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Pharmacological Management of the Patient with Neurological and/or Central Nervous System Disorders

Enhancing pharmacological and rehabilitation therapies through understanding of meds

Rosanne Thomas PT, MS, PhD

Objectives

1) Given the name of a drug commonly prescribed for a patient with neurological and/or CNS dysfunction, be able to classify the drug according to category, general mechanism of action, mode of administration, contraindications and synergistic as well as side effects.

2) Articulate pharmacological interventions’ effect on PT treatment as well as physical therapy’s effect on drug metabolism to optimize both interventions.

3) Perform a preliminary screening of a patient’s medications appropriate for an initial point of contact within the scope of PT practice.

4) Begin to develop an arsenal of accurate, comprehensive and professional on-line resources to use in everyday practice to continue to grow in one’s knowledge of ever changing neurological medications.
Pharmacology and non-prescribing Healthcare practitioners

Why???

Overview

• Pharmacology Review
• Structure of presentation
• Pharm management of specific aims within dx
• Patient Problems
• Commonalities
• Finding Good Drug Websites
Pharmacology

Pharmacotherapeutics
- Drug absorption
- Distribution
- Metabolism
- Excretion

Pharmacodynamics
- Cellular effects
- Systemic effects

What does the Body do to the drug?
What does the DRUG do to the body?
Drug Mechanism of Action

The means by which the presence of a drug produces an alteration in function

Drugs usually must combine with a cellular receptor to produce an effect

Pharmacotherapeutics

Dose of Drug Administered
- Enteral
- Parenteral

Drug concentration in systemic circulation

Drug concentration at site of action

Pharmacologic effect

Clinical Response

Summary

Pharmacokinetics
- Absorption
- Distribution
- Elimination

Pharmacodynamics
- Side effects/
  Toxicity
- Efficacy

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http://citadel.uci.edu/~n黑客/vsg/vsg/vsg.html
Drugs for Neurological Disorders

1. Minimize secondary damage acutely –
   • Spinal Cord Injury (SCI)
   • Ischemic Cerebral Vascular Accident (CVA)
   • Traumatic Brain Injury (TBI)
2. Manipulate neurotransmission –
   • Parkinson’s disease (PD)
   • Alzheimer’s disease (AD)
   • Psychiatric diseases
3. Slow disease progression –
   • Multiple Sclerosis (MS)
   • Amyotrophic Lateral Sclerosis (ALS)
4. Minimize signs/symptoms and secondary problems
   • Tone/spasticity

1 - Minimize secondary damage following an acute event

- Ischemic CVA
- Traumatic Brain Injury (TBI)
- Traumatic SCI

- CNS
- Acute Event, then static
- Primary, then secondary damage
Events after a CNS injury

**Penumbra** — areas adjacent to initial injury that may die secondarily

**Diaschisis** — interconnected areas that eventually may die

**Central Core** — initial injury due to ischemic cell death

**Excitotoxicity**

- Ischemia
- Ca influx
- Release of EAA’s
  - NMDA receptor activation
- Arachidonic acid release
- Free radical production
- Lipid peroxidation
- Apoptosis
- Necrosis

**Inflammation**

- ↑ Lesion growth
- ↑ed functional deficits

**Brain**

**Spinal Cord**
Events after a CNS injury – w/ acute Intervention

Minimize secondary damage acutely – Acute SCI
Glucocorticoids (steroids)

**Anti-inflammatory effects**
- Inhibits pro-inflammatory agents such as prostaglandins & leukotrienes
- Inhibits macrophages
- Inhibits inflammatory cells from secreting platelet activating factors, necrosis factor
- Stabilizes lysosomal membranes

**Methylprednisolone (MP)**
- NASCIS 2 standards
- Standard protocol
- High dosage bolus IV followed by infusion x 23h

- Treatment MUST be initiated within 8 hours of injury
Minimize secondary damage acutely – 
Acute TBI

Pharmacological Purposes:

- **BP Control (normotensive), maintain oxygenation**
  - each 10-point increase in systolic pressure associated with a decrease of 18.8% in the adjusted odds of death.

