

Objectives

- Describe the clinical progression of PD and the pharmacological treatment plan for early PD.
- Discuss the management of “off time” motor symptoms.
- Identify the advantages of atypical antipsychotic therapies in the management of Parkinson’s related
- psychosis and dementia.
- List the differences in dopamine agonist agent dosage forms that can be utilized to improve therapy.
- Explain the role of over the counter vitamins and supplements in the treatment of Parkinson’s Disease

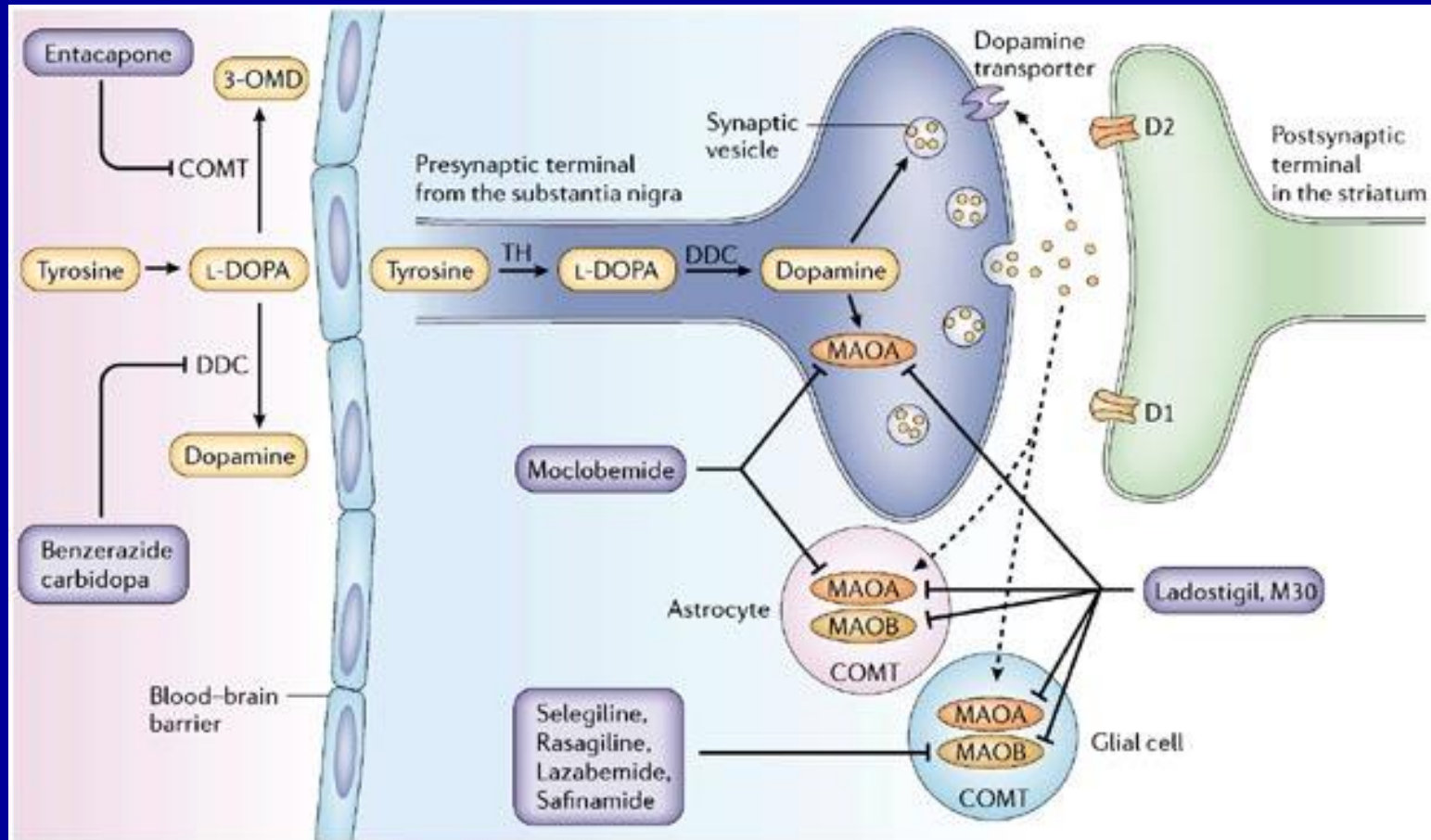
TREATMENT OF PARKINSON DISEASE

- MEDICAL
 - DOPAMINERGIC AGENTS
 - ANTI-CHOLINERGICS;
etc.
- SURGICAL
 - ABLATIVE
 - RESTORATIVE
 - D.B.S.
- PHYSICAL THERAPIES
 - P.T.
 - O.T.
 - SPEECH
 - OMT, BIOFEEDBACK
 - EXERCISE Rx, TAI-CHI
- PSYCHOTHERAPIES
 - COUNSELLING
 - SOCIAL WORK
 - MEDS., etc.

Pharmacological Treatment of Parkinson's Disease

- Goals:
 - Primary = restore dopamine receptor function.
 - Secondary = inhibition of muscarinic cholinergic receptors.
- Several types of drugs:
 - Levodopa
 - Dopamine Receptor Agonists
 - Monoamine Oxidase Inhibitors (MAOIs).
 - Catechol-*O*-Methyltransferase (COMT) inhibitors.
 - Muscarinic Cholinergic Receptor Antagonists.
 - Amantidine.

Drug Therapy



Early Parkinson's

- Initiate therapy once functional disability is present
- Decision of therapy needs to take into account
 - Predominate motor symptom
 - Physiologic age
 - Safety/efficacy of selected therapy

Tremor Predominant Disability

Muscarinic Cholinergic Receptor Antagonists.

- Muscarinic Receptors – localized to striatal neurons.
