RECENT ADVANCES

ANTI PARKINSONIAN DRUGS

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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

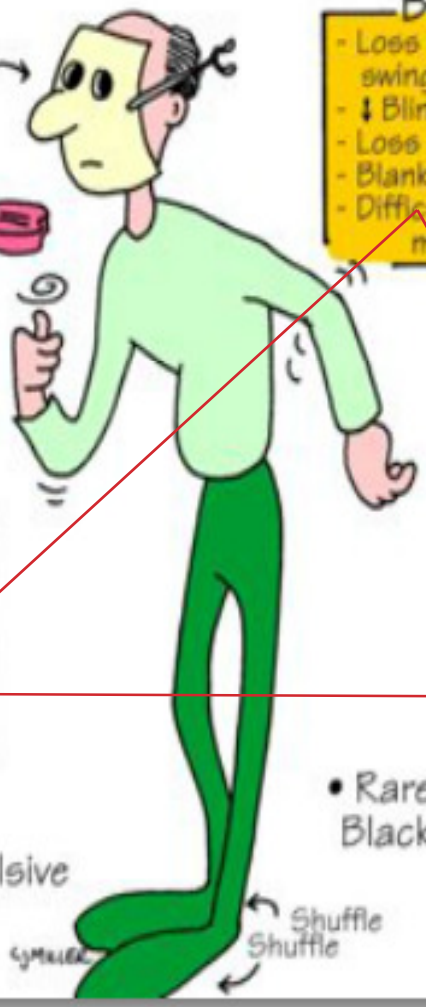
- Possible Mental Deterioration
- Depression

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

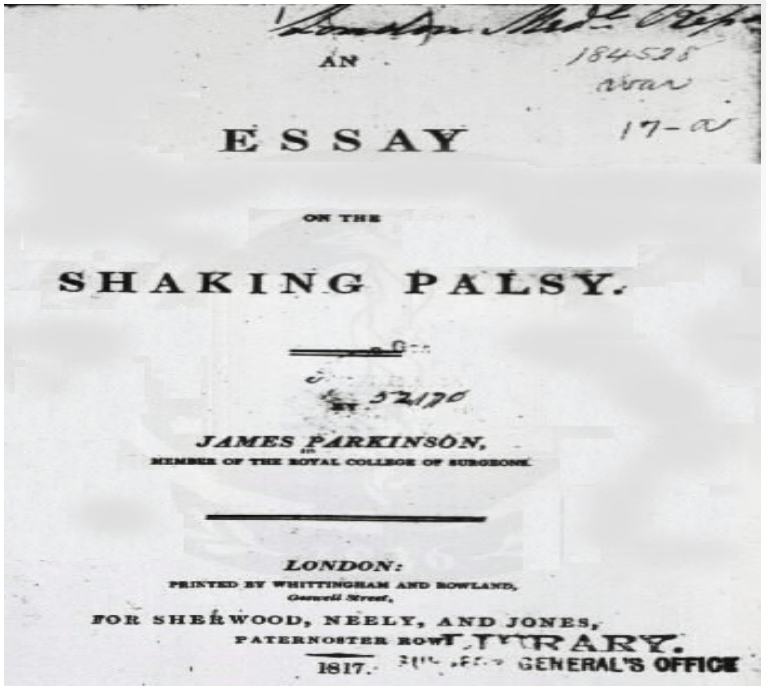
Muscle Rigidity
- ↑ Resistance to passive movement
- Cog wheel, jerky slow movement

- Rarely Occurs In Black Population

- Shuffling, Propulsive Gait



Brief overview



AN

ESSAY

ON THE

SHAKING PALSY.

JAMES PARKINSON,

LONDON:

FOR SHERWOOD, NEELY, AND JONES,

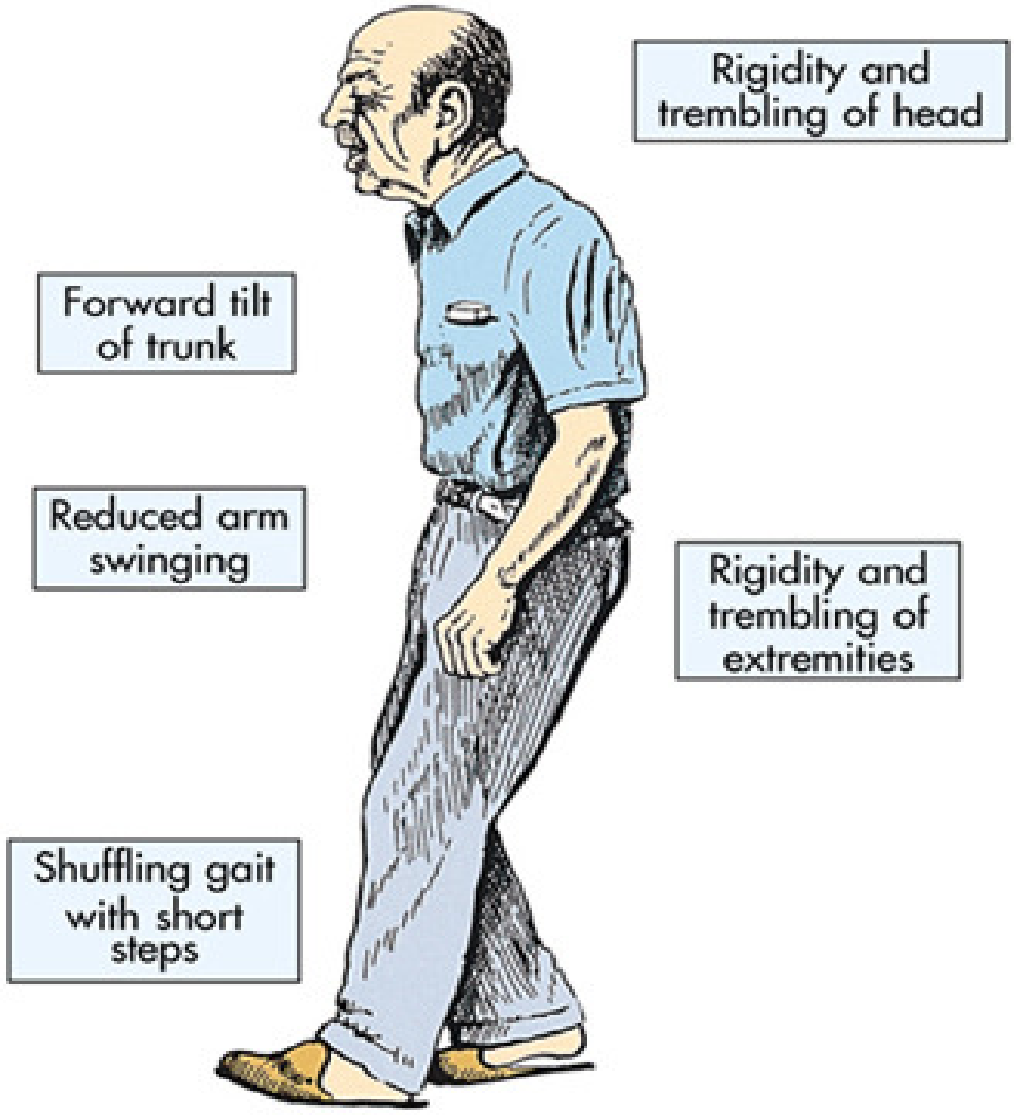
1817.