- **Osmotic agents- control ICP**

- **Barbituates- control ICP**

  - **Phenylephrine HCL → BP control**
    - A sympathomimetic with alpha 1 agonist effects
    - Raises BP via vasoconstriction of peripheral blood vessel smooth muscle
    - ↑’s total peripheral vascular resistance without affecting cerebral vessels
    - Administered IM or IV

Mannitol –
- Predictably lower ICP <15 mm Hg
- Poorly absorbed, given IV
- Osmotic diuretic used to ↓ intracranial pressure by:
  - ↑’s intravascular osmotic load pulling fluid from brain parenchyma
  - May ↓ blood viscosity → better blood flow & oxygenation
- Must have an intact BBB
- May exacerbate ICP if given chronically

**Side Effects:**
- Pulmonary edema
- Hypotension
- Renal injury

**Steroids**
- NOT CURRENTLY RECOMMENDED IN TBI
- Evidence → ↑ mortality
Minimize secondary damage acutely – TBI – Barbituates

High doses lower ICP by altering vascular tone

Mechanism –

- Facilitate GABAergic neuronal transmission → ↑ Cl channel activity → membrane hyperpolarization = ↓ excitability
- Depress actions of excitatory NT
- Exert nonsynaptic membrane stabilization effects

Result – very long T 1/2

- Suppression of brain stem reticular-activating system
- Sedation
- Amnesia
- LOC
- Anticonvulsant
- Mm relaxation
- Reflex suppression

Specific Examples –
- Pentobarbital – short acting
- Secobarbital – medium acting

Minimize secondary damage acutely – Acute Ischemic Stroke

- Blood Pressure Control – similar to TBI
- Clot Breakdown – fibrinolytic drugs
- Anti-coagulation – prevent further clots
- Prevention of secondary damage – save the penumbra and diaschisis

https://www.healthtap.com/topics/acute-cerebral-vascular-accident
Acute Ischemic Stroke – Meds to minimize secondary damage acutely -
Fibrinolytic Agents – “clot busters”

Streptokinase
Mechanism – Nonenzymatic protein substance that forms a complex with plasminogen converting plasminogen to plasmin
Clinical uses – lysis of acute DVT, pulmonary emboli & acute arterial thrombi
Side effects – bleeding
Administration - IV
Contraindications – bleeding, hemorrhagic stroke

TPA (Tissue plasminogen activator) (Alteplase)
Mechanism – Recombinant human thrombolytic enzyme that activates plasminogen bound to fibrin
Clinical uses – DVT, multiple pulmonary emboli
Side effects – Bleeding
Administration - IV
Contraindications- bleeding, hemorrhagic stroke

Must be administered within 3 hours of symptom onset

Acute Ischemic Stroke – Meds to minimize secondary damage -
Anticoagulants

- Parenteral
  - Heparin
- Subcutaneous
  - Lovenox
  - Arixtra
- Oral
  - Vitamin K antagonists – Coumadin/Warfarin
Summary- Acute Meds to minimize secondary damage

• SCI – minimize inflammation
  • Methylprednisolone (MP) IV infusion
• TBI – minimize brain edema, maintain brain perfusion
  • Normotensive - Phenylephrine HCL IV or IM
  • ICP reduction
    • Mannitol – osmotic agent
    • Barbituates - ↓ICP, sedation, CNS depression
      • Pentobarbital – short acting
      • Secobarbital – medium acting
• Ischemic CVA –
  • tPA/ Streptokinase – eliminate clot, reestablish BF
  • Anticoagulants – prevent further clots
    • Heparin – IV short term
    • Lovenox, Arixtra – subcutaneous
    • Warfarin/ Coumadin – Oral- long term

Acute Meds to prevent secondary damage – Rehab implications (screen share)

• Acute treatment – medically stable patient, passive, dependent activities
• Subacute Example – Lovenox

<table>
<thead>
<tr>
<th>Check Drug</th>
<th>Check Interactions</th>
<th>Precautions</th>
<th>Rehab Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>potential additive effects with NSAIDs</td>
<td>Easy bruising</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Coumadin – INR monitoring)</td>
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• Patient Example
Patient Example #1

- Mrs. Blue is a 76-year-old woman who has a history of hypertension and diabetes mellitus and had a myocardial infarction 2 years ago. She arrives at her local emergency room 4 hours after an acute onset of weakness in her left arm and leg. She fell at home after trying to get up, and it was only after her neighbors heard her calls for help that the emergency services rescue team came to her aid.