 - Mediate cholinergic tremor
 - May cause presynaptic inhibition of dopamine release.
- Trihexyphenidyl and Benztropine
 - Therapeutic Effectiveness –
 - Useful in patients administered neuroleptics as anti-dopaminergic properties of these drugs antagonize effects of levodopa.
 - Improve muscle rigidity and tremor but have little effect on bradykinesia.
 - Adverse Effects –
 - Characterized as “atropine-like” = dry mouth, inability to sweat, impaired vision, urinary retention, constipation, drowsiness, confusion.

Monoamine Oxidase Inhibitors (MAOIs)

- Two types of MAO have been characterized.
 - MAO-A – primarily metabolizes NE and 5-HT.
 - MAO-B – primarily metabolizes dopamine.
- Selegiline and Rasagiline.
 - Selective, irreversible inhibitors of MAO-B.

Selegiline or Rasagiline

- Both have been proven to be safe and effective therapies in PD. There are no head to head clinical trials.
- Selegiline has a pharmacokinetic profile which is characterized by low oral bioavailability and production of amphetamine metabolites.
- Rasagiline has demonstrated a benefit to early versus delayed start monotherapy in PD.
- Rasagiline offers advantages over the first-generation MAO-B inhibitor selegiline in its lack of tyramine reactions.
- Other benefits of rasagiline include a potential benefit on cognition hypothesized from a post hoc analysis of the TEMPO and PRESTO studies. Rasagiline long term data is derived from follow-up observation of the patients enrolled in the TEMPO trial and shows efficacy and safety for up to 6.5 years of therapy.

