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DISEASE MODIFICATION TRIALS IN PARKINSONS DISEASE: A REVIEW

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ABSTRACT:

Among the common neurological disorders worldwide, Parkinson's disease has a major share. Currently, only symptomatic therapies are available for it without any approved neuromodulation drugs as all the previously done disease modification trials have failed. There is a dire need for such therapies. Disease modification trials include all types of intervention targeting the degeneration process which underlies the disease process and thus slows it down or the treatment aim to regenerate or replace the neurons which are lost. There are many reasons for the failure of trials. This review emphasize the need for disease modification trials, causes of failure of trials, few prominent previously failed trails and review on-going clinical trials for disease modification. The aim of this review article is to highlight the importance and utmost need of development of neuroprotective agents for Parkinson's disease through future research.

KEY WORDS: parkinson's disease, Neuroprotective therapies, Neuromodulation therapies for Parkinson's disease.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative process after Alzheimer's disease. It was introduced by Dr. James Parkinson in 1817, who called him as a "shaking palsy." [1] It is a chronic, progressive neurodegenerative disorder characterized by clinical features involving both motor and non-motor systems. Consequently, a significant clinical impact is seen on patients, families, and caregivers of patients as a result of limited patients' mobility leading to additional social and economic burden. The presence of Non-motor features is due to neuronal loss in nondopaminergic areas while the motor symptoms of PD are attributed to the striatal dopaminergic neurons loss. Parkinsonism is a symptom complex used to describe the motor features of PD, which include bradykinesia, muscular rigidity and resting tremor. Among the list of causes of Parkinsonism which causes secondary Parkinsonism, Idiopathic Parkinson is the major cause of Parkinsonism [2] .Literature search shows that non-motor presentations of Parkinson appear far before the motor feature which is the time when pathogenesis of Parkinson start and is the focus of neuromodulation therapies.[3] Currently, no long term and neuroprotective therapies are available. There is the utmost need of time to search for the disease modification therapies to meet the challenge of neurodegeneration. By searching literature, we are hopeful that such strategies will lead to the development of disease modifying therapies 4.This is supported by previous studies that shows that identification of decreased neuronal loss will be most fruitful [5]. Our aim of writing this review article is to critically analyze the clinical trials which have been done and are ongoing currently in this field.

NEED OF DISEASE MODIFICATION TRIALS IN PARKINSONS DISEASE

Unfortunately, despite the promise of many therapies in preclinical trials, to date there is failure of any available approved drug for this purpose. Inevitable factors include irresistible dependency on animal models which are mostly toxin based along with insufficient knowledge of underlying pathogenesis[6]. Other drawbacks in previous clinical trials are discussed below which should be optimized through proper study

designs to get more successful results[7].

MATERIALS AND METHODS

Our article is narrative review. A detailed evaluation of articles published within last twenty five years on disease modification trials in Parkinson disease was undertaken. It included following steps: (1) a systematic search of review articles, (2) a critical appraisal of identified studies. Sources included mainly PubMed articles and clinicaltrials.gov. Using the key words mentioned above. To our knowledge, no previous article on this topic is available from Pakistan, which is our rationale for writing this review.

TARGETS FOR NEUROPROTECTION

The crucial steps in PD pathogenesis are outlined in FIGURE -1 while the targets of disease modification in Parkinsons disease and complex interaction of these steps which give rise to PD pathology and its neurodegeneration are presented in FIGURE 2.

WHY CLINICAL TRIALS OF PARKINSON DISEASE MODIFICATION FAILED?

There is no neuromodulation treatment yet in Parkinson disease as per American academy of Neurology, recent practice parameter[8].

It's worth appreciating to have such trials on board but inevitable step is to keep in mind the numerous other approaches that have failed. There are many reasons for failures.(FIGURE 3)

1. Insufficient understanding of PD pathogenesis as it undoubtedly represents more than one disease.
2. Ongoing dependence on animal models which are poorly predictive of neuroprotection in humans.
3. Need of better biomarkers for fruitful evaluation of therapy outcomes.

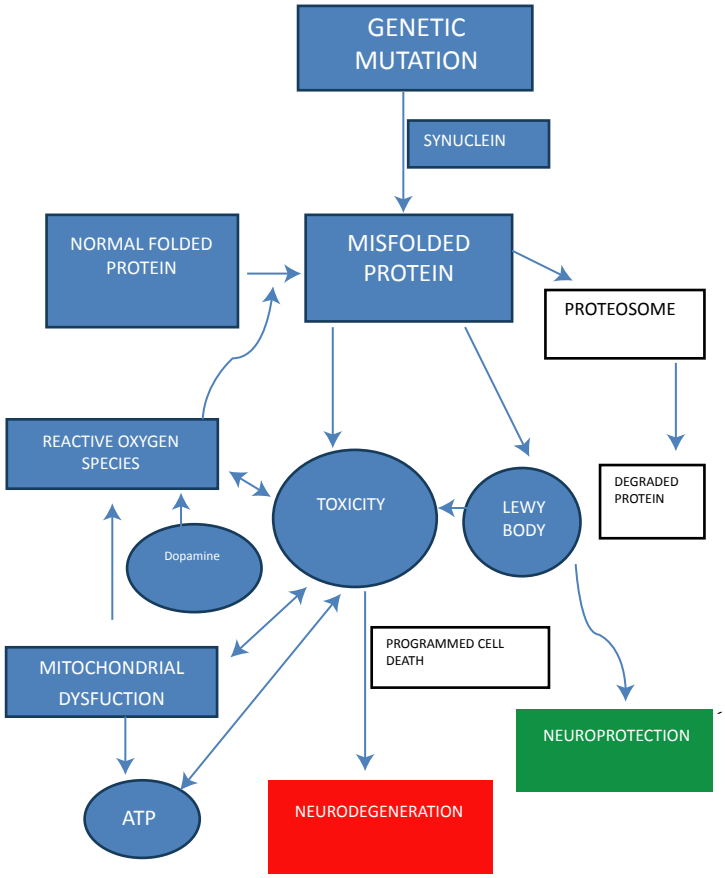

FIGURE 1: Mechanisms of PD pathogenesis

4. Inaviodable negative outcome even in well-designed and rational trials, treatments may still fail.

5. Lack of financial and institutional supports as well as inadequate research grants.

FAILED CLINICAL TRIALS

ELLDOPA trial (earlier verus later L-Dopa trial) was published in 1999.Levodopa (L-dopa) is the well-established and most efficacious symptomatic therapy in Parkinson. Due to the well understood role of dopamine catabolism producing free radicals, the hope generated for the neuroprotective role of levodopa [9,10] as a variety of preclinical data has predicted its neuroprotective effect [11,12].

