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
Hospice Patients by Diagnosis

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%)

Rilutek (riluzole)

- Has been found to prolong survival by 2-3 months
- Has never been studied for more than 18 month duration\(^1\)
  - Many recommend to re-evaluate and discontinue if use greater than 18 months
- May be appropriate to continue in some patients\(^2\)
  - 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\(^1\)
  - Goal to given 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\(^2\)

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 1-4gtts SL q4hr prn</td>
<td>Increase fluid intake (if appropriate) and air humidification</td>
</tr>
<tr>
<td>Hyoscycamine 0.125mg PO/SL q4hr prn</td>
<td>Guaiifenesin 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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</table>

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 with hold 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>
</thead>
<tbody>
<tr>
<td>➢ Phenytoin</td>
</tr>
<tr>
<td>➢ Penicillin, tetracycline and quinolone antibiotics</td>
</tr>
<tr>
<td>➢ Narrow Therapeutic Drugs</td>
</tr>
<tr>
<td>➢ warfarin, digoxin, carbamazepine, etc.</td>
</tr>
</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/anxiety associated with dyspnea

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

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 BID1 (renal insufficiency, seizures)
  • Aspirin 1300mg/day2 ???

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 5% of ALS or MS patients (though not all require treatment)
• Treatment:
  • Nuedexa 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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<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>
</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 only
- Severe: typical antipsychotic
  - Haloperidol, fluphenazine, chlorpromazine
  - +/- Amantadine 200-400mg/day (conflicting evidence as to benefit)
  - +/- Riluzole 50mg BID (conflicting evidence as to benefit)


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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