PARKINSONISM

- ✓ Parkinson disease is a slowly progressive degenerative neurological disease characterized by tremor, rigidity, bradykinesia (sluggish neuromuscular responsiveness), and postural instability.
- ✓ **Parkinson's disease** (PD) is the most common example of a family of neurodegenerative disorders characterized by a neuronal accumulation of the presynaptic protein α-synuclein and by variable degrees of **parkinsonism**, defined as a paucity and slowness of movement (**bradykinesia**), tremor at rest, rigidity, shuffling gait, and flexed posture. Nearly all forms of parkinsonism result from a reduction of dopaminergic transmission within the basal ganglia.
- ✓ Parkinson also noted the development of several nonmotor symptoms (e.g., constipation, drooling, dysphagia, speech and sleep disturbances), the profound adverse impact on quality of life, and the importance of caregiver support.
- ✓ The majority of parkinsonism cases are of the idiopathic type, in which the cause is unknown; it is commonly referred to as **Parkinson disease (PD)**.
- ✓ Less common forms of parkinsonism are classified under **secondary parkinsonisms** (e.g., drug-induced), multisystem Parkinson plus syndromes, or hereditary parkinsonisms.
- ✓ Since the 1950s, drug-induced parkinsonism has been the second most common form of parkinsonism.
- ✓ The **two major types** of parkinsonism-inducing agents are those that deplete central stores of dopamine (e.g., reserpine, methyldopa, tetrabenazine) and those that antagonize central dopamine receptors (e.g., chlorpromazine, haloperidol, metoclopramide).
- ✓ For all patients who present with signs and symptoms of parkinsonism, an inquiry should be made to assess for current use of the agents.
- ✓ If drug-induced parkinsonism is suspected, discontinuation of the offending agent will result in improvement within 3 months; complete resolution usually occurs within 1 year.
- ✓ In a case-controlled study, older adults on metoclopramide were three times more likely to be on the antiparkinson drug levodopa than those not on metoclopramide.
- ✓ This observation suggests that drug-induced parkinsonism is often misdiagnosed and treated as idiopathic PD.
- ✓ Multisystem Parkinson plus syndromes are uncommon and characterized by the presence of parkinsonian motor features along with other unique autonomic, neurologic, and psychiatric abnormalities.
- ✓ Several variants have been characterized, such as corticobasal degeneration, multiple-system atrophies, and progressive supranuclear palsy. In general, these atypical parkinsonisms are unresponsive or at best transiently responsive to antiparkinson therapy.

CLASSIFICATION OF PARKINSONISM

PRIMARY PARKINSONISM

- ✓ Idiopathic Parkinson disease

SECONDARY PARKINSONISM

- ✓ Brain neoplasm
- ✓ Drugs (e.g., haloperidol, metoclopramide, phenothiazines)
- ✓ Infections (e.g., postencephalitic, human immunodeficiency virus associated, subacute sclerosing panencephalitis)
- ✓ Metabolic (e.g., hypothyroidism, hepatocerebral degeneration, parathyroid abnormalities)
- ✓ Normal-pressure hydrocephalus

- ✓ Toxins (e.g., carbon monoxide, manganese, methanol, MPTP, organophosphate insecticides)
- ✓ Head trauma (e.g., "punch drunk" syndrome)
- ✓ Vascular (e.g., multi-infarct, Binswanger disease)

MULTISYSTEM PARKINSON PLUS SYNDROMES

- ✓ Corticobasal degeneration
- ✓ Multiple-system atrophies (e.g., olivopontocerebellar atrophy, Shy-Drager syndrome, striatonigral degeneration)
- ✓ Progressive supranuclear palsy (i.e., Steele-Richardson-Olszewski syndrome)

DEMENTIA/PARKINSONISM SYNDROMES

- ✓ Alzheimer's disease with parkinsonism
- ✓ Creutzfeldt-Jakob disease
- ✓ Guamanian amyotrophic lateral sclerosis-parkinsonism dementia ("Lytico-Bodig")
- ✓ Dementia with Lewy bodies
- ✓ Frontotemporal dementia

HEREDITARY PARKINSONISMS

- ✓ Autosomal Dominant
- ✓ α-synuclein gene mutation (PARK1)
- ✓ Frontotemporal dementia parkinsonism (FTDP–17)
- ✓ Huntington disease (juvenile form or Westphal variant)
- ✓ Levodopa-responsive dystonia
- ✓ LRRK2 (dardarin) mutation
- ✓ Rapid-onset dystonia parkinsonism (DYT12)
- ✓ Spinocerebellar ataxias (SCA2, SCA3)
- ✓ Autosomal Recessive
- ✓ Hallervorden-Spatz disease
- ✓ Neuroacanthocytes
- ✓ Niemann Pick type C
- ✓ Wilson disease
- ✓ Young-onset parkinsonism (DJ–1, parkin, PINK1)
- ✓ X-linked Recessive
- ✓ Fragile X tremor/ataxia syndrome (FXTAS)
- ✓ Lubag (DYT3 or Filipino dystonia parkinsonism)
- ✓ Waisman syndrome (X-linked parkinsonism with mental retardation)

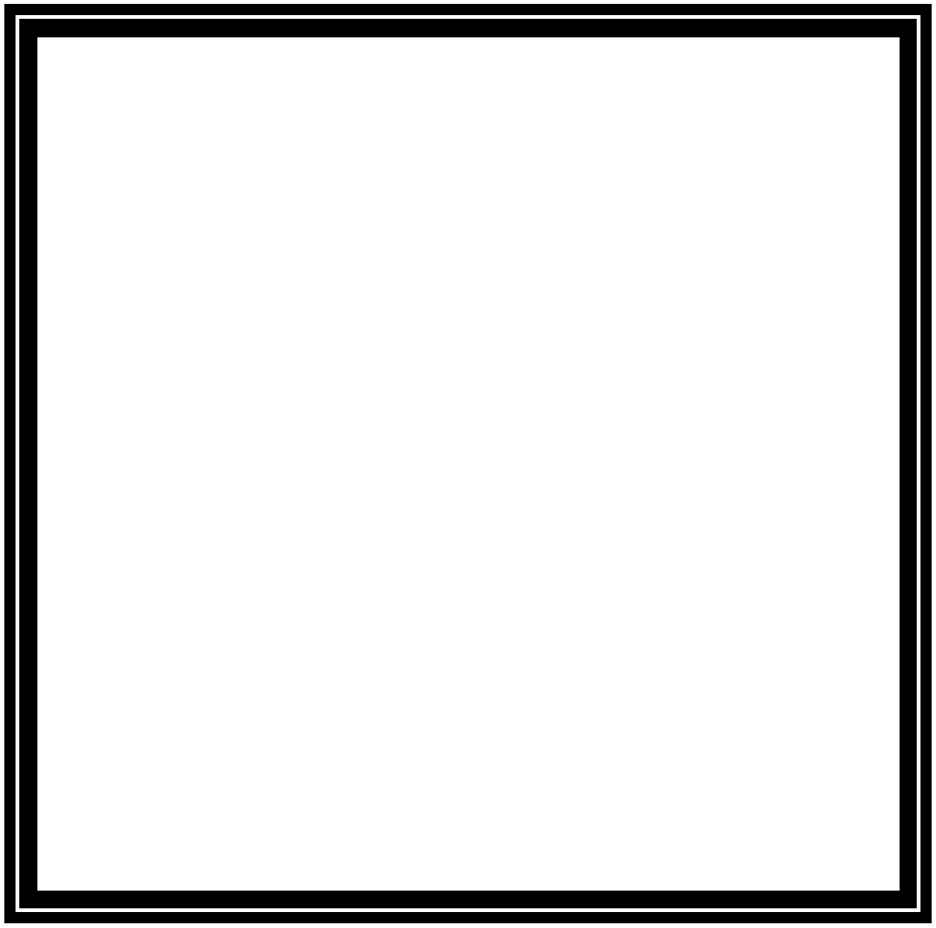
DRUGS COMMONLY ASSOCIATED WITH PARKINSONISM

- ✓ Cinnarizine and flunarizine[a]
- ✓ Haloperidol
- ✓ α-Methyldopa
- ✓ Metoclopramide
- ✓ Phenothiazines (e.g., chlorpromazine, mesoridazine, perphenazine, thioridazine)
- ✓ Reserpine (Rauwolfia serpentina)
- ✓ Tetrabenazinea

EPIDEMIOLOGY

- ✓ PD afflicts >1 million individuals in the United States (~1% of those >55 years). Its peak age of onset is in the 60s (range is 35 to 85 years), and the course of the illness ranges between 10 and 25 years.

