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Novel therapeutic strategies in the management of PD

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Abstract:

Parkinson's disease (PD) is a neurodegenerative condition that poses a serious threat to patients' quality of life. The progressive loss of dopaminergic neurons in the substantia nigra and the development of Lewy bodies that are high in -synuclein are the primary pathologies of PD development.The available therapeutic options are clinically beneficial because they enhance patients' quality of life and symptom severity.The goal of current scientific research is to identify disease biomarkers that will enable accurate and prompt diagnosis and to develop more potent treatments that will address current clinical needs. This review is taken through the recent strategies in the management of Parkinson's disease and is then given the opportunity to apply those ideas to routine clinical practice.

Introduction:

Parkinson's disease (PD) is a multifactorial neurodegenerative condition that gradually impairs voluntary motor control. Separated to the primary clinical feature of the disease [1].The impaired voluntary motor control is characterized by Akinesia, bradykinesia, hypokinesia, postural instability, rigidity, stooped posture, and tremor at rest. They frequently coexist with gait impairment [2, 3].

According to estimates, Parkinson's disease affects 0–3% of the general population and roughly 1% of people over 60 in industrialized nations[4]. The condition can affect people of all ethnic backgrounds, while men are slightly more likely to get it than women [5]. According to one study, there are roughly 13 incidences of Parkinson's disease for every 100,000 people. The average age at which this condition manifests was formerly predicted to be in the late 50s but is now believed to be in the early to mid-60s [6, 7].

Pathological in PD

The loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) area of the brain and the development of intracytoplasmic proteinaceous inclusions known as "Lewy bodies" are the main pathogenic features of Parkinson's disease (PD) [8]

Loss of dopaminergic neurons: The major diseased characteristic of SNpc depigmentation in PD is a result of the loss of nigrostriatal neurons in SNpc resulting in disarraying of neuronal circuits in the target regions of basal ganglia of these neurons [9]. There may also be some loss in other regions, including the ventral tegmental area and the central grey substance. Loss of SNpc neurons is accompanied by a drop in dopamine transporter (DAT) mRNA levels and a reduction in the amount of dopamine generated by these neurons [9].

Lewy bodies: Lewy Neurites (LN) and LB, which are recognisable, occur at different phases of Parkinson's disease (PD). Between cellular processes, LNs exist as spindle- or thread-like branching entities, whereas LBs are eosinophilic, proteinaceous intracytoplasmic inclusions that were seen in the cell bodies of the affected nerve cells. In pigmented nigral neurons, LBs are characterized by an eosinophilic spherical body with a dense core and a halo around it [9 ,10]. D-syn are the main components of aberrant cytoskeletal neurofilament proteins seen in LBs and LNs. Additionally, it has been demonstrated that LBs include E-amyloid precursor protein, tubulin, and microtubule associated protein. LB development has been documented in a number of PD patients with particular mutations in genes including D-syn and LRRK2. However, with the autosomal recessive young onset Parkinsonism, parkin mutation does not result in the creation of LB.