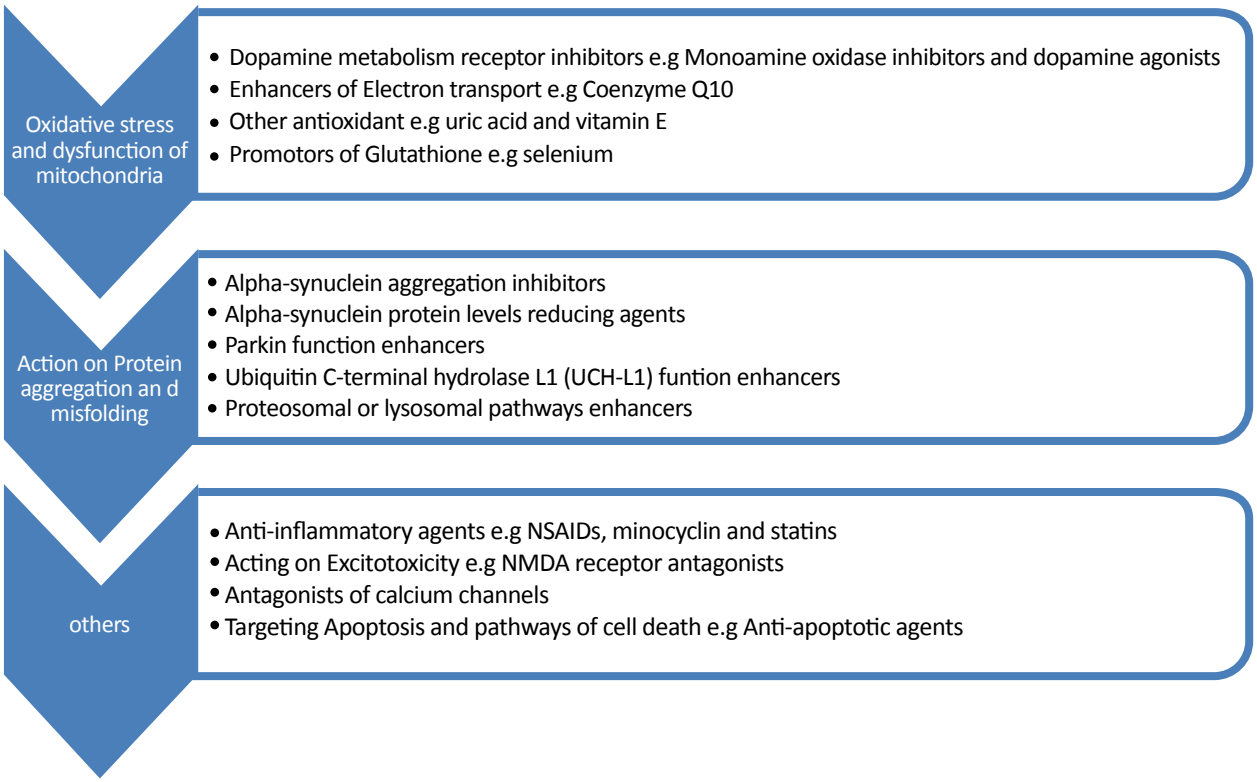

FIGURE 2: Targets of disease modification in Parkinsons disease

Placebo or L- dopa was given to at dose of 150 mg,300 mg or 600 mg per day to 361 patients for 40 weeks. It was followed by a washout period of 2 weeks. No significant difference was shown between the group of patients who were treated early with levodopa (n = 222) or in a delayed fashion (n = 223) in Unified Parkinson's Disease Rating Scale (UPDRS) score (P = .44)[13].

FIGURE 3: Main determinants for previous PD Neuroprotection trials failures

The results are shown in (Figure 4). The drawback of the study leading to controversial interpretation was ambiguity whether the effects of L-dopa outlasted the chosen 2 weeks washout period in the study which affects the results. The reliability of these neuroimaging techniques as measures for PD progression are still uncertain [14,15]