- On admission to the emergency room, she has an elevated blood pressure of 200/100 mmHg and is alert and oriented. Her initial physical exam reveals left-sided weakness and sensory loss that is greater in her arm than her leg. A CT scan is performed which reveals a clear, acute infarct in the right temporoparietal area with associated edema and no mass effect or hemorrhage.

- The neurologist and cardiologist concur on anticoagulation with heparin followed by conversion to warfarin.

1- Why was a fibrinolytic agent not prescribed for this patient? When would it be appropriate? What must be checked first?

2- Explain the anticoagulant regime used for Mrs. Blue—heparin followed by warfarin.

3- List 2 PT precautions while you treat Mrs. Blue during the acute phase.

4- What follow-up pharmacological treatment may be appropriate for Mrs. Blue once she returns home?

Minimize secondary damage following an acute event

Experimental Pharmacological Management

- NMDA receptor Blockers
  - Require intracranial admin due to BBB
  - Systemic, unproven results

- Ca channel Blockers - nimodepine

- Antioxidants - Vit E, Glutathione

- Free Radical Scavengers
  - Ginkgo biloba (EGb761) – can inhibit action of substances that adversely affect BBB
  - GM1 ganglioside - controversial

- Trophic Factors
  - NGF – delayed neuronal death when admin intraventricularly
2- Manipulate neurotransmission

Treatable neurotransmitter diseases fall into 2 categories:

![A Simple Synapse](http://fblt.cz/en/skripta/regulacni-mechanizmy-2-nervova-regulace/5-neurotransmisni-systemy/)

- **Too MUCH neurotransmission**
- **Too LITTLE neurotransmission**

**General Mechanisms**

**Too LITTLE neurotransmission due to:**

- Too few NT molecules binding to postsynaptic receptors (ex – PD, depression)
- Rx - Drugs that cause release of NT stores from presynaptic terminals
  - NT precursors
  - Drugs that inhibit the enzymes that degrade NT
  - Agonist that act at postsynaptic receptors

**Too MUCH neurotransmission due to:**

- A focus of hyperexcitable neurons that fire in the absence of appropriate stimuli (ex- seizures)
  - Rx - Blocking automaticity of these cells
- Too many NT molecules binding to postsynaptic receptors (ex-psychoses)
  - Rx – Administration of antagonists which block postsynaptic receptors

Manipulating transmission in a diseased pathway simultaneously affects synapses of normal neurons

Side Effects

Normal Synaptic Transmission

1. Presynaptic AP
2. Synthesis of NT
3. Storage of NT
4. Release
5. Reuptake
6. Degradation
7. Post synaptic receptor
8. Presynaptic autoreceptor
9. Membrane effects

http://people.fmarion.edu/tbarbeau/physio_neuro_supplements.htm
2- Manipulate neurotransmission

- PD – too little dopamine
- AD – too little acetylcholine
- Schizophrenia -Too much dopamine?
- Bipolar – Na channels?
- Depression – Serotonin modulation?
2- Manipulate neurotransmission

- PD – too little dopamine
- AD – too little acetylcholine
- Schizophrenia – Too much dopamine?
- Bipolar – Na channels?
- Depression – Serotonin modulation?

