Parkinson's Disease

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Session out line

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Introduction

- Parkinson's disease (PD) is one of progressive neurodegenerative disorders
- It is characterized by the clinical features of parkinsonism:
  - Bradykinesia (a paucity and slowness of movement)
  - Rest tremor, muscular rigidity, shuffling gait,
  - And flexed posture.

Con`t…

- Although defined clinically as a movement disorder, it is now widely appreciated that IPD can be accompanied by a variety of non-motor symptoms,
- Nearly all forms of parkinsonism result from a reduction of dopaminergic transmission within the basal ganglia.
- These clinical features of IPD were adeptly described in 1817 by James Parkinson

Epidemiology

- Up to 1 million individuals in the United States have IPD.
- The approximate annual incidence of IPD is age dependent
- The prevalence of IPD increases with age, affecting 1% of people older than age 65 years and 2.5% of those older than age 80 years.
- The usual age at time of diagnosis ranges 55 to 65 years.
- A higher incidence is reported among males, with a male-to female ratio of up to 2:1.

Etiology

- The true etiology of IPD is unknown,
- But is likely the result of interactions between aging, genetic constitution, and environmental factors.
- In IPD, a key histopathologic feature is degeneration of dopaminergic neurons in the substantia nigra
- Additionally, neuronal vulnerability in IPD extends beyond the nigrostriatal pathway
- And includes specific neurons in autonomic ganglia, basal ganglia, spinal cord, and neocortex

Con`t…

- Although IPD is sporadic, extensive epidemiologic research associates environmental factors with increased risk of IPD

These includes :

- Chronic exposure to pesticides and heavy metals
- Rural living, and drinking well water,

- Interestingly, epidemiologic studies have consistently associated an inverse correlation between cigarette smoking and caffeine consumption for development of IPD

Con`t…

- Intrinsically, the substantia nigra pars compacta (SNc) is a region characterized by high levels of oxidative stress
- Because free radicals are generated from dopamine auto oxidation mediated by MAO
- Several ant oxidative molecules (e.g., glutathione) are present in the SNc
- These molecules limit damage produced by free-radical attack,

Con`t…

- But in IPD, such protection might be overwhelmed
- Thus cellular damage from oxidant stress has long been discussed as an etiopathologic component of IPD.
- The SNc is also rich in iron and copper, essential cofactors in the biosynthesis and metabolism of dopamine
- The oxidation–reduction cycle of iron can also generate free radicals and toxic metabolites

Con`t…

In addition:

- Apoptosis , excitotoxicity, inflammation, mitochondrial dysfunction, nitric oxide toxicity, proteosomal dysfunction,
- and autophagic cellular mechanisms are also implicated etiopathologic mechanisms in IPD.
- Genetics may play a significant role, particularly if IPD begins before age 50 years.

Pathophysiology

- In the SNc, the two hallmark histopathologic features of IPD are :

  - Depigmentation of dopamine-producing neurons and

  - Presence of Lewybodies in the remaining SNc neurons.

- Lewybodies appear in degenerating neurons in association with adjacent gliosis.
- Lewypathology has been proposed to develop in a predictable anatomic distribution within the parkinsonian brain.

Con`t…

- In the premotor stage of IPD, Lewybodies are initially found in the medulla oblongata, locus coeruleus, raphe nuclei, and olfactory bulb
- This may correlate with observations that anxiety, depression, and impaired olfaction is detectable in premotor stages of IPD.
- As IPD progresses, Lewypathology ascends to the midbrain (particularly the SNc) and accounts for development of motor features.

Con`t…

- In advanced stages, Lewy pathology spreads to the cortex, and this may correlate with cognitive and additional behavior changes.
- Pathologic findings reveal a correlation between the extent of nigrostriatal dopamine loss and the severity of certain IPD motor features (e.g., bradykinesia
- The threshold for onset of clinically detectable IPD appears to be the loss of 70% to 80% of SNc neurons

Con`t…

- Functional neuroimaging studies suggest compensatory responses,
- Which are up regulation of dopamine synthesis and down regulation of synaptic dopamine reuptake,
- These occur as adaptive mechanisms beginning in the premotor stage of IPD.
- These adaptive responses may help to explain why the motor features are not clinically detectable until profound depletion (70%–80%) of SNc neurons has occurred.