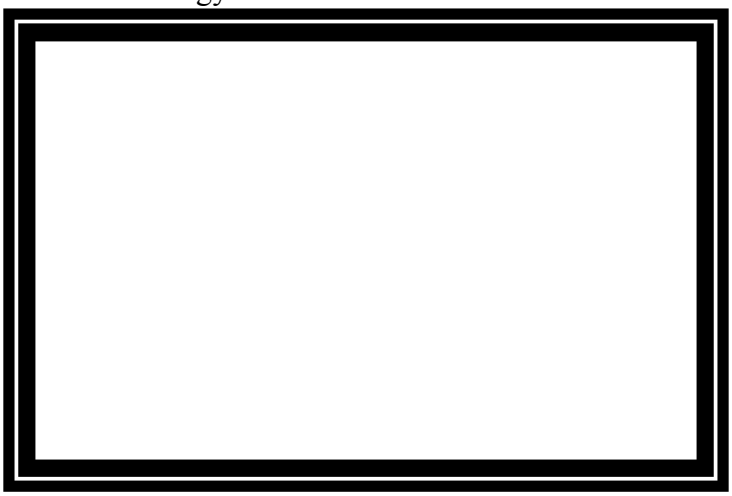
- ✓ Familial clusters of autosomal dominant and recessive forms of PD comprise 5% of cases.
- ✓ These are characterized by an earlier age of onset (typically before age 50 years) and a longer course than the more typical "**sporadic**" PD.
- ✓ Although most patients with PD appear to have no strong genetic determinant, epidemiologic evidence points to a complex interaction between genetic vulnerability and environmental factors.
- ✓ Risk factors include a positive family history, male gender, head injury, exposure to pesticides, consumption of well water, and rural living.
- ✓ Factors linked to a reduced incidence of PD include coffee drinking, smoking, use of nonsteroidal anti-inflammatory drugs, and estrogen replacement in postmenopausal women.



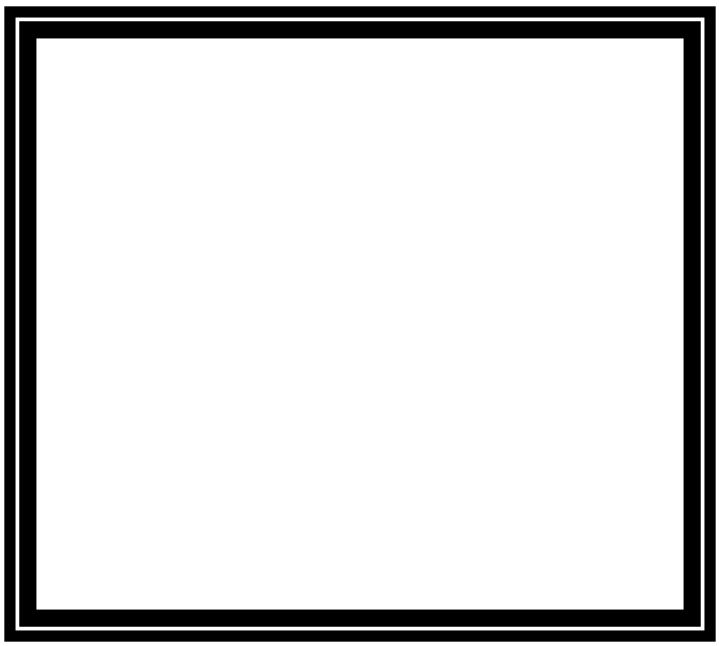
ETIOLOGY

- ✓ Many theories have been advanced regarding the origin of PD.
- ✓ Environmental factors have been implicated since it was discovered that many patients developed a parkinsonian syndrome following the epidemic of encephalitis lethargic in the United States between 1919 and the early 1930s.
- ✓ Attempts to isolate a virus as a causative agent of the disease have been unsuccessful, however. Renewed interest in environmental factors resurfaced with the discovery that ingestion of a meperidine analog, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), causes irreversible parkinsonism.

- ✓ The discovery of an autosomal dominant familial form of PD caused by a mutation in the α-synuclein gene has sparked interest in genetic constitution as a factor explaining the development of PD.
- ✓ In addition to environment and genetics, it has also been reported that byproducts of normal dopamine metabolism (e.g., hydrogen peroxide) can lead to the production of free radicals that cause peroxidation of cell membranes and cell death.
- ✓ Thus, the most attractive hypothesis for the etiology of PD is that the disease results from a complex interplay of age-related changes to the nigrostriatal tract, genetic predisposition, and toxin exposure.
- ✓ Neurotoxins highly selective for substantia nigra pars compacta (SNc) dopaminergic neurons are instructive because animal models of parkinsonism can be created with 6-hydroxydopamine and with 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine (MPTP).
- ✓ The latter compound is converted by monoamine oxidase (MAO) type B to the toxic 1-methyl-4- phenylpyridinium ion (MPP+).
- ✓ MAO-B inhibition by selegiline eliminates the toxicity of MPTP. MPP+ is toxic to neurons by interfering with mitochondrial metabolism.
- ✓ Another mechanism of toxicity that has received consideration for the pathogenesis of IPD is cellular damage from oxyradicals.
- ✓ Dopamine generates free radicals from autooxidation and from MAO metabolism.
- ✓ Several antioxidative mechanisms are present within and outside neurons to limit any damage that might be produced by free-radical attack, but one possibility is that such protection might be overwhelmed or impaired in IPD.
- ✓ Excitotoxicity, programmed cell death activation, and chronic infection are also under consideration for IPD etiology.



- ✓ The cause of Parkinson's disease is unknown.
- ✓ Yet several factors may be involved:
  - Excitotoxicity
  - Oxidative stress
  - Genetic



- **GENETIC**
  - ✓ It has been long suspected that genetics plays an important role in the etiology of neurodegenerative disorders.
  - ✓ More than 20 different genes have been identified in which mutations, cause an inherited form of a neurodegenerative disorders.
  - ✓ In these includes familial PD; Caused by mutation in genes encoding the proteins.
    - Alpha-synuclein
    - Parkin
  - ❖ **ALPHA-SYNUCLEIN**
  - ✓ Mainly three type mechanisms are involved in the parkinson's disease.
    - **FIRST MECHANISM**
      - Three **missense mutation** in alpha-synuclein (A53T, A30P & G 209A) lead to dysfunction and degeneration of dopaminergic neuron in PD.
      - Expression of alpha synuclein mutation increases vulnerability of cells to oxidative stress and apoptosis.
      - Overexpression of wild type or mutant alpha synuclein induces apoptosis.
      - Cells overexpressing mutant alpha synuclein exhibit decreases proteasome actly and increase vulnerability to mitochondrial dysfunction and apoptosis.
      - Alpha synuclein mutation results in loss of dopaminergic neuron and lewy body like cytoplasmic influsion.
      - Thus alpha synuclein knock out exhibit a detect in dopamine release.
    - **MITOCHONDRIAL PATHWAYS:**
      - Injured mitochondria causes released cytochrome C in to the intermediated cells.
      - Release cytochrome C which binds to the APaf 1 (Adaptor protein factor 1)
      - Apaf 1 than binds with the procaspases 9 and forms a multicomplex, called apoptosome.

- Than activation of the procaspases 9 and leads to activation of the caspases 3.
- Activation of the caspases 3 causes DNA fragmentation which Leads to neuronal cell death.

➢ **MECHANISM OF ALPHA-SYNUCLEIN:**

- Forms aggregates that exhibit toxic properties such as production of reactive oxygen supplement and increase membrane permeability.
- Alpha synuclein mutation also promote neuronal degeneration by causing abnormalities in protein degradation & oxidative stress.

❖ **ROLE OF PARKIN**

- ✓ Parkin is a ubiquitin protein ligases.
- ✓ Parkin mutation result in loss of ubiquitin protein ligase actly.
- ✓ Parkin can ubiquitin alpha synuclein suggesting a link between impaired proteasomal degradation of alpha synuclein and neurodegenerative process.
- ✓ Thus a defect in protein degradation is central to pathogenesis of PD.
- ✓ Strong mechanistic interaction b/w oxidative stress and protein degradation in neurodegenerative disorder in general since oxidative damage to parkins make them target for ubiquitinnation & proteasomal degradation.

❖ **DJ-1**

- ✓ The DJ-1 (PARK7) gene has been linked to another early onset of PD.
- ✓ This protein is involved in regulating gene activity and in protecting cells from a damaging process called oxidative stress.

❖ **PINK 1**

- ✓ Mutation in a gene called PTEN- induced kinase 1 (PINK 1), also known as PARK6; have been identified in PD.
- ✓ This gene involved in the regulating the protein function in both normal and disease states.
- ✓ The PINK 1 gene codes for a protein active in mitochondria, which convert food into energy inside the cell.

❖ **DRDN**

- ✓ Mutation in a gene called DRDN that appear to cause a late onset form of PD.
- ✓ This gene involved in the regulating the protein function.
- ✓ It is located in a chromosomal region formerly called PARK 8.
- ✓ DRDN codes for a protein called dardarin.
- ✓ Function of this protein is still unknown.

➢ **ENVIRONMENTAL TRIGGERS**

- ✓ Infectious agents, environmental toxins and acquired brain injury have been proposed to have a role in the etiology of neurodegenerative disorders.
- ✓ Here there is alteration in dopamine metabolism & or exposure to environmental toxins such as rotenone & MPTP (1-Methyl-4- phenyl 1,2,3,6, tetra hydropyridine) which induce the oxidative stress in dopaminergic neuron resulting in their dysfunction & death.
- ✓ Rotenone & MPTP both are inhibit the tyrosine hydroxylase, which is essential for the formation of dopamine. It could cause the parkinson's disease.

➢ **EXCITOTOXICITY**

- ✓ The term excitotoxicity is the neural injury that results from the presence of excess glutamate in the brain.

- ✓ Excitotoxicity causes excessive release of the glutamate from presynaptic neurons.
- ✓ Which leads to overstimulation of the glutamate receptor like NMDA & non NMDA receptor.
- ✓ Causes the activation of the Ca influx into the neuron via NMDA chain.
- ✓ Leads to cell death & causes the neurodegenerative disease like Parkinson's disease.

