Managing the Neuromuscular Conditions ALS, MS and Huntington's Disease: A Case-Based Approach

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Disclosures

Off-label use of medication will be discussed in this presentation.

Objectives

• Review the pharmacologic management of symptoms that are common to a patient with amyotrophic lateral sclerosis (ALS).
• Review the pharmacologic management of symptoms that are common to a patient with multiple sclerosis
• Review the pharmacologic management of symptoms that are common to a patient with Huntington’s disease
ALS Patient Case

- HPI: 69 year old nursing home patient admitted for ALS. Prognosis is weeks to months.
- PMH: Tube feeding started 6 months ago. All medications via G-tube.
- CC: Recurrent UTIs.
- Medications:
  - Albuterol nebulizer 0.083% q4hr prn
  - Riluzole 50mg BID (started 2+ years ago)
  - Olanzapine 5mg qday
  - Lorazepam 1mg q4hr prn
  - Atropine 1% ophth solution 2-4gtts q2hr prn secretions
  - Ciprofloxacin 250mg/5ml give 500mg BID x7 days (most recent course started 3 days ago)

Amyotrophic Lateral Sclerosis (ALS) or Lou Gehrig’s Disease

- Progressive neurodegenerative disorder (nerve cell break down) affecting both upper and lower motor neurons
- Most common age of onset is between 55 – 75 years old
- Median survival 3-5 years from diagnosis
  - 10-20% of patients may survive up to 10 years
  - Longer survival may be associated with younger age at onset, male, limb type ALS
Amyotrophic Lateral Sclerosis (ALS) or Lou Gehrig’s Disease

- Rate of decline tends to be linear and fairly constant
  - Patient history can help prognostication
  - Periods of mechanical ventilation, tubing feeding and hydration can make prognostication more difficult
- Common disease course (limb-onset):
  - General muscle weakness and atrophy.
  - Symptoms worsen and spread to throat, tongue, jaw, facial muscles
  - Spread to respiratory muscles leading to respiratory failure

General Guidance for Hospice Eligibility: ALS

- Rapid disease progression in the past 12 months:
  - To wheelchair or bed-bound
  - Speech barely intelligible or unintelligible speech
  - Pureed diet
  - ADLs assistance required
- At least one of the following in the past 12 months:
  - Critically impaired breathing, poor oral nutrition, life-threatening complication such as aspiration pneumonia, upper UTI, sepsis, fever after antibiotics, stage III-IV pressure ulcer

ALS Symptom Management

- Rilutek (riluzole)
- Dyspnea / Respiratory Failure
- Sialorrhea (Hypersalivation)
- Fatigue
- Muscle weakness / muscle wasting
- Dysphagia
- Constipation*
- Pseudobulbar affect*
Rilutek (riluzole)

- Only medication FDA approved to treat ALS
- Mechanism of action is unknown
- Usual dosing 50mg PO BID
  - This dose appears to slow the progression of ALS
- More effective for patients with bulbar-onset disease compared to limb-onset disease
- SE: nausea (16%), weakness (19%)

Has been found to prolong survival by 2-3 months
Has never been studied for more than 18 month duration
  - Many recommend to re-evaluate and discontinue if use greater than 18 months
  - May be appropriate to continue in some patients
    - Higher functional level, duration less than 12 months, symptoms less than 5 years, forced vital capacity >60%, less than 75yo


Dyspnea

- Dyspnea and anxiety are the 2 most prevalent symptoms in terminal phase
- Trial of oxygen
- Systemic opioids and benzodiazepines are standard of care
  - Goal to give low dose at frequent intervals
  - Morphine is used most often but can use any opioid
  - Many patients with dyspnea at EOL benefit from only 10mg/day morphine

1. American College of Chest Physicians, American Thoracic Society, NCCN
Sialorrhea

- Common symptom in ALS. Often what is most frequently thought of in ALS patient.
- Must distinguish between sialorrhea and thick mucus production.

