Neurol Ther (2025) 14:1769–1781
https://doi.org/10.1007/s40120-025-00800-3

REVIEW

Update on the Present and Future Pharmacologic Treatment of Parkinson's Disease

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Received: June 10, 2025 / Accepted: July 10, 2025 / Published online: July 18, 2025

ABSTRACT

Symptomatic drug treatment of Parkinson's disease combines various pharmacological principles for a patient-tailored drug combination. Development of more continuous delivery modes of dopamine-substituting drugs with formulations with better pharmacokinetic properties has enabled less frequent dosing and thereby provided further benefit for patients. Peripheral weakening of dopa decarboxylase activity with nutrients, such as short fatty acids, may enhance levodopa efficacy. A future concept may be mandatory combined central inhibition of catechol-*O*-methyltransferase, monoamine oxidase B and tyrosinase in levodopa-treated patients, if tolerated. This approach may hypothetically protect against toxins resulting from catecholamine metabolism. Beneficial modification of disease progression and cure is an unmet need. High expectations were mainly generated by promising positive experimental research outcomes. The employed models of Parkinson's disease provide uniform trial conditions. Drug safety and the side effect profile have minor importance. Subsequently performed translational clinical trials failed. Examples are studies with iron chelators, glucagon-like peptide 1 receptor agonists and free radical scavengers, particularly when levodopa-naïve patients were included. Multifactorial heterogeneity of disease mechanisms, variability of symptoms and their progression are the main causes for these negative results. Additionally an impact of symptomatic dopamine-substituting treatments on the course of Parkinson's disease was demonstrated in clinical studies with monoamine oxidase B inhibitors and dopamine agonists with levodopa therapy as comparator. Neuron transplantation, application of stem cells and their secreted exosomes, or secretomes, are still mainly considered by experimental researchers. Translation into clinical practice is complex or has failed. Stimulation of an existing endogenous repair system in the peripheral and central nervous system is an alternative. Repulsive guidance molecule A (RGMa) inhibits physiologic regeneration in peripheral and central neurons. Blocking of the physiologic effects of this protein initiates endogenous repair in models of acute and chronic neuronal dying as a more general therapeutic concept for chronic neurodegenerative and inflammatory disease.

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Keywords: Acetyl-DL-leucine; Deferiprone;

Dopaquinones; Levodopa; Parkinson's disease; Neuroprotection; Repair; Toxins

Key Summary Points

Dopamine-substituting drugs were improved by formulations with better pharmacokinetic behaviour.

Levodopa is the therapeutic gold standard but may accelerate ageing mechanisms, i.e. oxidative stress generation.

Future symptomatic treatment concepts may be central inhibition of catechol-*O*-methyltransferase and tyrosinase.

Progression-modifying trials failed because of the heterogeneity of Parkinson's disease among others.

Blocking of repulsive guidance molecule A may stimulate a physiologic repair mechanism as a future approach in Parkinson's disease.

INTRODUCTION

Ageing associated with accelerated cell death in the peripheral and central nervous system characterizes the onset of chronic neurodegenerative diseases. Genetic predisposition and limited detoxification, repair and regeneration capacity against exogenous and endogenous toxins are discussed as the disease onset-causing phenomena. They affect mitochondrial and cellular dysfunction and essentially contribute to the final, well-characterized modes of cell death (Fig. 1) [1]. Among the various chronic neurodegeneration disorders, Parkinson's disease (PD) is the second most common degenerative brain disease [2].

Symptoms and PD Originating Mechanisms

A smouldering, sometimes relapse-like progression is typical for the individual variable appearance of predominant motor, vegetative and psychopathological features in PD [3]. Current hypotheses also discuss environmental factors, i.e. acute, respectively chronic intoxication with pesticides. The main routes of toxin uptake are via the gastrointestinal or the bronchial system with further spread via the blood. As a consequence, one theory even proposes a rise of chronic neurodegeneration from the gastrointestinal tract via the vagal nerve to the brain, particularly in PD [4]. A typical neuropathological feature of the disease entity PD is an elevated neuronal occurrence of Lewy bodies with misfolded proteins, particularly α-synuclein protein enrichment. However it is far from clear whether this spread of Lewy bodies as a ubiquitous phenomenon in the nervous system results from the neurodegenerative disease process itself. It may also represent a defence against chronic neuronal death and its progression. Further essential neuropathological characteristics are nigral depigmentation and microglial activation in postmortem PD brain tissue [5]. More recent findings reported accumulating evidence for an association between disease intensity, described by clinical rating and functional neuroimaging techniques, and alteration of the immune system function in untreated patients with PD [6, 7]. This well-known phenomenon of endogenous inflammatory activation in the microglia and T cells may also be a physiologic clearance mechanism against the slowly evolving

