Drugs and the Extra pyramidal system

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The extra pyramidal system

- Separation of cortico-spinal system (pyramidal system, (PS)) from the basal ganglia (extra pyramidal motor system (EPS)) because they produce different symptoms
- Extra pyramidal motor system: All portions of the brain and brainstem that contribute to motor control
- Not part of the direct cortico-spinal system but linked to it
- EPS controls automated or involuntary movements, muscle tone and posture
- PS controls voluntary movements

The extra pyramidal system

- The *extrapyramidal system* (EPS)is composed of motor fibers which do not pass through the medullary pyramids
- EPS is difficult to describe, partly because of the complexity of pathways and feedback loops which compose it
- It can be divided into three controlling systems:
  - the cortically originating indirect pathways
  - the feedback loops
  - the auditory-visual-vestibular descending pathways

The extra pyramidal system

- Important in the control of movements
- EPS works by modifying neural impulses originating in the cerebral cortex
- Impulses generated at the primary motor strip are sent via the extrapyramidal fibres to the basal ganglia
- In a complex network of pathways, the structures of the basal ganglia modify impulses and send information to each other
- Some fibres will be directed down to synapse with the lower motor neurons
- Other fibres are routed through the thalamus and back up to the cortex

The extra pyramidal system

The role of the extrapyramidal system includes the following:

- Selective activation of movements and suppression of others
- Initiation of movements
- Setting rate and force of movements
- Coordinating movements

Clinical Signs of Basal Nuclei and Related Brainstem Dysfunction

- Damage to the extrapyramidal system, but especially damage to the basal ganglia, will result in movement disorders (dyskinesias)

Different types of dyskinesias include:

- **Myoclonus** - involuntary single or repetitive jerks of a body part
- **Tics** - rapid, repeated coordinated or patterned movements
- **Chorea** - rapid, involuntary, random, purposeless movements of a body part

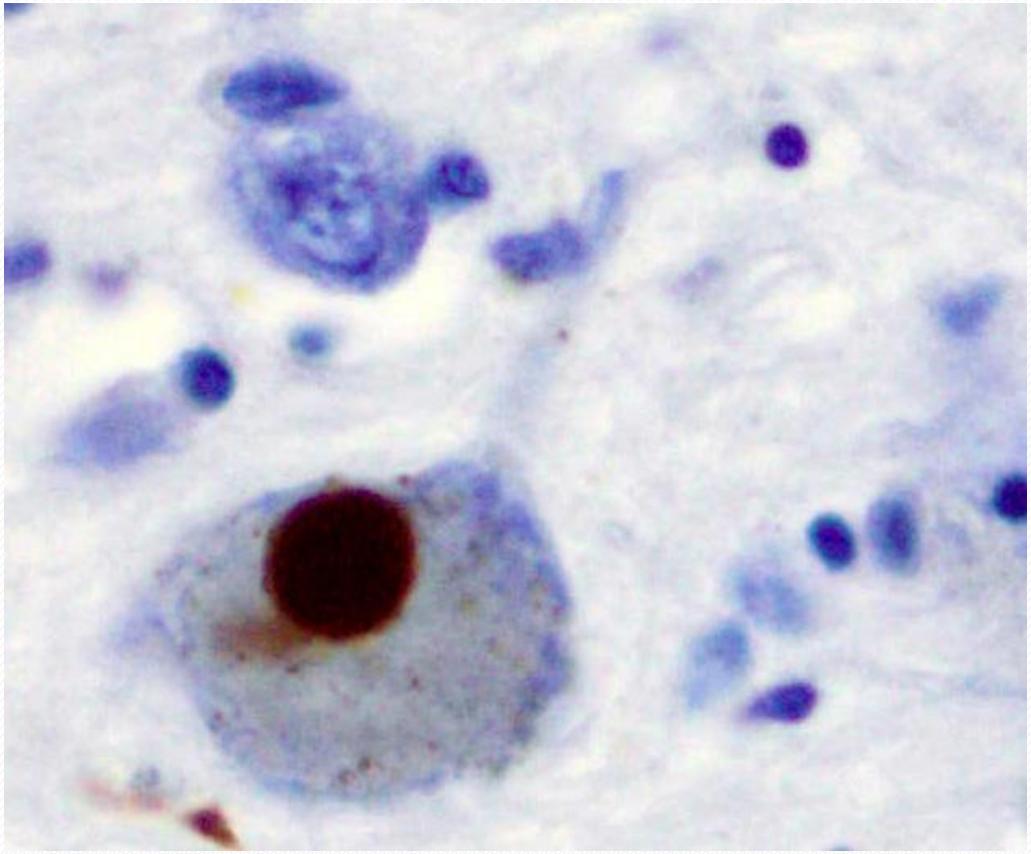
Clinical Signs of Basal Nuclei and Related Brainstem Dysfunction