- Other nervous system disorders including PNS
  - Myasthenia Gravis
  - Guillain Barre
  - Lambert Eaton

Covered in a future webinar
Not covered in this webinar

Manipulate neurotransmission
Common PD Drugs – replace dopamine (DA)

- Levodopa
- Levodopa/carbidopa
- DA receptor agonists
- Other
Levodopa

- Rapidly absorbed from small intestine by active transport
- Dietary AA compete with LDA for transport (protein restricted diet)
- Very limited bioavailability
- Short T½ - 1–3 h

Dopa-decarboxylate is the enzyme that converts L-DOPA to DA

Levodopa w/Carbidopa

LDA alone:
- 70% metabolized in GI, liver, kidney
- 27% SE in peripheral circulation – nausea
- 1 – 3% reaches brain

LDA & Carbidopa:
- Peripherally active inhibitor of dopa decarboxylate
Carbidopa’s effect on Levodopa administration

Prevents the conversion of LDA into Dopamine until it reaches the Substantia Nigra in the Basal Ganglia

- ↓ periph metab
- ↑ plasma levels
- ↑ T1/2
- ↑ LDA to brain

Levodopa Formulations

**Carbidopa/Levodopa (Sinemet)**

- 25mg/100mg TID = 1:4 ratio
- 25/250mg TID, QID = 1:10 ratio

**Clinical Effects –**

- Significant ↓ s/s
- Diminished efficacy/time
  (due to continued loss of DA neurons to convert L-dopa)

**Stalevo** = carbidopa, levodopa, entacapone

Supplied in 3 strengths

- **Stalevo 50** = 12.5 mg CD
  - 50 mg LD
  - 200 mg entacapone
- **Stalevo 100** = 25 mg CD
  - 100 mg LD
  - 200 mg entacapone
- **Stalevo 150** = 37.5 mg CD
  - 150 mg LD
  - 200 mg entacapone
Manipulate neurotransmission
Dopamine Receptor Agonists

• Alternative to LDA therapy – can be monotherapy or adjunct with LDA
• Act directly at DA-R
• Do not require metabolic conversion by DA neurons thus effect does not diminish as DA neurons continue to degenerate
• Can be targeted to particular DA-R subtypes
• Have longer duration of action

Dopamine Receptor Agonists

• Bromocriptine (Parlodel) – Potent D2R agonist
• Pramipexole (Mirapex) – selective D2R agonist
  • Effective monotherapy, delaying need for LDA
  • In combo - ↓ flux
  • Most freq rx agonist

• Ropinirole Hydrochloride (Requip)
  • DAR agonist used as monotherapy early in disease process
  • SE – somnolence, syncope, hypotension, may + dyskinesias

Well absorbed orally
Long T ½ 3-7 h
Manipulate neurotransmission
Other PD meds

- Selegiline (Deprenyl, Eldepryl)
  - MAO-B inhibitor – more DA around presynaptically

- Tolcapone (Tasmar)
  - COMT inhibitor – more DA around in the synapse

- Entacapone (Comtan)
  - COMT inhibitor - more DA around in the synapse

Alzheimer’s Disease - CHEI’s = Cholinesterase Inhibitors

- Theory – AD → altered Ach transmission
- Benefits temporary – do not address underlying cause
- Effective at all stages with improved cognitive performance and improved behavioral manifestations
- Helpful with ALL types of dementia
- Side effects – Nausea, vomiting, diarrhea, dizziness

http://filipinohomecaregiver.com/alzheimers-disease/
Manipulate neurotransmission AD Medication effect on Acetylcholine

- Improve efficiency of Ach
  - Cholinesterase inhibitors (CHEI's)
  - Slow breakdown of Ach at the synaptic cleft

맨 | enzyme in synaptic cleft that breaks down Ach

Common CHEIs

- Donepezil (aricept)
- Rivastigmine (Exelon)
- Galantamine (Galanthamine Reminyl)

All administered orally, Q 12-24 h
All for mild to moderate dementia
Manipulate neurotransmission - AD
NMDA antagonist - Menantine (Namenda)

- Modulates Glutamate transmission by blocking it’s receptors
- Recommended in moderate to late stage disease
- Maybe used in conjunction with CHEI’s
- May be neuroprotective
- Few side effects
  - Dizziness, rare – confusion, hallucinations