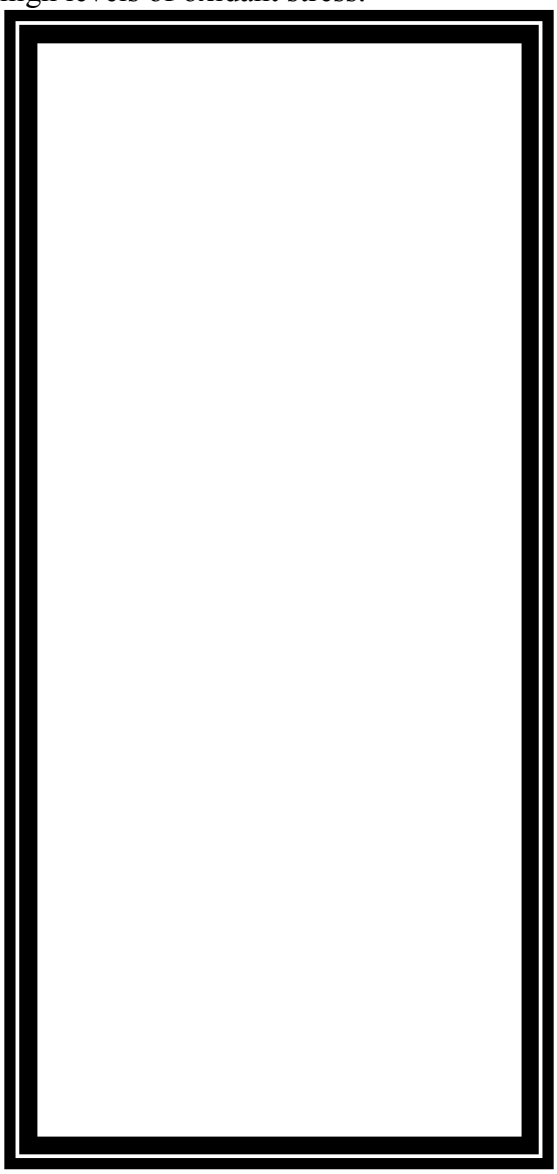
➢ **OXIDATIVE STRESS**

- ✓ Which is in the form of increase reactive oxygen (ROS), which is common apoptotic trigger.
- ✓ Causes several acute & chronic neurodegenerative disorders.

PATHOPHYSIOLOGY

- ✓ The pathophysiology underlying the motor and nonmotor features of PD is complex.
- ✓ A major pathologic process is neuronal degeneration of the pigmented substantia nigra pars compacta (SNpc), a region of the basal ganglia that produces dopamine and is intrinsically involved in motor control.
- ✓ Dopamine modulates the direct and indirect pathways of the extrapyramidal motor circuit, which are mediated by γ-aminobutyric acid (GABA) and glutamate.
- ✓ Inhibitory GABA-ergic pathways contribute to the major outflow pathways in the basal ganglia and striatum; as a result of dopamine depletion, the thalamus is over-inhibited and movement becomes abnormal.
- ✓ It is estimated that parkinsonian features are not clinically apparent until a critical threshold of 80% loss of dopamine concentration has occurred.
- ✓ In addition to depigmentation of the SNpc, another defining histopathologic hallmark is the presence of Lewy bodies (LBs).
- ✓ LBs are spherical, intracytoplasmic aggregates found in the remaining neurons of the SNpc and are composed of ubiquitin-positive proteinaceous aggregates of α-synuclein (a substance also found in amyloid plaques of Alzheimer's disease) and other misfolded proteins.
- ✓ Previously, LBs were believed to be detrimental; however, current evidence suggests that they may be a protective mechanism whereby intracellular neurotoxic products are isolated and prevented from causing further damage.
- ✓ Lewy pathology has been proposed to develop in a predictable anatomic distribution within the parkinsonian brain.
- ✓ In the preclinical stages of PD, LBs are initially found in the medulla oblongata, locus ceruleus, raphe nuclei, and olfactory bulb.
- ✓ This may correlate with observations that anxiety, depression, and impaired olfaction occur in preclinical stages of PD.
- ✓ As PD progresses to clinical stages, Lewy pathology ascends to the midbrain (particularly the SNpc), accounting for motor features.
- ✓ In advanced stages, Lewy pathology spreads to the cortex and may account for behavioral and cognitive changes.
- ✓ Thus, the pathology in PD affects not only dopaminergic SNpc cells but also nonnigral cell bodies that are involved in regulating acetylcholine, GABA, glutamate, norepinephrine, serotonin, and a range of other neuropeptides.
- ✓ The presence of nonnigral cell pathology may correlate with the development of various autonomic, behavioral, and cognitive symptoms in PD.

- ✓ Normally, the SNpc is endowed with a variety of protective mechanisms, as it is a region inherently subjected to high levels of oxidant stress.



- ✓ Whether triggered by toxin exposure or genetic susceptibility or a combination of factors, the available evidence suggests that intracellular redox potential is altered due to a cascade of events involving mitochondrial complex I dysfunction, free radical generation, oxidant stress, and dysfunction of the ubiquitin-proteasome system (UPS) that ultimately results in cell death.
- ✓ Other events including excitotoxicity, inflammation, and toxic effects of nitric oxide have also been implicated.
- ✓ In the SNpc of patients with PD, concentrations of protective antioxidants (e.g., glutathione) are reduced and reactive oxidants (e.g., peroxynitrite, O_2^-, ^-OH, Fe^{3+}) are elevated.
- ✓ This results in a change in the redox state to a more oxidizing environment.
- ✓ Glutathione is a major antioxidant, and depleted levels are consistently found in patients with PD.

- ✓ The cause of glutathione depletion is unknown, but it renders the dopaminergic neurons more vulnerable to oxidant stress induced by reactive nitrogen and oxygen species.
- ✓ The neurons of the SNpc possess disproportionately long dendrites that are poorly myelinated; this also enhances vulnerability to toxic factors.
- ✓ In addition to oxidant stress and altered redox potential, accumulation of intracellular protein aggregates occurs.
- ✓ Within the brain, misfolded proteins are normally tagged by ubiquitin and targeted for degradation by the UPS.
- ✓ The UPS is the major route through which intracellular proteolysis is regulated.
- ✓ However, in PD, a malfunction or overload of the UPS system results in accumulation of unfolded or mutated proteins that are toxic.
- ✓ Ultimately, disruption of the intracellular milieu results in activation of surrounding microglia, which release cytokines, glutamate, and reactive nitrogen and oxygen species that induce apoptotic and necrotic cell death.

➢ **DIRECT PATHWAY**

- ✓ In the normal brain, dopamine activates the D_1 receptor which results in activation of the striatum.
- ✓ The activated striatum inhibits the GPi/SNpr which disinhibits the thalamus.
- ✓ Disinhibits of the thalamus results in excitatory stimulus to the motor cortex.
- ✓ In Parkinson's disease, denervation of the striatal D_1 pathway results in excessive GABA outflow to the thalamus and reduced outflow to the motor cortex.

➢ **INDIRECT PATHWAY**

- ✓ In the normal brain, dopamine activates the D2 receptor which results in inhibition of the striatum. The inhibited striatum disinhibits the GPe.
- ✓ The didinhibited GPe results in more GABAergic activity to the STN and subsequently less activation of the GPi/SNpr.
- ✓ The reduced GABAergic outflow from the GPi/SNpr results in disinhibition of the thalamus and an increase in excitatory stimulus to the motor cortex.
- ✓ In Parkinson's disease, denervation of the striatal D2 pathway also ultimately results in excessive GABA outflow to the thalamus and reduced outflow to the motor cortex.

- **GABA**: γ-aminobutyric acid,
- **GPi**: Globus pallidus intema,
- **GPe**: Globus pallidus extema,
- **SNpc**: Substania nigra pars compacts,
- **SNpr**: Substantia nigra pars reticularis
- **STN**: Subthalamic nucleus

CLINICAL PRESENTATION AND DIAGNOSIS

- ✓ The initial cardinal motor features of PD are tremor at rest, rigidity, and bradykinesia.

- ✓ Initially these motor features develop unilaterally and then spread to contralateral extremities.
- ✓ As the disease progresses, postural instability (i.e., balance problem) develops.
- ✓ In addition to the primary motor features, nonmotor symptoms are also very common and significantly impair the patient's quality of life.
- ✓ Examples include bladder incontinence, constipation, dementia, drooling, dysphagia, erectile dysfunction, olfactory deficit, orthostatic hypotension, pain, paresthesias, seborrheic dermatitis, sleep disturbances, sweating, and temperature intolerances.
- ✓ Anxiety and depressive syndromes are also very common, and periodic screening for these conditions should be conducted.

