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RECENT TRENDS AND ADVANCES USED IN THE PARKINSON'S DISEASE

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BRIEF SUMMARY OF PARKINSON'S DISEASE

Parkinson's disease

The other names of this disease are **"Primary parkinsonism, paralysis agitans, idiopathic parkinsonism, shaking palsy"** and in ayurveda it is referred to as **Kampavata** as Kampa means tremor in Sanskrit.

Definition

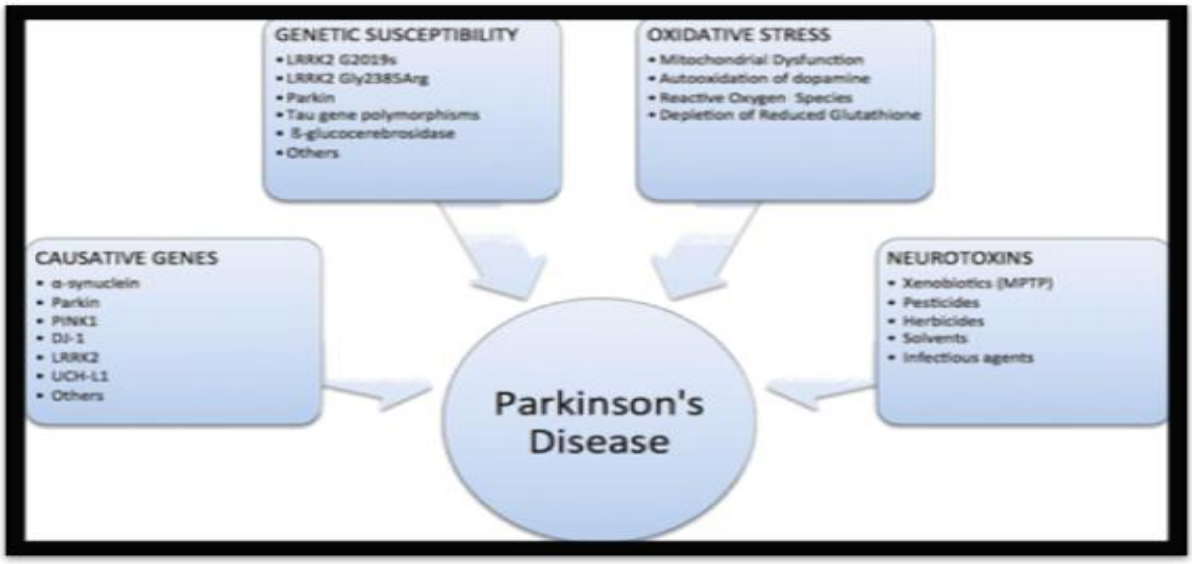
The Parkinson's disease is a long term progressive type of neurodegenerative disorder of the central nervous system that mainly affects the motor system

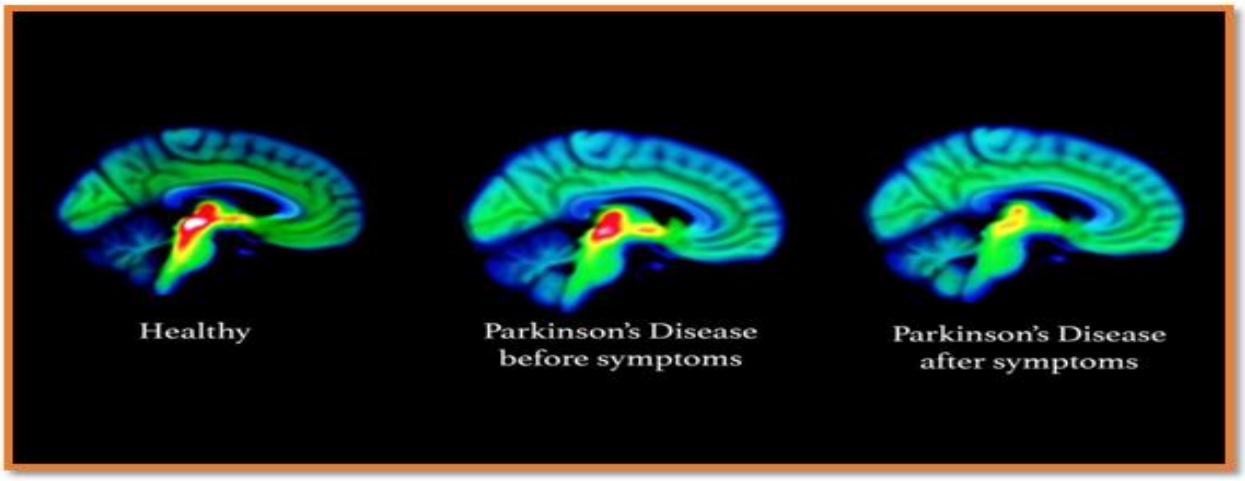
The **Epidemiology** of the parkinson's disease is among 1,00,000 population about 4.5 to 21 cases are estimated per year

