection and increasing numbers of injections. All participants received bilateral injections into the cervical spinal cord (C3-C5). The final group received injections into both the lumbar (L2-L4) and cervical cord through 2 separate surgical procedures. Participants were assessed for adverse events and progression of disease, as measured by the ALS Functional Rating Scale–Revised, forced vital capacity, and quantitative measures of strength. Statistical analysis focused on the slopes of decline of these phase 2 trial participants alone or in combination with the phase 1 participants (previously reported), comparing these groups to 3 separate historical control groups.

Results: Adverse events were mostly related to transient pain associated with surgery and to side effects of immunosuppressant medications. There was one incident of acute postoperative deterioration in neurologic function and another incident of a central pain syndrome. We could not discern differences in surgical outcomes between surgeons. Comparisons of the slopes of decline with the 3 separate historical control groups showed no differences in mean rates of progression.

Conclusions: Intraspinal transplantation of human spinal cord–derived neural stem cells can be safely accomplished at high doses, including successive lumbar and cervical procedures. The procedure can be expanded safely to multiple surgical centers.

Classification of evidence: This study provides Class IV evidence that for patients with ALS, spinal cord transplantation of human stem cells can be safely accomplished and does not accelerate the progression of the disease. This study lacks the precision to exclude important benefit or safety issues. Neurology® 2018;87:392-400
Amyotrophic Lateral Sclerosis (ALS)

- Treatment
  - Stem cell therapy
    - 2 open label trials completed
    - 30 patients injected
    - Phase I – safe to inject single concentration of HSSCs per injection
    - Phase II – increasing doses, increasing numbers of cells per injection, increasing injections and numbers of procedures
      - 18 procedures
      - 1 patient with post-op cord swelling resulting in paraparesis and pain
      - 1 patient with central pain syndrome
      - Both patients received highest dose of cells into cervical cord (20 injections, 400,000 cells/injection)
Future Directions

• Biologics
  • Targeted immune therapies
    • Antibody-specific
    • Cell-specific
    • Rituximab, Eculizumab, CFZ533
  • Vaccines
  • GM-CSF
  • Improved efficacy
  • Reduced adverse effects

• Genetic therapies
  • Stem cells, gene replacement, nerve growth factors, anti-sense oligonucleotides, autologous stem cell transplant