Adverse effects anorexia, dizziness, hyperhidrosis, insomnia, nausea, somnolence, and vomiting

Dopamine Receptor Agonists

- Pramipexole – preferential affinity for D3 receptor (also D2/D4).
 - Used primarily in patients with advanced Parkinson’s disease.
 - Possibly neuroprotective – scavenge H₂O₂.
- Ropinirole – D2 receptor agonist.
 - Effective as monotherapy in patients with mild disease.
- Rotigotine –transdermal patch stimulate dopamine receptors within the caudate–putamen in the brain
- Apomorphine – potent D1 /D2 agonist.
 - Given via subcutaneous injection to provide temporary relief of “off” periods of akinesia.
 - Short period of effectiveness (~ 2 h).
 - Associated with several side effects (i.e., dyskinesias, drowsiness, sweating, hypotension).
 - Adverse effects somnolence, edema, compulsive behaviors, hallucinations

**Bradykinesia, rigidity, tremor
(moderate/severe impairment)**

Issues to consider

- Physiologic age
- Presence of cognitive impairment
- Why?
 - Severity of adverse effects
 - Impact of age and development of levodopa related motor complications

Levodopa – Adverse Drug Effects

- Dyskinesias – occur in 80% of patients on long-term levodopa therapy.
 - Choreiform movements
 - Dose-related – higher doses = increased risk.
 - Occur more frequently in younger Parkinson’s patients.
- “On-off” Effect – fluctuations in clinical response to levodopa.
 - “Off” = marked akinesia.
 - “On” = improved mobility but marked dyskinesia.
 - Thought to be related to fluctuations in levodopa plasma concentrations.
 - Fluctuations can be “smoothed out” by incorporating a dopamine receptor agonist into pharmacotherapy.
 - Pramipexole.
 - Ropinirole.
 - Apomorphine.

1. Levodopa – Adverse Drug Effects.

- Acute side effects – related to increased peripheral concentrations of dopamine.
 - Nausea
 - Anorexia – treated with peripherally-acting dopamine antagonist (i.e., Domperidone).
 - Hypotension – particularly in patients on anti-hypertensives.
- Other common side effects:
 - Confusion.
 - Insomnia
 - Nightmares.
 - Schizophrenic-like syndrome – delusions and hallucinations due to enhanced CNS concentrations of dopamine.

Potential ways to increase levodopa effects

- Seltzer water, Parcopa
- Limit dietary protein
- Use CR formulation at bedtime
- Morning dose includes immediate release and CR forms

Catechol-*O*-Methyltransferase (COMT) Inhibitors

- Inhibition of L-aromatic amino acid decarboxylase is associated with compensatory activation of COMT.
 - Increased plasma levels of 3-OMD = poor response to levodopa (competition for active transporter in the gut and at the BBB?).
- Adjunctive therapy in patients treated with levodopa.

Catechol-*O*-Methyltransferase (COMT) Inhibitors.

- Selective COMT inhibitors – diminish peripheral metabolism of levodopa.
- May also reduce “on-off” fluctuations.
- Adverse Effects:
 - Related to increased plasma concentrations of levodopa.
 - Include dyskinesias, nausea, and confusion.
 - Other side effects: diarrhea, abdominal pain, orthostatic hypotension, sleep disorders, orange urine discoloration.
 - Tolcapone – potentially hepatotoxic.

Motor complications include

- Involuntary choreic or athetoid movements
- **Motor fluctuations “WEARING-OFF”**
- Acute dystonias
- “ON-OFF” period with rapid fluctuations
- “PEAK-DOSE”
- Diphasic dyskinesias
- Gait freezing

Strategies for treatment of motor fluctuations

- Development of peak dose dyskinesia
 - Reduce levodopa dose and dosing interval
- Reduce off time
 - add COMT inhibitor
 - add dopamine agonist
 - add MAO-B inhibitor
 - decrease levodopa dosing interval
 - consider apomorphine

APOMORPHINE	INJ,SOLN	Restricted to neurology for treatment of acute hypomobility episode of advanced Parkinson's disease.
CARBIDOPA /LEVODOPA	TAB,SA	
CARBIDOPA/LEVODOPA	TAB	-
ENTACAPONE	TAB	Neurologist treating Parkinson
RASAGILINE	TAB	Restricted to neurology, movement disorder specialist
ROPINIROLE	TAB	-
SELEGILINE HCL	CAP OR TAB	