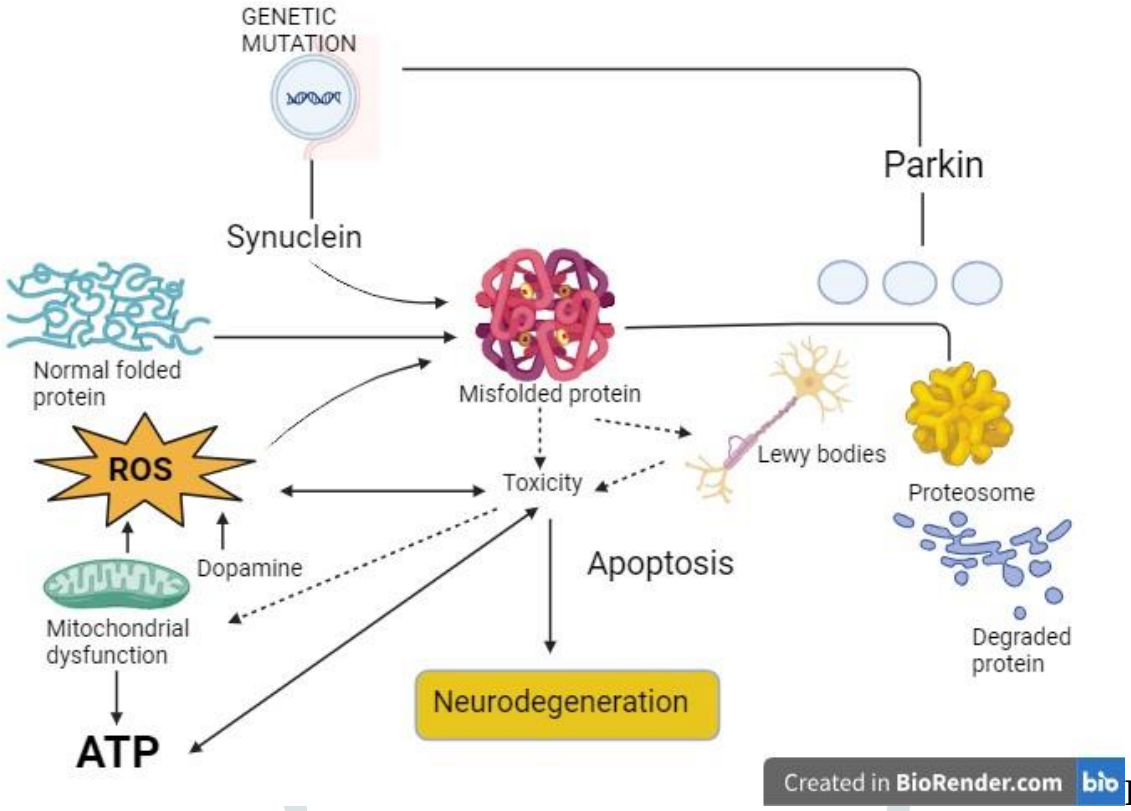
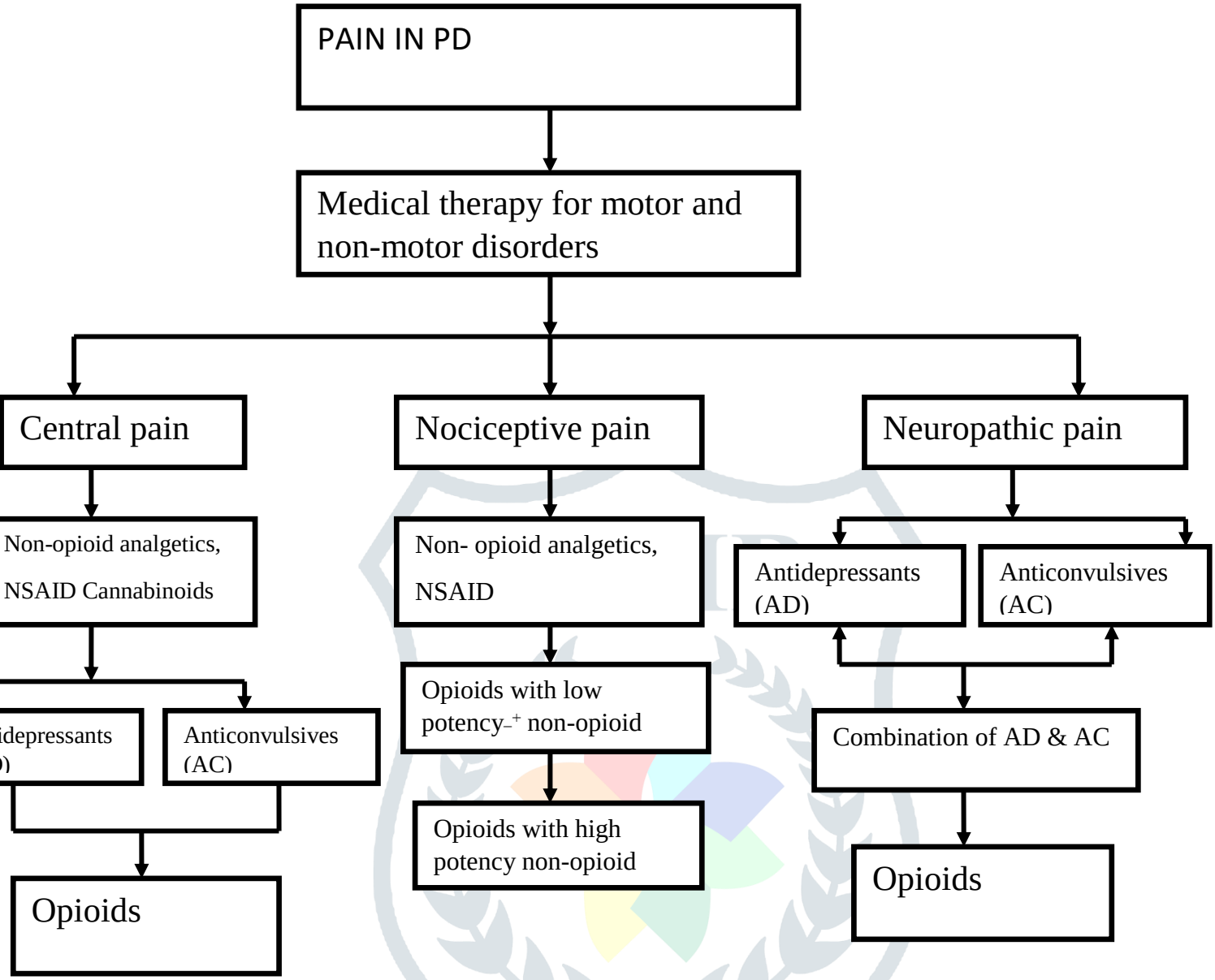