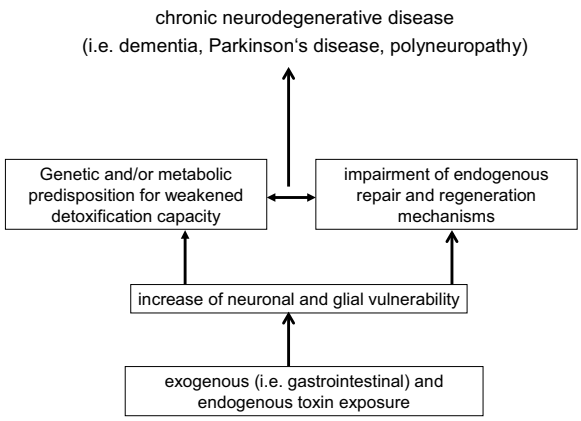

Fig. 1 Chronic neurodegenerative disease: a more general concept of disease in the peripheral and central nervous system

neurodegenerative process. Nevertheless the innate immune system is actively involved. Increased synthesis of cytokines, such as interleukin-1β or interleukin-6, particularly occurs in the early PD stages [7]. Oxidative stress generation additionally is also considered an important phenomenon [8]. Over the past 50 years, extensive experimental and neuropathological research has provided distinct and better insights and understanding of chronic neuronal and associated glial cell death. The predominant final mechanisms responsible for these processes are well identified. Investigations were mainly performed in treated but not in drug-naïve patients with PD [7]. Nowadays it is well accepted that the most important neurochemical PD feature is the nigrostriatal dopamine deficit. It is mainly responsible for the disturbances of motor behaviour [3, 5]. Chronically applied symptomatic, dopamine-substituting PD drugs induce, influence or aggravate aspects of these demonstrated metabolic changes [8]. In conclusion, the exact pathological PD aetiology is unknown. A multifactorial disease origin is likely.

PD: A Genetically Determined Disorder?

In fact the term PD describes a disease entity. It consists of different, heterogeneous subtypes, each other overlapping and not well described. More than 20 predisposing so-called PD genes with a different extent of penetration have been identified to date. They are also discussed as responsible components for onset of sporadic PD [9, 10]. Currently research still focuses on genetic alterations and mutations particularly in inherited PD. Popular ones are mutations of α-synuclein, Parkin, leucine-rich repeat kinase 2, Park-7, PINK-1, and ubiquitin carboxy-terminal hydrolase. They approximately occur 10% of idiopathic patients with PD only [9, 10]. Even in these genetic PD subtypes, age of onset and clinical symptoms are variable. This was convincingly shown in glucocerebrosidase mutation carriers. Heterogeneity was reported in terms of manifestation of motor and non-motor features, their onset at the moment of diagnosis and their progression [9–11].

Problem of Early Diagnosis

So-called cardinal motor symptoms are rigidity, akinesia and resting tremor. It is believed that their initial temporary occurrence results from neuronal death of approximately 50–60% of dopamine-synthesizing cells in the nigrostriatal system. Unspecific non-motor symptoms, such as depression or apathy, precede this impairment of motor behaviour. Clinical researchers occupied themselves with non-motor PD symptoms in more recent years. The focus on dopamine deficiency with associated motor symptom appearance has been replaced by a more widespread view of an altered, heterogeneous neurotransmission. Since the 1950s, it has been known that an individual different decline of neurotransmitters, such as serotonin, norepinephrine etc., occurs in PD and Alzheimer's disease [12]. The missing specificity of the initial non-motor signs for the evolving neurodegenerative process is one reason for initial diagnostic difficulties. In clinical practice, onset of motor symptoms, like the typical one-sided rest tremor, is the most common symptom raising suspicion of PD. Indeed the moment of diagnosis often reflects a relative advanced stage of PD [13]. Onset of balance problems is a further essentially quality of life-limiting symptom. It mostly reflects a later stage of PD. These postural disturbances do not respond to dopamine substitution in contrast to the motor symptoms. Their improvement, i.e. following application of the blood–brain-crossing dopamine precursor levodopa (L-dopa) or the dopamine agonist apomorphine, serves as diagnostic criterion in the clinical practice [13].