Clinical presentation

General Features

- For clinically probable IPD, the patient exhibits at least two of the following:
  - resting tremor, rigidity, or bradykinesia.
- Asymmetric onset and severity of these features is typical.
- Postural instability is more common in advanced IPD.

Motor Symptoms

- The patient experiences decreased manual dexterity, difficulty arising from a seated position, diminished arm swing during ambulation, dysarthria, dysphagia ,festinating gait, flexed posture ,"freezing" at initiation of movement, hypomimia , hypophonia , and micrographia

Con`t…

Autonomic and Sensory Symptoms

- The patient experiences bladder and anal sphincter disturbances, constipation, diaphoresis, fatigue, olfactory disturbance, orthostatic blood pressure changes, pain, paresthesia, paroxysmal vascular flushing, seborrhea, sexual dysfunction, and sialorrhea.

Mental Status Changes

- The patient experiences anxiety, apathy, bradyphrenia, confusionalstate, dementia, depression, hallucinosis/psychosis (typically drug induced), and sleep disorders

Con`t…

Laboratory Tests

- No laboratory tests are available to diagnose IPD.

Other Diagnostic Tests

- Genetic testing is not routinely helpful.
- Neuroimaging may be useful for excluding other diagnoses.
- Medication history should be obtained to rule out drug induced parkinsonism.

Treatment

Desired Outcomes

- The goal in the management of IPD is to improve motor and non motor symptoms
- Specific objectives to consider when selecting an intervention include:
- Preservation of the ability to perform activities of daily living; improvement of mobility;
- Minimization of adverse effects, treatment complications,
- Putative disease modification; and
- Improvement of non motor symptoms

Con`t…

- Once a correct diagnosis of IPD is made, nonpharmacologic and pharmacologic interventions must be considered.
- In the absence of functional impairment, initial monotherapy may be initiated with an MAO-B inhibitor,
- Addition of other therapeutic agents as IPD motor symptoms progressively worsen.
- Therapy with rasagilinein early stage PD has been demonstrated to slow the decline of motor function and is well tolerated

Con`t…

- The definition of functional impairment is highly patient specific
- Factors such as comorbid conditions, cognitive status, employment, lifestyle, and patients' desires must be considered when initiating pharmacotherapy.
- In a "physiologically" young patient experiencing functional impairment, monotherapy with a dopamine agonist or rasagiline is preferred.

Con`t…

- For patients who are older, cognitively impaired, or experiencing moderately severe functional impairment, L-dopa (e.g., carbidopa/levodopa) is preferred
- Ultimately, all patients will require the use of L-dopa (either as monotherapy or in combination with other agents)
- With the development of motor fluctuations, addition of COMT) inhibitor should be considered to extend L-dopa duration of activity, or