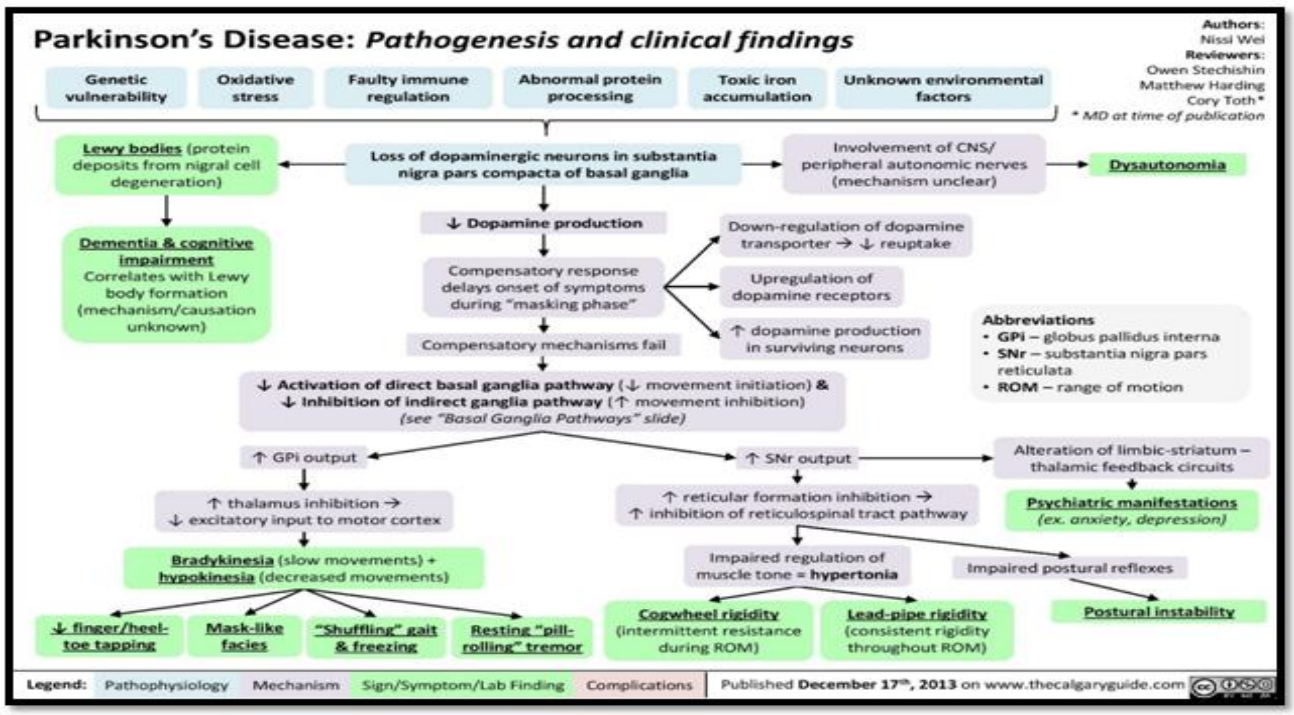
- Nearly 1 million will be living with parkinson's disease in US by 2020
- In India there is a crude type of prevalence rate of 14.1 rate in 1,00,000 among the kashmir population in North India
- It is increasing by the advance age present in 1% of the people with age over 65 years
- Early onset PD will be starting at age range of 40 years and it is of 3 to 5 % cases and juvenile occurring before age 21 years and young onset of age 21-40 years
- More than 10 million worldwide are living with PD
- Men are 1.5 times more likely to have Parkinson's disease than women.

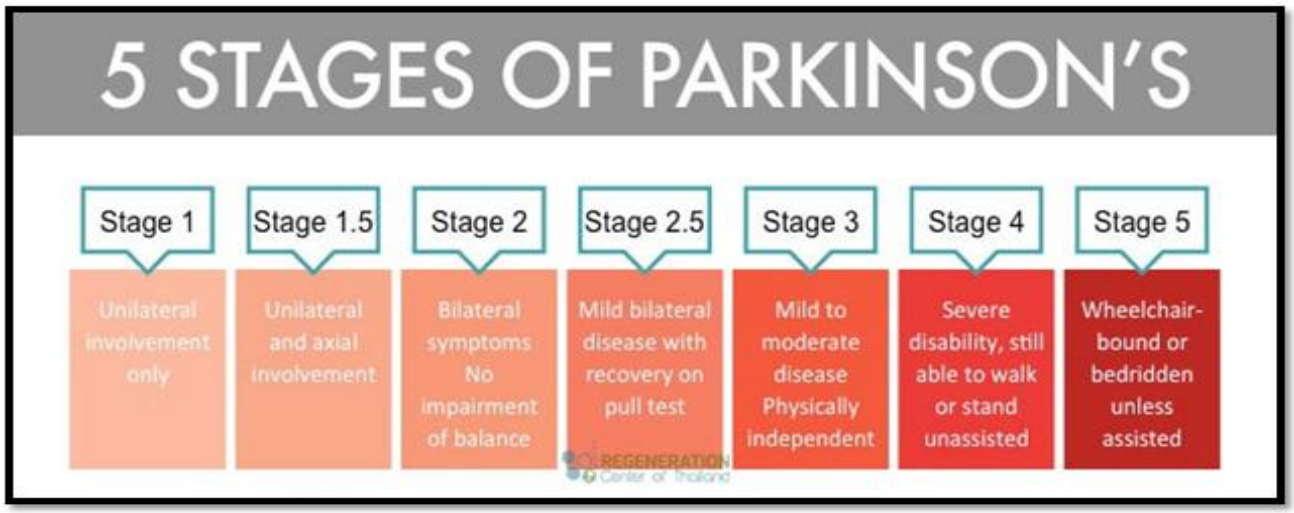
Etiology

There are genetical and environmental types of causes but mostly cause will be loss of dopaminergic neurons of substantia pars nigra, presence of lewy bodies , autoimmune factors etc.,









Risk factors for parkinson's disease

The risk factors for parkinson's disease are

1. Age
2. Sex
3. Heredity
4. Exposure to chemicals and toxic metals like herbicides , fungicides , agent orange , mercury , bismuth , lead , aluminium , iron , copper etc.,
5. History of head trauma and smoking
6. Drugs or medication like synthetic heroin etc.,

The Diagnosis is based upon the view of signs and symptoms , medical history , physical examination , neurologic examination , blood and other lab tests , MRI , PET scan , ultrasound of brain and in most cases a **SPECT**scan i.e., single photon emission computerized tomography scan called as dopamine transporter scan [**Dat scan**] is done but mostly the physical examination , neurological examination and signs and symptoms will tell the proper diagnosis rather if the scans are suggested

TREATMENTS USED IN PARKINSON'S DISEASE

The goals of PD treatment are to minimize symptoms, disability and side effects while maintaining the quality of life

Education of patients and caregivers, exercise and proper nutrition are essential

