Learning Objectives:
1. Describe the neurochemical basis for Parkinsonism and the mechanisms, benefits and adverse effects of agents used in its treatment
2. Describe the physiological basis for muscle spasm and spasticity and the mechanisms, benefits and adverse effects of agents used in its treatment

I. Parkinson’s Disease (PD)
- Neurodegenerative disorder
- Treatments alleviate symptoms, but do not alter the underlying course or progression of the disease
- Primarily a disease of later life (~1-3% of individuals over age 65 and 0.3% of general population)
- Parkinsonism: some symptoms of PD, but the pathology and causes differ

- Clinical Symptoms: four cardinal features:
  - bradykinesia: slowness and poverty of movement
  - muscular rigidity: increased resistance to muscle stretch
  - resting tremor: usually abates during voluntary movement
  - postural instability leading to disturbances of gait and falling
- Complications: inability to walk, mask-like expression, impairment of speech and skilled acts, possible death (from immobility or falls), depression common and dementia may occur

II. Pathophysiology
- Progressive and irreversible loss of dopamine neurons in the substantia nigra
  - Loss of dopaminergic neurons in the substantia nigra that provides dopaminergic innervation of the caudate-putamen (striatum)
- Symptomatic PD occurs with 70-80% loss
- May have an excess of acetylcholine as a consequence of the dopamine loss

III. Possible Causes of Parkinson’s Disease

IV. Treatment: increase dopamine levels
A. Increase Dopamine Biosynthesis
   Tyrosine → Dopa → Dopamine

<table>
<thead>
<tr>
<th>Tyrosine</th>
<th>L-Dopa</th>
<th>Dopamine</th>
<th>Hydroxydopamine</th>
<th>Dopamine</th>
<th>Hydroxydopamine</th>
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B. Decrease Dopamine Metabolism
   - DOPAC: 3,4-Dihydroxyphenylacetic acid; HVA: 3-methoxy-4-hydroxyphenylacetic acid

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<tr>
<th>DOPAC</th>
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<th>HVA</th>
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<tr>
<td>DOPAC</td>
<td>COMT</td>
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<td>Monoamine oxidase</td>
<td>HVA</td>
<td>Aldehyde dehydrogenase</td>
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V. Treatment of Parkinson’s Disease:
A. Carbidopa/levodopa (Sinemet) most often prescribed
   - Therapeutic Use: dopamine precursor; used because dopamine does not cross the blood brain barrier. In early PD, symptoms may be almost completely alleviated by L-DOPA treatment

Levodopa (Dopar)
- Mechanism: metabolic precursor of dopamine; uptake across blood brain barrier and conversion to dopamine in brain

Carbidopa or benserazide:
- Mechanism: peripherally acting aromatic L-amino acid decarboxylase inhibitor decreases peripheral conversion to dopamine
L-DOPA Adverse effects
- conversion to dopamine can produce side effects
  - CNS: psychiatric reactions (visual pseudohallucinations, confusion)
  - GI: nausea, vomiting, anorexia
  - Cardiovascular: tachycardia, arrhythmia due to increased catecholamines
  - Dyskinesias: excessive and abnormal involuntary movements
- Fluctuation of effect ("wearing off" phenomenon) each dose improves mobility for 1-2 hours, then rigidity and akinesia return
- Long-term: over time, dosing is difficult due to "on-off" phenomenon in which there are dramatic swings in motor function
  - Drug interactions: MAO inhibitors (synergize), antipsychotics (nullify)
  - Not recommended for psychotic patients or those with melanoma

B. Dopamine receptor agonist
- Therapeutic Effect: mimic dopamine by binding to receptor
  - Advantages:
    1. enzymatic conversion is not required and doesn't depend on functional capacity of nigrostriatal neurons
    2. does not compete for active transport across blood-brain barrier
    3. more selective for receptor subtypes (D1 vs. D2)
    4. longer duration of action than levodopa
    5. less generation of free radicals
    6. lower incidence of response fluctuations and dyskinesias with long term use