Con`t…

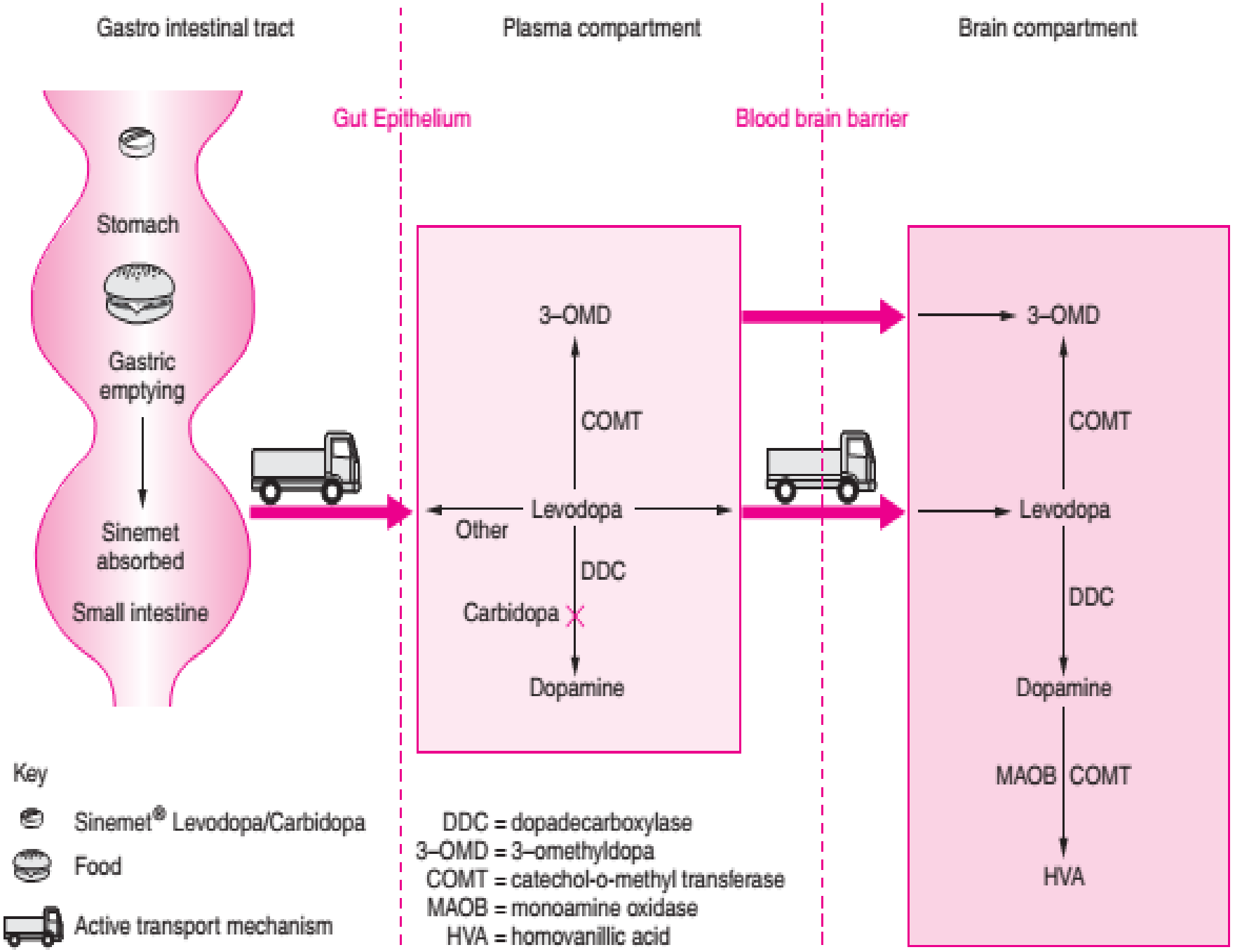
- If the patient is not already on an MAO-B inhibitor or dopamine agonist, addition of either one should be considered.
- For management of L-dopa induced peak-dose dyskinesias, the addition of amantadine should be considered.
- Surgery is considered only in patients who need more symptomatic control or who are experiencing severe motor complications despite pharmacologically optimized therapy

Con`t…

- The treatment plan evolves as the disease progresses and must include consideration of short-term symptomatic relief as well as long-term effects.
- Patient specific factors that guide selection of therapies include the "functional" age of the patient, patient's desired outcomes, cognitive status, severity of motor features, and response to any previous IPD therapies.
- Patient education should be communicated with realistic optimism.

Con`t…

- For example, it should be explained that although there is no cure for IPD, modern medicine has many medications that can provide relief of symptoms.
- Nonpharmacologic interventions such as exercise should be encouraged, and attention to non motor features of IPD should not be neglected


Gastro intestinal tract
Plasma compartment
Brain compartment
Gut Epithelium
Blood brain barrier
Stomach
Gastric emptying
Sinemet absorbed
Small intestine
3–OMD
COMT
Other
Levodopa
DDC
Carbidopa
Dopamine
3–OMD
COMT
Levodopa
DDC
Dopamine
MAOB
COMT
HVA
Key
Sinemet® Levodopa/Carbidopa
Food
Active transport mechanism
DDC = dopadecarboxylase
3–OMD = 3–omethyldopa
COMT = catechol-o-methyl transferase
MAOB = monoamine oxidase
HVA = homovanillic acid

Anticholinergic

- Dopamine provides negative feedback to acetylcholine neurons in the striatum,
- Degeneration of nigrostriatal dopamine neurons also results in a relative increase of striatal cholinergic interneuron activity.
- This increased cholinergic activity is believed to contribute to the tremor of IPD.