Figure 1. pathway of dopamine biosynthesis in dopaminergic neurons and dopamine release in the brain.

Pain Prevalence in Parkinson's disease

The prevalence of PD-related chronic pain varies according to the patient's age, disease stage, and concomitant factors and comorbidities.[11] The patient has stated that pain is a symptom of an early motor stage (for example, shoulder discomfort affecting localised rigidity and akinesia).[12] A prevalence of 60% for PD-related aches has been noted in middle stages.[13]Up to 80% of the population may experience altered pain perception as the disease progresses, along with an increase in pain prevalence.[14]



Novel neuroprotective and neurorestorative drugs for parkinson disease

1.Ladostigil and M30's neuroprotective and neurorestorative properties.

Ladostigil and M30 share many of rasagiline's molecular processes and neuroprotective activities in cultured neuronal cells and in vivo.[19,20] They include the inhibition of mitochondrial potential decline and cytotoxicity in SY5Y and PC12 cells in response to oxidative stress caused by peroxynitrite or glucose oxygen deprivation.[21]Ladostigil also has neuroprotective properties in vivo, greatly decreasing hippocampus cell damage caused by global ischemia in gerbils and cerebral edoema caused by closed head injury in mice.[21]Ladostigil and M30 may be able to slow the course of PD and DLB due to their neuroprotective properties against oxidative stress. Because these medications specifically inhibit MAO-A and -B and, unlike selective MAO-B inhibitors, raise brain levels of dopamine, they may give symptomatic relief of extrapyramidal symptoms.[19,20,22,23]

2. Cannabidiol neuroprotective properties.

Cannabidiol also has neuroprotective properties against MPP+, a neurotoxic that causes Parkinson's disease via increasing the expression of axonal and synaptogenic proteins and activating the nerve growth factor receptor (NGF), also known as Tropomyosin receptor kinase A (TRKA),as well as an increase in axonal and synaptogenic protein expression[24] Several chemicals present in Cannabis sativa, such as -caryophyllene and 9-tetrahydrocannabivarin (9-THCV), have shown promise in preventing the onset of Parkinson's disease. β-caryophyllene stimulates CB2, which decreases oxidative/nitrosative stress, proinflammatory cytokine release, and gliosis, which reduces neuroinflammation and nigrostriatal degeneration [25,26]