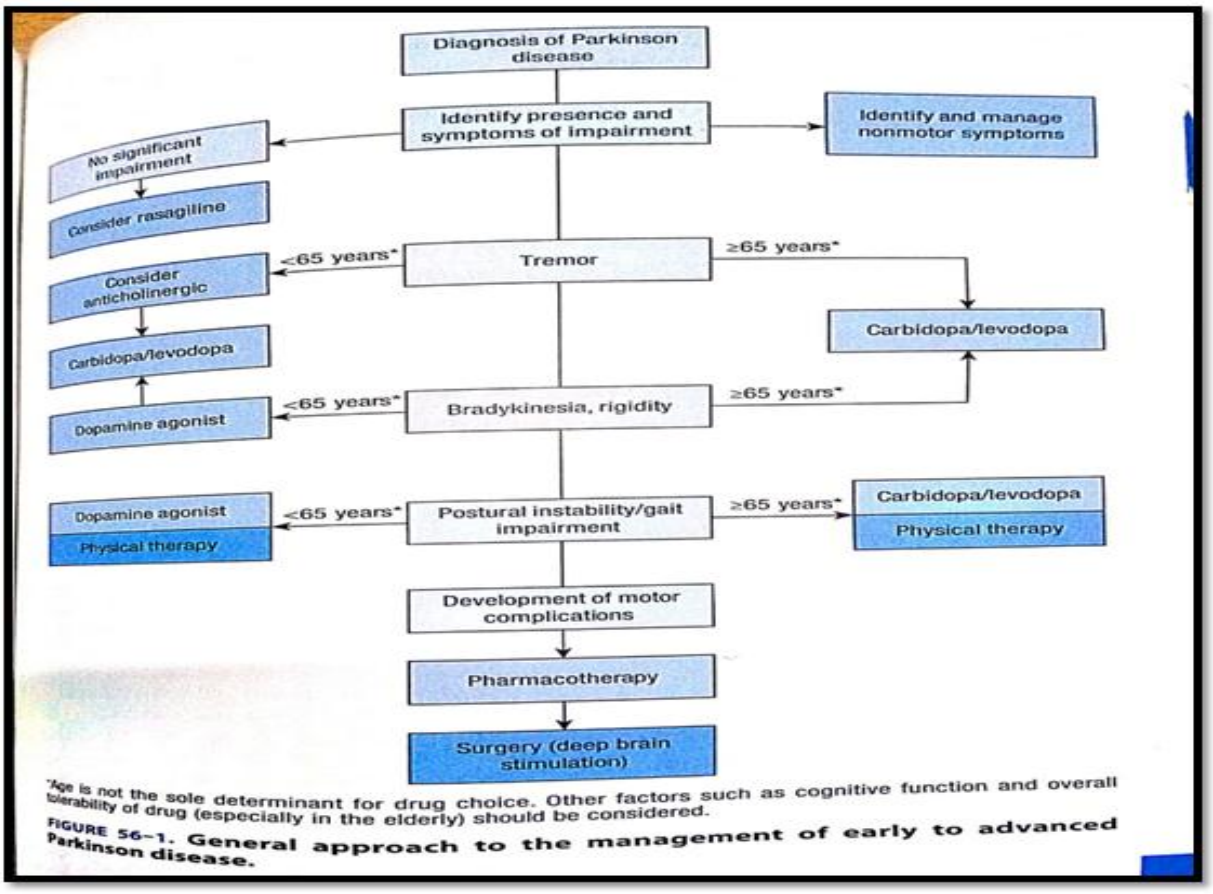


FIGURE 56–1. General approach to the management of early to advanced Parkinson disease.

The above diagram is the algorithm for management of early to advanced PD and their doses are given below at **Fig no 2**

- **Anticholinergic drugs** can improve tremor and sometimes **dystonic** [involuntary muscle movements] features , improve bradykinesia or other disabilities and patients with pre existing cognitive deficits and elders are at a greater risk for central anti cholinergic side effects
- **Amantadine** provides most benefits for tremor,rigidity,bradykinesia and mostly used for **L-Dopa induced dyskinesia** and it's doses should be reduced in **renal dysfunction patients with creatinine clearances** and for **haemodialysis patients** i.e., **[100 mg/day with creatinine clearance of 30-50 ml/min (0.50-0.84 ml/s) , 100 mg every other day for**

creatinine clearances of 15-29 ml/min (0.25-0.49 ml/s) and 200 mg every 7 days for creatinine clearance less than 15 ml/min (0.25 ml/s)] and **Livedoreticularis** [a diffuse mottling of skin in upper or lower extremities] is a common but reversible side effect

TABLE 56–2 Dosing of Drugs Used in Parkinson Disease[a]

Generic Name	Trade Name	Starting Dose[b] (mg/day)	Maintenance Dose[b] (mg/day)	Dosage Forms (mg)
Anticholinergic drugs				
Benztropine	Cogentin	0.5–1	1–6	0.5, 1, 2
Trihexyphenidyl	Artane	1–2	6–15	2, 5; 2.5 mL
Carbidopa/Levodopa products				
Carbidopa/L-dopa	Sinemet	300[c]	300–2000[c]	10/100, 25/100, 25/250
Carbidopa/L-dopa ODT	Parcopa	300[c]	300–2000[c]	10/100, 25/100, 25/250
Carbidopa/L-dopa CR	Sinemet CR	400[c]	400–2000[c]	25/100, 50/200
Carbidopa/L-dopa IR/ER	Rytary	435[c]	435–2450[c]	23.75/95, 36.25/145, 48.75/195, 61.25/245
Carbidopa/L-dopa enteral suspension	Duopa	1000[c]	1000–2000[c]	4.63/20 per mL
Carbidopa/L-dopa/entacapone	Stalevo	600[c]	600–1600[c]	12.5/50/200, 18.75/75/200, 25/100/200, 31.25/125/200, 37.5/150/200, 50/200/200
Carbidopa	Lodosyn	25	25–75	25
Dopamine agonists				
Apomorphine	Apokyn	1–3	3–12	30/3 mL[d]
Bromocriptine	Parlodel	2.5–5	15–40	2.5, 5
Pramipexole	Mirapex	0.125	1.5–4.5	0.125, 0.25, 0.5, 1, 1.5
Pramipexole ER	Mirapex ER	0.375	1.5–4.5	0.375, 0.75, 1.5, 3, 4.5
Ropinirole	Requip	0.75	9–24	0.25, 0.5, 1, 2, 3, 4, 5
Ropinirole XL	Requip XL	2	8–24	2, 4, 6, 8, 12
Rotigotine	Neupro	2	2–8	1, 2, 3, 4, 6, 8
COMT inhibitors				
Entacapone	Comtan	200–600	200–1600	200
Tolcapone	Tasmar	300	300–600	100, 200
MAO-B inhibitors				
Rasagiline	Azilect	0.5–1	0.5–1	0.5, 1
Selegiline	Eldepryl	5–10	5–10	5
Selegiline ODT	Zelapar	1.25	1.25–2.5	1.25, 2.5
Miscellaneous				
Amantadine	Symmetrel	100	200–300	100, 50/5 mL

(COMT, catechol-O-methyltransferase; CR, controlled release; IR/ER, immediate-release/extended-release; MAO, monoamine oxidase; ODT, orally disintegrating tablet.)
[a]Marketed in the United States for Parkinson disease.
[b]Dosages may vary.
[c]Dosages expressed as L-dopa component.
[d]Dosages of Rytary were developed to avoid confusion with other oral carbidopa/L-dopa products that contain L-dopa in multiples of 50 mg.
[e]Dosages expressed as entacapone component.
[f]Sterile solution of subcutaneous injection with supplied pen injector.