Manipulate neurotransmission Summary for Neurological Disorders PD and AD

**PD**
- Replace diminished endogenous DA
  - Sinemet – levodopa/carbidopa
  - Stalevo – levodopa/carbidopa/entacapone
- Act in place of DA – dopamine receptor agonist
  - Bromocriptine (Parlodel)
  - Pramipexole (Mirapex)
  - Ropinirole Hydrochloride (Requip)
- Slow DA breakdown
  - Selegiline (Deprenyl, Eldepryl) – *presynaptic inhibition of MAO-b*
  - Tolcapone (Tasmar) – *inhibition of COMT in synaptic cleft*
  - Entacapone (Comtan) – *inhibition of COMT in synaptic cleft*

**AD**
- Cholinesterase Inhibitors (CHEIs)
  - Donepezil (Aricept)
  - Rivastigmine (Exelon)
  - Galantamine (Galanthamine Reminyl)
- NMDA antagonist – *modulates Glutamate action*
  - Menantine (Namenda)
Manipulate neurotransmission
Rehab Implications

• Most common side effect of meds for PD and AD?
  • Blood pressure changes
  • Orthostatic Hypotension → falls
  • When is this the most problematic?

• Other commonalities
  • Alcoholic beverages or sedatives don’t mix well with these meds
  • May produce anticholinergic s/s – dry mouth, lack of sweating, nausea

• How do you deal with the fluctuating s/s of PD with medication half-lives?
  • On-off times
  • Levo-dopa induced dyskinesias

Manipulate neurotransmission
Patient Example # 2

• Mr. Red has an eight year history of PD and has been on sinemet QID for the past 5 years. He is receiving PT following a fall at home. After a few PT sessions, the PT noticed that there were certain days when the patient was able to actively and vigorously participate in the therapy program. On other days, the patient was essentially akinetic, and his active participation in exercise and gait activities was virtually impossible. There did not seem to be a pattern to his good and bad days, and the beneficial effects of the rehabilitation program seemed limited by the rather random effects of his levodopa medication. The patient stated that these akinetic episodes sometimes occurred even on nontherapy days.

1-Assuming that the patient’s PT was scheduled in the morning, WHAT could be going on with his morning akinesia?
2- What modifications would you recommend?
3- Describe the benefit of using DA agonists such as pramepexole.
4- What other meds could have been prescribed?
Manipulate neurotransmission
Patient Example # 3

• Mrs. Pink is a 77 y/o woman who was recently diagnosed with Alzheimer’s Disease and lives with her son and his family. Her concurrent dx include DM, HTN, depression and she sustained her 2nd CVA one month prior. Her medications include aspirin 325 mg/day, citalopram 40 mg QD, metformin 500 mg BID, Lisinopril 20 mg/day, Toprol XL 25 mg/day.

• She has been receiving physical therapy to assist recovery from her latest CVA. Her physician has prescribed an Exelon patch QD and Namenda daily for the AD dx.

• Her son called to cancel PT today as Mrs. Pink reports nausea, vomiting and c/o “weakness.”

1- List the probable indication for each med.


3- What is the likely culprit for these new s/s?

4- What could you recommend regarding her new medications?

3- Slow disease progression

• Multiple Sclerosis (MS)
• Amyotrophic Lateral Sclerosis (ALS)
Slow disease progression- MS

Interferons:
A family of soluble proteins – cytokines
• Act as chemical messengers between cells
• Essential role in the immune system by repairing damage and helping destroy infecting material
• “Interfere” with replication of genetic material in foreign cells
• Three main types - α, β, gamma
• Interferon Beta – only interferon beneficial in rx of MS

• Methylprednisolone
• Glatiramer Acetate (Copaxone)
• Interferon Beta 1b (Betaseron)
• Interferon Beta 1a (Avonex)
• Interferon Beta 1a (Rebif)
• Mitoxantrone (Novatrone)

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Methylprednisolone
• High dose corticosteroid given IV over course of 4 days during MS exacerbation
• Can shorten an exacerbation but NOT change disease progression
• Tapering oral dose of corticosteroid given after 4 day IV regimen

Glatiramer acetate (Copaxone)
• Synthetic mix of polypeptides containing 4 amino acids: glutamine, alanine, tyrosine, lysine.
• $10,000/year for rx
• Reduces incidence of relapse without affecting disease progression
• Daily SC injection
• SE: pain, erythema, pruritus, flushing, chest tightness, anxiety, dyspnea (30 min)