C. COMT (catechol-O-methyltransferase) inhibitors
- Tolcapone (Tasmar): longer duration of action, acts peripherally and centrally
- Entacapone: short duration of action (~2 hrs), mainly peripheral actions
  - These drugs differ in pharmacokinetic properties and adverse effects
  - Therapeutic effect: often combined with L-DOPA when "on-off" becomes a problem
  - Mechanism: COMT catabolizes dopamine (and levodopa), therefore, inhibiting COMT prolongs duration of action of L-DOPA
  - Side Effects: same as levodopa/carbidopa alone: nausea, orthostatic hypotension, vivid dreams, hallucinations, confusion, dyskinesias
  - Tolcapone may produce hepatotoxicity, therefore is used only in patients that do not respond to other therapies

D. MAO-B inhibitor: Selegiline (Eldepryl®)
- Therapeutic Effect: Used as an adjunct therapy with L-DOPA in patients with declining or fluctuating response; not therapeutically effective alone
  - Mechanism: Increases dopamine levels and prolongs effects of levodopa
  - Two forms of MAO:
    - MAO-A: non-selective (DA, NE, 5-HT); more prevalent in periphery
    - MAO-B: more DA-selective; prevalent in brain
      - does not inhibit peripheral catecholamine metabolism
  - Side Effects: nausea, headache, dizziness, confusion
  - Dosing important: may also affect MAO-A at high concentrations
  - Drug interactions: Not recommended for patients on meperidine, tricyclic agents, serotonin reuptake inhibitors
E. **Muscarinic Acetylcholine Antagonists** (anti-cholinergic):
   - *Trihexyphenidyl* (Artane®), *benztropine mesylate* (Cogentin®), *diphenhydramine hydrochloride* (Benadryl®)
   - **Therapeutic Use:** Modest anti-parkinsonian action, used in early PD, as an adjunct to dopaminergic therapy and to treat tremor caused by anti-psychotic drugs
   - Improve tremor and rigidity, little effect on bradykinesias
   - Side Effects: sedation, mental confusion, mood changes, blurry vision, dry mouth, nausea, arrhythmias

F. **Amantadine** (Symmetrel)
   - **Mechanism:** Antiviral agent; mechanism of anti-parkinsonian effects not clear- antagonist activity at NMDA receptors may augment dopamine release
   - **Therapeutic Use:** Modest effects, used only for mild PD or as adjuvant to levodopa
   - Benefits are short-lived, but it may improve bradykinesia, rigidity and tremor
   - Side effects: CNS effects: depression, irritability, agitation, confusion, hallucinations

G. **Surgery**
   - **Therapeutic Use:** used primarily for advanced and drug-resistant cases
   - Ablative surgery may be replaced by brain stimulation
   - Autologous transplantation from adrenal medulla: not used much now
   - Possible Future treatment: Transplantation of fetal mesencephalon (SN-contains dopaminergic neurons) or stem cells

VI. Treatment of PD treatment drug side effects:
   - **Domperidone**
     - **Therapeutic use:** nausea, vomiting (reduces peripheral side effects of levodopa)
     - **Mechanism:** peripheral D2 antagonist
   - **Clarithromycin**: treat hallucinations and psychotic symptoms of levodopa
   - **Mechanism:** Atypical neuroleptic with minimal D2 blocking properties

VII. Parkinsonism
   - **A. MPTP:**
     - MPTP is closely related to MPPP, a derivative of meperidine (Demerol)
     - MPPP was synthesized as a designer drug and also a heroin contaminant (heroin was cut with MPPP which is cheaper)
     - Sloppy synthesis of MPPP produces MPTP contamination
   - **B. Drugs may cause PD symptoms:**
     - Antipsychotic: haloperidol, chlorpromazine, thorazine
     - Antiemetic: prochlorperazine (Compazine) and metoclopramide (Reglan)
   - **Mechanism:** block dopamine receptors
   - **Treatment:** anticholinergics (Cogentin) or lower dose of antipsychotic

