RECENT ADVANCES
ANTI PARKINSONIAN DRUGS

1Swetha E.S, 2Sathisha Aithal, 3Ayesha Rubina
1,3 – Postgraduates, 2 – Professor
Department of Pharmacology, SSIMSRC, Davangere
PARKINSON'S DISEASE

- Onset usually gradual, after age 50.
  (Slowly progressive)

- Mask-Like, Blank Expression
- Stooped Posture
- Pill Rolling Tremors

Bradykinesia
- Loss of normal arm swing while walking
- Blinking of the eyelids
- Loss of ability to swallow
- Blank expression
- Difficulty initiating movement

- Possible Mental Deterioration
- Depression

Tremor
- Commonly in hands and arm
- Pill rolling motion with the fingers
- Occurs most often at rest
- May involve diaphragm, tongue, lips and jaw
- Increases with stress

- Shuffling, Propulsive Gait

Muscle Rigidity
- Resistance to passive movement
- Cog wheel, jerky slow movement

- Rarely Occurs In Black Population
Brief overview

• Introduction
• Symptoms
• Causes
• Dopamine neurotransmission
• Pathological basis of pharmacotherapy
• Treatments available at present
• Advanced pharmacotherapy
Introduction

• A progressive neurological condition, resulting from the degeneration of dopamine producing neurons in the substantia nigra.

• Parkinson’s affects functional activities and many other simple or complex but familiar and routine activities

• Cumulative effect on patients, their families and the healthcare and social care systems

• An estimated 7 to 10 million people worldwide are living with Parkinson's disease.
Motor symptoms

- Forward tilt of trunk
- Reduced arm swinging
- Shuffling gait with short steps
- Rigidity and trembling of head
- Rigidity and trembling of extremities
Non motor symptoms

**Neuropsychiatric**
- Anxiety disorders
- Apathy
- Depression
- Psychosis and visual hallucinations
- Dementia

**Autonomic disturbance**
- Urinary dysfunction
- Constipation
- Sexual dysfunction
- Orthostatic (postural) hypotension
- Weight loss
- Dysphagia
- Hyperhidrosis
- Sialorrhoea

**Sensory disturbance**
- Pain
- Olfaction

**Sleep disturbances**
- Nocturnal non-motor symptoms
  - (RLS, REM, RBD).
- Excessive daytime sleepiness
What causes Parkinson’s?

- Genetic factors
- Environmental factors
  - MPTP, use of herbicides and pesticides
- Mitochondrial dysfunction and oxidative stress
- Ubiquitin-proteasome system
- Parkinsonism
Dopamine neurotransmission
Parkinson's disease
Available treatments

**Dopaminergic therapy**
- **Dopamine replacing therapy**
  - Levodopa along with dopa decarboxlase inhibitors
- **Dopamine agonists**
  - Ergot derivatives
    - Bromocriptine, pergolide
  - Non ergot derivatives
    - Pramipexole, ropinirole, lisuride, cabergoline, rotigotine
- **Dopamine releasing drug**
  - Amantadine

**Monoamine oxidase inhibitors**
- Selegeline, rasageline
# Available treatments

## Anticholinergics

- Procyclidine, trihexphenydyld, benztropine, bipiriden

## Non motor symptoms

- **Dementia** – memnatine and galantamine
- **Orthostatic hyptension** – midodrine, fludrocortisone
- **Depression** – venlafaxine, paroxetine, duloxetine
- **Psychosis** – clozapine

## For motor complications

- Oral or transdermal dopamine agonists
- **Monoamino oxidase inhibitors**
- **COMT inhibitors**
  - Entacapone, tolcapone
- **Apomorphine**: to reduce the off phenomenon
- **Amantadine**
Advanced pharmacology

Medicines in Development For Parkinson’s Disease

- Application Submitted
- Phase III
- Phase II
- Phase I

23

Parkinson’s Disease
Diagnosis
Related Conditions

11
Newer targets

- Stem cell therapy
- Neuroprotective factors
- Neuroprotective agents
- Alpha 2 receptor
- Glutamate receptor
- Adenosine receptor
- Serotonin
- Miscellaneous
- Gene therapy
- Protein and enzymes
Gene therapy

• AADC – codes for 1-aminoacid decarboxylase
  • preclinical: direct administration into brain- ↑DA synthesis