Con`t…

- The anticholinergic drugs are considered effective against tremor
  - Eg. Benztropine and trihexyphenidyl
- Sometimes dystonic symptoms associated with IPD are also improved by anticholinergic agents
- Use of anticholinergic agents is limited due to the development of intolerable side effects, necessitating dosage reduction or drug discontinuation

Con`t…

- Common adverse effects include blurred vision, confusion, constipation, dry mouth, memory difficulty, sedation, and urinary retention.
- Younger patients are better able to tolerate anticholinergic side effects, whereas patients with preexisting cognitive deficits and advanced age are less tolerant.
- Anticholinergic drugs can be used alone or in conjunction with L-dopa and other antiparkinson agents.

Amantadine

- Amantadine provides modest symptomatic benefit for tremor, as well as rigidity and bradykinesia.
- The precise mechanism of action of amantadine is unknown, but dopaminergic and non dopaminergic mechanisms, such as inhibition of glutamatergic NMDA receptors, are implicated.
- Amantadine is typically administered 300 mg/day in divided doses.

Con`t…

- Amantadine is also useful for suppressing L-dopa– induced dyskinesia.
- The antidyskinetic properties of amantadine are presumed to be mediated by antiglutamate activity
- Amantadine is eliminated renally, and a reduced dose should be administered when renal dysfunction is present

Con`t…

- Common side effects of amantadine include confusion, dizziness, dry mouth, and hallucinations.
- The elderly are particularly prone to develop confusion.
- Not uncommonly, amantadine may cause livedo reticularis, a reversible condition characterized by diffuse mottling of the skin affecting the upper or lower extremities and often accompanied by lower-extremity edema.

Carbidopa/levodopa

- L-Dopa is the immediate precursor of dopamine and, in combination with carbidopa or benserazide remains the most effective drug for the symptomatic treatment of IPD.
- L-Dopa crosses the blood–brain barrier, whereas dopamine, carbidopa, and benserazide do not.
- The combination of L-dopa with carbidopa or benserazide, reduces the unwanted peripheral conversion of L-dopa to dopamine.

Con`t…

- As a result, increased amounts of L-dopa are transported into the brain,
- peripheral adverse effects of dopamine, such as nausea, are reduced.
- In the SNc, L-dopa is converted, via decarboxylation, to dopamine by the enzyme L-amino acid decarboxylase
- The converted dopamine is stored in the presynaptic SNc neurons

Con`t…

- Then released into the synaptic cleft whereupon it binds to the D1 and D2 postsynaptic receptors.
- Dopamine activity is terminated primarily by reuptake back into the presynaptic neuron by means of a dopamine transporter.
- The enzymes MAO and COMT also inactivate dopamine.
- All patients with IPD will require L-dopa at some point

Con`t…

- An initial maintenance L-dopa regimen of 300 mg/day (in divided doses and in combination with carbidopa or benserazide) often is adequate.
- About 75 mg/day of carbidopa is required to sufficiently inhibit the peripheral activity of L-amino acid decarboxylase, but some patients require more.
- Therefore, the usual initial maintenance carbidopa/L-dopa regimen is 25/100 mg 3 times daily.

Con`t…

- As the motor features of IPD become progressively more severe, use of higher dosages is required.
- There is no maximum allowable total daily L-dopa dose;
- However, the usual maximal dose needed by patients, even those with severe IPD, is 800 to 1,000 mg/day

Con`t…

Pharmacokinetics

- There is marked intra- and intersubject variability in the time to peak plasma concentrations after oral Ldopa,
- This variation may in part be attributed to differences in gastric emptying.
- L-Dopa is absorbed primarily in the proximal duodenum by a saturable large neutral amino acid transport system.