Non Motor Symptoms of Parkinson's Disease

Cognitive impairment

- Dementia
 - R/o other causes (metabolic, structural etc.)
 - Reduce medications as much as possible
 - Consider rivastigmine, donepezil, galantamine

Orthostatic Hypotension

- Up to 60% with Advanced PD will have autonomic dysfunction
- Fludrocortisone, midodrine
- Droxidopa has orphan Drug designation gives preferential patent protection to drugs that are intended to treat disorders affecting fewer than 200,000 people in the US. It is under review for an ANDA

Psychosis, Depression

- Hallucinations
 - D/C selegiline, anticholinergics, amantadine
 - lower dopaminergic medications (agonist 1st)
 - clozapine, quetiapine
- Depression
 - serotonin uptake inhibitor, nortriptyline, NA/Serotonergic uptake inhibitors
 - Desipramine and citalopram are equally efficacious
 - Nortriptyline was proven efficacious in comparison to paroxetine extended release
 - Paroxetine and venlafaxine improve depression without compromising motor function

Urinary dysfunction

- Drugs affecting detrusor overactivity may be useful but at the cost of AE
- Botulinum injections have some evidence
- Sacral nerve stimulation

Constipation

- Colonic transit time may slow down as a result of PD
- A pilot study has shown benefit with probiotics
- PEG products may also be of benefit

Daytime drowsiness

- Improve nocturnal sleep hygiene
- Data supporting use of modafinil is conflicting
- Methylphenidate may offer some benefit but AE may out weigh benefit

Insomnia, vivid dreams

- Sleep dysfunction is considered an intrinsic part of PD and the prevalence rates range from 75 to 98% in the PD population
- Disorders of sleep may be affected by motor symptoms and dyskinesias
- Night time dosing of levodopa, dopamine agonists may help
- Comorbid conditions, such as OSA and RLS should be identified by means of polysomnography and treated with continuous positive airway pressure and dopaminergic agents, respectively. When present, depression and psychosis may be appropriately treated with the result of a consolidation of the sleep/wake cycle. Control of nocturia also may improve sleep quality.

Impulse Control

- The prevalence rates reported for ICDs are quite variable ranging from 6 to 25% and this heterogeneity might be due to methodological differences such as the measures used for screening
- Predisposition may be seen in males, have younger age at PD onset, longer duration, early disease onset, have a personal or immediate family history of alcohol–use disorders or a prior history of ICDs
- Compulsive behaviors often resolve or improve with dopamine agonist reduction, switching to a different agonist or discontinuing agonist treatment entirely
- psychoactive drugs and psychotherapy provides a secondary course of treatment

Pain

- Four different types of pain have been categorized in PD:[305] musculoskeletal (due to Parkinsonian rigidity, rheumatologic disease or skeletal deformity), dystonic, radicular–neuropathic (due to a root lesion, focal or peripheral neuropathy) and central pain.
- Dystonic pain is the one more frequently associated with motor fluctuations and the effects of dopaminergic drugs.[303] Central pain is defined as a painful, burning, stabbing, aching, itching or tingling sensations in undefined and peculiar body regions or a vague overall sensation of tension and discomfort that responds
- Tricyclic antidepressants, carbamazepine, gabapentin may provide relief

Atypical Antipsychotics

	OLANZAPINE	INJ,PWDR
	OLANZAPINE	TAB
	PALIPERIDONE	INJ,SUSP,SA
	QUETIAPINE FUMARATE	TAB
	RISPERIDONE	INJ,SUSP,SA
	RISPERIDONE	SOLN,ORAL
	RISPERIDONE	TAB
	ZIPRASIDONE	CAP,ORAL