- **Levodopa or L-Dopa with carbidopa** combination and in CNS and peripherally this L-Dopa is converted **by L-amino acid decarboxylase [L-AAD]** to dopamine
- In periphery the carbidopa or benserazide can block **L-AAD thus increasing CNS penetration of administered L-Dopa** and **decreasingdopamine** adverse effects like nausea, cardiacarrhythmias,postural hypotension and **vivid dreams** and **elimination ½ life of levodopa is about 1 hour and adding of carbidopa or benserazide can extend ½ life of 1.5 hours and adding of COMT inhibitor can extend it to 2 to 2.5 hours.**

There are some responses like

1. **End of dose wearing off** is related to increasing loss of neuronal dopamine storage capability and short ½ life of L-Dopa
2. **Delayed on or no on** can result from delayed gastric emptying or decreased absorption in duodenum
3. **Dyskinesias**– involuntary choreiform movements usually involving neck , trunk and extremities
4. **Freezing** – Episodic inhibition of lower extremity motor function
5. **Off period dystonia** – Muscle contractions most commonly in distal lower extremities like feet or toes occurs often in early morning

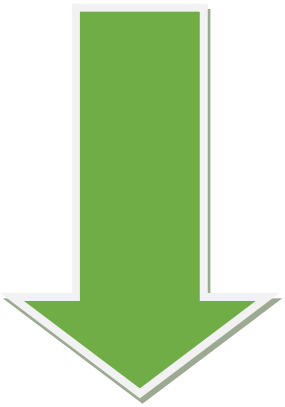
TABLE 56–4 Common Motor Complications and Possible Initial Treatments

Effect	Possible Treatments
End-of-dose "wearing off" (motor fluctuation)	Increase frequency of carbidopa/L-dopa doses; add either COMT inhibitor or MAO-B inhibitor or dopamine agonist; add or switch to extended release carbidopa/L-dopa (ie, Rytary)
"Delayed on" or "no on" response	Give carbidopa/L-dopa on empty stomach; use carbidopa/L-dopa ODT; avoid carbidopa/L-dopa SR; use apomorphine subcutaneous
Start hesitation ("freezing")	Increase carbidopa/L-dopa dose; add a dopamine agonist or MAO-B inhibitor; utilize physical therapy along with assistive walking devices or sensory cues (eg, rhythmic commands, stepping over objects)
Peak-dose dyskinesia	Provide smaller doses of carbidopa/L-dopa; reduce dose of adjunctive dopamine agonist; add amantadine

(COMT, catechol-O-methyltransferase; MAO, monoamine oxidase; ODT, orally disintegrating tablet; SR, sustained release.)

- **MAO-B inhibitors** i.e., **Monoamine oxidase B**inhiblike selegiline blocks dopamine breakdown and can extend on time of L-Dopa up to 1 hour and it often permits reduction of L-Dopa dose by as much as 1 half and combining MAO-B inhib with meperidine& opioid analgesics is contraindicated because of a small risk of **serotonin syndrome**
- **COMT inhib i.e., Catechol-O-Methyltransferase inhibitors** are used in conjunction with carbidopa / levodopa to prevent peripheral conversion of L-Dopa to dopamine and **tolcapone** use – limited potential for fatal liver toxicity and monitor LFT's and **brownish orange urine colouration** occur and **entacapone has shorter ½ life**
- The dopamine agonists like **ergot derivatives – bromocriptine and non ergots likepramipexole,rotigotine and ropinirole** are beneficial adjuncts in patients experiencing fluctuation in response to L-Dopa and they decrease frequency of off periods and provide an L-Dopa sparing effect and one of the drug like **apomorphine** iscontraindicated with **serotonin 3 receptor blockers** like **ondansetron**

The below figures are the side effects of the drugs and some of the non motor symptoms and their possible treatments