Con`t…

- Competition for this transporter by dietary or supplemental large neutral amino acids can interfere with L-dopa bioavailability
- L-Dopa is not bound to plasma proteins.
- Active transport across the BBB occurs by the large neutral amino acid transporter system
- Separation of L-dopa administration with high protein meals has been recommended

Con`t…

- Because large amounts of dietary large neutral amino acids may compete for transport across the blood–brain barrier
- However, in patients with early IPD, this interaction is generally not significant.
- In advanced IPD, special diets involving protein restriction or redistribution may improve L-dopa responsiveness and are sometimes implemented.

Con`t…

- A metabolite of L-dopa, 3-O-methyldopa, also competes for transport, but it is not clear how this affects L-dopa clinical response.
- When peripheral decarboxylation of L-dopa is inhibited by carbidopa or benserazide, 3-O-methylation (via COMT) becomes the predominant catabolic pathway.
- The elimination half-life of L-dopa is about 1 hour,

Con`t…

- It is is extended to about 1.5 hours with the addition of carbidopa or benserazide.
- With the addition of a COMT inhibitor such as entacapone to carbidopa/L-dopa, the elimination half life is extended to about 2 to 2.5 hours
- Long-term L-dopa therapy is associated with a variety of motor complications

Con`t…

- End-of-dose "wearing off" (motor fluctuations) and L- dopa peak-dose dyskinesias are the two most commonly encountered.
- These motor complications can be disabling and challenging to manage.
- The approximate risk of developing either motor fluctuations or dyskinesia is 10% per year of L-dopa therapy.

Table 68-3 Common Motor Complications and Possible Initial Treatments

Effect	Possible Treatments
End-of-dose "wearing off" (motor fluctuation)	Increase frequency of carbidopa/L-dopa doses; add either COMT inhibitor or MAO-B inhibitor or dopamine agonist
"Delayed on" or "no on" response	Give carbidopa/L-dopa on empty stomach; use carbidopa/L-dopa ODT; avoid carbidopa/L-dopa CR; use apomorphine subcutaneous
Start hesitation ("freezing")	Increase carbidopa/L-dopa dose; add a dopamine agonist or MAO-B inhibitor; utilize physical therapy along with assistive walking devices or sensory cues (e.g., rhythmic commands, stepping over objects)
Peak-dose dyskinesia	Provide smaller doses of carbidopa/L-dopa; add amantadine

COMT, catechol-O-methyltransferase; CR, controlled release; MAO, monoamine oxidase; ODT, orally disintegrating

MAO B inhibitors

- Selegiline, also known as L-deprenyl, is marketed for extending L-dopa effects and is typically administered 5 mg twice daily.
- Selegiline is also available as an orally disintegrating tablet formulation administered 1.25 to 2.5 mg once daily.
- A transdermal formulation of selegiline is also available but is not indicated for IPD.
- As monotherapy in early IPD, conventional selegiline provides modest improvements in motor function.

Con`t…

- In more advanced IPD, the adjunctive use of conventional selegiline can provide up to 1 hour of extended on time for patients with wearing off,.
- This inconsistent effect of conventional selegiline may be explained, in part, by poor and erratic bioavailability of the parent drug
- As an amphetamine pharmacophore, selegiline undergoes first-pass hepatic metabolism

Con`t…

- Adverse effects of selegiline are minimal but can include insomnia ,hallucinations, and jitteriness.
- Selegiline also increases the peak effects of L-dopa and can worsen preexisting dyskinesias or psychiatric symptoms such as delusions.
- With the selegiline orally disintegrating tablet formulation, first-pass hepatic metabolism is bypassed as a consequence of transmucosal absorption of the drug

Con`t…

- Hence, bioavailability characteristics of the parent drug are improved and formation of amphetamine metabolites is reduced.
- Thus, the selegiline orally disintegrating tablet formulation may provide an improved response relative to conventional selegiline

Con`t…

- Rasagiline is a second-generation, irreversible, selective MAO-B inhibitor administered at 0.5 or 1 mg once daily.
- Rasagiline is effective as monotherapy in early IPD and also as add-on therapy for managing motor fluctuations in advanced IPD.
- Patients initiated on rasagiline monotherapy early in IPD had less functional decline than did patients whose treatment was delayed