SYMPTOMATIC THERAPIES IN PD: DOPAMINE SUBSTITUTION

Considerable research activities in the past 60 years led to the development of PD symptom-alleviating therapies by dopamine substitution with drugs. The initial and most essential

breakthrough was made with L-dopa in the 1960s: it ameliorates motor and to a considerable extent associated non-motor symptoms in PD [14, 15]. Drug development started with L-dopa alone, followed by the dopamine reuptake inhibitor and *N*-methyl-D-aspartate antagonist amantadine. Then ergot and later non-ergot dopamine agonists and enzyme blockers of dopa decarboxylase, monoamine oxidase B (MAO-B) and catechol-*O*-methyltransferase (COMT) were introduced. A certain debate on the use of L-dopa is still ongoing in the scientific community due to the onset of fluctuations of motor behaviour, acceleration of ageing processes and assumptions about L-dopa neurotoxicity [16]. In particular, plasma fluctuations of L-dopa, which are believed to be closely associated with dopamine oscillations in the synaptic cleft, counteract the well-accepted concept of "continuous dopaminergic stimulation" for PD treatment [17]. Many lines of evidence showed that constant delivery of dopamine-replacing drugs is an essential precondition for nearly normal movement behaviour in patients with PD. Therefore PD drugs with long half-life, i.e. delayed release formulations, are advantageous. Compensation capacity of persistent oral L-dopa intake-related central synaptic dopamine oscillations diminishes after a certain individually varying interval. The consequence is slowly evolving onset of so-called motor complications. Their characteristics are changes between adequate motor behaviour, recurrence of motor impairment, the so-called OFF, and too high dopamine stimulation, causing involuntary movements. They are referred to as dyskinesia [17]. These motion alterations are associated with non-motor fluctuations [18]. As an example, frequently apathy appears within OFF states. Dyskinesia may be related to manic episodes. OFF episodes are less well tolerated by patients than dyskinesia [18]. Treatment of these ups and downs of motor and non-motor PD features is still in the focus of current ongoing drug research in PD [17, 18]. Accordingly innovation has focussed on novel formulations of L-dopa, dopamine agonists and amantadine with improved pharmacokinetics [19]. Continuous, subcutaneous apomorphine or L-dopa brain delivery by pump devices improve motor fluctuations considerably [20, 21]. An alternative is the use of on-demand therapies. They aim to get patients quickly out of quality of life-limiting OFF states. Application of fast release and quickly acting PD drugs is performed. Various drug administrations are used. Mechanisms are circumvention of the impact of gastric emptying and gastrointestinal absorption on drug efficacy. Soluble L-dopa/benserazide, inhalation of L-dopa alone or sublingual application or subcutaneous injection of the dopamine agonist apomorphine were developed. They have in common that the patients themselves or their caregivers must recognise the onset of the OFF interval as early as possible. Moreover they must be able to learn the application mode. To date no comparative analysis exists which shows the superiority of one treatment paradigm over the other in terms of continuous versus on-demand administration of dopamine-substituting compounds in the short and long term. Pivotal trials with these on-demand therapeutics showed the efficacy of each approach [19, 22, 23]. Well-selected advanced PD patient cohorts were included. Only well-known PD compounds were investigated within these new application modes. Mainly the interval to normal movement behaviour, termed ON, was measured and reported. The effort required for intake was not considered; however, it varies, e.g. sublingual application versus subcutaneous injection of apomorphine [19].

Impact of Therapeutic Dopamine Substitution Approaches on PD Progression

Out of the symptomatic PD drug portfolio is L-dopa—the most commonly applied compound, but its use is a double edged sword. On the one hand it is well tolerated, very efficacious and therefore improves quality of life. Therefore its use should not be delayed, particularly when access to medication is limited and the initiation of L-dopa therapy often occurs many years after onset [24, 25]. On the other hand one frequently discussed long-term side effect of oral L-dopa is the onset of motor complications. Moreover chronic L-dopa metabolism via COMT consumes methyl groups. Methyl groups play numerous physiological roles in humans, such as affecting gene function. Consequently chronic L-dopa

