An Update on Present and Future Parkinson’s Disease 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
    - Levodopa
      - Increases L-Dopa levels
- Dopamine
  - MAO-B
    - Inhibits MAO-B
  - Selegeline
- Amantidine
  - Stimulates release of DA
  - 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

Parkinson’s disease
# 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)
Carbidopa/ Levodopa

- Sinemet or Rytary
- L-dopa
- Levodopa
- Immediate, Extended 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 → Tyrosine → L-Dopa → Dopamine

Levodopa increases L-Dopa levels

Selegeline inhibits MAO-B

Amantadine stimulates release of DA, inhibits reuptake

DA Agonists bind to DA receptors

Release → Reuptake → Degradation

DA receptors

COMT inhibitors block degradation of DA and L-Dopa

Acetylcholine inhibitors block action of ACh in striatum

Parkinson’s disease
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 – speech, cognition, mood
- Some gait improvement
Carbidopa/Levodopa

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

- 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
- “kick in quicker” and “last longer”
- Available February 2015
- 95, 145, 195, 245
Dopamine Agonists

Sites of action of common therapies for Parkinson’s disease

Tyrosine → Tyrosine → L-Dopa → Dopamine → Degradation

Levodopa Increases L-Dopa levels

Selegeline Inhibits MAO-B

Amantidine Stimulates release of DA
Inhibits reuptake

DA Agonists Bind to DA receptors

Release → DA → Reuptake → Degradation

DA Receptors

COMT Inhibitors Block degradation of DA and L-Dopa

Acetylcholine Inhibitors Block action of ACh in striatum

P...
Dopamine Agonists

- Pramipexole
- Ropinerole
- Rotigotine
- Mirapex
- Requip
- Neupro
- Aphmorphine = Apokyn Injectable

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

- Somnolence – Sleep attacks
- Nausea
- Vomiting
- Hypotension
- Edema
- Impulse control disorders
- Punding
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

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- L-Dopa
- Dopamine
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- Selegeline
- Amantidine
- DA Agonists
- COMT Inhibitors
- Acetylcholine Inhibitors

Parkinson’s disease
Entacapone & Stalevo

- 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
Amantadine

Sites of action of common therapies for Parkinson’s disease

- **Tyrosine**
  - Leads to **L-Dopa**
  - **Levodopa** increases L-Dopa levels

- **Dopamine**
  - **Selegeline** inhibits MAO-B
  - **Amantadine** stimulates release of DA, inhibits reuptake

- **DA Receptors**
  - **DA Agonists** bind to DA receptors
  - **Acetylcholine Inhibitors** block action of ACh in striatum

- **Degradation**
  - **COMT Inhibitors** block degradation of DA and L-Dopa

Parkinson’s disease
Amantadine (Symmetrel)

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

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- Stimulates release of DA
- Inhibits reuptake

Amantidine
- Stimulates release of DA
- Inhibits reuptake

Selegeline
- Inhibits MAO-B

MAO-B
- Degradation
- DA Agonists
- Binding
- Reuptake
- Degradation

COMT Inhibitors
- Block degradation of DA and L-Dopa

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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
Duopa

- Duopa
Future Therapies

- Motor symptoms
- Non-motor symptoms
- Medicines that may slow the progression of Parkinson’s disease – Disease Modifying
Disease Modifying

- Alpha-synuclein
- Neurotrophic - chloroquine and amodiaquine
- Anti-inflammatory
- Anti-oxidant
- Miscellaneous
- Tasigna – Nilotinib (PD, PDD, LBD)
PD01A

- “Vaccine “
- AFFITOPE Trial
- Immunotherapy vaccine against Parkinson’s disease that targets the protein alpha-synuclein.
- Vienna Austria by AFFiRiS
- Phase IB
- PD and MSA
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
Motor Symptoms

- levodopa
- Accordion Pill
- Carbidopa/levodopa patch
- Dyskinesia
- Postural Instability
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
Non-Motor Symptoms

- LIP – psychosis
- Dysphagia/Sialorrhea
- Cognition/ Memory
Pimvaserin

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