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARK 1,4</td>
<td>α- synuleicin – death of dopaminergic neurons</td>
</tr>
<tr>
<td>PARKIN</td>
<td>Ubiquitin ligase - translates to a protein helping in the breakdown of recycled proteins</td>
</tr>
<tr>
<td>DJ-1,</td>
<td>mitochondrial protein – protection from oxidative stress</td>
</tr>
<tr>
<td>PINK</td>
<td></td>
</tr>
<tr>
<td>LRKK-2-</td>
<td>disease-modifying pathways</td>
</tr>
</tbody>
</table>

GBA gene

GM-1 ganglioside – cell growth, development and repair- preclinical:

• AT2101 – 1st generation pharmacological chaparone - - improved motor function, stopped inflammation in the brain and reduced levels of alpha-synuclein

• CERE-120 - Adeno-associated virus (AAV) that was engineered to carry the human gene for neurturin - phase1/2
Proteins

α-synuclein - sticky protein that clumps in the cells of people with Parkinson’s disease.

• Vaccine
  • copolymer-1 – modifies the behaviour of the supporting glial cells
  • PD01A – induction of antibodies against alpha-synuclein accumulation, phase 1: success.

• Antibody – binds to defective proteins - effective in preclinical studies.

• NPT200-11- α- synuclein stabilizer – binds to defective protein: reduces neuinflammation and neurodegeneration. Effective in preclinical studies, dose was also found to be safe. It could prevent the progression

• GM608 - endogenous human embryonic stage neural regulatory and signaling peptide - controls the development, monitoring and correction of the human nervous system – phase 2
Nerve growth factors

• MM – 201 – a small molecule activator of neurotrophic factor, a blood brain barrier permeant, potently neurotrophic and neuroprotective, and capable of reversing cognitive and motoneuron deficits.

• GDNF- glial cell derived neurotrophic factor
  • Halts the degeneration and helps in repair of brain cells
  • Currently 2 studies PHASE1
    • Chronic administration directly to brain
    • Implantation under the skin

• Other neurotrophic targets studied
  • NT-4: neurotropin 4 – protection from oxidative stress in cell culture
  • FGF-2: fibroblast growth factor- defect led to defective DA neurons- long term survival in preclinical studies
  • BDNF – brain derived neurotrophic factor – increased DA neuron survival
Neuroprotective agents

- **NET – PD** (Neuroprotection exploratory trials) funded by NIH
- **Co-enzyme 10** – ubiquinone, cofactor in electron transport chain
- **GP-1485** - novel neuroimmunophilin-ligand – antiinflammatory
- **Creatine** a nutritional supplement, Creatine is effective in improving mitochondrial function
- **Minocycline** – caspase inhibitor, also inhibits the iNOs - important for apoptotic cell death – set for Phase3.

- **Rofecoxib** – prevented 50% degeneration of dopaminergic neurons in mouse model
Neuroprotective agents

• **Isradepine** – CCB- Calcium entry through LTCCs in SNc DA neurons measurably increases oxidation of mitochondrial matrix proteins likely contributing to accelerated cell death - **STUDY- PD**, Phase3

• **Inosine** – **SURE-PD** – phase2

• **Exenatide** has beneficial effects on nerve cells when tested in the laboratory - Phase 2

• **Pioglitazone** – **FS-ZONE** study – phase 2
Adenosine

- Adenosine A2A receptor - concentrated in the motor control part of the brain that is most affected in PD
- Antagonistic interaction between adenosine and dopamine

- Istradefylline – phase 3
- Tozadenant – phase 3
  - mGluR5 receptor antagonist

- Fipamezole – phase 1, SCH-420814, BIIA-014, Lu AA4707 and V81444 - Phase 2
  - Also an α₂ antagonist
  - NE – facilitates DA neurotransmission, deficiency – non-motor symptoms
Glutamate

- Oxidative stress
- Degeneration of dopaminergic neurons
- Glutaminergic neurons become overactive
- Excitotoxic
- Acceleration of neurodegeneration
  Also causes dyskinesia in levodopa treated patients

AMPA
- Telampanel – phase 1&2
- Perampanel phase 2
- Riluzole – phase 2

• LY300164 - Metabotropic receptor (mGlu receptor) modulators
  • AFQ056 –

NMDA
- Dextromethorphan – phase 2
- Pramipexole
- Remacimide – phase 1

• FP0011 - small molecule glutamate release inhibitor in Phase 2
Nicotine

- Stimulation of nicotinic receptors and the release of dopamine in the striatum

- Neuroprotective
  - Preserve nigral neurons - may help improve memory loss and cognitive impairment
  - modulate the entry of calcium into cells - increases the amount of intracellular calcium - appears to improve cellular survival
  - Nicotine may have an antioxidant effect

