An Update on Parkinson’s Disease Treatment
An Update on Present and Future Therapies

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Overview

Cardinal Symptoms
- Bradykinesia
- Rigidity
- Tremor
- Postural Instability

Non-Motor Symptoms
- Fatigue
- Cognitive Disorders
- Hypophonia
- Depression
- Anxiety
- Constipation
How do we treat PD?

Sites of action of common therapies for Parkinson’s disease

- Tyrosine
  - Tyrosine
  - L-Dopa
  - Dopamine

- Amantadine
  - Stimulates release of DA
  - Inhibits reuptake

- DA Agonists
  - Bind to DA receptors

- MAO-B
  - Inhibits MAO-B

- Selegeline
  - Inhibits MAO-B

- COMT Inhibitors
  - Block degradation of DA and L-Dopa

- Acetylcholine Inhibitors
  - Block action of ACh in striatum
## Medical Therapies

- Carbidopa/Levodopa
- Stalevo
- Pramipexole (Mirapex)
- Ropinirole (Requip)
- Rotigotine (Neupro)
- Bromocriptine (Parlodel)
- Rasagiline (Azilect)

- Amantadine (Symmetrel)
- Selegiline (Eldepryl)
- Zydis Selegiline (Zelapar)
- Entacapone (Comtan)
- Trihexyphenidyl (Artane)
- Benztropine (Cogentin)
- Apokyn (Apomorphine)
Sinemet

- Carbidopa/ Levodopa
- L-dopa
- Levodopa
- Regular and Controlled Release
- “Active” component is the levodopa which is converted to dopamine in the brain
- Carbidopa is given to decrease nausea, vomiting and decreased blood pressure.
Levodopa

Sites of action of common therapies for Parkinson’s disease

- Tyrosine to L-Dopa
- Dopamine
- Selegeline inhibits MAO-B
- Amantadine: stimulates release of DA, inhibits reuptake
- DA Agonists: bind to DA receptors
- DA Receptors
- COMT Inhibitors: block degradation of DA and L-Dopa
- Acetylcholine Inhibitors: block action of ACh in striatum

Parkinson’s disease
Sinemet (Carbidopa/Levodopa)

- Remains far and away the best medication available for Parkinson’s disease
- Improves most motor symptoms including slowness, stiffness, resting tremors etc.
- Some non-motor symptom benefit
- Some gait improvement
Sinemet

- Levodopa induced dyskinesias
- Motor Fluctuations
  1. Wearing off
  2. Sudden offs / unpredictable offs
  3. Dose failures/ “dud pills”
Dopamine Agonists

Sites of action of common therapies for Parkinson’s disease

Tyrosine

L-Dopa

Levodopa
Inhibits MAO-B

Selegeline

DA

Amantidine

Stimulates release of DA
Inhibits reuptake

DA Agonists

Bind to DA receptors

DA Receptors

Binding

Reuptake

Degradation

MAO-B

COMT Inhibitors
Block degradation of DA and L-Dopa

COMT

Acetylcholine Inhibitors
Block action of ACh in striatum

Parkinson’s disease
Pramipexole (Mirapex)

- Good when used in combination with levodopa
- Can reduced motor fluctuations
- Lots of side effects
- Higher costs
Pramipexole Side Effects

- Somnolence – Sleep attacks
- Nausea
- Vomiting
- Hypotension
- Edema
- Impulse control disorders
- Punding
Ropinirole (Requip)

- Similar side effect profile
- Dopamine agonist
- Immediate release is dosed 5 times daily
- Available in an extended released form dosed once daily
Rotigotine (Neupro)

- Transdermal patch
- Novel delivery method
- Dosed once daily
- Avoids peaks and troughs
- Compliance improved
- Similar side effects
- Red Squares
Apokyn

- Apomorphine (injection)
- Almost immediate effect (3-5 min)
- Only works for a short time
- Particularly helpful for dose failures, morning akinesia and sudden offs
- Apokyn pump available overseas
- Lots of nausea, vomiting and hypotension
COMT Inhibitors

Sites of action of common therapies for Parkinson’s disease

Tyrosine → Tyrosine → L-Dopa → Levodopa

Levodopa Increases L-Dopa levels

Selegeline Inhibits MAO-B

Amantidine Stimulates release of DA

Inhibits reuptake

DA Agonists Bind to DA receptors

Reuptake

DA Receptors

Degradation

COMT Inhibitors Block degradation of DA and L-Dopa

Acetylcholine Inhibitors Block action of ACh in striatum

Parkinson’s disease
Entacapone (Comtan)

- COMT inhibitor
- Only works when dosed with levodopa
- Increases the availability of levodopa in the brain
- Prevents breakdown of levodopa
- Allows levodopa to last for longer time (60-90 min)
Comtan

- Helpful in motor fluctuations
- Orange colored urine and sweat
- Diarrhea
- Worsening dyskinesias
Stalevo