- 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





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

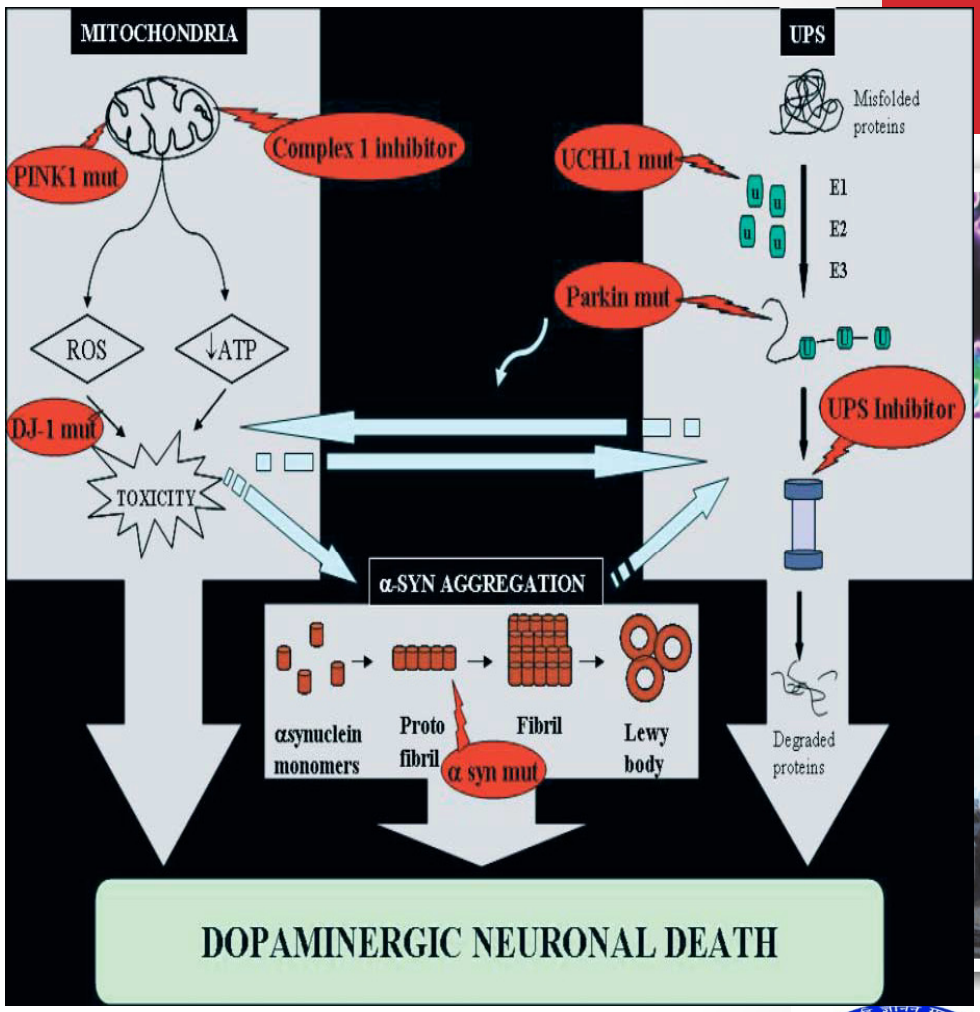
- Pain
- Olfaction

Sleep disturbances

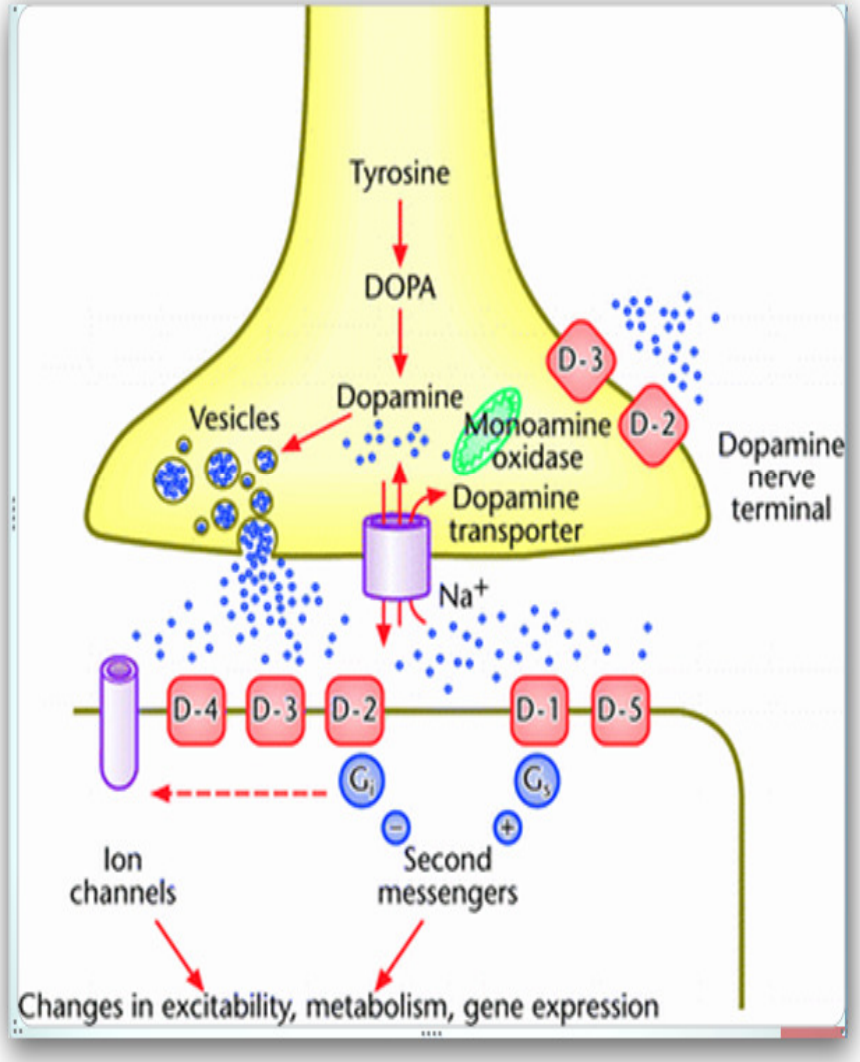
- Nocturnal non-motor symptoms
  - (RLS,REM, RBD).
- Excessive daytime sleepiness