- **Ballism** - gross, abrupt contractions of the extremities
- **Athetosis** - relatively slow, writhing, purposeless movement of a body part
- **Dystonia** - a slow form of hyperkinesia
- **Spasm** - a general term that designates a variety of muscular contractions
- **Tremor** - Rhythmic (periodic) movement of a body part

Clinical Signs of Basal Nuclei and Related Brainstem Dysfunction

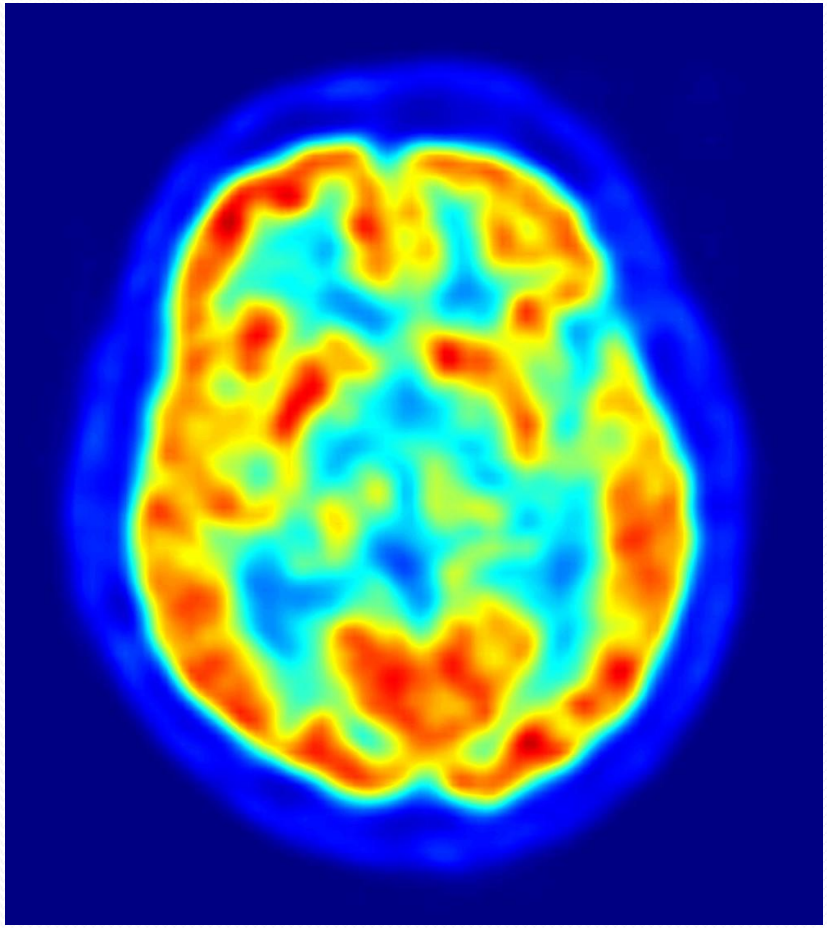
- Perhaps the most familiar disease condition in this group is *Parkinson's disease* (paralysis agitans)
- Characterized by a combination of rigidity, bradykinesia, tremor and postural instability
- Cognitive decline occurs in many patients as the disease advances

The pathology of the disease is characterized by the accumulation of a protein called alpha-synuclein into inclusions called Lewy bodies in neurons, and from insufficient formation and activity of dopamine produced in certain neurons of parts of the midbrain.



A Lewy body (stained brown) in a brain cell of the substantia nigra in Parkinson's disease. The brown colour is positive immuno histochemistry staining for alpha-synuclein.

Diagnosis of typical cases is mainly based on symptoms, with tests such as neuro-imaging being used for confirmation.



Fludeoxyglucose (18F) (FDG)] PET scan of a healthy brain. Hotter areas reflect higher glucose uptake. A decreased activity in the basal ganglia can aid in diagnosing Parkinson's disease.