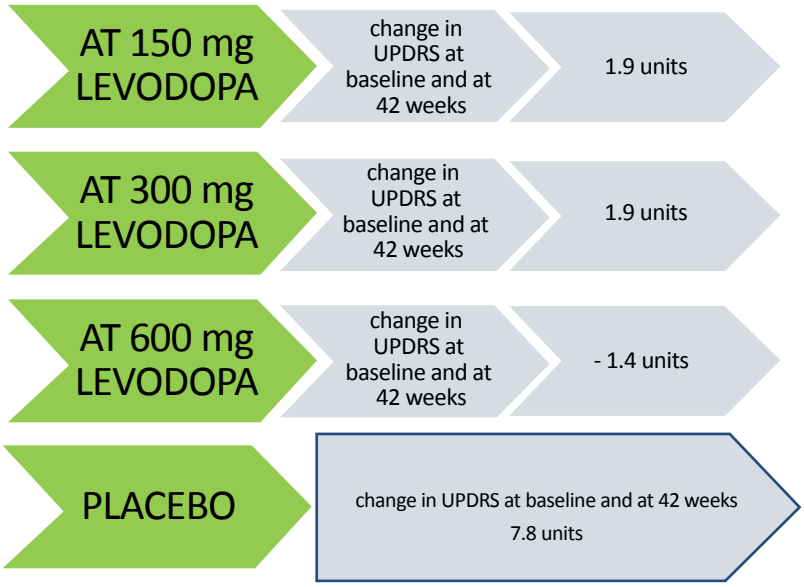

FIGURE 4 : RESULTS OF ELLDOPA STUDY

Another trial was conducted on 800 patients in 1987 on Deprenyl and Tocopherol for the treatment of early Parkinson's disease. Results showed no significant effect. Deprenyl is a monoamine oxidase inhibitor while tocopherol is a vitamin E component acting as a free radical trap.The beneficial effect of deprenyl remains unclear based on the outcome of study as concluded that 10 mg/day of Deprenyl delays the onset of disability associated with early Parkinson's disease

that was otherwise untreated in contrast to 2000 IU/ day of tocopherol. Suppression of dopamine release result in reduction of oxidative stress. By its action at D2 autoreceptors, found on Dopamine receptor agonists were considered to be potentially neuroprotective. Certain agonists, such as Pramipexole, have hydroxylated benzyl ring structure and may also act as direct antioxidants [16,17].So , a study, **CALM-PD trial (Comparison of the agonist pramipexole with levodopa on motor complications of Parkinson's disease)** was carried out in order to compare Pramipexol with levodopa[18]. Patients on Pramipexol showed less decrease in β-CIT uptake rather than those on levodopa alone. Another trial named **Ropinirole as Early Therapy versus L-dopa Positron Emission Tomography (REAL-PET)** trial showed same results. A decrease in putaminal[18] Fdopa uptake was found in ropinirole group versus levodopa group. Drawbacks like extended washout of medications, lack of placebo control along with other limitations question the neuroprotective role of Dopamine agonist as depicted by both mentioned study trials[14,15]. Rasagiline , Selegiline and vitamin E are the agents used as antioxidant agents in many studies. Mechanism underlying is monoamine oxidase B inhibition which leads to reduction in dopamine oxidation. Selegiline and Vitamin E neuroprotective effect in early PD patients was tested by the **DATATOP trial (Deprenyl and tocopherol antioxidative therapy of parkinsonism)**[20,21]. Results showed that as compared to patients given placebo, vitamin E did not show any improvement neither positively affected selegiline's effect while selegiline significantly delayed the time of onset of levodopa treatment. The limitation of study is that selegiline improve PD symptoms by exerting mild symptomatic effect that improves motor symptoms in PD. This created bias in study. To decrease the confounding effect of symptomatic efficacy, study was conducted on Rasagiline which is a newer MAO-B inhibitor, more efficacious than selegiline. With antioxidant characteristics of its metabolite. (FIGURE 5).

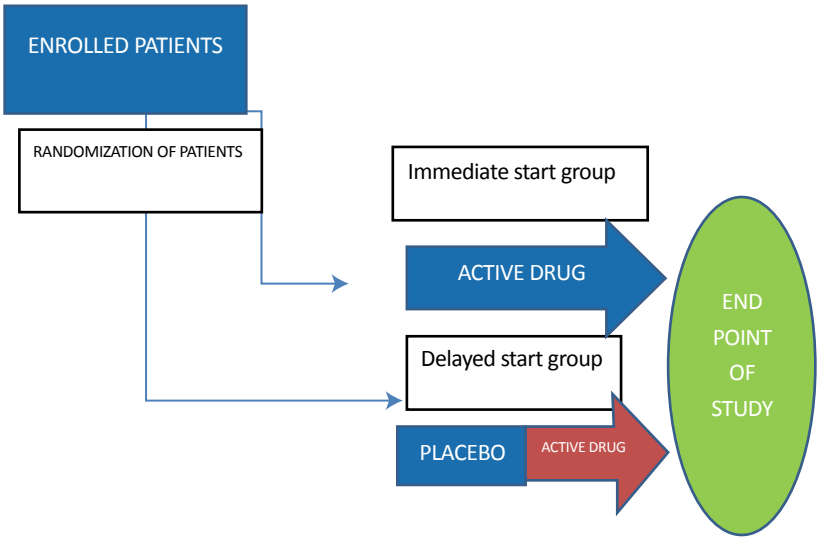

FIGURE 5 : The delayed-start design diagram .

One of the study with delayed start design was **TEMPO study (Rasagiline in Early Monotherapy for Parkinson's Disease Outpatients)**. Patients were subjected to placebo or rasagiline for 6 months followed by another 6 months treatment on Rasagiline [22]. Results suggested that a long-lasting improvement is obtained through early treatment. Limitation was short duration of study, and limited sizes of groups. A study, **ADAGIO (Attenuation of Disease Progression with Azilect Given Once-daily trial)** with a larger sample size and extended duration was conducted for analyzing these initial results but also turned out unsuccessful.In ADAGIO trial newly diagnosed patients with PD were given once daily either 1 mg rasagiline, 2 mg rasagiline, or placebo [23] .Switching of placebo arm to the active treatment arm was done after 9 months while continuing those patients on rasagiline on it for further 9 months.Results are shown in Figure 6 and 7.After 18 months, the 1 mg rasagiline treatment arm fulfilled all three pre-specified endpoints which were considered to reflect a disease-modifying effect were fulfilled by 1 mg rasagiline but not by 2 mg rasagiline after 18 months[24]. The reason for such difference is not known. Food and Drug Administration (FDA) in the US did not approve for rasagiline as a disease-modifying therapy. A trial on Coenzyme Q10

was carried out.Electron transport chain in mitochondria has a cofactor , Coenzyme Q 10 that has been shown to reduce dopaminergic neurodegeneration in PD mouse models[25].