Interferon Beta – 1b (Betaseron)
• Synthetic mixture of proteins that exert antiviral activities through cellular metabolic processes involving RNA synthesis & protein
• Produces a ↓ in exacerbations, a longer time between exacerbations, & less severe exacerbations
• Administered every other day SC
• SE: Flu-like s/s (fatigue, chills, fever, mm aches, sweating), inj site rea. Depression including suicidal ideation/attempt
• Avoid use during pregnancy

Interferon Beta – 1a (Avonex)
• As 1b above but Depression not as severe
• Administered once-a-week IM injection

Interferon Beta – 1a (Rebif)
• 3 x wk SC injection
<table>
<thead>
<tr>
<th><strong>Slow disease progression- MS</strong></th>
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<tbody>
<tr>
<td><strong>Mitoxantrone (Novatrex)</strong></td>
</tr>
<tr>
<td>• A DNA reactive agent approved for use as chemotherapy – an antineoplastic</td>
</tr>
<tr>
<td>• Suppresses activity of T cells, B cells &amp; macrophages</td>
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<tr>
<td>• Limits MS exacerbation through unknown mechanism</td>
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<tr>
<td>• Administered IV once every 3 months for a 24 month period</td>
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<table>
<thead>
<tr>
<th><strong>Ampyra (Dalfampridine)</strong></th>
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<tbody>
<tr>
<td>• 10 mg twice a day – <strong>ORAL</strong> administration</td>
</tr>
<tr>
<td>• Potassium channel blocker that assists AP propagation along demyelinated nerves</td>
</tr>
<tr>
<td>• Improve walking speed</td>
</tr>
<tr>
<td>• SE – seizures at high doses. Can not be used with kidney disease</td>
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<table>
<thead>
<tr>
<th><strong>Tysabri (Natalizumab)</strong></th>
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<tr>
<td>• Monoclonal antibody affecting leukocytes</td>
</tr>
<tr>
<td>• Withdrawn in 2005 reintroduced in 2006</td>
</tr>
<tr>
<td>• 300 mg IV infusion Q 4 wk</td>
</tr>
<tr>
<td>• SE – headache, fatigue, UTI, depression, jt pain</td>
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<thead>
<tr>
<th><strong>Slow disease progression- ALS</strong></th>
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**Riluzole (rilutek) – Hypothesized mode of action:**

- Inhibitory effect on glutamate release
- Inactivation of voltage dependent Na channels
- Interfere with intracellular events after NMDA & AMPA receptor binding

[Fig L-3: Riluzole Inhibits Glutamate Release](http://web.stanford.edu/group/hopes/cgi-bin/hopes_ISO/riluzole/)
Slow disease progression - ALS

- **Radicava (edaravone)** – Approved by FDA on 5/5/2017 after 13 y of testing
- First ALS med approved by FDA in 22 years
  - Have completed several Phase 3 trials BUT none in U.S. yet
- Hypothesized mode of action:
  - A free radical scavenger, thought to decrease effects of oxidative stress on cells
  - Slows decline in physical function
- Administered via IV in 28 day cycles - 14d of daily infusion/ 14d of rest
- Very costly ~ $1000 per infusion → > $150,000 per year
- Potentially life threatening Side Effects including allergic reactions
- Common Side Effects – bruising, gait problems, headaches

MT Pharma America: [https://www.multivu.com/players/English/8047051-mt-pharma-america-radicava-fda-approval/](https://www.multivu.com/players/English/8047051-mt-pharma-america-radicava-fda-approval/)

3- Slow disease progression - Summary

**MS**
- Methylprednisolone
- Glatiramer Acetate (Capaxone)
- *Interferon Beta 1b (Betaseron)*
- *Interferon Beta 1a (Avonex)*
- *Interferon Beta 1a (Rebif)*
- Mitoxantrone (Novatrone)
- Dalfampridine (Ampyra)
- Natalizumab (Tysabri)

**ALS**
- *Riluzole (Rilutek)*
- Edaravone (Radicava)
Slow disease progression Rehab Implications

• Multiple side effects with MS disease modifying meds
  - Immediate post-injection reactions consisting of symptoms such as flushing, chest pain, dyspnea, and hives have been reported, often several months after treatment initiation

• Mild Side Effects – flu like s/s
• Moderate Side Effects include OHT
• May help to take at HS

• ALS
  - Rilutek only med available to impact dx
  - Prolongs life approx. 3-6 months

Slow disease progression Patient Problem #4

1. What other options of disease modifying meds might be better suited for Mrs. Black? Why?
2. What other suggestions do you have?