Con`t…

- Earlier initiation with rasagiline is associated with better long-term outcomes.
- For motor fluctuations, the efficacy of rasagiline appears similar to that of entacapone,
- With offering approximately 1 hour of extra on time during the day

Con`t…

- when an adjunctive agent is required for managing motor fluctuations, rasagiline is considered a first-line agent (as is entacapone).
- Overall, rasagiline is well tolerated with minimal gastrointestinal or neuropsychiatric side effects.
- Rasagilineis metabolized by hepatic CYP1A2 to aminoindan, which is inactive and devoid of amphetamine-like properties

COMT inhibitors

- Entacapone and tolcapone, have been developed to extend the effects of L-dopa
- They are indicated for managing wearing off.
- Both reduce the peripheral conversion of L-dopa to dopamine,
- Thus enhancing central L-dopa bioavailability. Consequently,
- In the absence of L-dopa, they have no effect on IPD symptoms.

Con`t…

- For patients with wearing off, these agents can decrease off-time significantly
- COMT inhibition is considered more effective than controlled-release carbidopa/L-dopa in providing consistent extension of L-dopa effect.
- triple-combination product of carbidopa/Ldopa/entacapone offers convenience for some patients

Con`t…

- Tolcapone inhibits both peripheral and central COMT.
- Its use is limited by reports of fatal hepatotoxicity,
- So that strict monitoring of hepatic function, especially is required.
- Because of the hepatotoxicity risk, tolcapone is reserved for patients that are not responding to other therapies.

Con`t…

- Entacapone has a shorter half-life than tolcapone,
- 200 mg needs to be given with each dose of carbidopa/L-dopa
- Dopaminergic adverse effects may occur and generally are manageable by reduction of the carbidopa/L-dopa dosage
- With both agents, brownish-orange urinary discoloration may occur

Con`t…

- Also, delayed onset of diarrhea (weeks to months later) can occur in up to 5% of patients.
- Unlike tolcapone, entacapone is not associated with hepatotoxicity
- If an adjunctive agent is needed for managing motor fluctuations, entacapone is considered one of the first choices

Dopamine Agonists

- Dopamine agonists fall into two pharmacologic subtypes:
  - Ergot-derived agonists (bromocriptine) and
  - nonergotagonists (pramipexole, ropinirole).
- The nonergot dopamine agonists are safer than the ergotderived agonists
- And are useful as monotherapy in mild-moderate IPD, and also as adjuncts to L-dopa therapy in patients with motor fluctuations.

Con`t…

- For younger patients dopamine agonists are preferred over L-dopa.
- Older patients are more likely to experience intolerable side effects from the dopamine agonists;
- Consequently, carbidopa/L-dopa is preferred, particularly if cognitive problems or dementia is present.
- In terms of disease-modifying effects, the clinical data with dopamine agonists are inconclusive

Con`t…

- **Common adverse effects** :
- nausea, confusion, hallucinations, light-headedness,
- lower-extremity edema, postural hypotension,
- sedation, and vivid dreaming.

Less common but serious adverse effects:

- compulsive behaviors
- psychosis,
- and sleep attacks

Con`t…

- Hallucinations and delusion can be managed using a stepwise approach
- Often involves the use of an atypical antipsychotic medication, such as clozapine or quetiapine.
- The addition of a dopamine agonist to L-dopa therapy also can increase the frequency and severity of L-dopa induced dyskinesias,
- Especially in patients with preexisting dyskinesias

Con`t…

- Pramipexole is initiated at a dose of 0.125 mg 3 times a day and
- Increased every 5 to 7 days, as tolerated, to a maximum of 1.5 mg 3 times a day.
- An extended-release pramipexole formulation is also available for once-daily administration.

Con`t…

- Pramipexole is renally excreted with an 8- to 12hour half-life.
- The initial dosage must be adjusted in renal insufficiency
- 0.125 mg twice daily for creatinine clearances of 35 to 59 mL/min
- 0.125 mg once daily for creatinine clearances of 15 to 34 mL/min

Con`t…

- Apomorphine is an injectable nonergot dopamine agonist.
- It is an aporphine alkaloid originally derived from morphine but lacks narcotic properties.
- Because of extensive hepatic first-pass metabolism, apomorphine is not suitable for oral administration and is administered subcutaneously.
- Apomorphineis also available for continuous subcutaneous infusion with minipumps.