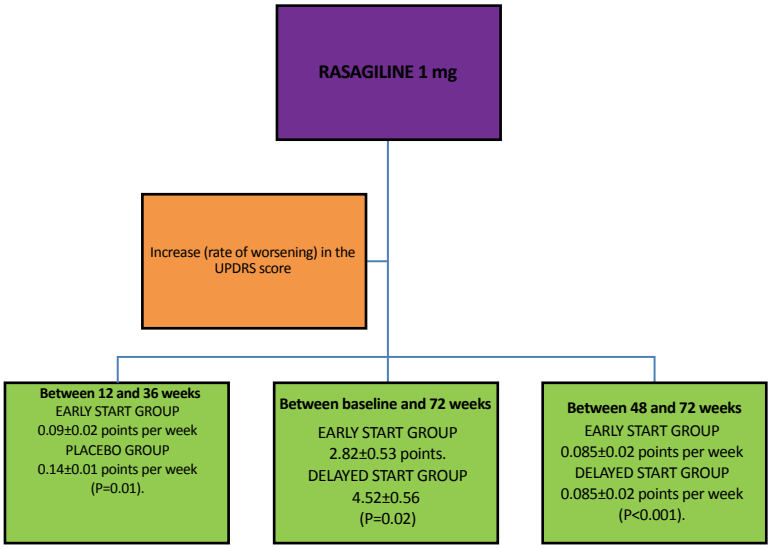

FIGURE 6: ADAGIO TRIAL: Rasagiline 1 mg Results

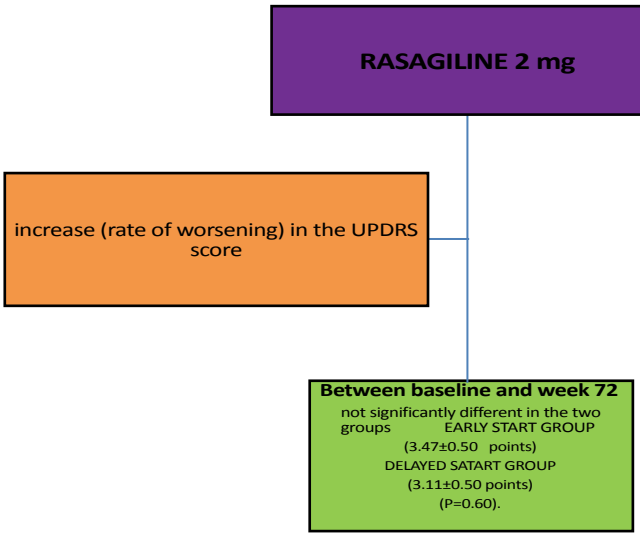

FIGURE 7 : ADAGIO trial: Rasagiline 2 mg Results

CoQ10 used in doses 300 mg, 600 mg, or 1200 mg versus placebo was studied for 16 months or until levodopa required26. Results showed reduction in UPDRS score in patients treated with CoQ10 treated patients as compared to placebo with most of the benefit was on 1200 mg of CoQ10. As it did not meet the criteria for futility, a larger, long-term study using high doses of CoQ10 versus placebo has recently been started. Another agent, Creatine was also studied in a trial. Animal models has shown neuroprotective effect of creatine which functions to promote mitochondrial ATP production[27].Creatine versus placebo in early PD patients was compared and followed for two years 28. UPDRS score or β-CIT uptake failed to show any difference between the control and creatine groups. A large phase III trial with different stages of PD is in progress. In literature, few trials using antiapoptotic agents are also mentioned like TCH346 and CEP-1347. The propargylamine TCH346 inhibits the apoptotic process by inihibiting glycolytic enzyme

glyceraldehyde-3-phosphate dehydrogenase (GAPDH) .A double-blind, randomized trial was carried out and followed over 12 to 18 months, but unlike animal models [29,30] this study failed to show a significant difference in clinical outcome[31]. Another trial , **Parkinson Research Examination of CEP-1347 Trial (PRECEPT)** was conducted although terminated early due to futility on interim analysis, to assess the efficacy and safety of CEP 1347, inhibitor of mixed lineage kinases inhibitor. It is also an anti-apoptotic factor that can activate the c-Jun N-terminal kinase (JNK) pathway involved in cell death and has turned out promising in preclinical studies [32-34]. Numerous trophic factors have also been studied in an attempt to develop PD disease modifying therapy.These agents factors promote the nigral dopaminagic neurons survival acting as neuroprotective in animal models [35-37]. Glial-Derived Neurotrophic Factor (GDNF) has been delivered so far primarily by direct infusion of the protein into the brain suggested to be effective in smaller studies 38 but a larger controlled study involving was halted because of lack of efficacy 39. Serious device-related adverse events and development of serum antibodies to GDNF was reported. Delivery of trophic factors by gene transfer approaches is alternative to its direct infusion. 40. Recently neurturin, a neurotrophic factor related to GDNF has been used [41,42]. Motor function in MPTP-treated monkeys 43 and in 6- OHDA-treated rats found to be improved by delivery of an adeno-associated viral (AAV-2) vector containing neurturin (CERE-120) [44, 45]. 12 patients with advanced PD tested for CERE-120 safety and found promising. 46Caution needed in interpretation of open - label trials data .A larger double-blind study is in progress. Neuroimmunophilins, intracellular receptor proteins promote neuronal growth independently of their immunosuppressive effects [47-49].This effect is shown in 6- OHDA and MPTP animal models [50-52], although neurodegeneration has not been reduced in all PD animal models [53,54]. In extension study, the effects of continued (prior GDNF patients) or new (prior placebo patients) exposure to GDNF, given as Intraputamenal glial cell line-derived neurotrophic factor (GDNF) were explored for another 40 weeks. Although, in nonhuman primate Parkinson's disease models[55], GDNF is shown to have neuroprotective and neurorestorative effects [56,57] but as neuromodulating treatment failed to show a significant clinical benefit till date[58,59]. Drugs which are used in other diseases have also been studied like pioglitazone. Patients with PD who were on regimen of rasagiline or selegiline as stable treatment were randomly assigned with (1:1:1) to 15 mg/day pioglitazone, 45 mg/day pioglitazone, or placebo and were followed from 2011 to 2013. Results were insignificant and further larger trial of pioglitazone is not recommended. Despite well recognized anti-inflammatory and antiapoptotic actions of minocycline [60], experiments failed to show beneficial effects. It was concluded that symptoms developed more rapidly and severely in minocycline /MPTP-treated animals. With the advancement in disease pathogenesis,based on the thought that to replace substantia Nigra pars compacta (SNc) dopamine neurons affected by the disease process, embryonic dopaminergic cells could be transplanted into the brain, cell-based transplantation strategies were initiated. Despite the popularity of stem cells among public, the stem cells found unsuccessful to provide further benefits versus fetal nigral dopamine cells in animal models. In addition, these trials also have risk of tumourogenesis.