Parkinsonism

- Normal high concentration of dopamine in the basal ganglia of the brain is depleted
- Various other neurotransmitters (i.e. Nor-epinephrine) are also depleted in the brain
- Pharmacologic attempts to restore dopamenergic activity with levodopa and dopamine agonists alleviate motor symptoms
- An alternative but complimentary approach is to restore the normal balance of cholinergic and dopamenergic influences on the basal ganglia with anti-muscarinic drugs

Treatment of Parkinson's: Levodopa and carbidopa

- Dopamine does not cross the blood-brain barrier
- But its immediate precursor levodopa is actively transported into the CNS and is converted to dopamine in the brain

Levodopa

- Is a metabolic pre-cursor of dopamine
- It restores dopaminergic neurotransmission in the corpus striatum by enhancing the synthesis of dopamine in the surviving neurons

Treatment of Parkinson's: Levodopa and carbidopa

Carbidopa

- Enhances the effects of levodopa
- A de-carboxilase inhibitor that does not cross the blood - brain barrier
- Diminishes the metabolism of levodopa in the GIT and peripheral tissues; increases availability of levodopa to the CNS
- Addition of carbidopa lowers the dose of levodopa 4 to 5x
- Decreases the severity of the side effects arising from peripherally formed dopamine

Treatment of Parkinson's: Levodopa and carbidopa

Side effects:

- Anorexia
- Nausea and vomiting
- Tachycardia
- Hypotension
- Adrenergic action on the iris causes mydriasis
- Saliva and urine are a brownish colour
- Visual and auditory hallucinations and abnormal involuntary movements may occur
- Levodopa can also cause mood changes, depression, psychosis and anxiety

Treatment of Parkinson's: Dopamine agonists

- Act directly on dopamine receptors

1. **Bromocriptine**

   - D_2 agonist
   - Peak plasma levels 1-2 hours after oral dose
   - Excreted in bile and faeces
   - Usual daily dose varies between 7.5 – 30 mg
   - To minimize side effects dose is built up slowly over 2 or 3 months; starting at 1.25 mg BD increasing with 2.5 mg every 2 weeks

Treatment of Parkinson's: Dopamine agonists

2. **Pramipexole**

- Preferential affinity for D_3 family of receptors
- Peak plasma concentration reached after ±2 hours
- Excreted largely unchanged in the urine
- Most patients require between 0.5 and 1.5 mg 3x per day
- Starting dose of 0.125 mg 3x per day, doubled after 1 week
- Further increments in daily dose are by 0.75 mg at weekly intervals, depending on response and tolerance

Treatment of Parkinson's: Dopamine agonists

3. **Ropinirole**

- Pure D_2 receptor agonist
- Metabolized by CYP1A2
- Daily dosage between 2 and 8 mg 3x per day is needed
- Introduced at 0.25 mg 3x per day; the total daily dose is increased by 0.75 mg at weekly intervals until the 4^{th} week and by 1.5 mg thereafter

Treatment of Parkinson's: Dopamine agonists

4. **Apomorphine and Rotigotine**

- Newer dopamine agonists
- Available in injectable and transdermal delivery systems
- Apomorphine is used in the acute management of the hypomobility or 'off' phase
- Rotigotine is used in the treatment in the early stages of the illness
- Administered through a once-daily transdermal patch that provides even pharmakokinetics over 24 hours

Pharmakokinetic properties of dopamine agonists

	Pramipexole	Ropinirole	Rotigotine
Bioavailability	>90%	55%	45%
V_d	7 L/kg	7.5 L/kg	84 L/kg
Half-life	8 hours[1]	6 hours	7 hours[3]
Metabolism	Negligible	Extensive	Extensive
Elimination	Renal	Renal[2]	Renal[2]

- V_d = volume of distribution
- [1] = increases to 12 hours in patients older than 65 years
- [2]= less than 10% excreted unchanged
- [3] = administered as a once-daily transdermal patch

Treatment of Parkinson's: Dopamine agonists

Side effects:

- Sedation
- Hallucinations
- Confusion
- Delusions
- Nausea
- Vomiting
- Anorexia
- Postural hypotension
- Dyskinesia
- Disorders of impulse control (compulsive gambling, shopping etc.)
- Headache
- Nasal congestion

Treatment of Parkinson's: Mono Amine Oxidase-inhibitors

2 types of monoamine oxidases in the nervous system:

- Monoamine oxidase A (MAO-A) metabolizes nor epinephrine, serotinin and dopamine
- Monoamine oxidase B (MAO-B) metabolizes dopamine selectively

Treatment of Parkinson's: Mono Amine Oxidase-inhibitors

1. **Selegiline** (deprenyl)