SIGNS AND SYMPTOMS

- ✓ A rhythmic, pill-rolling tremor of the hand and upper extremities is often the most visible yet least disabling symptom.
- ✓ This tremor generally occurs at rest and is of slower frequency (3 to 6 Hz) than the tremor associated with alcoholism, essential tremor, hyperthyroidism, or nervousness.
- ✓ Patients will commonly report that the tremor disappears during sleep and is worsened by stress or excitement.
- ✓ In addition to rest tremor, a postural tremor (observable when arms are outstretched in front of the patient) is also common.
- ✓ Action tremor (e.g., tremor during writing) is uncommon.
- ✓ In contrast to the other cardinal features, tremor severity generally remains stable over time.
- ✓ Muscular rigidity or stiffness commonly affects the upper and lower extremities and axial regions such as the face and trunk.
- ✓ Rigidity of the extremities interferes with range of motion and is detected upon passive flexion at the elbow, wrist, or knee with the patient in a seated position.
- ✓ In the presence of tremor, the rigidity is associated with a cogwheel or ratchet-like quality upon examination.
- ✓ Rigidity of the face and trunk is often observable as a lack of facial expression (masked facies) and stooped posture. The masking of facial expression may be misinterpreted as apathy, unfriendliness, or depression.
- ✓ Bradykinesia is defined as slowness of movement.
- ✓ On neurologic examination, bradykinesia is often assessed by finger taps performed with each hand separately (patient taps thumb with index finger in rapid succession with widest amplitude possible).
- ✓ Hand movements (patient opens and closes hands in rapid succession with widest amplitude possible) and leg agility (patient taps heel on ground in rapid succession, picking up entire leg; amplitude should be about 3 inches) are also assessed.
- ✓ Difficulty in initiating and executing learned movements contributes substantially to functional impairment (e.g., significant interference with performing activities of daily living and walking).
- ✓ The combination of bradykinesia and rigidity often contributes to a characteristic slow, shuffling gait and reduced arm swing.
- ✓ Patients commonly report a worsening of handwriting, with small and illegible letters.
- ✓ Postural instability or poor balance is a disabling symptom of advanced disease.

- ✓ Often a slow, shuffling gait is transformed into a rapid, festinating gait with a tendency to fall forward.
- ✓ Retropulsion with a tendency to fall backward also occurs.
- ✓ As a result, patients are at greater risk for falls and injuries and are less able to ambulate without assistance.
- ✓ This symptom is difficult to treat and is often resistant to pharmacotherapy.
- ✓ Although not considered a cardinal feature, "freezing," or a sudden, episodic inhibition of lower extremity motor function, may occur and interferes with ambulation.
- ✓ Patients may report that their "feet are stuck to the floor" and that they have difficulty initiating steps (start hesitation) or turns (turn hesitation).
- ✓ Freezing often is exacerbated by anxiety or when perceived obstacles (e.g., doorways, turnstiles) are encountered. This symptom is also difficult to treat pharmacologically.

DIAGNOSIS

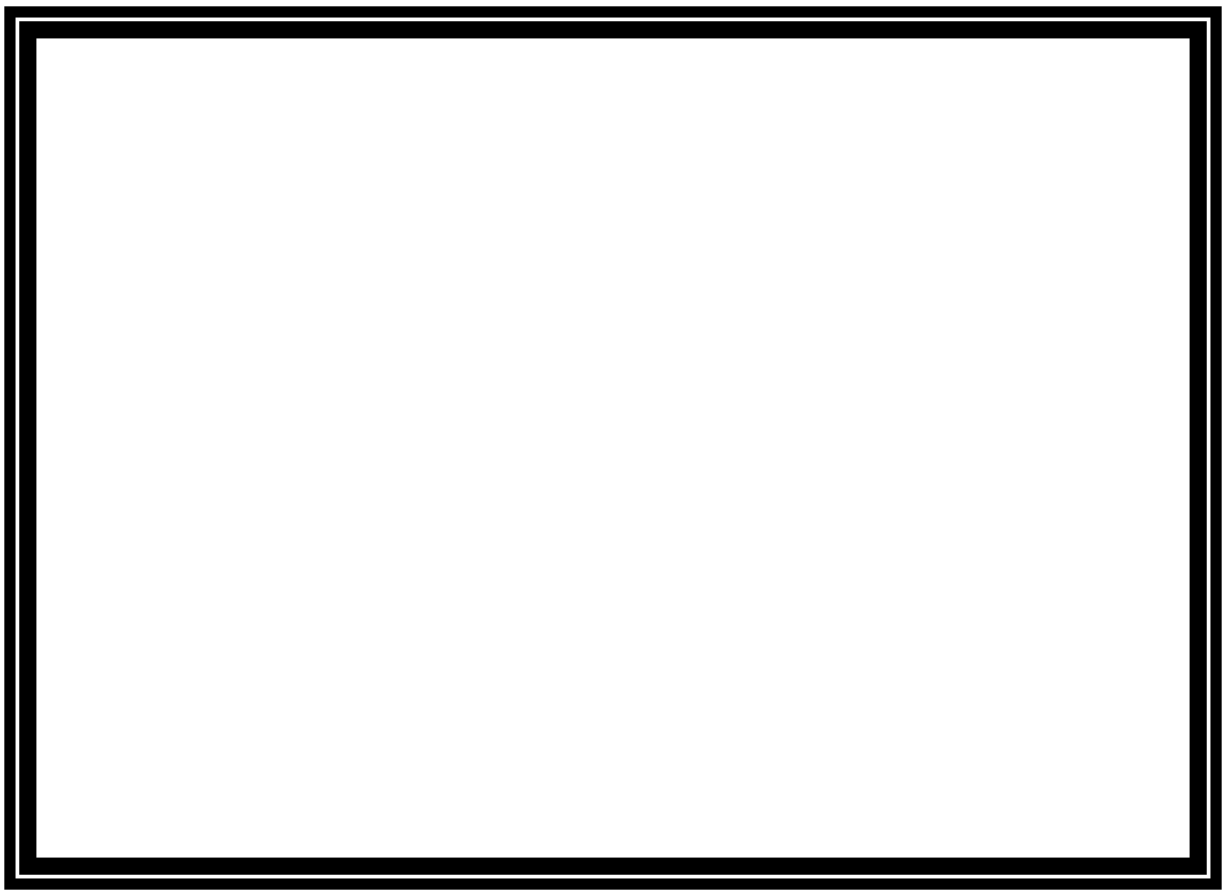
- ✓ Universally applicable preclinical tests or screens for PD remain an unmet need. Neuroimaging techniques, such as magnetic resonance imaging, positron emission tomography, and single photon emission computed tomography, in combination with various radiotracers as biomarkers for PD, have emerged as promising diagnostic and screening tools.
- ✓ However, these techniques require refinement before they can be used widely in the assessment of PD.
- ✓ Screening for impaired olfaction has been suggested for detection of increased PD risk later in life, but this method also requires additional validation.
- ✓ Currently, the diagnosis of PD depends on clinical findings based on neurologic assessment.
- ✓ A definitive diagnosis of PD is possible only upon postmortem confirmation of LBs and depigmentation of the SNpc.
- ✓ A careful clinical diagnosis is essential because the treatment and prognosis of idiopathic PD differ markedly from that of drug-induced parkinsonism or multisystem Parkinson plus syndromes.
- ✓ Even when drug-induced parkinsonism is ruled out, misdiagnosis occurs in up to 25% of cases.
- ✓ However, a clinical diagnosis of PD can be made with high probability if the patient presents with bradykinesia and either rest tremor or rigidity; motor features are initially unilateral; motor features are progressive; and there is an absence of early falls, dementia, or cerebellar (e.g., ataxia) or pyramidal (e.g., spasticity) signs.
- ✓ The diagnosis is confirmed if there is an excellent and sustained symptomatic response to dopaminergic therapy.
- ✓ In the early stages of PD, telltale features are slight and may be difficult to detect, but as the disease progresses, the signs and symptoms become unmistakable.
- ✓ If action tremor is present in the absence of bradykinesia or rigidity, the diagnosis of essential tremor should be considered.
- ✓ Once a clinical diagnosis of PD is made, assessment scales are useful for monitoring disease progression.
- ✓ The **Hoehn and Yahr scale** is a user-friendly, multistaging system based essentially on the presence and severity of postural instability.

- ✓ The Unified Parkinson's Disease Rating Scale (UPDRS) is a sensitive method for evaluating functional status, disease progression, and effectiveness of antiparkinson therapy.
- ✓ Neurologists specializing in PD often include portions of the UPDRS in the neurologic examination.
- ✓ Currently, the UPDRS is undergoing revision, particularly in assessment of nonmotor features.
- ✓ The Schwab & England Activities of Daily Living scale and the Parkinson's Disease Quality of Life scale (PDQUALIF) are useful tools for assessing quality-of-life parameters specific to the disease (e.g., independence, personal hygiene, physical function, self-image, sexuality, sleep, and social function).