TABLE 1: PREVIOUS TRIALS FOR PARKINSONS DISEASE MODIFICATION

PREVIOUS CLIICAL TRIALS FOR DISEASE MODIFICATION IN PD

TARGETS/MECHANISM OF ACTION	THERAPEUTIC AGENT	TRIAL
EARLYVERSUS LATE LEVODOPA USE	LEVODOPA 150 mg, 300 mg, 600 mg per day	ELLDOPA trial
USE OF TO COPHEROL AND DEPRENYL	Deprenyl (10 mg per day) Vitamin E (2000 IU per day)	
DOPAMINE RECEPTOR AGONISTS	compared pramipexole with L-dopa	CALM-PD trial
ANTIOXIDANT THERAPIES	Selegiline, Vitamin E, Rasagiline.	DATATOP trial TEMPO study ADAGIO trial
COENZYME Q10		
CREATINE		
ANTI-APOPTOTIC AGENTS	TCH346 CEP-1347	PRECEPT trial
TROPHIC FACTORS	Gilal-derived neurotrophic factor (GDNF)	
	Neurturin (CERE-120)	
	Neuroimmunophilins	
PIOGLITAZONE IN EARLY PARKINSON'S DISEASE		
MINOCYCLINE		
DOPAMINE CELL TRANSPLANTATION		

ONGOING PD MODIFICATION CLINICAL TRIALS
TRIALS /DRUG IN ADVANCED STAGES OF STUDY

Isradipine, currently approved as antihypertensive, is a dihydopyridine calcium channel blocker.It acts preferably on Cav1.3 channels which are the calcium channels expressed in many regions of body including many areas of brain too. Neuroprotection is shown in PD mouse models through substantia nigra pacemaker activity inhibition by CaV1.3 channel blockade. Isradipine causes blockade of calcium entry into brain cells thus preventing brain cell death.It has also being studied for neuromodulation in PD. Urate is one of the main antioxidant found in plasma.Its precursor is Inosine which ultimately has some neuroprotective effects. **SURE-PD3 (Study of Urate Elevation in Parkinson's Disease, Phase 3)** is ongoing in people of 30 years ages .It was started in June 2016 and it has been estimated to complete on October 31, 2019. Unfortunately, National Institute of Neurological Disorders and Stroke (NINDS) announces early study closure of SURE-PD3 Trial , after an interim analysis showed futility.The trial was testing whether a treatment that raises blood levels of the natural antioxidant urate (from ≤5.7 mg/dL to 7.1-8.0 mg/dL) for two years slows the rate of worsening in PD Movement disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Urate has antioxidant properties in substantia nigra pars compacta dopaminergic neurons in animal models .In conclusion, whether inosine has disease-modifying potential or not remains to be evaluated. Deferiprone act as a strong chelator of iron and is being studied. Exenitide is approved for Type 2 diabetes treatment. In animal models neuroprotective, and neurorestorative effect is found which leads to learning, and memory, behavior and motor function improvement [61]. Exenitide ,exendin synthetic form and human glucagon –like peptide -1 naturally found analogue. Oxidative and cellular stress activates the protein Abelson (c-Abl) , a non-receptor tyrosine kinase [62]. C-Abl has different location in the cell which affects its function.Actions includes parkin inactivation, , toxic elements autophagy impairment and alpha synuclein aggregation, role in cellular adhesion and survival pathways in the cell cytoplasm [63].By using 1-methyl-4phenylpyridinium and in vitro using MPTP toxin ,c-Abl can be activated [64,65]. Its role in the pathogenesis of PD and other α-synucleinopathies is established [66,67] (FIGURE 8) summarizes its role.Further larger clinical trials of neuromodulation are recommended. Tyrosine kinase enzymes can be selectively inhibited by a group of drugs labeled as Tyrosine kinase inhibitors (TKIs), a group of drugs inhibiting tyrosine kinase selectively [68] showed a neuroprotective potential in MPTP mouse models against dopaminergic toxins [69].