I. **Skeletal Muscle Relaxants**
   - **1. Neuromuscular Blockers:**
     - **Site of action:** neuromuscular endplate
     - **Clinical use:** adjunct to general anesthesia during surgery or in ICU to produce muscle paralysis
   - **2. Spasmolytics**
     - **Site of action:** considered “centrally acting” but not all act on CNS (i.e. dantrolene)
     - **Clinical use:** reduce spasticity due to muscle spasm or disease

II. Overview: Neural Control of Skeletal Musculature
   - Muscle relaxants and drugs used to treat motor disorders can act at a number of points
   - **A. Descending motor pathways** (upper motor neurons)
     - Originate in brain and terminate in spinal cord
     - Voluntary movement control
   - **B. Local Spinal pathways** (lower motor neurons)
     - Spinal cord to muscles
     - Disease/injury leads to flaccid paralysis of muscles, atrophy
   - **C. Skeletal Muscle: neuromuscular junction**
### III. Muscle Spasm: use spamolytics as adjunct therapy to rest and physical therapy

**A. Propanediols**  
- **Drugs:** methocarbamol (Robaxin), chlorzoxazone (Paraflex), metaxalone (Skelaxin), carisoprodol (Soma)  
- **Therapeutic Use:** acute, painful muscle spasms  
- **Mechanism:** interneuron blocking agent  
- **Side Effects:** drowsiness, headache, dizziness, blurred vision, nausea, vertigo

**B. Cyclobenzaprine (Flexeril)**  
- **Therapeutic Use:** reduces increased muscle tone associated with skeletal muscle spasm; not effective in patients with CNS disorders or lesions  
- **Mechanism:** acts on neurons in brainstem  
- **Side Effects:** constipation, anti-cholinergic effects

### IV. Spasticity

- **Characterized by** an increase in tonic stretch reflexes and flexor muscle spasms together with muscle weakness  
- **Results from** an upper motor neuron lesion (i.e. pathways that descend from brain and normally exert inhibitory control are damaged, resulting in hyperexcitability of motoneurons in the spinal cord)  
- **Associated with** cerebral palsy, multiple sclerosis, stroke, spinal trauma  
- **Symptoms:** decreased muscle control, rigidity, weakness  
- **Pharmacotherapy:** decrease muscle contraction; increase inhibitory inputs, decrease excitatory inputs

#### A. Baclofen (Lioresal)
- **Therapeutic Use:** spinal cord lesions, trauma, multiple sclerosis  
- **Mechanism:** GABA\(_A\) agonist, inhibitory system that decreases release of excitatory neurotransmitters in brain and spinal cord, may also reduce pain due to effects on substance P  
- **Side Effects:** nausea, drowsiness, weakness, confusion  
- **Contraindicated in** epileptic patients (may increase seizures)  
- **Benzodiazepines (Diazepam)**  
- **C. Tizanidine (Zanaflex)**  
- **Therapeutic Use:** due to pathological condition of brain or spinal cord (multiple sclerosis, injury)  
- **Effect:** short acting muscle relaxant  
- **Mechanism:** congener of clonidine, has \(\alpha_2\) adrenergic agonist actions to increase inhibitory effects in spinal cord, may also inhibit nociception via dorsal horn  
- **Side Effects:** hypotension, sedation, dizziness  
- **D. Dantrolene (Dantrium)**  
- **Therapeutic Use:** upper motor neuron disease (spinal cord injury, cerebral palsy, multiple sclerosis), also malignant hyperthermia (anesthetics)  
- **Mechanism:** reduces skeletal muscle contraction by interfering with release of calcium via sarcoplasmic reticulum; spasmylostatic actions outside CNS  
- **Side Effects:** generalized muscle weakness, sedation, nausea, occasionally hepatitis; cardiac and smooth muscle are only very slightly depressed