HOEHN AND YAHR STAGING OF PARKINSON'S DISEASE	
Stage 1	Unilateral Disease
Stage 2	Bilateral disease without balance impairment
Stage 3	Mild to moderate bilateral disease, some postural instability; physically independent
Stage 4	Severe disability; unable to live alone independently
Stage 5	Unable to walk or stand without assistance

UNIFIED PARKINSON DISEASERATING SCALE (UPDRS)

- ✓ To evaluate the clinical efficacy of antiparkinson drugs and to monitor disease progression, most investigators have used the UPDRS.
  - The disadvantages associated with the use of scales for rating the functional and motor disabilities of patients with Parkinson disease include the potential of interrater variability and imprecision because of the semiquantitative scoring.
  - The result of testing depends highly on the stage of the disease, whether the patient is being evaluated during an on or off period, and the relative distribution of the improvement across al l the items evaluated.
- ➢ UPDRS
- ➢ **Part I:** An evaluation of mentation, behavior, and mood.
- ➢ **Part II**: A self - reported evaluation of the activities of daily living (ADLs) and includes speech, swallowing, handwriting, ability to cut food, dressing, hygiene, falling, salivating, turning in bed, and walking.
- ➢ **Part III:** A clinician-scored motor evaluation.
  - ✓ Patients are evaluated for speech, rest - tremor facial expression and mobility, action or postural tremor of hands, rigidity, finger taps, hand movements, rapid alternative pronation-supination movement of hands, leg agility, ease of arising from a chair , posture, postural stability, gait , and bradykinesia.
  - ✓ Each item is evaluated on a scale of 0-4.
    - A rating of 0 on the motor performance evaluation scale indicates normal performance.
    - A rating of 4 on the motor performance evaluation scale indicates severely impaired per formance.
- ➢ **Part IV:** the Hoehn and Yahr staging of severity of Parkinson disease.
- ➢ **Part V:** The Schwan and England ADL scale.



Differential Diagnosis

- ✓ The differential diagnosis of parkinsonian syndromes requires a careful historyand physical examination.
- ✓ Neuroimaging with magnetic resonance imaging (MRI) is useful to rule out disorders such as normal pressure hydrocephalus, vascular disease, or mass lesions. Positron emission tomography (PET) is helpful in confirming suspected atypical forms.
- ✓ Essential tremor (ET) is sometimes confused with rest tremor in PD, but the absence of other signs of parkinsonism and
- ✓ The bilaterality, higher frequency (8 to 10 Hz), and postural dependency of ET plus significant relief with even a small amount of alcohol help differentiate this from the rest tremor of PD.
- ✓ In individuals under 40 it is important to rule out Wilson's disease.
- ✓ In younger individuals Huntington's disease (HD) sometimes presents with prominent parkinsonian features.
- ✓ Although parkinsonian features are often present in AD, they are greatly outweighed by the cognitive and behavioral disturbances.
- ✓ In DLB, the parkinsonian features are compounded by the early appearance of hallucinations and disturbances in arousal and behavior.
- ✓ Parkinsonism may also develop following exposure to certain neurotoxins such as carbon monoxide or manganese.
- ✓ The differentiation of sporadic PD from atypical parkinsonism is the most difficult task, since early in their course these atypical forms often meet diagnostic criteria for PD.

- ✓ Accordingly, it is important not to settle on a definite diagnosis at the first visit.
- ✓ The development of early imbalance and falls suggests progressive supranuclear palsy(PSP); early urinary incontinence, orthostatic hypotension, and dysarthria suggest multiple system atrophy (MSA).
- ✓ The early appearance of drug-induced hallucinations strongly favors the diagnosis of DLB.
- ✓ As a rule the different forms of atypical parkinsonism can be reliably differentiated from sporadic PD within the first 3 to 4 years.

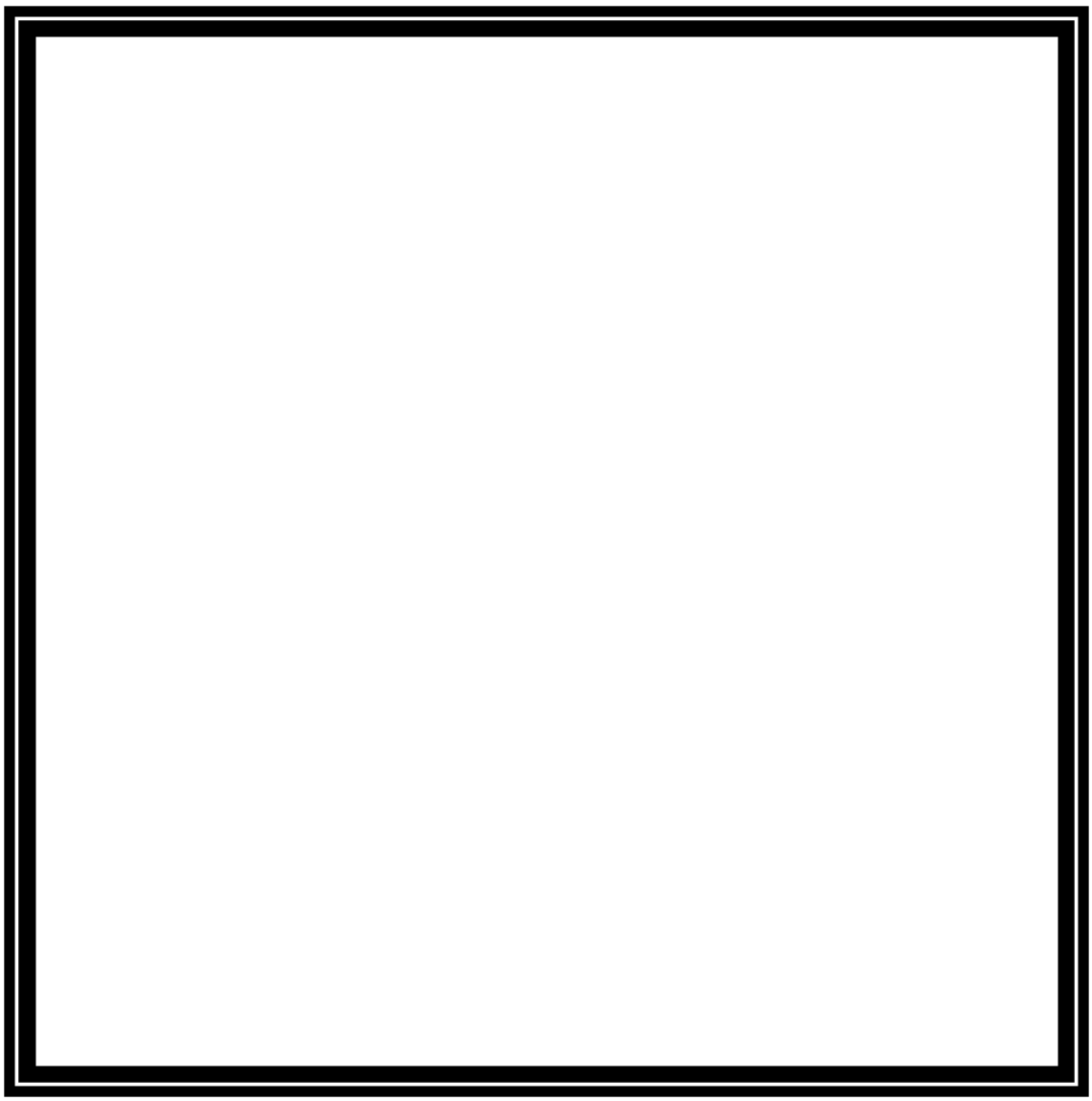
TREATMENT

NONDRUG TREATMENT

- ✓ **Exercise**
  - It is an important adjunctive therapy and is most beneficial.
  - Although exercise does not help with the symptoms of Parkinson disease, regular focused exercise, stretching, and strengthening activities can have a positive effect on mobility and mood.
- ✓ **Nutrition**
  - Patients with Parkinson disease are at increased risk of poor nutrition, weight loss, and reduced muscle mass.
  - Examples of the beneficial effects of proper nutrition in this group of patients include the following:
    - Sufficient fiber and fluid intake help prevent constipation associated with Parkinson disease and the medications used to treat the disease.
    - Calcium supplementat ion helps maintain the existing bone structure.
    - Excessive dietary protein in the late stages of the disease causes erratic responses to levodopa therapy.
    - A large body of literature supports the pathophysiological role of antioxidants in the neuroprotective role and decrease in progression in Parkinson disease.
- ✓ Products such as α- tocopherol or vitamin, creatine, coenzyme Q10 act as scavengers of free radical which are harmful to cells.

DRUG THERAPY

- ✓ Drug therapy for symptomatic relief.
- ✓ Treatment is divided into two generalized categories:
  - Symptomatic therapies
  - Preventive or protective measure
- ✓ Neuroprotective strategies are used to slow the development and progression of the disorder.