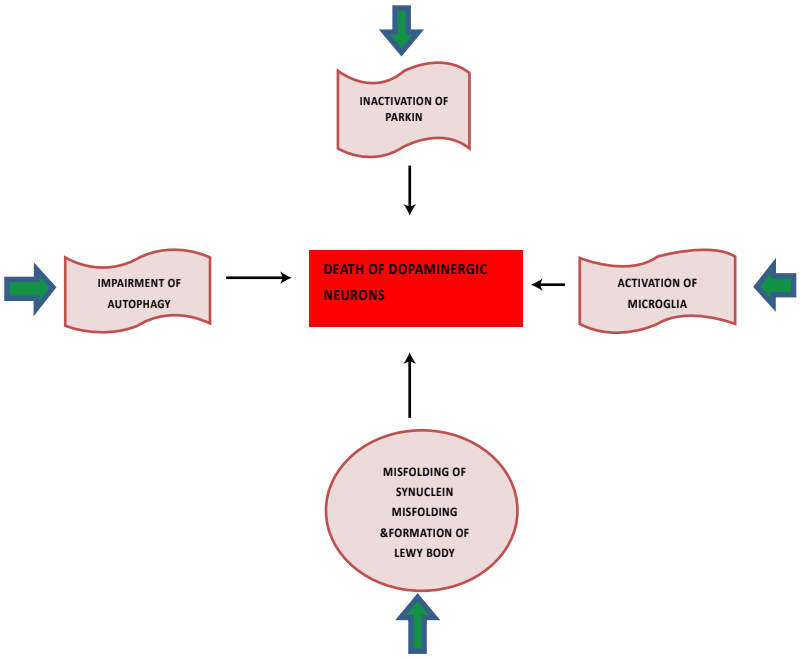

FIGURE 8: Mechanism of action of c- ABL

Low doses of **nilotinib** over long periods enhance Alpha synuclein autophagic degradation [70]. Another agent, bafetinib prevent parkin inactivation and dopaminergic neuron loss as suggested by Imam et al. [71] Imatinib produced the similar

neuroprotective effects but it had lower bioavailability in the brain leading to less potency. During the analysis, only one patient developed a serious cardiac adverse event[72]. Various recommendations are given for nilotinib use [73]. Care and liver functions monitoring is needed [74]. Although, no convincing evidence of its efficacy in PD patients has been found yet but trials are ongoing [75]. Restoration of dopaminergic deficits has also been considered. Off-target effects can be minimized with oral dopamine replacement which can act by providing the regenerative treatments to the striatum. So far, with varying success rate, different cell sources for transplantation in PD have now been investigated [76].Many critical features of PD can be treated by such cell based approaches like use of human fetal ventral mesencephalon (VM) tissue grafts in humans. The drawbacks include ethical and others such as unexpected insufficient fetal tissue supply leading to unpromising results [76]. Stem cells is now considered as the most likely approach of delivering a clinically useful and cell-based ,clinically useful therapy for [77].The risk of tumour formation can be avoided by by thorough investigation of safety, and proper surveillance. Another approach toward a regenerative treatment for PD includes viral vectors. As per viral gene-delivery trials; Lentivirus vectors have much larger capacity for genetic cargo than Adeno-associated virus (AAV).It can be used as are integrating viral vectors[78] .**ProSavin,** a lentiviral product carrying the genes for aromatic amino acid decarboxylase, tyrosine hydroxylase and cyclohydrolase-1. Although, a phase I/II trial have shown its well tolerance but unfortunately, many patients experienced an increased on-medication dyskinesias[78]. In United Kingdom and France, a further trial of **OXB-102**, a new version of **ProSavin** is near initiation. For developing agent havng PD disease-modifying effect that targets alpha synuclein, various experimental approaches are either have been investigated or are currently ongoing.

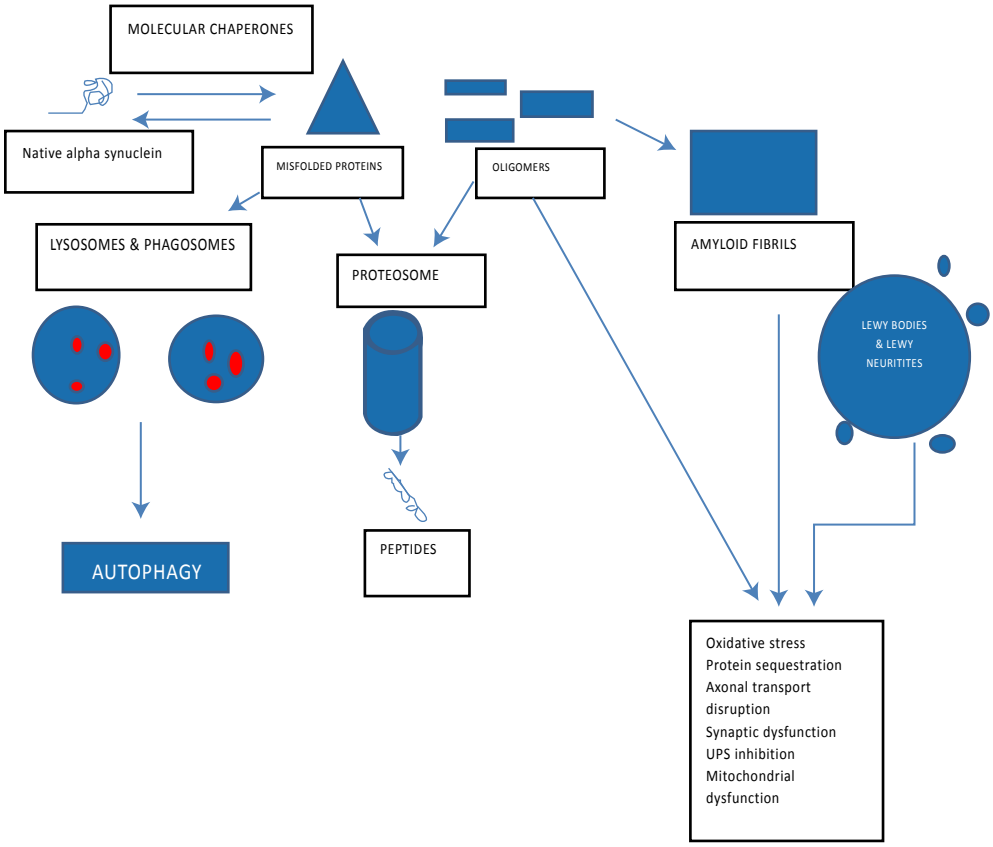

Figure 6. Diagrammatic representation of alpha synuclein as target of drug.