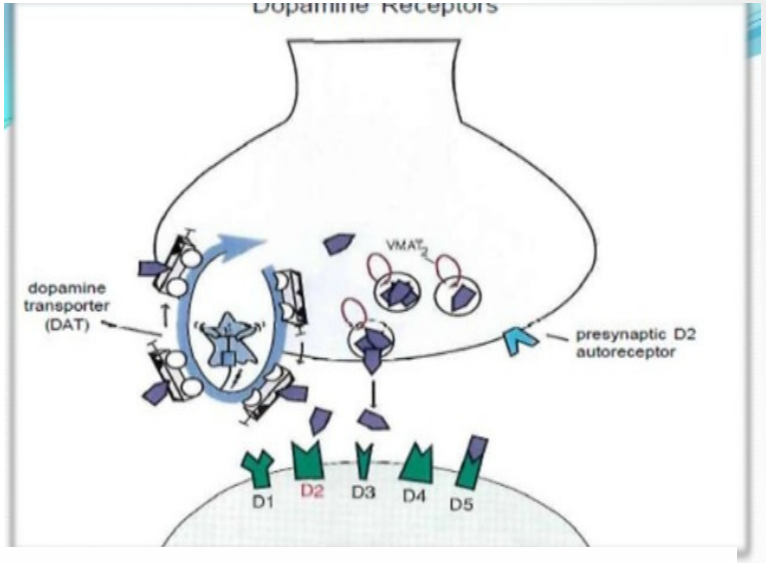
What causes Parkinson's?

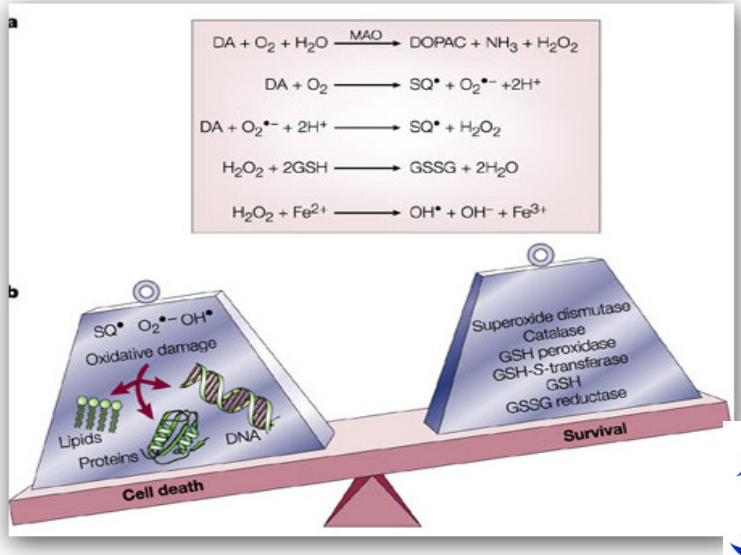
- Genetic factors
- Environmental factors
  - MPTP, use of herbicides and pesticides
- Mitochondrial dysfunction and oxidative stress
- Ubiquitin-proteasome system
- Parkinsonism