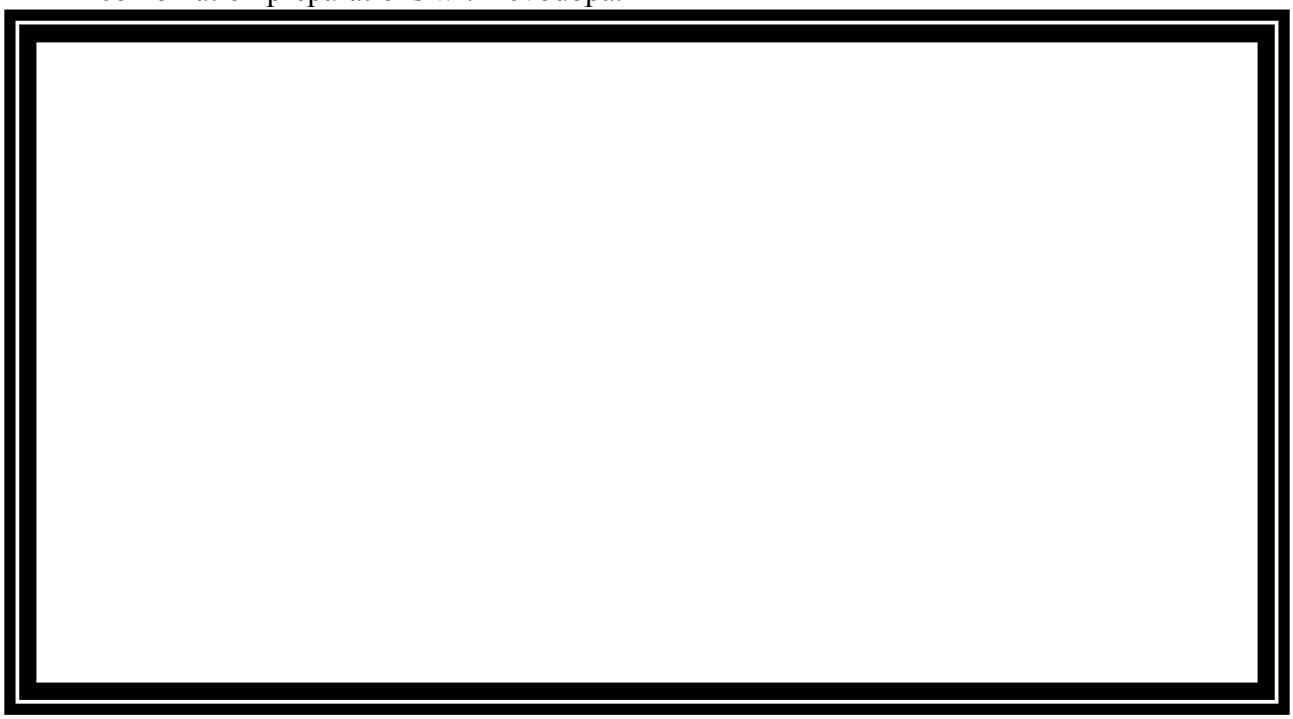


DRUG THERAPY

LEVODOPA

- ✓ **Levodopa** combined with a peripheral-acting dopa-decarboxylase inhibitor provides the mainstay of treatment in Parkinson's disease but should only be started to help overcome significant disability.
- ✓ Other agents include anticholinergic drugs, dopamine receptor agonists, selegiline, COMT inhibitors and amantadine.
- ✓ Although the number of dopamine-releasing terminals in the striatum is diminished in Parkinson's disease, remaining neurons can be driven to produce more dopamine by administering its precursor, levodopa.
- ✓ If levodopa is administered orally, more than 90% is decarboxylated to dopamine peripherally in the gastrointestinal tract and blood vessels, and only a small proportion reaches the brain.
- ✓ This peripheral conversion of levodopa is responsible for the high incidence of side-effects if it is used alone.

- ✓ The problem is largely overcome by giving a decarboxylase inhibitor that does not cross the blood-brain barrier along with the levodopa.
- ✓ Two peripheral decarboxylase inhibitors, carbidopa and benserazide, are available as combination preparations with levodopa.



1. Decarboxylase inhibitors (carbidopa and benserazide) decrease side-effects by reducing peripheral conversion of levodopa to dopamine by aromatic amino acid decarboxylase (AAAD).
2. Active transport of levodopa into the brain may be inhibited by competition from dietary amino acids after a high-protein meal.
3. In the nigrostriatal neurons, levodopa is converted into dopamine.
4. Amantadine enhances the release of dopamine at the nerve terminal.
5. Dopamine agonists act directly on striatal receptors.
6. The monoamine oxidase type B (MAO-B) inhibitor selegiline increases the availability of neuronal dopamine by reducing its metabolism outside the neuron.
7. The catechol-O-methyl-transferase (COMT) inhibitor entacapone prolongs the availability of dopamine by inhibiting the metabolism of dopamine and levodopa outside the neuron.

- ✓ The initiation of levodopa therapy should be delayed until there is significant disability, since there is concern that its use makes long-term side-effects more likely.
- ✓ With this in mind, some authorities suggest that it is advisable to initiate treatment with a dopamine agonist or a slow-release preparation of levodopa in order to minimise or delay the onset of long-term side-effects, but evidence for this is not strong.
- ✓ The important point is to treat with as little medication as possible consistent with the patient being able to perform the activities of daily living.
- ✓ Levodopa is particularly effective at improving bradykinesia and rigidity.
- ✓ Tremor is also helped but rather unpredictably.
- ✓ The initial dose is 50 mg 8- or 12-hourly, increased if necessary.

- ✓ The total levodopa dose may be increased to over 1000 mg/day if necessary.
- ✓ **Side-effects** include postural hypotension, nausea and vomiting, which may be offset by the use of a peripheral dopamine antagonist such as domperidone.
- ✓ Other dose-related side-effects are involuntary movements, particularly orofacial dyskinesias, limb and axial dystonias, and occasionally depression, hallucinations and delusions.
- ✓ Unusual but important side-effects include change in personality with increased (sometimes pathological) gambling, hypersexuality and drug (levodopa)-seeking behaviour.
- ✓ Late deterioration despite levodopa therapy occurs after 3-5 years in one-third to one-half of patients.
- ✓ Usually this manifests as fluctuation in response.
- ✓ The simplest form of this is end-of-dose deterioration due to progression of the disease and loss of capacity to store dopamine.
- ✓ More complex fluctuations present as sudden, unpredictable changes in response, in which periods of severe parkinsonism alternate with dyskinesia and agitation (the 'on-off' phenomenon).
- ✓ End-of-dose deterioration can often be improved by dividing the levodopa into smaller but more frequent doses, or by converting to a slow-release preparation.
- ✓ The 'on-off' phenomenon is difficult to treat, but sometimes subcutaneous injections of apomorphine (a dopamine agonist) are helpful to 'rescue' the patient rapidly from an 'off' period.
- ✓ Involuntary movements (dyskinesia) may occur as a peak-dose phenomenon, or as a biphasic phenomenon (occurring during both the build-up and wearing-off phases).
- ✓ Management is difficult, but involves modifying the way levodopa is administered to obtain constant levels in the brain, and the use of alternative drugs, including amantadine and dopamine agonists.
- ✓ Continuous infusion of apomorphine may be particularly helpful in this situation.

ANTICHOLINERGICS

- ✓ Before the advent of levodopa, centrally acting anticholinergic agents such as benztropine, biperiden, procyclidine, and trihexyphenidyl were mainstays of therapy.
- ✓ Symptomatic improvement with these agents is modest and favors tremor control. The most suitable candidates for the anticholinergics are younger patients with tremor-predominant disease.
- ✓ Common side effects include blurred vision, dry eyes, dry mouth, drowsiness, confusion, memory impairment, tachycardia, constipation, and urinary retention.
- ✓ Because of side effects, therapy generally is short-lived, particularly in older adults.
- ✓ However, in the absence of troublesome side effects, anticholinergic agents can be helpful.
- ✓ If therapy is to be discontinued after prolonged treatment, a downward dosage titration is recommended because abrupt withdrawal may result in severe agitation and confusion.

AMANTADINE

- ✓ Amantadine hydrochloride is an antiviral agent that was serendipitously found to have antiparkinson activity.

- ✓ The mechanism of antiparkinson activity remains unknown but may involve potentiation of neuronal dopamine release, blockade of dopamine reuptake, or antagonism of cholinergic or glutamatergic receptors.
- ✓ For patients with mild signs and symptoms, amantadine monotherapy may be considered.
- ✓ Within days of initiation, modest improvements in bradykinesia, rigidity, and tremor can be expected.
- ✓ With prolonged amantadine monotherapy, tachyphylaxis has been reported to occur, but discontinuation for a few weeks often restores responsiveness.
- ✓ Amantadine also demonstrates antidyskinesia effects and is useful for managing levodopa-induced dyskinesias.
- ✓ In general, side effects are mild.
- ✓ Central side effects include confusion, hallucinations, hyperexcitability, insomnia, and nightmares.
- ✓ These side effects often remit with a dosage reduction.
- ✓ If insomnia occurs, late-evening doses should be avoided.
- ✓ Other side effects include dizziness, nausea, orthostatic hypotension, and dry skin or eczema.
- ✓ Patients may also develop a benign form of livedo reticularis, a vascular cutaneous reaction characterized by a reddish-purple, fishnet-patterned mottling of the upper or lower extremities, often accompanied by ankle edema.
- ✓ This condition resolves upon discontinuation of amantadine.
- ✓ Abrupt discontinuation of therapy after prolonged treatment should be avoided due to the risk of withdrawal encephalopathy.
- ✓ Because amantadine is renally excreted as unchanged drug and high plasma levels may precipitate toxic delirium, a dosage reduction is recommended for patients with creatinine clearance less than 50 mL/minute/1.73 m.2,54

SELECTIVE MONOAMINE OXIDASE TYPE B INHIBITORS

- ✓ Inhibition of MAO_B is associated with reduced synaptic degradation of dopamine and prolonged dopaminergic activity.
- ✓ Two selective MAO_B inhibitors, **Rasagiline** and **Selegiline**, are available in the United States for management of PD.
- ✓ Both contain a propargylamine moiety, which is essential for conferring irreversible inhibition of MAO_B.
- ✓ At therapeutic doses, these agents preferentially inhibit MAO_B over MAO_A.
- ✓ Unlike the nonselective $MAO_{A/B}$ inhibitors, these agents do not require tyramine restriction when administered at therapeutic dosages.
- ✓ Because of the risk of serotonin syndrome, concomitant use of either rasagiline or selegiline with meperidine is contraindicated.
- ✓ Caution is urged with concomitant use of selective serotonin reuptake inhibitors (SSRIs), imipramine, clomipramine, lithium, sibutramine, and high-dose dextromethorphan.
- ✓ However, SSRIs are commonly used in selegiline-treated patients, and serious serotonin syndrome is rare.
- ✓ When combined with carbidopa/levodopa, dyskinesias may emerge or become worse and may require reduction of the levodopa dose.