Antidepressants

CITALOPRAM HYDROBROMIDE	SOLN,ORAL
CITALOPRAM HYDROBROMIDE	TAB
FLUOXETINE	CAP,ORAL
FLUOXETINE	SOLN,ORAL
FLUOXETINE	TAB
MIRTAZAPINE	TAB
PAROXETINE	TAB
SERTRALINE	SOLN,ORAL
SERTRALINE	TAB
TRAZODONE	TAB
VENLAFAXINE (ER)	CAP,SA/TAB, SA
VENLAFAXINE (IR)	TAB

Additional Agents

DEXTROAMPHETAMINE	CAP,ORAL
DEXTROAMPHETAMINE	CAP,SA
DEXTROAMPHETAMINE	ELIXIR
DEXTROAMPHETAMINE	TAB
METHYLPHENIDATE	CAP,SA
METHYLPHENIDATE	TAB
METHYLPHENIDATE	TAB,SA
CAFFEINE/SODIUM BENZOATE	INJ
DONEPEZIL (5MG AND 10MG ONLY)	TAB
ERGOLOID MESYLATES	TAB,ORAL
GALANTAMINE	CAP,SA
GALANTAMINE	TAB
MEMANTINE HCL	TAB
OXYBUTYNIN	TAB,SA
OXYBUTYNIN CHLORIDE	TAB

Nutraceuticals

- Patients frequently use alternative therapies and do not recognize them as medications
- Supplement products are not approved or regulated as a drug
- Mixed evidence available for common therapies

Antioxidants

- DATATOP study – tocopherol supplementation was not found to reduce the probability of requiring levodopa. It did not enhance treatment effects of selegiline
- Prevention–NHS, HPFS– neither intake of tocopherol or ascorbic acid was significantly associated with risk of PD
- A meta–analysis of studies from 1966–2005 found no beneficial effects of ascorbic acid or beta carotene

Coenzyme Q10

- Shults et al studied 80 pts with early PD. Primary outcome was UPDRS. Doses of 1200mg per day were associated with a reduced rate of motor dysfunction. Same findings were shown by Muller.
- Strijks and Horstink did not demonstrate clinically significant findings on nonstandard motor tests or UPDRS
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New Research

- Different approaches to dopaminergic delivery
- Antiglutamergic drugs
- Drugs targeting adenosine, alpha adrenergic and seritonergic receptors
- Gene therapies
- Development of neuroprotective therapies