supplementation reduces the methylation capacity. As shown in chronic L-dopa/dopa decarboxylase inhibitor (DDI)-treated patients with PD, the methylation deficit may accelerate ageing processes, neuronal dysfunction and oxidative stress generation etc. [8]. The discussion on the detrimental effects of L-dopa on the progression of PD did not consider these more holistic consequences of long-term metabolic aspects of L-dopa/DDI administration. The main focus was chronic degradation of nigrostriatal dopamine-generating neurons and experimental research in isolated neuron models of PD [26, 27]. However actually outcomes of the LEAP (levodopa in early Parkinson's disease) study propose a certain PD progression-accelerating effect of chronic L-dopa/DDI therapy. Only L-dopa-naïve patients were included. PD progression was faster in the second half of the trial between week 44 and 90 in the patient cohort with early L-dopa/DDI start and longer intake, compared with the study arm with a delayed and thus shorter L-dopa/DDI exposure [28]. This is discussed in detail by the authors of the LEAP study. They write that one interpretation of the outcome of the non-inferiority analysis during phase 2 of the trial, during which both groups were exposed to L-dopa/DDI and during which the rate of change in the Unified Parkinson's Disease Rating Scale (UPDRS) score was faster in the early-start group than in the delayed-start group, is that disease progression was more rapid in the early-start group. The observation that 48 patients in the early start arm and 62 patients in the delayed start group need additional antiparkinsonian drug therapy is not worth mentioning in this discussion. The dosing of this supplementation of PD therapy is also not reported [28]. Therefore the published data of the LEAP study did not allow any firm conclusions on chronic L-dopa/DDI treatment effects on the PD course from the clinical point of view. However an interesting result was earlier shown with L-dopa-sparing treatments, i.e. with the MAO-B inhibitor selegiline. Initially, trials convincingly showed motor symptom-ameliorating effects of selegiline. It delayed the need to initiate L-dopa therapy. Combined with L-dopa/DDI only over an up to 5-year treatment interval, selegiline improved PD-associated, reduced end-of-dose motor fluctuations, and the need for dosing and intake frequency of L-dopa. Diverging curves in terms of L-dopa/DDI dosing over 5 years appeared in this SELEDO (from selegiline plus L-dopa) study [29]. One may discuss this outcome as a beneficial PD progression-modifying benefit. A controversial discussion on putative cardiotoxicity and the availability of the better-tolerated and safer rasagiline with its similar mode of action limit the clinical use of selegiline nowadays. Similar results were shown with the dopamine agonists ropinirole and pramipexole. Their chronic intake was related to lower progression of presynaptic, nigrostriatal dopaminergic neurodegeneration compared with L-dopa/DDI therapy. Diverging curves appeared in terms of radiotracer uptake with the applied functional imaging techniques [30, 31]. This was not the case when monotherapy with pramipexole was investigated within a delayed start design without comparison against L-dopa/DDI treatment [32].

Failures of Disease Modification in PD

To date the most unmet treatment need in PD is still beneficial disease modification or cure. Direct therapeutic interventions on the various aforementioned disease mechanisms in PD were tested. The list of clinical trial failures is long. It includes free radical scavengers, such as tocopherol or coenzyme Q, or antibodies against misfolded α-synuclein [1]. This latter therapeutic approach causes decline of the ubiquitous, multifunctional, soluble, monomeric protein α-synuclein. It is transformed to an abnormal, insoluble, amyloid state. Many reasons, such as exposure to toxins or infectious pathogens, are believed to cause the loss of soluble α-synuclein by misfolding [5]. The negative study outcomes suggest that antibodies against α-synuclein, like cinpanemab or prasinezumab, and the α-synuclein-degrading nilotinib do not support beneficial modification of the PD course. All the tested α-synuclein metabolism-impacting compounds had one thing in common: they were safe, but provided no symptomatic benefit in the clinic [19].

Examples of Questionable Trial Designs and Conclusions

Trial inclusion criteria may also contribute to negative clinical study outcomes. An example is a trial on iron chelation with deferiprone within the context of the decades-old debate on an increased free radical generation as an essential characteristic of PD pathology. It involved a discussion on the role of iron [33].