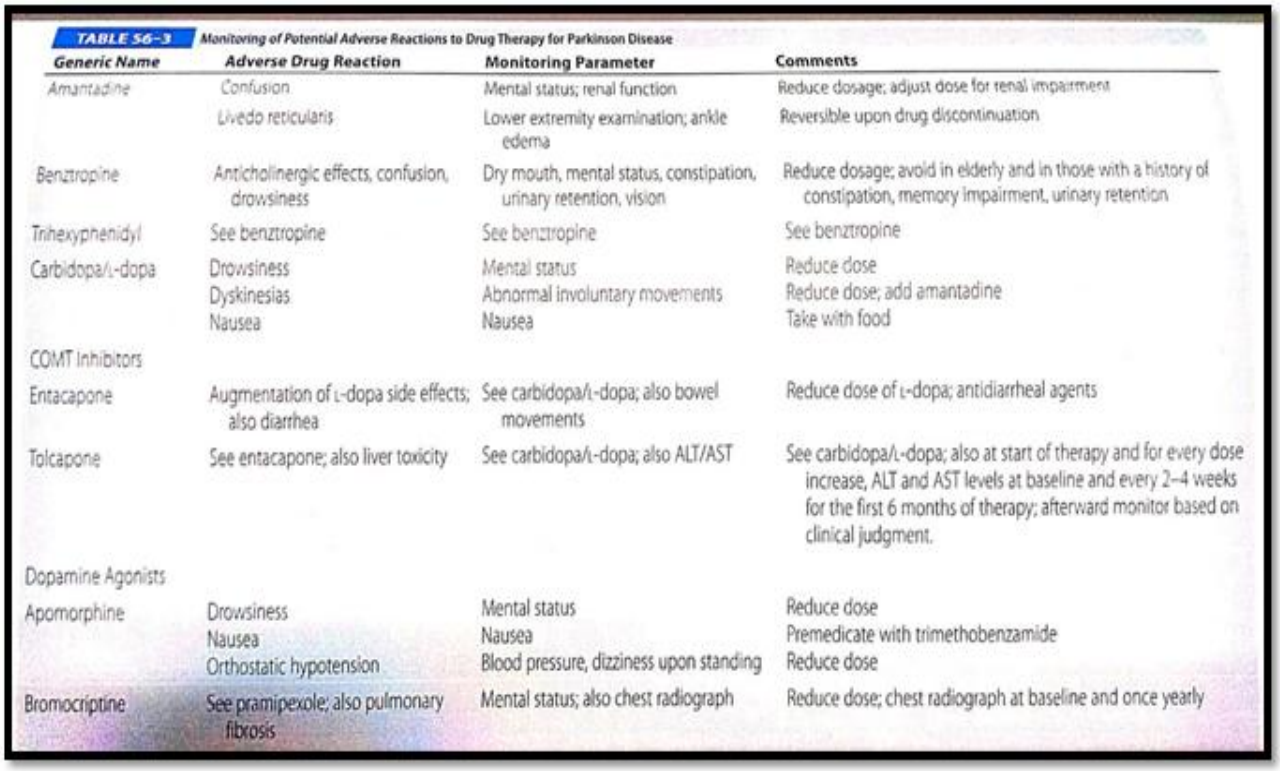


TABLE 56-3 *Monitoring of Potential Adverse Reactions to Drug Therapy for Parkinson Disease*

Generic Name	*Adverse Drug Reaction*	Monitoring Parameter	Comments
Amantadine	Confusion	Mental status; renal function	Reduce dosage; adjust dose for renal impairment
	Livedo reticularis	Lower extremity examination; ankle edema	Reversible upon drug discontinuation
Benztropine	Anticholinergic effects, confusion, drowsiness	Dry mouth, mental status, constipation, urinary retention, vision	Reduce dosage; avoid in elderly and in those with a history of constipation, memory impairment, urinary retention
Trihexyphenidyl	See benztropine	See benztropine	See benztropine
Carbidopa/L-dopa	Drowsiness	Mental status	Reduce dose
	Dyskinesias	Abnormal involuntary movements	Reduce dose; add amantadine
	Nausea	Nausea	Take with food
COMT Inhibitors			
Entacapone	Augmentation of L-dopa side effects; also diarrhea	See carbidopa/L-dopa; also bowel movements	Reduce dose of L-dopa; antidiarrheal agents
Tolcapone	See entacapone; also liver toxicity	See carbidopa/L-dopa; also ALT/AST	See carbidopa/L-dopa; also at start of therapy and for every dose increase, ALT and AST levels at baseline and every 2–4 weeks for the first 6 months of therapy; afterward monitor based on clinical judgment.
Dopamine Agonists			
Apomorphine	Drowsiness	Mental status	Reduce dose
	Nausea	Nausea	Premedicate with trimethobenzamide
	Orthostatic hypotension	Blood pressure, dizziness upon standing	Reduce dose
Bromocriptine	See pramipexole; also pulmonary fibrosis	Mental status; also chest radiograph	Reduce dose; chest radiograph at baseline and once yearly

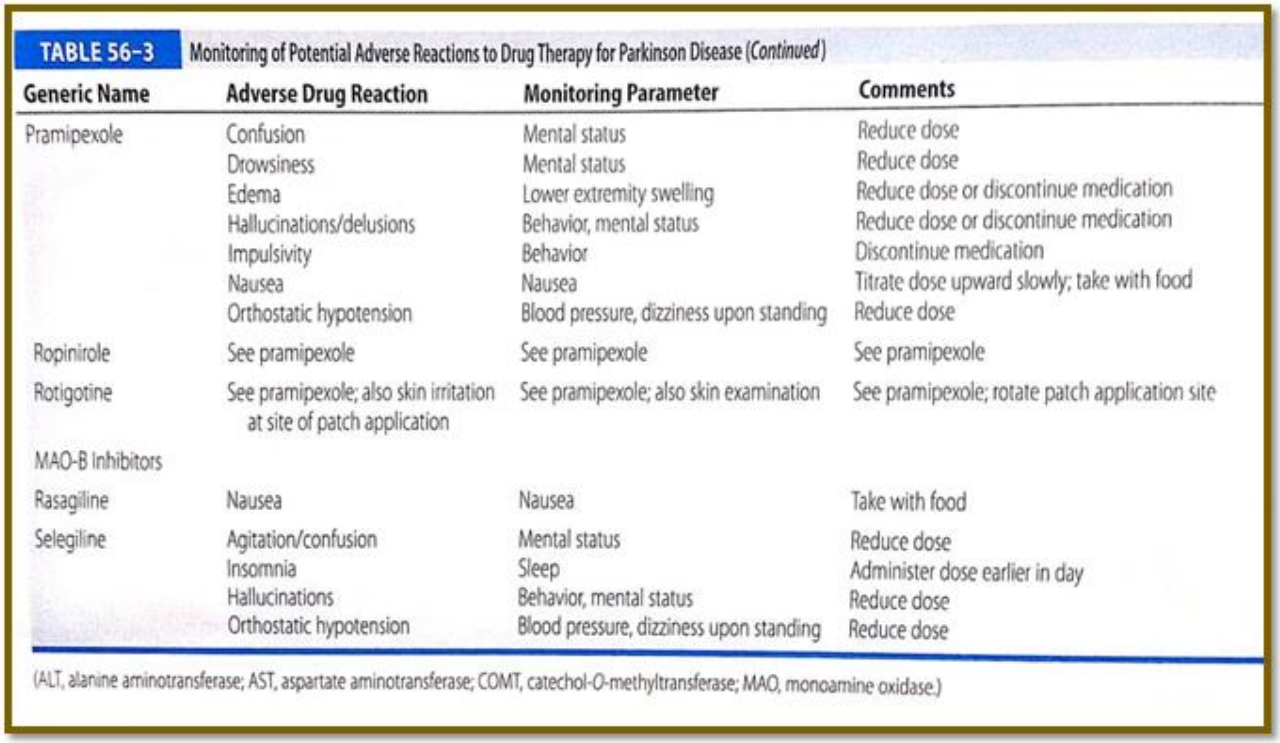


TABLE 56-3 Monitoring of Potential Adverse Reactions to Drug Therapy for Parkinson Disease (*Continued*)