Con`t…

- Apomorphine should not be injected intravenously.
- For patients with advanced IPD who are experiencing intermittent off episodes despite optimized therapy, administration of subcutaneous apomorphine effectively triggers an "on" response within 20 minutes.
- The effective dose ranges from 2 to 6 mg per injection, with most patients requiring approximately 0.06 mg/kg.
- Sites of injection should be rotated to avoid development of subcutaneous nodules.

Con`t…

- The metabolic pathway of apomorphine remains unknown.
- Apomorphine elimination half-life is approximately 40 minutes, and the duration of benefit can be up to 100 minutes.
- Nausea and vomiting are common side effects,
- Patients should be premedicated with the antiemetic trimethobenzamide.

Con`t…

Other side effects include :

- Dizziness, hallucinations, injection-site irritation,
- orthostatic hypotension, somnolence, and yawning.
- severe hypotension and syncope,
- Thus apomorphine is contraindicated with drugs in the serotonin (5HT3)-receptor blocker class,
- Including dolasetron, granisetron, and ondansetron.

TABLE 29–2. Management of Motor Complications in Advanced Disease[2,15,16,44–46]

I. Motor Fluctuations
- A. Suboptimal or delayed peak response
  1. Take Sinemet® on an empty stomach
  2. Use rapid-dissolving tablet (Parcopa™), crush Sinemet®, or make liquid Sinemet®
  3. Decrease dietary protein around the dose that is delayed
  4. Substitute standard Sinemet® for some of the Sinemet CR®
- B. Optimal peak but early wearing off
  1. Decrease dose and increase frequency of standard Sinemet®
  2. Substitute Sinemet CR® for some of the standard Sinemet®
  3. Add other PD medications (dopamine agonist, selegiline, amantadine, or COMT inhibitor)
- C. Optimal peak but unpredictable offs
  1. Adjust time with meals and avoid high-protein meals or redistribute the protein in meals
  2. Substitute or add rapid-dissolving tablet form or liquid form of Sinemet®
  3. Rescue with a dopamine agonist (apomorphine) given with domperidone or trimethobenzamide
  4. Sinemet® via intraduodenal tube
  5. Deep brain stimulation procedure
- D. Freezing
  1. Gait modifications (use visual cues such as walk over lines, tapping, rhythmic commands, rocking; use rolling walker)
  2. Difficult to treat so adjust current medication up or down based on other PD symptoms
  3. Treat anxiety with benzodiazepine

II. Dyskinesias
- A. Peak dose chorea
  1. Decrease risk by lowering Sinemet® dose when adding other PD medications
  2. Smaller doses more frequently (liquid Sinemet®)
  3. Decrease Sinemet® dose and add dopamine agonist
  4. Amantadine
  5. Add propranolol, fluoxetine, buspirone, or clozapine
  6. Deep brain stimulation
- B. Off period dystonia in the early morning (i.e., foot cramping)
  1. Add Sinemet® CR or dopamine agonist at bedtime if having nighttime offs
  2. Morning Sinemet® dose should be immediate-release with or without CR
  3. Selective denervation with botulinum toxin
- C. Diphasic dyskinesia
  1. Avoid controlled-release preparations; consider liquid Sinemet®
  2. Add dopamine agonist, amantadine, or COMT inhibitor
  3. Deep brain stimulation

III. Akathisia
1. Benzodiazepine
2. Propranolol
3. Dopamine agonists
4. Gabapentin

Evaluation of therapeutic outcomes

- Monitor medication administration times
- Monitor to ensure that the patient and/or caregivers understand the prescribed medication regimen
- Monitor for nonadherence and, if present, inquire for possible reasons
- Monitor and inquire specifically about dose-by-dose effects of medication
- Monitor for presence of drugs that can exacerbate idiopathic Parkinson's disease motor features

THANK U