3. Parkinson's Disease with Amphetamine-Type Stimulants.

Amphetamine-type stimulants have been used recreationally to boost physical and mental performance in tired individuals.Allied and Axis armies utilised amphetamine and methamphetamine extensively throughout World War II for their stimulant and performance-enhancing benefits.[27]Amphetamine-type stimulants share twelve transmembrane (TM) helices organised in a barrel-like bundle with catecholamine neurotransmitters such as noradrenaline and dopamine.[28] An aromatic ring and a nitrogen on the aryl side-chain are required for competitive binding to the monoamine reuptake transporters, noradrenaline transporter (NET), dopamine transporter (DAT), and 5-HT transporter (SERT)[28] The molecular processes that underpin stress-induced protection have been linked to (i) reduction in baseline ERK 1/2 and kinase b levels, which are important for a variety of cellular processes include apoptosis (ii) Protein phosphatase 2, a protein 13 of 35 phosphatase involved in ERK1/2 dephosphorylation, showed decreased activity, preventing it (iii) BCL-2, a protein that promotes survival and has anti-apoptotic properties, is upregulated [29]

New physiotherapy techniques

Physical therapy for Parkinson's disease patients is defined by systematic reviews and clinical recommendations as therapies aimed at improving muscular strength, aerobic capacity, balance, gait, and functional mobility through cueing, cognitive movement methods, and physical exercises[30,31]

This notion of physical therapy management is also used by us, and auxiliary workouts such as tai chi and dance are considered separately.

1. Interventions in multimodal physical therapy.

The long-term consequences of multimodal physical therapy have only been covered in a small number of research.Multimodal physical treatment increased gait speed, Unified PD Rating Scale Activities of Daily Life subscale (UPDRS-II) scores, and UPDRS overall scores in a 6-week supervised programme observed by physiotherapists. The effects were felt for three months.[32]In another trial, individuals with moderate Parkinson's disease were given supervised physical therapy consisting of either balance and mobility training or aerobic exercise three times per week for four months, followed by one session per month for a year[33]Improvements in UPDRS-II and UPDRS Motor subscale (UPDRS-III) scores in the balance and

mobility training group, as well as walking economy in the aerobic group, were observed after 4 months, when compared to an active control group; however, only the improvements in walking economy were maintained at 16 months.[34]

2. Resistance exercise that is progressive.

Many meta-analyses support the use of progressive resistance training in Parkinson's disease rehabilitation due to its moderate short-term advantages.[35,36]The long-term advantages of this strategy, however, remain unknown. The subjects' exercise doses were increased utilisingthe notion of repeated maximum (40-80% of the amount of force that may be generated in one maximal muscular contraction).[37,38,39,40]

PRT dramatically boosted muscular strength and power in the subjects. Two investigations looked at muscular strength while without taking medication Dibble et al. observed no significant gain in muscular strength after 3 months of PRT, while Corcos et al discovered greater peak torque after 12 and 24 months of PRT.[41]

To develop off-medication muscular strength, a training duration longer than three months may be necessary. PRT for 12 weeks improved physical ability in people with Parkinson's disease as measured by the 6-minute walk test82,87 and the 2-minute step test80 immediately following training. However, Prodoehl et al. showed substantial improvements in 6-minute walk test performance after 6 months but not after 24 months of PRT.[42]

3. Aerobic endurance training.

The AET was limited to a training intensity of 60-75% of maximal heart rate or 40-50% of heart rate reserve.[43,44] The training lasted either 12 or 24 weeks. After 4 months, Schenkman et al. introduced a monthly training session that lasted up to 16 months.[45] In terms of VO2max walking economy and stress test length, as well as physical capability as determined by the 6-min walk test and 2-min step test, AET outperformed general exercise or usual care.[42,44]Numerous studies involving aerobic walking found that participants' gait performance improved in terms of walking speedstride length gait stability (as evidenced by a reduction in gait variability) and shorter double-support time.[43]

4. Patterned exercise experiments that are formalized

Tai chi has been studied in two high-quality research, with contradictory outcomes.[46]A low-quality research compared tai chi to qi-gong, with unfavourable results in both groups.[47] The same group reported two favourable but low-quality studies on power yoga.[48,49] Dancing has also been utilised as an intervention, and while the outcomes for a range of dance modalities, including tango and Irish dancing, are favourable when compared to the active comparator, the studies are of low quality.[50] One low-quality research comparing tango to regular exercise was unfavourable.[51] Because the results of studies examining organised patterning workouts varied, the effectiveness conclusion cannot be drawn "inadequate data," however the consequence for therapeutic treatment is "potentially beneficial.

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CONFLICT OF INTEREST

No conflict of interest associated with this work.

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