Generic Name	Adverse Drug Reaction	Monitoring Parameter	Comments
Pramipexole	Confusion	Mental status	Reduce dose
	Drowsiness	Mental status	Reduce dose
	Edema	Lower extremity swelling	Reduce dose or discontinue medication
	Hallucinations/delusions	Behavior, mental status	Reduce dose or discontinue medication
	Impulsivity	Behavior	Discontinue medication
	Nausea	Nausea	Titrate dose upward slowly; take with food
	Orthostatic hypotension	Blood pressure, dizziness upon standing	Reduce dose
Ropinirole	See pramipexole	See pramipexole	See pramipexole
Rotigotine	See pramipexole; also skin irritation at site of patch application	See pramipexole; also skin examination	See pramipexole; rotate patch application site
MAO-B Inhibitors			
Rasagiline	Nausea	Nausea	Take with food
Selegiline	Agitation/confusion	Mental status	Reduce dose
	Insomnia	Sleep	Administer dose earlier in day
	Hallucinations	Behavior, mental status	Reduce dose
	Orthostatic hypotension	Blood pressure, dizziness upon standing	Reduce dose

(ALT, alanine aminotransferase; AST, aspartate aminotransferase; COMT, catechol-*O*-methyltransferase; MAO, monoamine oxidase.)

TABLE 56–1 Nonmotor Symptoms and Possible Treatments

Symptom	Possible Treatments
Anxiety	Cognitive behavioral therapy, selective serotonin reuptake inhibitors, venlafaxine, minimize "off" times.
Cognitive impairment	Eliminate anticholinergic agents. Add cholinesterase inhibitor.
Constipation	Fiber, hydration, exercise, laxatives, stool softeners.
Daytime sleepiness	Proper night time sleep hygiene, reduce dose of dopamine agonist, referral to sleep specialist to rule out apnea and sleep disorders.
Depression	Selective serotonin reuptake inhibitor, newer-generation serotonin norepinephrine reuptake inhibitor, cognitive behavioral therapy.
Drooling	Local injection of botulinum toxin, atropine sublingual drop, glycopyrrolate, ipratropium sublingual spray.
Dysphagia	Referral to speech therapist, dysphagia diet, avoid anti-cholinergic medications, manage dry mouth.
Fatigue	Caffeine, armodafinil, modafinil, proper night time sleep hygiene, referral to sleep specialist to rule out sleep disorder.
Falling	Referral to physical therapy; assistance with ambulation, minimize risk for bone fractures, treat osteoporosis.
Hallucinations/psychosis	Eliminate adjunctive medications, especially anticholinergic agents and dopamine agonists. Add clozapine, quetiapine pimavanserin.
Impulse control disorder	Discontinue dopamine agonist or add clozapine, quetiapine or naltrexone
Insomnia	Nonbenzodiazepine $GABA_A$ agonists, trazodone.
Orthostatic hypotension	Reduce dose of alpha-blockers, dopamine agonist, diuretics vasodilators. Abdominal compression, add salt and water to diet, water boluses, fludrocortisone, midodrine, droxidopa, pyridostigmine.
Overactive bladder	Behavioral therapies (eg, bladder training, fluid management, pelvic floor muscle exercises), antimuscarinic agents, mirabegron, intradetrusor injections of botulinum toxin
Pain	Treatment as per type of pain (eg, dystonic, musculoskeletal, neuropathic), minimize "off" times, appropriate referral to orthopedics, physical therapy, pain specialist, rheumatology.
REM sleep behavior disorder	Clonazepam, melatonin.
Restless legs syndrome	Dopamine agonist at bedtime; gabapentin.

(GABA, γ-aminobutyric acid; REM, rapid eye movement.)

Educate the patients and caregivers about recording medication doses & administration times and duration of on & off periods

Monitor symptoms, side effects and activities of daily living and individualize therapy and other medications that may worsen motor symptoms,memory,falls or behavioural symptoms should be discontinued if possible

NEW/RECENT TRENDS/ADVANCES INTRODUCED TO THIS DISEASE

The recent type of trends that which are introduced in PD are like

- In August 2019, FDA has approved a drug i.e., Istradefylline of Nourianz brand for parkinson's off time when the symptoms return between medication doses
- This Istradefylline belongs to adenosine A2A antagonists which work by blocking adenosine chemical and boosts the dopamine i.e., brain chemical that decreases in PD and this Istradefylline is OD type of drug that can be added to a medication regimen consisting of levodopa/ carbidopa to decrease "off time." Common side effects may include dyskinesia (abnormal, involuntary movement), dizziness, constipation and other symptoms like insomnia, hallucinations etc.,

The other recently approved type of drugs are

1. INBRIJA [Levodopa oral inhalation powder] – 21/12/2018 approved by FDA& it is indicated for the intermittent treatment of off episodes in patients with Parkinson's disease treated with carbidopa/levodopa and it is contraindicated with thepatients currently taking a nonselectiveMAOinhibitor or who have recently (within 2 weeks)taken a nonselective MAO inhibitor and it's mechanism of action will be as a the metabolic precursor of dopamine, crosses the blood-brain barrier and after it is converted to dopamine in the brain.
2. Xadago [Safinamide] is another drug from Newron Pharmaceuticals approved byFDA [US Food and drug administration]& it is a MAO-B type of inhibitor & indicated for adjunctive treatment to levodopa/carbidopa in patients with PDexperiencing "off" episodesand it's dose is 50 mg OD oral and it can be increased upto 100 mg and it's particular mechanism is not known but as it is a MAO-B inhibitor it inhibits MAO-B activity byblocking the catabolism of dopamine, as a result to increase in dopamine levels andsubsequent increase in dopaminergic activity in the brain. It is contraindicated with other MAO inhibitors,opioiddrugs,dextromethomorphan and a history of hypersensitivity etc.,
3. In 2019 the CDER [Center for drug evaluation and research – Division of FDA] has approved a drug i.e., FluorodopaF 18injection, a radioactive diagnostic agentfor use in positron emission tomography [PET] studies to help diagnoseadult patients with suspected Parkinsonian syndromes,a group of disorders, that includes Parkinson's diseasethat may occur when there is a reduction in the ability ofdopamine, an essential chemical in the body that works inthe brain, to function normally.
   The other kinds of treatments that are recently and in few years are like use of electrical neuromodulation in Parkinson's disease and techniques of electrical neuromodulation are" Deep brain stimulation , transcranial direct current stimulation , transcranial alternating current stimulation, direct cortical stimulation.