Mrs Black is a 62 y/o female with a PMH of RRMS x 19 years. She is still ambulatory with a STCN and independent with self-care, though with constant fatigue and intermittent spasticity. Since diagnosis, she has been prescribed several interferon beta formulations (IFN) and currently has been taking Avonex.

She admits to non-compliance with the medication injections, some weeks only self-administering twice.

She now reports increasing weakness BLE and N & T in her RUE. Mrs. Black spoke to her physician on the phone and she prescribed a Depo-Medrol pack (methylprednisolone acetate.)
4. Minimize signs/symptoms and secondary problems - Hypertonicity

**Hypertone develops when there is:**

- ↓ in inhibition from cortex and inhibitory sp cord interneurons
- Following an Upper Motor Neuron lesion
  - **Spasticity** – velocity dep hypertone, on the against gravity mm side of a joint
  - **Rigidity** – not velocity dependent, on both sides of a joint, not due to an UMN lesion

**Multiple Medication Options:**

- Baclofen
- Tizanidine
- Dantrolene
- Diazepam
- Botox

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**Spasticity Management**

Legend:
- Mo = Motor neuron in Sp Cord
- Ii = Inhibitory interneuron
- Ie = Excitatory interneuron
- NMJ = Neuromuscular Junction

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Spasticity Management - Baclofen

- GABA-B agonist
- + hyperpolarization
- ↓s release of excitatory NT
- ↑ neuronal inhibition

Baclofen Intrathecal Administration

**The Programmer**
- Externally programmed via computer software
- Instructions transmitted through a “wand” by radio telemetry to the infusion pump
- Can be programmed for a continuous dose over 24 hours up to 12 specific dosages throughout the day
  - Simple continuous
  - Periodic Bolus
  - Complex-Continuous
- Average doses – 300-1000mcg
- Refill every 4 – 12 weeks

**The Pump**
- Surgically implanted SC in abdomen
- Stores & releases prescribed amounts of drug
- Holds 18 ml (3.5 teaspoons)
- Refilled q 1-5 months depending on pump size, concentration, and dose

**The Catheter**
- Small diameter, silicone rubber tube
- Travels from pump, under skin, to delivery site in spinal cord
- Catheter introduced below L3, advanced to T8-10
Intrathecal Pump

**Advantages**
1. Medicine is sent directly to the nerve cells
2. Medicine dosage can be adjusted
3. Less medication is needed, which reduces side effects.
4. Reservoir can be easily refilled when needed
5. Surgery is reversible

**Disadvantages**
1. Requires surgery to implant the pump
2. Expensive
3. Tubing can become disconnected or kinked
4. Risks
   a. Infection
   b. Baclofen overdose
   c. Pump dysfunction
   d. Symptoms of withdrawal

<table>
<thead>
<tr>
<th>S/S of Overdose</th>
<th>Baclofen</th>
<th>Intrathecal Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>Drowsiness</td>
<td></td>
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<tr>
<td>Seizures</td>
<td>Respiratory Depression</td>
<td></td>
</tr>
<tr>
<td>Hypertonia</td>
<td>Loss of consciousness</td>
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**Baclofen**

**Intrathecal Administration**

**Intrathecal Baclofen Candidates**
- Moderate to severe hypertonicity
- Potential to be more independent with ADL’s
- Non-ambulatory with tone interfering with caregiving
- Pain or at risk for skeletal deformity
- Committed support system
- Over 4 y/o
- Respond to intrathecal test dose < 100 micrograms
- One year post TBI

[Link: http://www.neuros.net/es/generalidades_dolor/]
Spasticity Management
– Dantrolene (Dantrium)