<table>
<thead>
<tr>
<th>Sialorrhea</th>
<th>Thick Mucus</th>
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<tbody>
<tr>
<td>Atropine 1-4 gtts SL q4hr prn</td>
<td>Increase fluid intake (if appropriate) and air humidification</td>
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<tr>
<td>Hyoscyanine 0.125mg PO/SL q4hr prn</td>
<td>Guaifenesin 400mg q4hr prn</td>
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<tr>
<td>Glycopyrrolate 1mg PO TID</td>
<td>Acetylcysteine 200-400mg via nebulizer TID. Most effective if given bronchodilator 10-15min prior to dose.</td>
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<tr>
<td>Transderm Scop patch 1.5mg q3days</td>
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<tr>
<td>Amitriptyline 10-150mg qHS</td>
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Fatigue

- Consider discontinuing riluzole?¹
- Pharmacologic treatment
  - Corticosteroids
    - Dexamethasone 4mg BID with last dose by 2pm
    - Prednisone 10mg qAM
  - Methylphenidate 5mg BID with last dose by 2pm
  - Megestrol acetate 160-800mg/day (best response seen in 480-800mg/day)


Muscle Weakness, Wasting and Spasticity

- Quinine sulfate 325mg BID used to be considered first line
  - Removed from market by FDA due to possible SE and DI
- Current first line options
  - Baclofen 5-10mg PO TID (max 80mg/day)
  - Baclofen 50-100mcg IT qDAY (may titrate by 10-30% per day)
  - Tizanidine 2-4mg PO BID (max 24mg/day)
Dysphagia / Feeding Tube

- Feeding tube placement is not recommended in palliative care
  - Small studies have found some benefit of PEG placement in ALS. May consider if vital capacity is above 50% of predicted
- Multiple large cohort studies have found that feeding tubes do not improved survival in dementia
  - Tube feedings have not been found to improve nutritional status or pressure ulcers
  - Feeding tubes have not been found to prevent aspiration in severely demented patients
  - Observational studies have found no measureable increase in discomfort following decision to withhold artificial nutrition or hydration in advanced dementia


Medications via Tube Feeding

**Step 1**: Is the medication necessary? Can it be stopped?
**Step 2**: Can the medication be given via the tube?

- Tablets/Capsules: confirm if it can be crushed/opened then grind to a fine powder and mix with 10-15ml of water
- Liquids: not always OK to just give via tube!!
  - Sorbitol content- greater 15gm/day from all sources will cause diarrhea
  - Sugar content- is the patient diabetic?
  - Hyperosmolality - >1000 mOsm/kg can cause cramping, diarrhea, vomiting. General rule is to dilute all liquids with 10-30ml water. Osmolality can be found in PI.

Feeding Tube Placement

- Most medications are absorbed systemically in the duodenum
- Intrajejunal administration of drugs with extensive first-pass metabolism (e.g., beta-blockers, nitrates, opioids, and tricyclics) can increase bioavailability.
Medications Likely to Interact with Tube Feeds

• Meds should not be mixed directly with tube feedings
• Tube should always be flushed before and after med administration with at least 15-30ml water
• Meds should not be mixed together and given at same time

<table>
<thead>
<tr>
<th>Medications Likely to Interact with Tube Feeds</th>
</tr>
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<tbody>
<tr>
<td>Phenytoin</td>
</tr>
<tr>
<td>Penicillin, tetracycline and quinolone antibiotics</td>
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<tr>
<td>Narrow Therapeutic Drugs</td>
</tr>
<tr>
<td>warfarin, digoxin, carbamazepine, etc.</td>
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</tbody>
</table>

Medication Specific Items

• Antacids, bismuth, and sucralfate act locally in the stomach, to be effective
• Itraconazole and ketoconazole require an acidic environment for absorption
  • Bioavailability might be reduced when they are administered as farther down the GI tract.
• PPIs via a tube that ends in the intestine
  • Requires a prepared suspension with sodium bicarbonate.
  • These suspensions may be less likely to clog feeding tubes.