DEEP BRAIN STIMULATION remains the most common and effective form of electrical stimulation for the treatment of PD.

- It is one of the most prevalent type of neurosurgical procedure for PD providing effective relief for some motor & non motor symptoms
- It is a good type of technique and it's successful chances are also good but it's limitation is invasive
- DBS involves the surgical implantation of electrodes that stimulate subcortical structures including the subthalamic nucleus and globuspallidusinternus
- It offers significant improvements in motor symptoms and fluctuations in comparison to best medical therapy in some advanced PD patients
- Exact mechanism of action of DBS is not known and now it is believed as DBS efficacy is rooted in a reversible information lesionthat disrupts the expression of pathological neural activityacross the motor circuit.

TRANSCRANIAL DIRECT CURRENT STIMULATION is non-invasive treatment & is a new type of treatment option for PD and neurological diseases

- It is easy to handle , low cost and fewer side effects and good changes or adherence is seen in the patients by this treatment
- The evidence suggests that transcranial direct current stimulation (tDCS) is a good evidence for clinical practice&most likely impacts on motor symptoms of the disease, withmost prominent results relating to rehabilitation
- It's use is applied in supplemental motor areas together with a gait training can facilitate motor learning and modulate neurons for better potentiation of exercises together with patients with walking difficulties due to PD
- Utility is limited due to its weak effects and high variability, with medication state.

DIRECT CORTICAL STIMULATION of the motor cortex in the treatment of PD has been trialled with varying success over the years

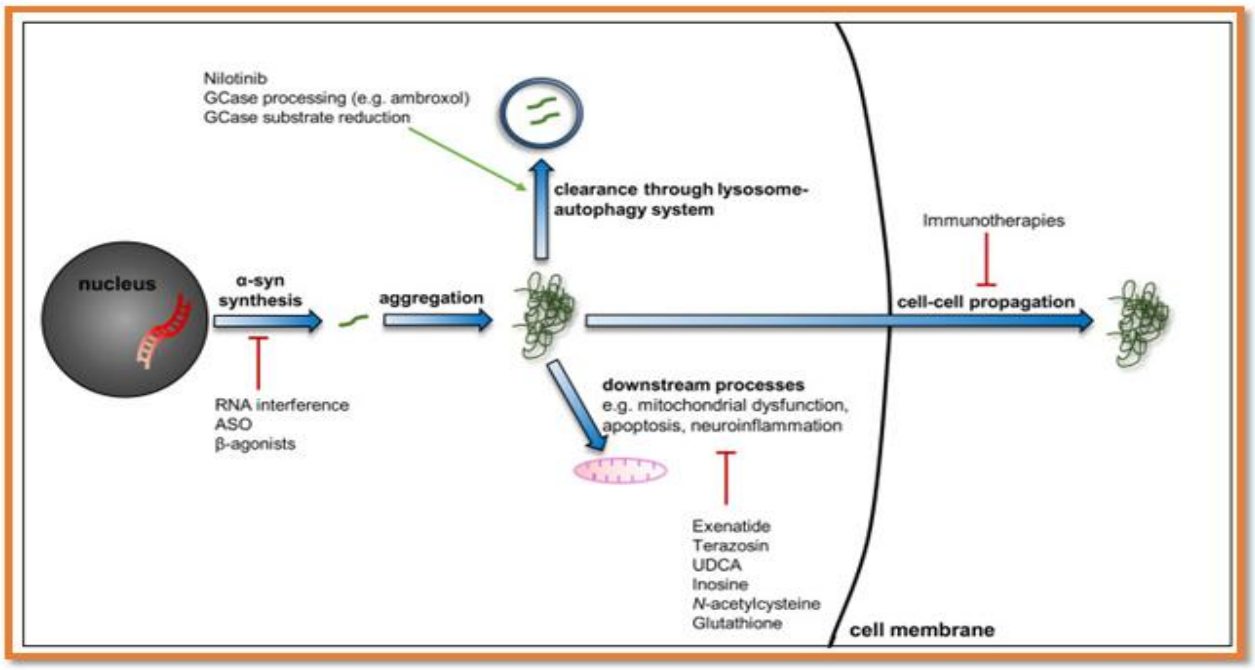
- Stimulation can be subdural, but minimally invasive epidural methods seem to be preferred due to reduced surgical risks
- Efficacy has been variable, but is generally considered less efficacious than DBS
- This is potentially due to the dependency between stimulation site (cortical or sub-cortical) and behavioural effects, and confounded by limits on stimulation intensity in order to prevent seizure onset.

- Stimulation efficacy could be improved by determining the optimum stimulation site according to patient specific brain connectivity in order to reveal the “sweet spot” for modulating downstream nuclei in the motor circuit.

TRANSCRANIAL ALTERNATING CURRENT STIMULATION application in parkinson’s symptomology has remained experimental and these treatments will be including electrodes producing the electric impulses and all these treatments provide actions like neurotransmitter concentration changes and both Tcs types & DBS will have complete field shaping by possible developments in hardware

- In this electrical neuromodulation techniques to achieve a effective neuromodulation– All forms have been associated with neuroplastic effects and pharmacological dependencies, and an emerging recognition that underlying brain state is an important and some times these factors may overlap also
- The Pharmacological impact of stimulation, either by director indirect methods, will affect the efficacy of subsequentperiods of stimulation.

The below diagram is **“PUTATIVE DISEASE MODIFYING THERAPIES FOR PD ”**



The other kind of treatments that are involved and are in clinical trials stage or going on are

- **Immunotherapies**
  A humanised monoclonal antibody prasinezumab or PRX002, Prothena brand has been shown to reduce free serum alpha synuclein at approximaately 97 percent and cleared phase 1 clinical trials and trial 2 is under way and other antibody or drugs like BIIB054 [Biogen] target n terminal portion of alpha synuclein and it’s 1st trial is good and it is undergoing 2nd trial and other approaches like antisense oligonucleotide and rnainterference techniques to reduce its synthesis but they remained in the pre clinical studies.
- **Drug repurposing**
  It is a technique in which use of drugs through which the reduction of alphasynucleinpathology or having anybeneficial effects other processesare implicated in Parkinson's disease. The following tablewill be giving the information regarding the most promising agents that are being consideredfor Parkinson's disease treatment or the putative or commonly accepted disease modifying therapies for Parkinson's disease table is given below

Clinical trials of putative disease-modifying treatments for Parkinson's disease.