- Carbidopa/ levodopa/ entacapone
- Side effect profile is the same as Sinemet plus Comtan
- Combination pill
Sites of action of common therapies for Parkinson’s disease

- **Tyrosine**
  - Converts to L-Dopa
  - Enzymatically converted to Dopamine
- **Levodopa**
  - Increases L-Dopa levels
- **Selegeline**
  - Inhibits MAO-B
- **Amantadine**
  - Stimulates release of DA
  - Inhibits DA reuptake
- **DA Agonists**
  - Bind to DA receptors
  - Stimulate DA receptor binding
- **COMT Inhibitors**
  - Block degradation of DA and L-dopa
- **Acetylcholine Inhibitors**
  - Block action of ACh in striatum

**Parkinson’s disease**
Amantadine (Symmetrel)

- Previously used in early stage PD before the era of levodopa
- Helpful for levodopa refractory tremor
- Reduces dyskinesias
- Inexpensive
- Lots of side effects: confusion, hallucinations, dry mouth, fatigue, livedo reticularis rash, swelling, nightmares
MAO Inhibitors

Sites of action of common therapies for Parkinson’s disease

- Tyrosine
- Levodopa
- Amantidene
- Selegeline
- DA Agonists
- COMT Inhibitors
- Acetylcholine Inhibitors

- Increases L-Dopa levels
- Inhibits MAO-B
- Stimulates release of DA
- Blocks degradation of DA and L-Dopa
- Block action of ACh in striatum

Parkinson’s disease
MAOIs

- Selegiline, rasagiline (Azilect)
- Small improvement in the UPDRS
- Has been used for freezing
- Package insert warns of food and drinks with tyramine
- Interactions with Demerol, pseudoephedrine, dextromethorphan, halothane
- Can be helpful for motor fluctuations
- NOT NEUROPROTECTIVE
Anti-cholinergics

Sites of action of common therapies for Parkinson’s disease

- Tyrosine
- L-Dopa
- Dopamine
- MAO-B
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- DA Agonists
- Amantadine
- COMT Inhibitors
- Acetylcholine Inhibitors

Pertinent processes:
- Release
- Reuptake
- Degradation
- Binding

Notes:
- Amantadine: Stimulates release of DA
- Amantadine: Inhibits reuptake
- DA Agonists: Bind to DA receptors
- COMT Inhibitors: Block degradation of DA and L-Dopa
- Acetylcholine Inhibitors: Block action of ACh in striatum
Artane

- Tryhexyphenidyl
- Early stages seem to have best benefit
- Can be used in levodopa refractory tremor
- Lots of side effects
- Less helpful in bradykinesia and rigidity
Future Therapies

- Motor symptoms
- Non-motor symptoms
- Medicines that may slow the progression of Parkinson’s disease
- Others
Levodopa Intestinal Gel

- Duodopa
Continuous Apomorphine

- CAI
- Subcutaneous infusion of apomorphine
- No surgical PEG tube required
- Needle changed daily
- Can cause skin breakdown and abscesses
- Requires co treatment with an anti-nausea medication.
APO-GO
NeuroDerm

- Pharmaceutical Company
- Liquid Levodopa/carbidopa
- Pumps and pump – patches
- Moderate to severe Parkinson’s disease
Rytary

- IPX066 – Impax
- Extended release capsule of carbidopa/levodopa
- Meant to release slowly in small “beads” as the drug passes through the small intestine
- Has a short acting component as well
- Hopefully will “kick in quicker” and “last longer”
- Last FDA update was April 2014.
Pimvaserin

- Nuplazid
- Completed Phase III clinical trial for parkinson’s disease psychosis
- Pending application with FDA
- FDA has granted Breakthrough Therapy designation for the treatment of PDP.
- Does not worsen motor symptoms
PD01A

- Vaccine
- AFF008 Trial
- Immunotherapy vaccine against Parkinson’s disease that targets the protein alpha-synuclein.
- Vienna Austria by AFFiRiS
- Phase I – evaluate if a booster needed and then move to phase II.
Inosine

- Elevates Blood Uric Acid Levels
- Higher uric acid associated with a lower risk of PD
- Risk of kidney stones and gout
- SURE-PD
- Antioxidant
- Not yet recommended for Neuroprotection
Isradipine

- Approved by the FDA for high blood pressure
- Calcium channel blocker
- Possibly disrupts the flow of toxic chemicals into dopamine-producing cells
- Reasonably well tolerated and safe
- Symptomatic benefits NOT proven
- Neuroprotective benefits NOT proven
others

- XP 21279 – motor symptoms
- XPRO 1595 – anti-inflammatory
- CVT-301 – inhaled levodopa
- Adenosine antagonists (A2A) – motor symptoms
- Opicapone – new COMT inhibitor, once daily
- Dipraglurant – dyskinesia
- Safinamide – MAOI, CCB, NaCB
Questions