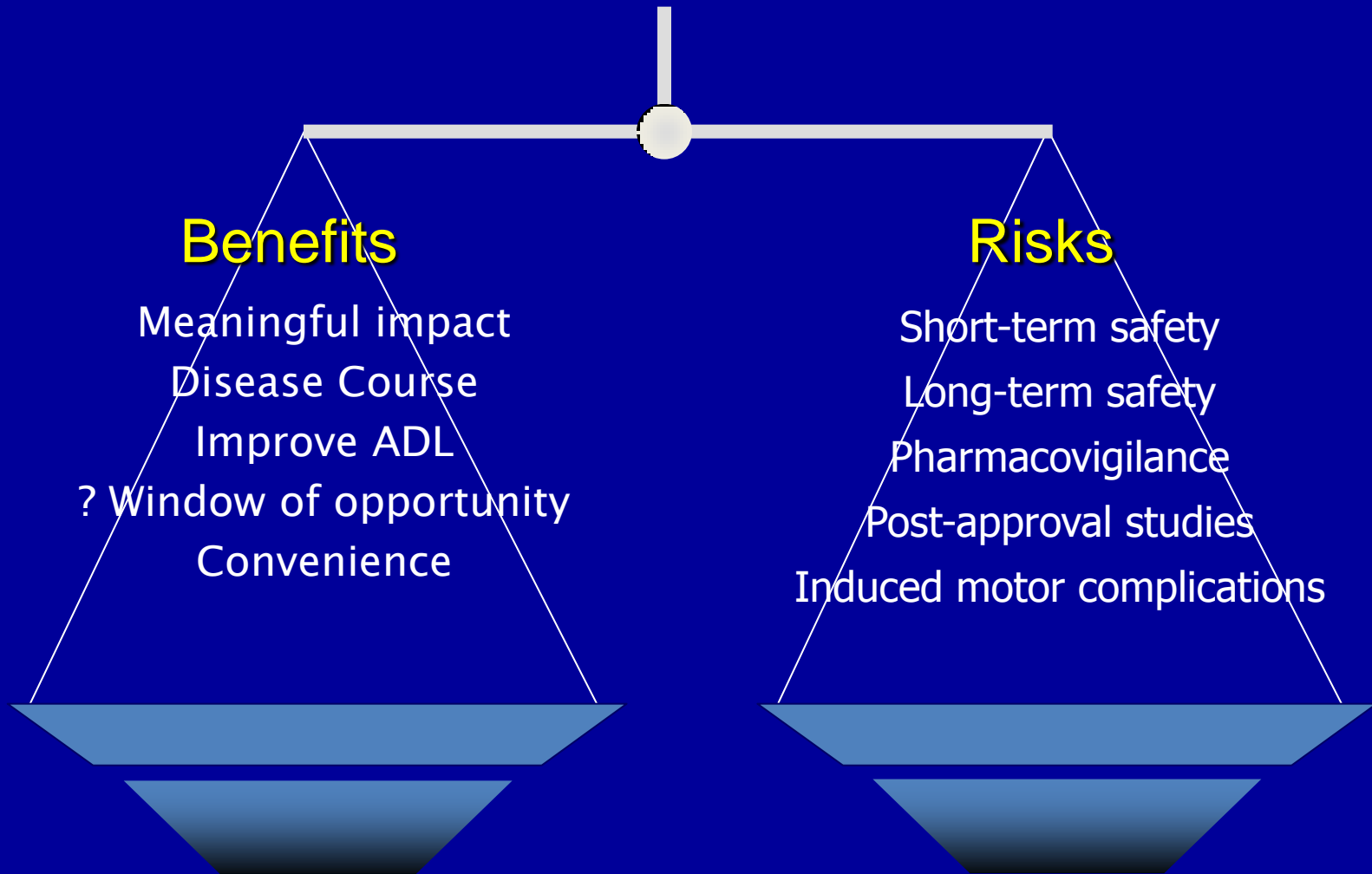
Summary– Treatment Selection

- Monotherapy with amantadine, monoamine oxidase type B (MAO–B) inhibitor or a dopamine agonist (DA) in the early stages of disease may delay the development of motor complications.
- Levodopa is the most effective therapy for treating PD symptoms. However, its use may be complicated by the development of motor dyskinesias after \pm 5 years of levodopa therapy.
- Neuropsychiatric complications are less likely with levodopa therapy than with DAs. DAs are also more likely to be associated with compulsive behaviors, excessive daytime sleepiness and sleep attacks.

Treatment–Motor Complications

- MAO–B inhibitors and catechol–O–methyl–transferase inhibitors (COMT) and DAs are effective at decreasing the motor fluctuations seen in patients treated with levodopa, once they arise.
- COMT inhibitors prolong the action of levodopa and may allow for a dose reduction which can aid in reducing motor fluctuations
- Rasagiline, DAs and COMT inhibitors may be employed to lower the dose of levodopa required on a daily basis. This may reduce the likelihood of levodopa induced dyskinesias.
- Entacapone, rasagiline (level I evidence) and selegiline are effective in reducing off time seen with levodopa therapy. Pramipexole and ropinirole have level II studies demonstrating benefit.
- Based on four level III studies, sustained release levodopa has not demonstrated a benefit in reducing off time.
- In late stage PD when off periods become frequent and unpredictable, apomorphine may be considered. The patient must be willing or have a caregiver to give the injections. Nausea may complicate therapy; however, prophylactic use of an anti–nausea agent may reduce this likelihood and is encouraged.

Treatment Decisions: Considering Benefits and Risks



Questions?