RNA interference technologies can be used to obtain this goal. In RNA interference, synthetic ribonucleic acid (RNA) molecules are introduced extrinsically which leads to messenger RNA (mRNA) degradation, ultimately triggering selective post-transcriptional silencing of the α-synuclein gene. Rodent model using Lentiviral delivery of a short-hairpin RNA (shRNA) offers support to this concept[79]. Direct infusion of a small-interfering RNA (siRNA) directed against α-synuclein into the mouse hippocampus has also been shown[80]. Clenbuterol , β2-adrenergic receptor agonists (β2

agonists) used in the asthma has been found to cause reduction in α-synuclein gene expression by 35% in a neuroblastoma cell line and in rat cortical neurons. Moreover, it can cross the blood brain barrier which is a necessary requirement for proposed treatment approaches [81]. Active and passive immunotherapies have been shown capable of targeting and degrading extracellular α-synuclein[82]. An active **immunotherapy vaccine (AFFITOPE PD03A, AFFiRiS, Austria)** phase I clinical trial has recently been completed. AFFiRiS , a synthetically produced vaccine containing an α-synuclein resembling peptide , has passed its safety testing in trial.Repeated subcutaneous injections of high dose or low dose AFFITOPE PD03A showed cross reactivity against α-synuclein and immune response depending on the dose against the peptide with increasing antibody titers over time. Other safe active immunotherapies in early PD include **PD01A**. Passive immunotherapeutic agent, humanized monoclonal antibodies against α-synuclein **PRX001** has also been tested. MEDI1341 for PD, additional immunotherapies targeting α-synuclein are under development. By using intravenous injections, two antibody Infusion trials are there. The current ntravenous trials are Biogen (phase 2a) and Roche (phase 2b). Despite the promising safety data, results as neuromodulating agent are insignificant. Both chaperone-mediated autophagy and macroautophagy plays significant role in alpha-synuclein degradation pathways [83]. Rapamycin , an immunosuppressant and is a recently known macroautophagy inducer [84]. Animal model of GBA1 (encoding for the lysosomal enzyme glucocerebrosidase) has shown to reduce alpha synuclein in mutation-associated PD [85].Trehalose and the tricyclic antidepressant nortriptyline increases autophagy activity like several compounds 86,87 therefore are being considered for clinical trials. Trehalose, a naturally occurring disaccharide with the ability to reduce protein aggregation as well as act via mammalian target of rapamycin for increased degradation[86,87] . Gaucher disease, a lysosomal storage disease results from homozygous mutation in Glucocerebrosidase 1 gene (GBA1 gene) which encodes for the enzyme β-glucocerebrosidase (GCase). Ongoing two clinical trials in PD patients aim to correct abnormalities in the lysosomal environment in such patients. Patients, in the first phase II trial of **MOVES-PD (Multicenter pharmacOkinetics and interVEntional Study in Parkinson's Disease - MOVES-PD)** , patients are receiving a compound called GZ/SAR4026715. It inhibits the glycosphingolipids production which build up in cells in PD patients with GBA1 mutations and are catabolized by GCase .Other clinical trials are under consideration as potential treatment for GBA1 mutation-associated PD using ambroxol[88], a Food and Drug Administration(FDA)-approved mucolytic. Ambroxol facilitates the pathway of misfolded GCase to the lysosome through its chaperone properties[89].

REPURPOSING OF OTHER DRUGS

Drug repositioning /drug repurposing or drug reprofiling is the redevelopment of a drug for its use in a different disease. Recent examples include Exanitide and Nilotinib in PD patients. Exenatide, a well known antidiabetic drug whereas nilotinib , the chronic myelogenous leukemia treatment. Currently an ongoing trial to evaluate the safety and tolerability of nilotinib in Parkinson's disease (NILO-PD) is in progress in the United States[75]. Statins has many mechanisms of actions which are cholesterol-independent and mostly have neuroprotective potential including proinflammatory molecules suppression & microglial activation, alpha -synuclein aggregation attenuation , endothelial nitric oxide synthase stimulation ,adaptive immunity modulation , neurotrophic factors enhanced expression , and inhibition of oxidative stress. An ongoing clinical trial has started in 2015 and with expected completion in 2020.It aims to determine whether protection against chronic neurodegeneration is provided by Simvastatin or not [90].

TRIALS FOR TACKLE THE PROBLEM "AT SOURCE"

Gut bacteria produce metabolites which have been identified to have a link with brain inflammation. A trial of giving PD patients, encapsulated fecal transplants from healthy individuals is under consideration. Although this approach has limitation and can contribute to ongoing neurodegeneration with time. To evaluate Fecal Microbiota Transplant (FMT) in PD management, a clinical is ongoing [91].

NANOTECHNOLOGY:

Nanoscience intends towards material manipulation at sub-atomic or atomic levels whose characteristics differ markedly as compared to the bulk matter whereas nanotechnology intends to utilize these manipulated materials for purposes like characterizing, designing and formation of improved structure, devices and systems with designated size and shape (1-100 nm) for various purposes[92]. Graphene quantum dots (GQDs) is emerging as showing some promise [93]. GQDs can block the formation of alpha synuclein fibrils and promote their disaggregation by interation with fibrils of alpha synuclein. This technology carries great promise for future health management perspectives. Although,

nanotechnology accounts only 5% in publications worldwide but this technology is at its budding level with the few products in the market [94].

OTHER AGENTS

DNL201 is a Leucine-rich repeat kinase 2 (LRRK2) inhibitor being tried in Parkinson's patients with the genetic mutation (LRRK2). Another such drug, DNL151 is being evaluated in the Netherlands96
Coffee drinking is long been known to be protective against PD[97]. Theoretically, Caffeine effects alpha-synuclein aggregation as well as on inflammatory processes in the gut. Unfortunately, clinical evidence of caffeine therapy in PD is lacking. The symptomatic effect of 200 to 400 mg per day caffeine in PD in a placebo-controlled randomized trial of 6 week showed improvement.[98] Further studies are needed. Nicotine role as a potential treatment for PD has been evaluated previously [99]. Numerous studies continued to show that PD is less prevalent among smokers than those who never smoked [100,101].