SELEGILINE

- ✓ Selegiline or L-deprenyl is a first-generation irreversible MAO_B inhibitor that is administered once or twice daily.
- ✓ Laboratory experiments demonstrate that selegiline and its metabolite, N-desmethylselegiline, also protect against apoptosis and free radical-induced neurotoxicity.
- ✓ Unfortunately, the DATATOP trial, designed to evaluate the neuroprotective effect of selegiline in as yet untreated PD patients, yielded inconclusive results.
- ✓ However, the trial did demonstrate that monotherapy with selegiline in early PD is associated with modest symptomatic benefits, a delay in the need for levodopa, and extended employability.
- ✓ In moderate to advanced disease, adjunctive selegiline can be used to treat wearing-off symptoms.
- ✓ However, the role of selegiline is complicated by clinical data suggesting that cumulative exposure increases the risk of mortality (when used in combination with levodopa), especially in patients with a history of dementia, frequent falls, and postural hypotension.
- ✓ Subsequent studies have failed to confirm an adverse effect of selegiline on mortality.
- ✓ Selegiline is metabolized to the amphetamine derivatives L-amphetamine and L-methamphetamine, which have been implicated in producing side effects such as insomnia and vivid dreaming.
- ✓ Some patients also report an increased sense of well-being. Other side effects include confusion, dizziness, dry mouth, hallucinations, nausea, and orthostatic hypotension.
- ✓ If insomnia occurs, patients should be instructed to take doses no later than noon. Uncommonly, exacerbation of peptic ulcer disease and elevations in liver enzymes may occur.
- ✓ An orally disintegrating formulation of selegiline that undergoes orobuccal absorption with reduced metabolism to amphetamine derivatives may be available in the near future.

RASAGILINE

- ✓ Rasagiline is a second-generation, irreversible MAO_B inhibitor that is more potent than selegiline.
- ✓ Rasagiline is administered once daily and is effective as monotherapy in early PD.
- ✓ Once-daily rasagiline is also effective as adjunctive therapy in patients with advanced PD who are experiencing wearing-off fluctuations.
- ✓ In one study of levodopa-treated patients with motor fluctuations, the efficacy of adding once-daily rasagiline was similar to that of adding entacapone to each levodopa dose.
- ✓ Rasagiline is metabolized by hepatic CYP-450 1A2, and concurrent use of potent CYP1A2 inhibitors (e.g., ciprofloxacin) may increase rasagiline levels significantly.
- ✓ The major metabolite of rasagiline is aminoindan, which is devoid of amphetamine-like properties.
- ✓ Caution should be used when initiating treatment with rasagiline in patients with mild hepatic insufficiency.
- ✓ Rasagiline administered once daily is well tolerated, with an incidence of side effects similar to placebo in clinical studies.

CATECHOL-O-METHYLTRANSFERASE INHIBITORS

- ✓ The highly selective, reversible, nitrocatechol-structured COMT inhibitors (entacapone and tolcapone) extend the therapeutic activity of carbidopa/levodopa and are indicated for the management of wearing-off episodes.

- ✓ In the presence of carbidopa, levodopa metabolism is shifted toward the COMT pathway.
- ✓ With the coadministration of a COMT inhibitor, the levodopa area under the concentration time curve (AUC) and elimination half-life are increased.
- ✓ For most patients experiencing wearing off, up to 2 hours or more of additional "on" time per day can be achieved with the addition of a COMT inhibitor.
- ✓ This extra "on" time is valued by patients and analogous to a sleep-deprived person getting an extra 2 hours of sleep per night.
- ✓ In general, COMT inhibitors do not significantly alter levodopa's absorption pharmacokinetics, peak plasma concentrations (C_{max}), and the time of peak occurrence (T_{max}).
- ✓ Upon addition of a COMT inhibitor, patients should be informed that levodopa-related side effects (e.g., dyskinesias, dizziness, hallucinations, nausea) may be enhanced.
- ✓ These side effects can be alleviated by reducing the levodopa dose. Other side effects include dry mouth, intensification of urine coloration (caused by nitrocatechol metabolites), and diarrhea.
- ✓ The diarrhea may occur after 1 to 3 months of therapy initiation; it is usually self-limiting and responds to antidiarrheal agents.
- ✓ COMT inhibitors may inhibit the metabolism of other drugs with catechol structures, such as dobutamine, epinephrine, fenoldopam, isoproterenol, methyldopa, and nadolol.
- ✓ Overall, COMT inhibitors are preferred adjunctive agents to carbidopa/levodopa to improve duration of "on" time in patients experiencing wearing off.

TOLCAPONE

- ✓ Tolcapone is a broad-spectrum (i.e., centrally and peripherally acting) COMT inhibitor with an elimination half-life of approximately 2 hours.
- ✓ As such, it is administered 100 to 200 mg three times a day (at 6-hour intervals).
- ✓ As an adjunct to carbidopa/levodopa, tolcapone can double the half-life and AUC of levodopa and is associated with significant improvements in "on" time and reductions in "off" time in patients experiencing wearing-off motor fluctuations.
- ✓ However, tolcapone use is associated with hepatocellular injury, and its use requires frequent assessment of liver function enzymes.

ENTACAPONE

- ✓ Entacapone is a peripherally acting COMT with an elimination half-life of approximately 30 to 45 minutes.
- ✓ As such, the drug is administered in conjunction with each dose of carbidopa/levodopa, up to a maximum of eight times per day.
- ✓ Entacapone increases levodopa's half-life and AUC by up to 50%.
- ✓ Entacapone is also available in combi- nation with carbidopa/levodopa as a three-drug-in-one tablet formulation marketed under the proprietary name Stalevo; this may offer a more convenient method of administration.
- ✓ Entacapone is eliminated primarily via biliary excretion, and mild to moderate hepatic impairment increases bioavailability twofold.
- ✓ In patients with hepatic insufficiency, the dosage should be halved.
- ✓ Entacapone is associated with few specific laboratory abnormalities. In clinical studies, the occurrence of significant liver enzyme elevations was low (<1%).
- ✓ Entacapone chelates iron, and administration with oral pharmaceutical iron preparations should be separated by at least 2 hours.

APOMORPHINE

- ✓ Apomorphine is the only injectable antiparkinson agent available in the United States; it was the first dopamine agonist to be evaluated for the treatment of PD.
- ✓ It is an aporphine alkaloid originally derived from morphine but lacks the narcotic properties of the parent compound.
- ✓ Apomorphine is considered the most potent agent in the dopamine agonist class.
- ✓ Due to extensive first-pass metabolism, apomorphine is commonly administered via subcutaneous injection.
- ✓ Apomorphine is an effective "rescue" drug for rapid relief of intermittent "off" episodes in advanced PD.
- ✓ For patients with advanced PD experiencing intermittent "off" episodes despite optimized therapy, administration of subcutaneous apomorphine consistently and effectively triggers an "on" response within 20 minutes.
- ✓ The effective dose ranges from 2 to 6 mg per injection; most patients require approximately 0.06 mg per kg.
- ✓ Sites of injection (abdomen, upper arm, and upper thigh) should be rotated to avoid the development of subcutaneous nodules.
- ✓ In some countries, apomorphine is also available for continuous subcutaneous injection with mini-pumps.
- ✓ Apomorphine should not be injected intravenously.
- ✓ Upon exposure to air, apomorphine rapidly oxidizes and will discolor fabrics a greenish color.
- ✓ The route of apomorphine metabolism is unknown.
- ✓ Its elimination half-life is approximately 40 minutes, and the duration of benefit is up to 100 minutes.
- ✓ These pharmacokinetic properties make apomorphine a suitable drug for intermittent "rescue" administration.
- ✓ Apomorphine should be initiated in a clinic or office setting for test dose administration, monitoring of blood pressure, determination of therapeutic dose, and patient/caregiver education.
- ✓ A test dose is administered, and if orthostatic hypotension develops, the patient should not receive outpatient apomorphine therapy.
- ✓ Otherwise, a therapeutic dose is determined, and the patient or caregiver administers the drug as needed for "rescue" therapy during "off" episodes.
- ✓ Nausea and vomiting are common side effects; prior to apomorphine initiation, the patient should be premedicated with an antiemetic such as trimethobenzamide for 3 days.
- ✓ The antiemetic may be continued for up to 2 months.
- ✓ Other side effects include dizziness, dyskinesia, hallucinations, injection site irritation, rhinorrhea, somnolence, and yawning at the onset of effect.
- ✓ Due to reports of severe hypotension and syncope, apomorphine is contraindicated with drugs in the serotonin ($5HT_3$)-receptor blocker class, including dolasetron, granisetron, and ondansetron.

BROMOCRIPTINE

- ✓ Bromocriptine is an ergot-derived agonist that stimulates D_2 receptors and mildly antagonizes D_1 sites.
- ✓ The drug possesses poor oral bioavailability and is highly protein bound.