Medications Likely to Clog Tube

• Bulk-forming laxatives (psyllium)
• Enteric coated tablets that are crushed (aspirin)
• Cholestyramine
• Sevelamer (Renagel)
• Antacids
• Syrup formulations
  ➢ Narrow tubes more likely to clog regardless of medication.
ALS Patient Case Follow-up

- **Order Clarification:**
  - Change to ciprofloxacin 250mg tablet crushed via PEG BID. Hold tube feeding for at least one hour prior to administration.
- **Discontinued:**
  - Riluzole
  - Atropine
- **Added:**
  - Glycopyrrolate 1mg TID
  - Hyoscyamine 0.125mg q4hr prn secretions
  - Morphine 20mg/ml concentrate give 0.25ml q2hr prn pain/dyspnea
  - Lorazepam 0.5mg q4hr prn anxiety

Multiple Sclerosis Patient Case

- **HPI:** 67 year old home patient admitted to hospice with MS. Patient is often found spitting and swearing/stuttering. The caregiver states that the patient was recently started on Nuedexta for this symptom. Patient prognosis weeks to months.
- **Medications:**
  - Albuterol nebulizer 0.083% q4hr prn
  - Nuedexta 20/10mg BID (started 2 weeks ago)
  - Donepezil 10mg qday
  - Olanzapine 5mg qday
  - Sertraline 100mg qday
  - Lorazepam 1mg q4hr prn

Multiple Sclerosis (MS)

- **Inflammatory disease of the CNS associated with destructive demyelination of neurons**
- **Characterized by recurrent attacks of progressive neurologic dysfunction**
- **Four types:**
  - **Relapsing-remitting:** episodes of neurologic dysfunction and stability
  - **Primary progressive disease:** progressive neurologic degeneration from onset
  - **Secondary progressive disease:** begins as relapsing-remitting but converts to progressive deterioration
  - **Progressive-relapsing:** begins as progressive but has occasional attacks
Neuron Demyelination

http://www.mayoclinic.org/diseases-conditions/multiple-sclerosis/symptoms-causes/dxc-20111884

Multiple Sclerosis (MS)

- Incidence, prevalence, and mortality associated with MS vary with latitude
  - Incidence rates increase with increasing latitudes
  - Higher incidence closer to the equator
- Affects women two to three times as often as men
- Onset usually between 20-45 yo, although late-onset (after age 50) is not uncommon
  - Late onset associated with more rapid decline

General Guidance for Hospice Eligibility: MS

- Rapid disease progression in the past 12 months:
  - To wheelchair or bed-bound
  - Speech barely intelligible or unintelligible speech
  - Pureed diet
  - ADLs assistance required
- Severe nutritional impairment OR life-threatening complication in the past 12 months
- All of the following:
  - Dyspnea at rest, vital capacity less 30%, oxygen at rest, declines artificial nutrition
MS Symptom Management

- Cognitive dysfunction / depression
- Fatigue / heat intolerance
- Gait impairment
- Seizures
- Pseudobulbar affect
- Ophthalmic (blindness/vision impairment)*
- Dysphagia*
- Incontinence*

Cognitive Dysfunction/Depression

- Neurophysiological testing shows up to 70% of patients have some cognitive impairment
  - Frank dementia is uncommon
  - Most common abstract conceptualization, recent memory attention, speed of information processing
- Treatment: no proven therapies
  - Cholinesterase inhibitors (donepezil)
    - Conflicting evidence. Most recent trials show no benefit
  - SSRIs/SNRIs

Fatigue

- Fatigue is reported in up to 78% of patients
- Exhaustion unrelated to the amount of activity performed
  - Often worse during an acute attack
  - Often aggravated by heat and/or humidity
- Treatment options:
  - Corticosteroids
  - Methylphenidate 5mg BID (max 60mg/day)
  - Amantadine 100mg BID (renal insufficiency, seizures)
  - Aspirin 1300mg/day* ???