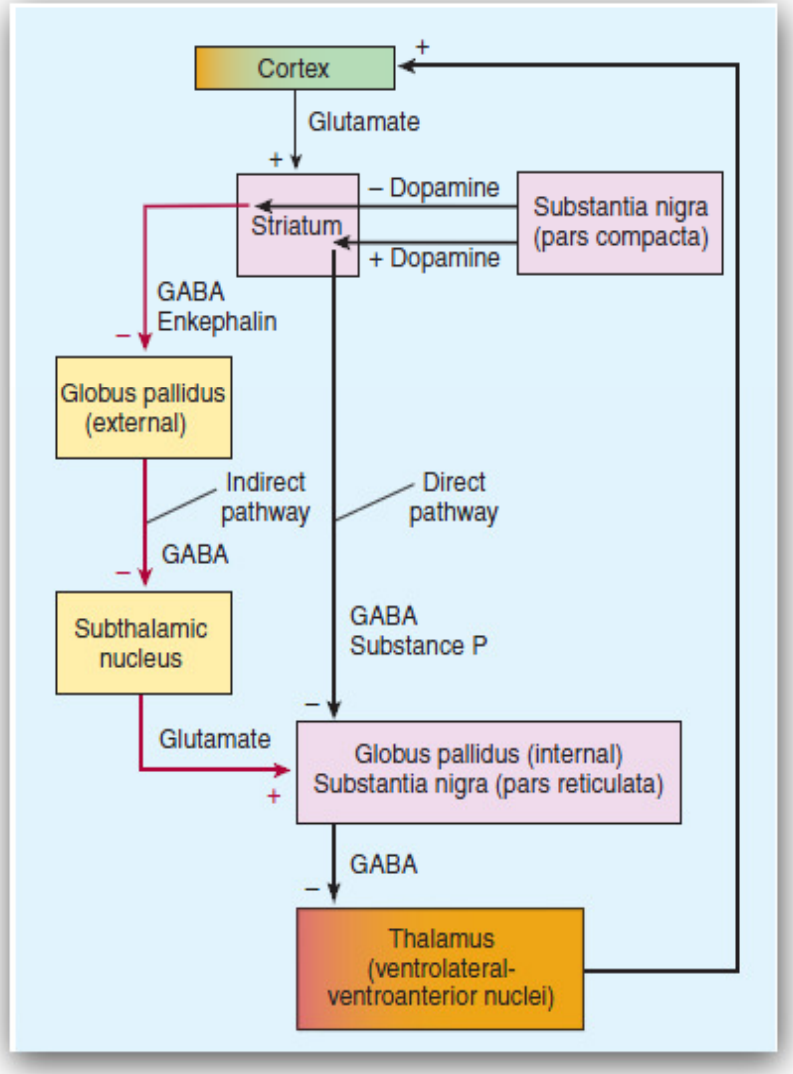
Dopamine neurotransmission

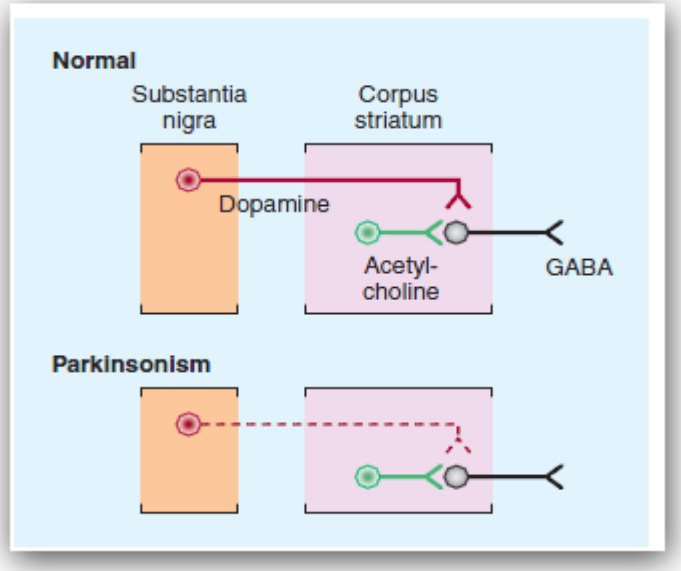


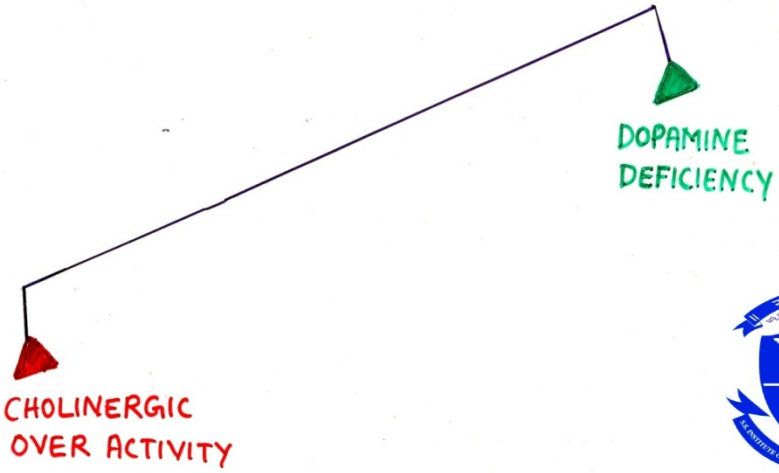




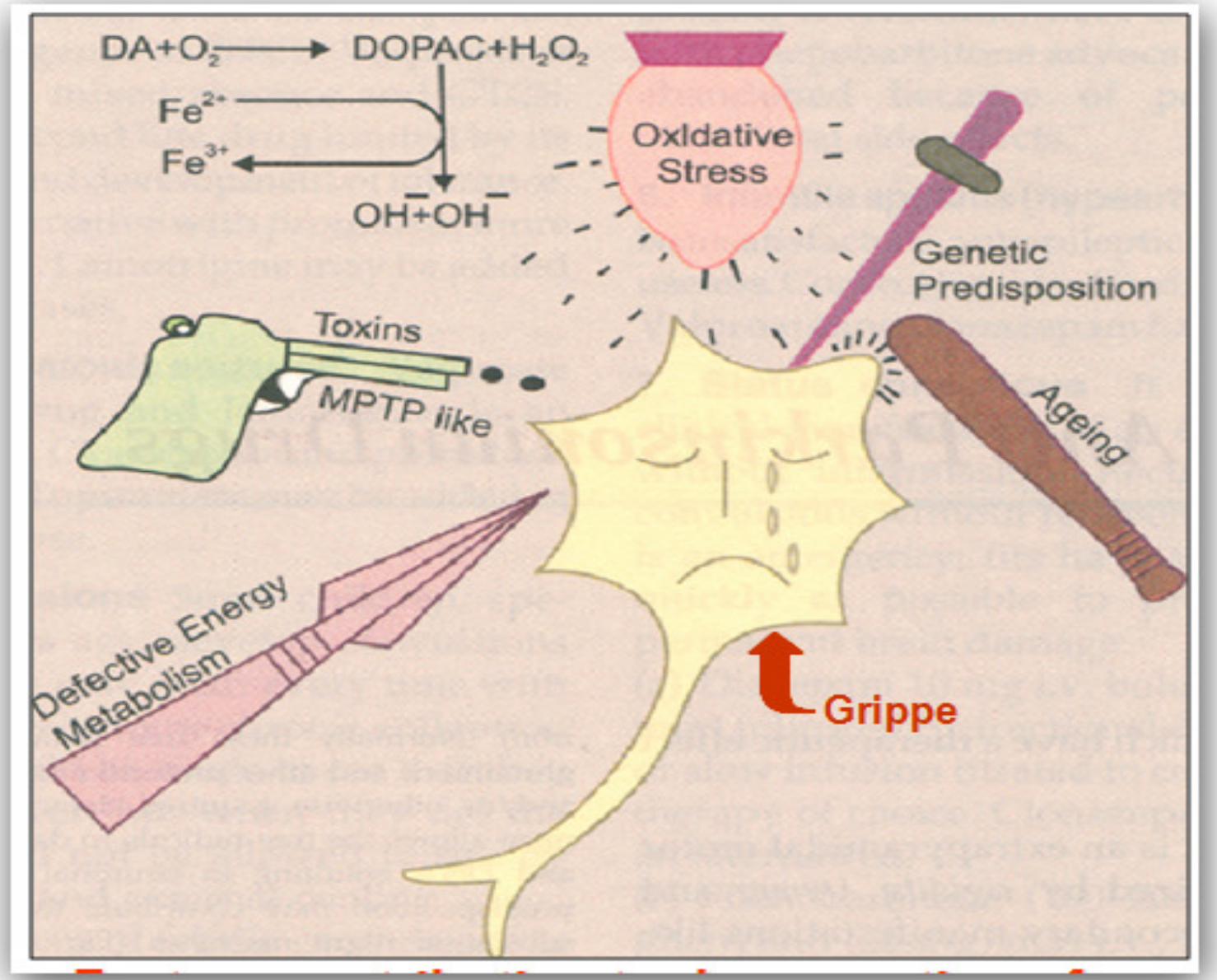
Parkinson's disease







ssms


DA+O2 → DOPAC+H2O2
Fe2+
Fe3+
OH+OH
Oxidative Stress
Genetic Predisposition
Toxins
MPTP like
Ageing
Defective Energy Metabolism
Grippe

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

Monoamino oxidase inhibitors

- Selegeline, rasageline

Available treatments

Anticholinergics

- Procyclidine, trihexiphenydyl, 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