Drug/class	Proposed mechanism	Progress in trials
α-synuclein reduction		
β-agonists	Reduced α-synuclein transcription through acetylation of promoters and enhancers of the *SNCA* gene [28]	Not started
Nilotinib	Inhibition of ABL tyrosine kinase activity and enhanced autophagy [34]	Safe and tolerable but no clinical benefit in phase II trial
Terazosin	Activation of PGK1 and HSP90, increased ATP levels, and reduced α-synuclein levels [35]	Single-centre randomised placebo-controlled trial currently enrolling patients
Mitochondrial function		
Ursodeoxycholic acid	Restoration of mitochondrial function	Randomised placebo-controlled trial currently recruiting patients
N-acetylcysteine	Antioxidant effect and elevation of glutathione levels [36]	Small open-label phase II study showed no changes in indicators of oxidative damage or brain glutathione levels [36]
Glutathione	Reduction in reactive oxygen species and free radical levels	Double-blind trial completed, with no clinical benefit demonstrated over placebo
Neuroinflammation		
Azathioprine	Modulation of peripheral immune system profile	Single-centre randomised placebo-controlled trial about to start enrolling patients
Sargramostim (G-CSF)	Induction of Treg immune responses [37]	Phase I placebo-controlled trial completed Generally well tolerated, with reported modest improvement in UPDRS part III scores [38]
AZD3241	Reduced oxidative stress and neuroinflammation through inhibition of myeloperoxidase	Phase 2a randomised placebo-controlled trial completed Safe and well tolerated with reduced nigrostriatal distribution of microglia [39]
Other		
Inosine	Elevation of urate levels	Randomised placebo-controlled phase III trial halted early in 2018, with results awaited
Exenatide	GLP-1 receptor activation leading to inhibition of apoptosis, reduced microglial activation and neuroinflammation, reduced oxidative stress, and promotion of neurogenesis	Well tolerated, with improvements seen in UPDRS part III scores in randomised controlled trial [40] Phase III trial currently in set-up
Isradipine	Neuroprotection through blockade of L-type calcium channels in substantia nigra [41]	Multicentre phase III trial recently completed, with no improvement in motor or quality of life outcomes
Deferiprone	Iron chelation	Phase II randomised double-blind placebo-controlled trial completed, demonstrating reduced iron content in caudate and dentate nucleus No significant clinical benefit [42]

Abbreviations: ATP, adenosine triphosphate; G-CSF, granulocyte colony-stimulating factor; GLP-1, glucagon-like peptide-1; HSP90, heat shock protein 90; PGK1, phosphoglycerate kinase-1; Treg, regulatory T cell; UPDRS, Unified Parkinson's Disease Rating Scale.

The other treatments are like

- **Targeting non dopaminergic neuro transmitter systems** like by using the drugs like Safinamide having multi modal actions & additionally cholinesterase inhibitors like rivastigmine& donepezil have been trialled for their ability to reduce falls in PD
- **Neurotrophic factors** such as **glial cell line derived neurotrophic factor [GDNF]** have beneficial effects on dopaminergic neurons in pre clinical models and there has been much interest in developing neuroprotective therapies based upon neurotropic factors & there is a GDNF analog i.e., **Neurturin** has also been trialled in patients with similar results to those who seen with GDNF namely promising open label trials that have failed to translate to clinical benefit in larger trials & it has recently been reported in a press release that the agent can be delivered without major side effects, although it is too early to say whether it has therapeutic benefits for patients.

3) Regenerative treatments

These treatments aim to restore dopaminergic tone in a more targeted and physiological manner than can be achieved with current dopaminergic therapies.

- Several of these approaches are now entering clinical trials
- Gene therapies may be used to increase dopamine levels instriatum through introduction of genes that mediate dopamine synthesis
- 2 gene therapies involving genes encoding these enzymes are currently undergoing clinical trials
- Cell based therapies offer another emerging approach for targeted replacement of dopamine to treat dopamine dependent aspects of PD

Current and planned trials of human stem cell-derived neuronal products.

Trial	Country	Cell source	Number of patients	Status
Center for iPS Cell Research and Application	Japan	Allogenic iPSCs	7	Started
NYSTEM-PD	USA	ESCs (H9 cell line)	10	Pending decision from FDA
Chinese Academy of Sciences	China	ESCs	50	Ongoing
European STEM-PD trial	UK and Sweden	ESCs (RC17 cell line)	To be confirmed	In set-up
Fujifilm cellular dynamics international	USA	Autologous iPSCs	To be confirmed	In set-up
Allife Medical Science and Technology Co., Ltd.	China	Autologous iPS-neural stem cells	10	In set-up
Aspen Neuroscience	USA	Autologous iPSCs	To be confirmed	In development
International Stem Cell Corporation	Australia	Parthenogenetic ESC-derived neural stem cells	12	Ongoing

Abbreviations: ESC, embryonic stem cell; FDA, US Food and Drug Administration; iPSC, induced pluripotent stem cell.

- A tricistroniclentivirus vector is also currently undergoing clinical trials & this treatment consists of genes encoding AADC,TH,GTP cyclohydrolase 1 which catalyses rate limiting step of tetrahydrobiopterin synthesis – A cofactor required for dopamine & serotonin synthesis
- There are somanytype of treatments that are in phase 1 clinical trials

There are some **Advances developed in DBS** like

- The pedunculopontine nucleus has recently been trialled as a new target for DBS particularly for gait problems seen in PD
- Initial trials are reported positive impacts on gait & postural instability& more rigorous subsequent trials were less promising
- More recently, stimulation of substantianigrareticularis has shown promising effects on axial symptoms in preliminary studies along with stimulation of basal forebrain with subthalamic nucleus for some of cognitive deficits in PD

- There is a great interest in adaptive DBSi.e., a system in which stimulation delivered to target is adjusted in response to physiological signals
- This type improves clinical response, limits adverse effects and reduces the requirements for battery charges and the associated cost& further work is required in identifying &hoped that such technologies will enhance clinical utility of DBS in future
- Non invasive DBS techniques involving the use ofexternal devices delivering electric fields to deep structures would overcome or circumvent need of neurosurgery & it's associated risks

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