Gait Impairment

- Leg weakness and spasticity results from lesions in the descending motor tracts of the brain
- Most common treatment is physical therapy and mobility aids (cane, wheelchair, etc.)
- Dalfampridine (Ampyra) 10mg BID
  - Improved walking ability better than placebo after 14 weeks
  - SE: UTI (12%), insomnia (9%), seizure (4%)
  - $$$ (AWP = $1,182 for 15 day supply)

Seizures / Paroxysmal Symptoms

- Paroxysmal symptoms: paroxysmal attacks of motor or sensory phenomena due a demyelinated lesion
  - Brief, almost stereotypic event occurring frequently and often triggered by movement or sensory stimuli
  - Often mistake for a seizure
  - Do not indicate a true exacerbation or loss of myelin
  - Seizures: more common in MS than the general population
  - Treatment: anticonvulsants for both paroxysmal symptoms and seizures

Pseudobulbar Affect

- Also called emotional liability or emotional incontinence
- Describes sudden uncontrollable outbursts of laughter or tearfulness
- Limited data suggests that pseudobulbar palsy may affect ~50% of ALS or MS patients (though not all require treatment)
- Treatment:
  - Nuedexta 20/10mg BID (see next slide)
  - TCAs (ex: amitriptyline 10-150mg qHS)
  - SSRIs (ex: fluvoxamine 100-200mg qDAY)
Nuedexta (dextromethorphan/quinidine)

- Only medication in its class. No other medication available for this indication.
- Early trials show it is the dextromethorphan that is providing benefit.
- Dextromethorphan is rapidly metabolized by the CYP2D6 enzyme.
- Quinidine is a selective CYP2D6 inhibitor.
  - Commercially available dose is 200mg.
  - Dose in Nuedexta is 10mg per dose.
- Thus co-administration reduces the metabolism of the dextromethorphan and maintains serum plasma levels.
- NOTE: fluoxetine (Prozac) and paroxetine (Paxil) are both strong CYP2D6 enzyme inhibitors.

MS Patient Case Follow-up

- Discontinued:
  - Donepezil
  - Nuedexta
  - Sertraline (to start a different SSRI)
- Added:
  - Dextromethorphan 30mg/5ml give 10ml BID (max 120mg/day)
  - Fluoxetine 20mg qDAY (given with dextromethorphan)
  - Methylphenidate 5mg bid with last dose by 2pm x14 days and re-evaluate
  - Lorazepam 2mg q15min prn active seizure with max 6mg/episode

Huntington’s Disease

- Inherited progressive, autosomal dominant neurodegenerative disorder characterized by movement abnormalities, psychiatric manifestations, and cognitive impairment.
- Normal onset between 35-44 years old
  - Can range from 2-80 years old
- Has been described as having ALS, Parkinson’s and Alzheimer’s simultaneously.
General Guidance for Hospice Eligibility: Huntington’s Disease

• Functional Assessment Staging Scale (FAST) stage IV or greater AND
  • Inability to ambulate without assist, inability to dress without assist, urinary or fecal incontinence, no consistent verbal communication

• AND one of the following in the past 12 months:
  • Aspiration pneumonia, pyelonephritis or UTI, sepsis, stage III-IV pressure ulcer, toxoplasmosis unresponsive to therapy, fever with antibiotics, inability to maintain intake with significant wt loss, low albumin, significant dysphagia

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Functional Assessment Staging Score (FAST)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>No difficulty either subjectively or objectively</td>
</tr>
<tr>
<td>2</td>
<td>Complains of forgetting location or objects. Subjective word finding difficulties</td>
</tr>
<tr>
<td>3</td>
<td>Decreased job functioning evident to co-workers. Difficulty in traveling to new locations. Decrease organizational capacity.</td>
</tr>
<tr>
<td>4</td>
<td>Decreased ability to perform complex tasks (e.g., planning dinner for guests), handling personal finances (forgetting to pay bills), difficulty marketing, etc.</td>
</tr>
<tr>
<td>5</td>
<td>Requires assistance in choosing proper clothing to wear for day, season, occasion.</td>
</tr>
<tr>
<td>6a</td>
<td>Difficulty putting clothing on properly without assistance.</td>
</tr>
<tr>
<td>6b</td>
<td>Unable to bathe properly; e.g., difficulty adjusting bath water temperature) occasionally or more frequently over the past weeks.*</td>
</tr>
<tr>
<td>6c</td>
<td>Inability to handle mechanics of toileting (e.g., forgets to flush the toilet, does not wipe properly or properly dispose of toilet tissue) occasionally or more frequently over the past weeks.*</td>
</tr>
<tr>
<td>6d</td>
<td>Urinary incontinence, occasional or more frequent.</td>
</tr>
<tr>
<td>7a</td>
<td>Ability to speak limited to approximately a half dozen different words or fewer, in the course of an average day or in the course of an intensive interview.</td>
</tr>
<tr>
<td>7b</td>
<td>Speech ability limited to the use of a single intelligible word in an average day or in the course of an interview (the person may repeat the word over and over.</td>
</tr>
<tr>
<td>7c</td>
<td>Ambulatory ability lost (cannot walk without personal assistance).</td>
</tr>
<tr>
<td>7d</td>
<td>Ability to sit up without assistance lost (e.g., the individual will fall over if there are no lateral rests [arms] on the chair).</td>
</tr>
<tr>
<td>7e</td>
<td>Loss of the ability to smile.</td>
</tr>
<tr>
<td>7f</td>
<td>Loss of ability to hold of head independently.</td>
</tr>
</tbody>
</table>