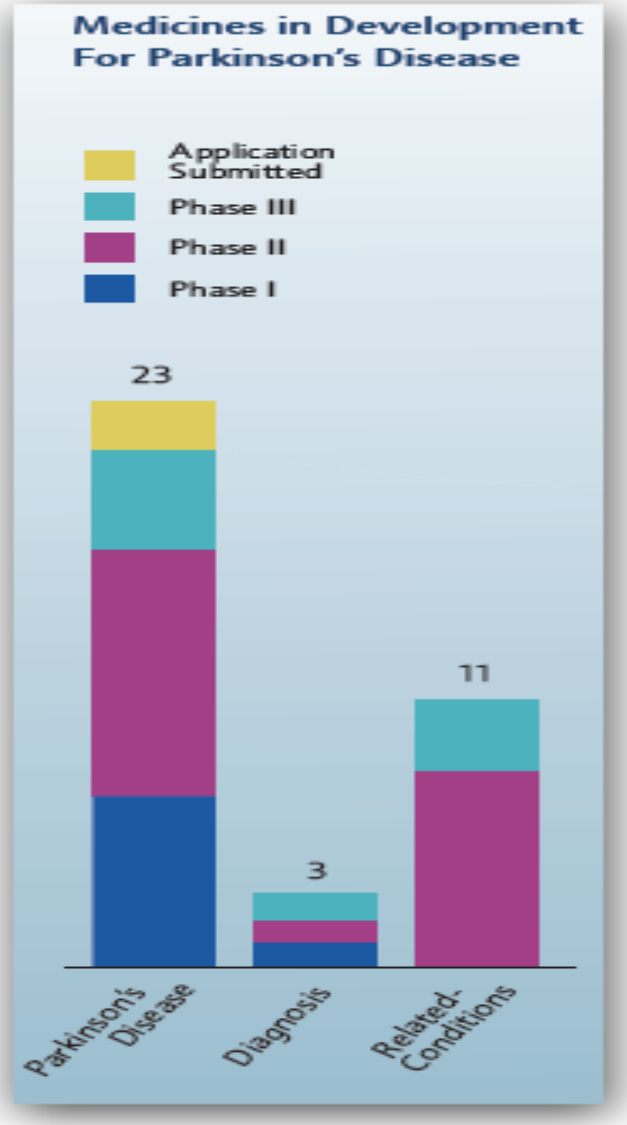
•Monoamino oxidase inhibitors COMT inhibitors

Entacapone, tolcapone

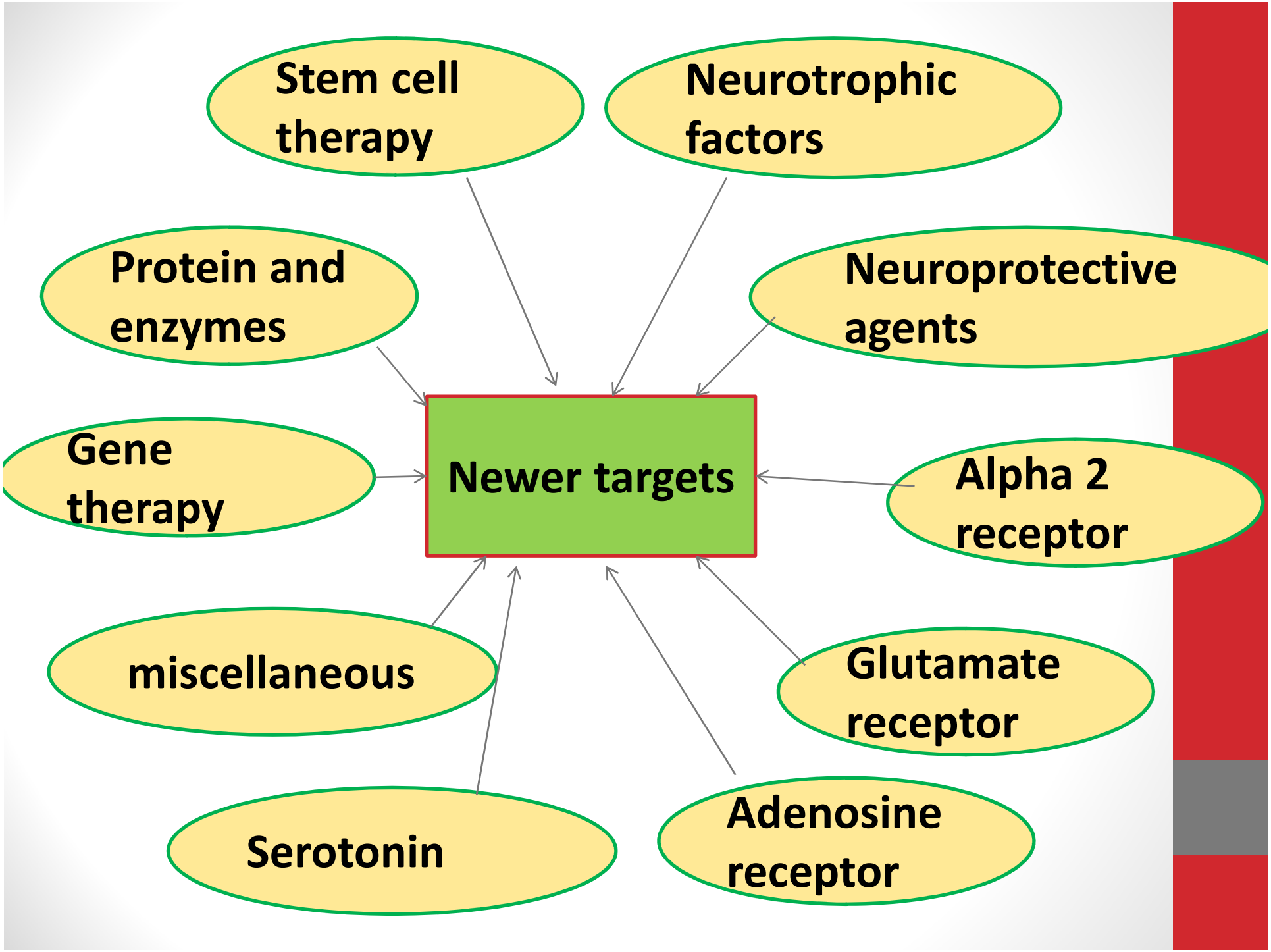
•Apomorphine : to reduce the off phenomenon