- Acts directly on mm
- An antagonist of the ryanodine receptor (Ca channel receptor in SR of skeletal mm)

Spasticity Management
- Diazepam

- ↑s GABA’s central inhib effect @ li
- CNS depressant
Spasticity Management – Zanaflex (Tizanidine)

- Central acting α2 agonist
- ↑ inhib effects of II

Spasticity Management – Botulinum Toxin

- Prevents release of acetylcholine vesicles from presynaptic axon @ NMJ
  - Toxin binds to presynaptic axon terminal
  - Internalization of toxin
  - Inhibition of NT release
- Administered IM in specific muscles
- Chemical denervation within days – lasts approx 3 months
Minimize signs/symptoms and secondary problems

Patient Example # 5

• Mr. Orange is a 30 y/o man who sustained complete paraplegia below L2 during a MVA. With rehab he became independent with self-care, and had begun to ambulate wearing KAFOs. During this time, spasticity had increased in his LEs to the point where dressing and self-care were often difficult. The tone also made it difficult to don/doff his KAFOs. He was begun on dantrolene (Dantrium) at an initial oral dosage of 25 mg/day, which was gradually increased to 400 mg/day.

• Although the dantrolene controlled his spasticity, he began to notice UE weakness and difficulty transferring and ambulating.

1- How does dantrolene modulate tone?
2- Why is it causing UE weakness?
3- What other medication options might be a better choice for Mr. Orange?
4- What would be your recommendation to the prescribing physician?

Modified from Pharmacology in Rehabilitation, CD Ciccone

4. Minimize signs/symptoms and secondary problems - Chronic Pharmacological Management

Meds for Behavioral Issues

• Anti-Psychotics
• Anti-Depressants
• Anti-Anxiety

Potential Impact on Rehab

• Sedation
• Akathisias
• Short term memory impairment
• Tardive dyskinesias
• Suicidal ideation
4. Minimize signs/symptoms and secondary problems - Chronic Pharmacological Management

**Bladder Control (neurogenic bladder)**
- Ditropan (oxybutynin chloride) oral BID-TID – *anticholinergic muscarinic receptor antagonist*

**Drooling**
- Cogentin (benztropine mesylate) *anticholinergic muscarinic receptor antagonist*

**Recurrent UTI**
- Cipro (Fluoroquinolone Antibiotics)

**DVTs**
- Anticoagulants
  - Coumadin, Xarelto, Pradaxa, Eliquis, etc

**Potential Impact on Rehab**
- Side effects of anticholinergics
  - Blurred vision
  - Constipation
  - Decreased sweating
  - Dizziness
  - Dry mouth

- Cipro SE
  - Tendonitis, rupture
  - Neurotoxicity in pts w/Neuro Dx

Finding Accurate Drug information

- **Anyone** can post information
- Don’t waste time on unreliable/ inaccurate sites

**Suggestions**
- What is the site’s domain? *Don’t make this your only criteria!*
  - .gov, .edu – almost always reliable
  - .org – often nonprofit, less reliable
  - .net, .com – least reliable
- Who wrote/sponsored/ published the site? *Check for biases or ulterior motives*
- When was the site last updated? *Is it current?*
- What links connect with the site? *Are they reputable?*
- Who is the site’s audience?

Drugs for Neurological Disorders

1. Minimize secondary damage acutely –
   • Spinal Cord Injury (SCI)
   • Ischemic Cerebral Vascular Accident (CVA)
   • Traumatic Brain Injury (TBI)

2. Manipulate neurotransmission –
   • Parkinson’s disease (PD)
   • Alzheimer’s disease (AD)
   • Psychiatric diseases

3. Slow disease progression –
   • Multiple Sclerosis (MS)
   • Amyotrophic Lateral Sclerosis (ALS)

4. Minimize signs/symptoms and secondary problems
   • Tone/spasticity
   • Neurogenic bladder
   • Drooling

Keep in mind -

• We’re not the expert
• There are multiple sources of information available
• Be pro-active and ready with information before it’s needed
• Be responsible and always screen your patient’s meds
• Establish relationships with prescribing healthcare professionals
References