*Scored primarily based upon knowledge obtained from a knowledgeable caregiver.
Huntington Patient Case

• HPI: A 55 year old male admitted to hospice with Huntington’s chorea.
• CC: Muscle rigidity and stiffness. Recently started on ropinirole for this. This is thought to be due to disease progression as well as due to antipsychotics.
• Medications:
  • Quetiapine 100mg BID
  • Baclofen 5mg BID
  • Paroxetine 20mg qDay
  • Glycopyrrolate 1mg TID
  • Hyoscyamine 0.125mg q6hr prn secretions
  • Ropinirole 0.25mg BID

Huntington’s Disease

• Symptom management:
  • Chorea
  • Rigidity
  • Cognitive dysfunction
  • Dementia
  • Sialorrhea

Chorea

• Brief, abrupt, irregular, unpredictable, non-stereotyped movements
• May be aggravated by stress, anxiety, depression
• Chorea may vary with changes in mood, posture or position
• Severe chorea may require padding chair/bed
• Treatment: dopamine antagonist and benzodiazepines
Chorea Treatment (labeled)

- Tetrabenazine (Xenazine) 12.5-25mg BID
- Shown to improve chorea severity
- MOA: depletes dopamine, norepinephrine and serotonin stores
- Recommended by AAN (American Academy of Neurology)
- Metabolized by CYP2D6
  - Recommend to decrease dose by ½ if patient also on strong CYP2D6 inhibitor
- AWP = $4,539 for 15 day supply (25mg BID)
  - Manufacturer offers patient assistance program

Proposed Chorea Treatment Algorithm

- Mild/moderate: tetrabenazine
- Moderate: atypical antipsychotic
  - Olanzapine, risperidone
    - High-dose quetiapine (600mg/day) reported to improved chorea in 1 case report only¹
- Severe: typical antipsychotic
  - Haloperidol, fluphenazine, chlorpromazine
  - +/- Amantadine 200-400mg/day (conflicting evidence as to benefit)
  - +/- Riluzole 50mg BID (conflicting evidence as to benefit)

¹ J Neurol. 2002;249(8):1114.

Rigidity

- Usually rigidity and bradykinesia do not require treatment
- Treatment: dopamine agonists
  - In rare cases where pharmacologic treatment is required
  - Levodopa, pramipexole (Mirapex), ropinirole (Requip)
  - Caution: use of these can worsen chorea and or agitation/psychosis
Cognitive Dysfunction / Dementia

- Psychosis, agitation and depression are all common
  - Quetiapine (Seroquel) may be particularly useful to manage agitation/psychosis as it does not worsen bradykinesia
  - However, many patients require an antipsychotic for the management of chorea

- Dementia
  - No effective therapy for dementia associated with HD
  - Small studies and case reports fail to show improvement of motor or cognitive impairment with cholinesterase inhibitors (donepezil, etc.)

Huntington Patient Case

Follow-Up

- Discontinue:
  - Quetiapine
  - Ropinirole

- Add:
  - Olanzapine 5mg BID (to replace quetiapine)
  - Baclofen 10mg TID (to maximize dose and replace ropinirole)

Questions?

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