- Transdermal nicotine patch – NICOPARK2 - phase 2
- NP002 – oral capsule phase 2
- SIB-1508Y - centrally acting, selective neuronal nicotinic acetylcholine receptor agonist - motor and cognitive benefits (RETEST-PD- phase 1)
Miscellaneous

• Hormones
  • Testosterone deficiency is seen in 20-60% of men above 60 years – may contribute for non motor symptoms
    • TEST – PD : phase2
  • Evidence indicates - higher risk for low bone mineral density - contribute to increased fractures compared to healthy subjects
    • Vitamin D - Phase 2 (in bone loss)
    • POETRY – estrogen replacement therapy - Phase 2

• EMD 128130 inhibits the function of serotonin, a chemical messenger thought to regulate dopamine release - Phase 2
Miscellaneous

- **Dalfampridine** - potassium channel blocker for gait impairment - Phase I/II

- AVE8112 – PDE 4 inhibitor – procognitive phase 2

- AZD3241 - Myeloperoxidase inhibitor phase 2

- Vatiquinone - oral small molecule targeting NAD(P)H dehydrogenase quinone that augments endogenous glutathione biosynthesis - phase 2
Stem cell therapy

• Grafting the fetal derived dopanergic tissue- increase dopamine production in the brain

• Mouse progenitor cells- induction of cells which has neuron like properties

• The transplanted dopamine neurons improved the performance of mice and rats in motor function tests for Parkinson’s.

• Stem cell derived from the bone marrow of the patient will be stereotactically transplanted in the striatum – phase 1

• Embryonic stem cell directly to brain

• Oligodendrocyte progenitor cell culture project - phase 2
  • Pyramidal cells, oligodendrocyte, and dopaminergic neuron differentiation protocol/projects
Phase IV trials – non motor symptoms

- Levetiracetam – SV2A inhibitor – dyskinesia
- Rasageline, MAO inhibitor is studied along with dopamine agonists
- Naltrexone - impulse control disorder
- Rivastigmine – improve cognition and dementia
- Lubiprostone – constipation
- Donepezil – dementia

Recent approval
- Droxidopa – orthostatic hypotension
- Ioflupane I 123 injection - first diagnostic imaging agent for evaluation of neurodegenerative movement disorders
Drugs that belong to currently approved class

- **Dopamine facilitator** - levodopa
  - Continuous infusion therapy: phase 1, inhalation – phase 2
- **MAO inhibitor** –
  - Safinamide – increase on and reduces off phase
- **Dopamine agonists**
  - Pardoprunox – partial dopamine agonist - phase 3 (dyskinesia)
  - aplindore, and transdermal lisuride – phase 2
  - Rotigotine extended release formulation
- **COMT inhibitor**
  - Nebicapone
  - Opicapone : phase 3
- **OS-320** - amantidine extended release preparation
Trials for non motor symptoms

- Pimavanserin - 5-HT2A receptor inverse agonist – psychosis – phase 3
- Quittiapine
- Clozapine – PSYCLOPS trial
- Pitolistant – first H3 inverse agonist to be introduced - tonic control of histamine release, The procognitive activity
  - Phase 3
- RM131- MOVE PD- constipation
- Acamprosate
- Lezabepide – MAO inhibitor – phase2
- Atomoxetine – ATM-cog – improve cognition, antidepressant
FDCs under trial

- Introdudenal levodopa/carbidopa gel – DUODOPA
- levodopa/carbidopa extended release
- pramipexole/rasagiline
- Newer delivery system
  - Transdermal – dopamine agonists
  - Intraduodenal – levodopa/carbidopa
  - Intranasal – levodopa
  - Amantadine - extended release
Summary

• The average age of onset of the disease is 60, with incidence increasing significantly with age. About 5 percent to 10 percent of people have “early-onset”

• The cost to the economy in direct and indirect expenses is more than $14 billion a year

• A gene therapy that targets the part of the brain that controls movement
• Receptors as new targets found in the brain where degeneration and abnormality are often seen
• New delivery mechanisms, new FDCs

• 43 active clinical trials
References

• Qayyum A. ETIOLOGY AND PATHOPHYSIOLOGY OF PARKINSON’S DISEASE.

THANK YOU