- ✓ Although originally indicated for disorders of hyperprolactinemia, bromocriptine was the first oral dopamine agonist to receive an FDA-approved indication for PD management.
- ✓ Overall, bromocriptine is generally considered to be less effective than pergolide, pramipexole, and ropinirole.
- ✓ This may be due, in part, to mild D_1 antagonism.
- ✓ Because of its ergotlike structure, bromocriptine also exerts agonist activity at α-receptors and serotonin receptors.
- ✓ This may contribute to other side effects such as vasoconstriction, rhinitis, erythromelalgia (a painful, reddish skin rash), pleuropulmonary disease, and retroperitoneal fibrosis.
- ✓ Bromocriptine-induced pleuropulmonary disease is reversible and occurs in about 2% to 5% of patients after 5 years of therapy.
- ✓ Patients receiving dosages greater than 20 mg per day for more than 6 months may be at increased risk.
- ✓ A baseline chest radiograph is recommended before initial therapy.
- ✓ Drugs that are potent inhibitors of the cytochrome P-450 3A4 enzyme (e.g., erythromycin, clarithromycin, nefazodone) may increase plasma bromocriptine levels by severalfold.

PERGOLIDE

- ✓ Pergolide was the second oral agonist to receive an FDA-approved indication for treating PD. Pergolide is a semisynthetic ergot derivative with strong D_2 receptor agonism.
- ✓ Unlike bromocriptine, pergolide also stimulates D_1 receptors. The therapeutic equivalency ratio of pergolide to bromocriptine is about 1:10.
- ✓ In early PD, pergolide is effective as monotherapy, but with more advanced disease, symptomatic benefit is best when combined with levodopa.
- ✓ Although pergolide has a long half-life, the duration of clinical activity is about 6 hours, and multiple daily doses are needed.
- ✓ Side effects are common but generally less frequent than with bromocriptine.
- ✓ As with bromocriptine, retroperitoneal fibrosis and other ergotamine-like side effects may occur.
- ✓ Pergolide use has been associated with the development of restrictive valvular heart disease, and monitoring for cardiac valvular dysfunction should be instituted.

PRAMIPEXOLE

- ✓ Pramipexole is a second-generation dopamine receptor agonist.
- ✓ Pharmacologically, pramipexole differs from the first-generation agonists, bromocriptine and pergolide, in several respects.
- ✓ Pramipexole is a nonergot agonist, and ergotamine-related side effects, such as retroperitoneal fibrosis, are not to be expected.
- ✓ Pramipexole is very specific for the D_3-subtype receptor (which belongs to the D_2 receptor family).
- ✓ The clinical effects associated with D_3-receptor specificity remain speculative, but they may include improved efficacy and antidepressant or mood-elevating activity.
- ✓ In a clinical study of depressed patients with PD receiving either pramipexole or pergolide, a significant improvement in depressive symptoms was observed only in the pramipexole-treated patients.

- ✓ Pramipexole is excreted renally as unchanged drug and exhibits no significant inhibition of hepatic cytochrome P-450 enzymes.
- ✓ In patients with a creatinine clearance less than 60 mL per minute, elimination of pramipexole is reduced.
- ✓ In early PD, pramipexole is effective as monotherapy, but with more advanced disease, symptomatic benefit is best when combined with levodopa.

ROPINIROLE

- ✓ Ropinirole is a nonergot second-generation agonist that exhibits high affinity for D_2 and D_3 receptor subtypes, with minimal activity at nondopaminergic receptor sites (i.e., α, histaminic, cholinergic, serotonergic).
- ✓ Side effects are similar to those of pramipexole. Unlike pramipexole, ropinirole elimination is not affected by renal function. Ropinirole is metabolized in part by the CYP-450 1A2 isoenzyme, and inhibitors of this enzyme may increase ropinirole levels.
- ✓ In early PD, ropinirole is effective as monotherapy, but with more advanced disease, symptomatic benefit is best when combined with levodopa.
- ✓ A sustained-release formulation of ropinirole is under development.

SURGERY

- ✓ Stereotactic thalamotomy can be used to treat tremor, though this is needed relatively infrequently because of the medical treatments available.
- ✓ Other stereotactic lesions are currently undergoing evaluation, in particular the implantation of stimulating electrodes into the globus pallidus to help in the management of drug-induced dyskinesia.
- ✓ The implantation of fetal mid-brain cells into the basal ganglia to enhance dopaminergic activity remains experimental.
- ✓ Over the past decade there has been a renaissance in the surgical treatment of PD and other movement disorders.
- ✓ Although both pallidotomyand thalmotomywere performed widely in the 1950s, the introduction of levodopa in the 1960s led to the virtual abandonment of surgery.
- ✓ The resurgence in the use of surgery has been motivated bythe fact that after 5 years of treatment, many patients develop significant drug-induced motor fluctuations and dyskinesias.
- ✓ Second, advances in understanding of the functional organization of the basal ganglia and the pathophysiologic basis of parkinsonism have provided a clearer rationale for the effectiveness of these procedures and guidance for targeting specific structures.
- ✓ The demonstration, in animal models of PD, that ablation of the STN (subthalamotomy) resulted in a dramatic reduction in all of the cardinal features of parkinsonism was a critical finding.
- ✓ The selection of suitable patients for surgery is most important, since in general patients with atypical Parkinson's do not have a favorable response.
- ✓ The major indications for surgery are
    - A diagnosis of idiopathic PD,
    - A clear response to levodopa,
    - Significant intractable symptoms of PD, and/or
    - Drug-induced dyskinesias and wearing-off

- ✓ Contraindications to surgery include atypical forms of PD, cognitive impairment, major psychiatric illness, substantial medical comorbidities, and advanced age (a relative factor).
- ✓ Signs and symptoms not responding to levodopa, such as postural instability and falling, hypophonia, micrographia, drooling, and autonomic dysfunction, are unlikely to benefit from surgery.
- ✓ As a rule of thumb, the benefits from surgery are unlikely to exceed the benefits of antiparkinson medication.
- ✓ In general, the decision for surgery should be made by a movement disorder neurologist who is part of a team including a neurosurgeon trained in functional neurosurgery, a psychiatrist, a neuropsychologist, and trained technicians.

ABLATION VERSUS DEEP BRAIN STIMULATION (DBS)

- ✓ The use of ablation (e.g., pallidotomyor thalamotomy) has decreased greatly since the introduction of DBS and is generally reserved for individuals who for medical or economic reasons cannot have DBS.
- ✓ Major advantages of DBS are that it is somewhat less invasive and more reversible than ablation, and in addition maybe adjusted to best effect following implantation.
- ✓ Although the choice between the STN and the internal segment of the globus pallidus for DBS has shifted toward the STN, the data to support this are lacking.
- ✓ Several clinical trials are now under way to compare these two targets.
- ✓ The available evidence suggests that both are effective for all the cardinal features of PD as well as for dyskinesias and motor fluctuations.
- ✓ Unilateral stimulation is appropriate for patients with asymmetric disease, although bilateral surgery is generally necessary for patients with more advanced disease and for those with significant bilateral manifestations.
- ✓ Reductions in drug dosages appear to be easier with STN than globus pallidus procedures.
- ✓ The mechanism of action of DBS remains controversial. Since clinically it appears that ablation and stimulation of a given target have a similar effect, it has been assumed that stimulation caused a functional blockade.
- ✓ It is likely, however, that multiple factors are involved.
- ✓ The basis for improvement maybe the replacement of abnormal neural activity by a more tolerable pattern of activity.
- ✓ Following ablation or DBS, the remaining motor systems in the brainstem, thalamus, and cortex are able to compensate more effectively for the abnormal activity associated with the parkinsonian state.
- ✓ Whatever the mechanism, it is clear that these approaches can offer impressive results in properly selected patients.

NEUROTRANSPLANTATION AND OTHER SURGICAL APPROACHES

- ✓ Despite highly encouraging open-label pilot studies of fetal cell transplantation, this approach has suffered considerable disappointment with the recent publication of the results from two large, well-controlled clinical trials.
- ✓ The first, using sham surgery, showed only modest benefit in patients under 60 and no benefit in those over 60.
- ✓ An unexpected complication in a number of patients was the development of symptomatic dyskinesias, occurring off medication.

- ✓ The second study has shown similar findings with regard to benefit and the development of dyskinesias.
- ✓ A puzzling feature of these studies is the apparent successful grafting observed by PET and autopsy.
- ✓ Because of these disappointing results, the considerable obstacles to obtaining sufficient fetal tissue, and opposition to the use of fetal tissue on ethical grounds, this approach is now viewed as purely investigational.
- ✓ It is hoped that these issues can be addressed with the development of other strategies to enhance dopaminergic cell function (e.g., carotid bodycells; stem cells; encapsulated and geneticallyengineered cells capable of producing levodopa, dopamine, and/or trophic factors).
- ✓ The favorable response from direct infusion of glial cell–derived neurotrophic factor (GDNF) to the putamen in a small number of patients with PD has raised hopes that this approach, or the use of gene-transfer of trophic factors such as GDNF, will succeed.
- ✓ Preliminarystudies in primate models of PD have been encouraging in this regard.

PHYSIOTHERAPY AND SPEECH THERAPY

- ✓ Patients at all stages of Parkinson's disease benefit from physiotherapy, which helps reduce rigidity and corrects abnormal posture.
- ✓ Speech therapy may help in patients where dysarthria and dysphonia interfere with communication.