- A selective irreversible inhibitor of MAO-B at normal doses (higher dose inhibits MAO-A) as well
- Only minor effect on its own
- It enhances and prolongs the effect of levodopa (dose reduction)
- Standard dose is 5 mg at breakfast and 5 mg at lunch
- Used as adjunctive therapy in patients with declining or fluctuating response to levodopa
- May slow disease progression

Treatment of Parkinson's: Mono Amine Oxidase-inhibitors

2. **Rasagiline**

- An irreversible and selective inhibitor of MAO-B
- Used for early symptomatic treatment
- Standard dose is 1mg per day
- Also used as adjunctive to levodopa-carbidopa at dosage of 0.5 or 1 mg per day to prolong effects in patients with advanced disease
- May slow disease progression
- 5 x more potent than selegiline

Treatment of Parkinson's: Mono Amine Oxidase-inhibitors

Side effects:

- Selegiline may cause insomnia when taken later during the day
- Adverse effects of levodopa may be increased by these drugs
- The combined administration of levodopa and an non-selective inhibitor may lead to hypertensive crises

Treatment of Parkinson's: Catechol-O-methyltransferase inhibitors

- Inhibition of dopa decarboxylase is associated with compensatory activation of other pathways of levodopa metabolism, especially Catechol-O-methyltransferase (COMT)
- COMT increases levels of 3 O-methyldopa (3-OMD) which is associated with poor therapeutic response to levodopa
- 3-OMD competes with levodopa for an active carrier
- Selective COMT inhibitors such as tolcapone and entacapone prolong levodopa action by decreasing peripheral metabolism

Treatment of Parkinson's: COMT

Tolcapone and entacapone

- Both are used, entacarpone preferred
- Levodopa clearance is decreased; bioavailability increased
- Peak concentration and maximal concentration is not increased
- Useful in patients who have developed levodopa response fluctuations; reducing the total daily levodopa dose

Treatment of Parkinson's: COMT

Pharmacokinetics: Tolcapone

- Oral absorption occurs readily, not influenced by food
- Extensively bound to plasma albumin (>98%) with limited volumes of distribution
- **Penetrates the blood-brain barrier** and inhibits COMT in the CNS
- Inhibition of COMT in the periphery; main therapeutic action
- Tolcapone has **a long duration of action**
- Extensively metabolized, eliminated in faeces and urine

Treatment of Parkinson's: COMT

Pharmacokinetics: Entacapone

- Oral absorption occurs readily, not influenced by food
- Extensively bound to plasma albumin (>98%) with limited volumes of distribution
- Entacapone **does not penetrate the blood-brain** barrier
- Inhibition of COMT in the periphery; main therapeutic action
- Entacapone has a **shorter duration of action**
- Extensively metabolized, eliminated in faeces and urine

Treatment of Parkinson's: COMT

Side effects:

- Diarrhoea
- Postural hypotension
- Nausea and vomiting
- Anorexia
- Dyskinesias
- Hallucinations
- Sleep disorders
- Fulminating hepatic necrosis is associated with tolcapone

Treatment of Parkinson's: Anti-muscarinic agents

- A number of centrally acting anti-muscarinic drugs are available
- Potency and efficacy differ in different patients
- May improve tremor and rigidity, little effect on bradykinesia
- Treatment is started with 1 of these drugs at a low dose; dosage gradually being increased until benefit occurs or adverse effects limit further increments

Treatment of Parkinson's: Anti-muscarinic agents

Side effects:

- CNS and peripheral effects
- Poorly tolerated by the elderly
- Dyskinesias occur in rare cases
- Acute suppurative parotitis sometimes occurs as a complication of dryness of the mouth

Treatment of Parkinson's: Anti-muscarinic agents

Some drugs with antimuscarinic properties used in parkinson's

Drug	Usual Daily Dose (mg)
Benztropine mesylate	1–6
Biperiden	2–12
Orphenadrine	150–400
Procyclidine	7.5–30
Trihexyphenidyl	6–20

Treatment of drug-induced extrapyramidal symptoms

- Reserpine and tetrabenazine deplete biogenic mono-amines from storage sites
- Haloperidol, metoclopramide and the phenothiazines block dopamine receptors
- Produce a parkinsonian syndrome, usually within three months of introduction
- Disorder tends to be symmetric with inconspicuous tremor

Treatment of drug-induced extrapyramidal symptoms

- Syndrome is related to high dosage and clears over several weeks or months after withdrawal
- Anti-muscarinic drugs used if treatment is necessary; levodopa has no effect

Thank you!