•Amantadine

Advanced pharmacology






Stem cell therapy
Neurotrophic factors
Protein and enzymes
Neuroprotective agents
Gene therapy
Newer targets
Alpha 2 receptor
miscellaneous
Glutamate receptor
Serotonin
Adenosine receptor

Gene therapy

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

Gene	Function
PARK 1,4	α- synuleicin – death of dopaminergic neurons
PARKIN	Ubiqutin ligase - translates to a protein helping in the breakdown of recycled protiens
DJ-1, PINK	mitochondrial protein –protection from oxidative stress
LRKK-2-	disease-modifying pathways

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-synuleicin - 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, phase1: success.

- Antibody – binds to defective protiens - effective in preclinical studies.

- NPT200-11- α- synuleicin 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 a signaling peptide - controls the development, monitoring and correction 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 suplement, 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 dopaminerg 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 – phase1, SCH-420814, BIIA-014 , Lu AA4707 and V81444 - Phase 2
  - Also an $\alpha_2$antagonist
    - NE – facilitates DA neurotransmission, deficiency – no motor symptoms

Glutamate

Oxidative stress

↓

Degeneration of dopaminergic neurons

↓

Glutaminergic neurons become overactive

↓

Excitotoxic

↓

Accleration 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 – phase2
- 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 -** phase2
- **NP002** – oral capsule phase 2
- **SIB-1508Y** - centrally acting, selective neuronal nicotinic acetylcholine receptor agonist - motor and cognitive benefits (RETEST-PD- phase 1)

Miscellaneous

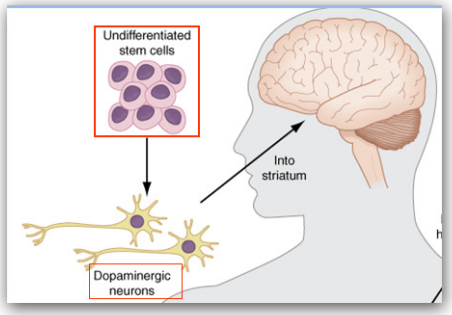
- Hormones
  - Testesterone deficiency is seen in 20-60% of men above 60years – may contribute for non motor symptoms
    - TEST – PD : phase2
  - Evidence indicates - higher risk for low bone mineral density - contribute to increased fractures compared to healthy subjects
    - Vitamin D - Phase 2 (in 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 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 inhibiotor – 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
- loflupane 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: phase1, inhalation – phase 2
- MAO inhibitor –
  - Safinamide – increase on and reduces off phase
- Dopamine agonists
  - Pardoprunox – parial 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
- Quitiapine
- 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

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THANK YOU