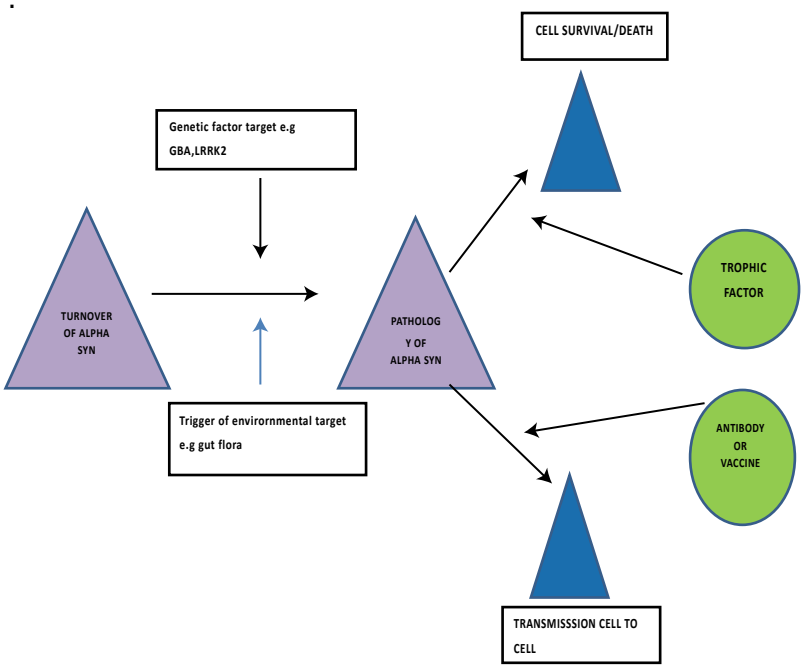

Figure 7 : PD progression impact by various agents

Nicotine experimentally did prevents or slow down neurodegeneration by up-regulating anti-apoptotic protein [102]. Moreover, cytochrome P450 enzymes family is also induced for detoxification of neurotoxin. Protection against toxin-induced nigrostriatal degeneration in a PD animal model is also provided [103]. A trial named **Disease-modifying Potential of Transdermal NICotine in Early Parkinson's Disease (NIC-PD)** has been done. The study was conducted from 2012 to 2016. In contrary to the hypothesis it was found that nicotine may accelerate the disease as shown by worsening of UPDRS scores versus placebo [104]

NATURAL COMPOUNDS

Newer researches aim for the identification of natural compounds which can of halt or slow down the neurodegeneration for example Polyphenols and flavonoids. Extracted chiefly from plants and microorganisms contain biological agents acting on multiple targets[105]. Currently, the data is scares further studies desired.

EXERCISE AND PHYSICAL THERAPY

Physical exercise, a well-recognized non-pharmacological form of PD treatment over 50 years [106] it results in improvement in functional capacity, strength, walking and balance of the patients [107,108].In rats , treadmill exercise effect were examined [109] and the results showed modulation of various factors including Brain-Derived Neurotrophic Factor (BDNF) in the basal ganglia ,changes in mitochondrial function balance and coordination. Moreover, other

animal model studies suggested that brain plasticity is also affected which in turn leads to neuromodulation.These are facilitated by Vascular Endothelial Growth Factor (VEGF) the Glial cell line-Derived Neurotrophic Factor (GDNF) release [109-111].There is also decreased formation of Reactive Oxygen Species (ROS) formation and reduced oxidative stress [112].

TABLE.5: RECENT CLINICAL TRIALS FOR DISEASE MODIFICATION IN PD

ONGOING CLINICAL TRIALS

TARGETS/MECHANISM OF ACTIONS	THERAPEUTIC AGENT	TRIALS
DOPAMINERGIC DEFICITS RESTORATIONS		
GENE DELIVERY APPROACHES	ProSavin	
TRIALS USING ALPHA-SYNUCLEINAS A THERAPEUTIC TARGET		
Alpha-Synuclein Production reduction	Clenbuterol	
Extracellular a-synuclein degradation Immunotherapies	active immunotherapy vaccine (AFFITOPE PD03A, AFFiRiS, Austria) PD01A PRX001 a-synuclein antibody MEDI1341 for PD	two antibody infusion trials Biogen (phase 2a) and Roche (phase 2b).
AUTOPHAGY ENHANCEMENT	Rapamycin	
	Trehalose and Nortriptyline	
	GBA1 mutation and Ambroxol	MOVES-PD
OTHER DRUGS REPURPOSING	Exanitide	
	Nilotinib	(NILO-PD)
	Simvastatin	
	Defiriprone	
	Isradipine	
"AT SOURCE" PROBLEM CONFRONTATION IMMUNOMODULATION TRIALS	Gut microbiome	
NANOTECHNOLOGY	Graphene quantum dots (GQDs)	
OTHER AGENTS		
URATE ELEVATION	Inosine	SURE-PD
CAFFENE		
NICOTINE		(NIC-PD)
LRRK2 INHIBITOR	DNL201, DNL151	
NATURAL COMPOUNDS	Polyphenols and flavonoids, saffron, turmeric, ginkgo, green tea/black tea	

CONCLUSION

Disease modification in PD remains an important but difficult to achieve target. Despite too many trials no agent has been approved as Parkinson disease modifying agent yet. Once this goal will be achieved successfully, neuroprotective treatment could transform PD patients' lives to a problem that can be managed rather than having a progressive and disabling disease. Most important barriers for development of disease modification drugs include PD pathogenesis knowledge limitations, lacking strategies and the study design for disease progression study. Encouragingly, there has been an increasing interest in understanding and treating PD which hopefully will lead to developing better therapies for PD. It is expected that further research focused on better elaboration at molecular level PD pathology will lead to the fruitful outcomes in understanding the main defining pathways of PD mechanisms; ultimately the efforts to develop disease modifying treatment can be advanced soon.

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