Deferiprone Failure

The main objective of the clinical deferiprone study was to show a certain disease-modifying effect. The outcomes were negative [34]. Only L-dopa-naïve patients were included. Oxidative stress resulting from chronic L-dopa/DDI intake was not considered. L-Dopa/DDI administration reduces cysteine and cysteinyl-glycine (Cys-Gly). Their occurrence indirectly reflects oxidative stress exposure. Cys-Gly and cysteine are needed for the generation of the radical scavenger γ-glutamyl-cysteine-glycine, also termed gluthathione (GSH) [8]. Many experimental and clinical investigations in PD relate nigrostriatal, dopaminergic neuronal degeneration to oxidative stress associated with neuronal dopamine metabolism, lower GSH content and concomitant iron increase [33]. These free radical generation-causing effects of L-dopa/DDI contribute to further neuronal damage in PD. Deferiprone generally decreases iron in tissue, but only free iron is related to oxidative stress. In contrast bound iron has many physiologic roles, e.g. in haemoglobin. It transports oxygen to all parts of the body in red blood cells. Iron is also present in myoglobin. This protein transports and stores oxygen, i.e. in muscles [33]. As a result, long-term deferiprone therapy may cause manifestation of various unspecific symptoms, such as weakness. Accordingly, patients with poorer PD rating scores compared to the placebo were found in the iron chelator-treated PD cohort [34]. Again here, this trial design equated symptomatic improvement in UPDRS scores with disease modification. This employed clinical assessment instrument essentially contributed to the negative outcomes.

Modification of Disease Progression by Lixisenatide?

A similar development occurred in the case of the glucagon-like peptide 1 (GLP-1) receptor agonist lixisenatide [35]. Mainly L-dopa/DDI-treated patients with PD were recruited (lixisenatide, 100; placebo, 97). A small difference of improvement (3.08, confidence interval [CI] 0.86–5.3 points) in the applied PD rating scale score was found compared with placebo after 12 months and 2 months later after the treatment stop of lixisenatide or placebo. Lixisenatide induced slight weight loss (common adverse effects 8%). Dosing changes of dopamine substitution in the second 6-month-long study were higher (4.4, CI – 39.5 to 30.6 mg L-dopa equivalents) in the lixisenatide-treated cohort. Nausea and vomiting was more frequent in the lixisenatide-exposed study arm (59%) compared with the placebo group (15%). Both characteristics are typical for dopamine substitution. Elevated dosing of dopamine substitution and the increase of L-dopa-associated onset of gastrointestinal side effects hypothetically complement each other. They may also serve as signs of higher L-dopa bioavailability. This hypothetically contributed to the observed improvement, which is per definition not regarded as a clinically relevant one [36]. Accordingly a further corresponding trial with a GLP-1 agonist in L-dopa-naïve patients was negative [37].

Revival of Nicotinamide

Nicotinamide adenine dinucleotide (NAD) is again mentioned as a further potential candidate for disease modification, because this compound may provide benefit on multiple potential pathways associated with PD. However the effects of NAD on increased L-dopa bioavailability are underestimated. They may complicate and interfere with the demonstration of a PD-modifying effect [38, 39].

Future Negative Result with Acetyl-DL-Leucine?

One more recent example is probably now started with case reports on two idiopathic patients with disturbed REM sleep behaviour

disorder (RBD). They took acetyl-DL-leucine (ADLL) 5 g daily. An improvement of dopamine-sensitive RBD symptoms was reported [40, 41]. A simultaneously occurring reversal of loss of striatal dopamine transporter binding was observed. ADLL is now proposed as a disease-modifying compound in PD. Clinical trials have been initiated and expectations are high. To date no one considers that long-term ADLL substitution will probably induce a central enzyme induction of amino acid decarboxylase. It transforms not only ADLL but also L-dopa to dopamine in nigrostriatal presynaptic neurons. Accordingly more dopamine is generated and released to the synaptic cleft. Therefore dopamine-sensitive RBD symptoms are improved. Dopamine transporter activity for dopamine reuptake from the synaptic cleft is upregulated. This effect was mirrored by the observed increased dopamine transporter binding in the nigrostriatal region of the two reported patients with idiopathic RBD over time [42]. One patient with RBD even performed a 10-day-long stop of ADLL intake. However its is well known that adaptive gene regulations of enzyme activities generally last considerable intervals. In conclusion these case reports only describe the phenomenon of enzyme induction with a symptomatic effect, but not a neuroprotective disease severity reversal [42].

Putative Reasons for Failed Translation into Clinical Valuable Results

Frequently, an increasing body of experimental and clinical publications report promising results. They are based on investigations in the uniform cell culture—and animal PD models for modification of progression. It is well known that they only partially reflect the heterogeneous, clinical picture of PD in patients. Then the translation into reliable clinical outcomes fails. The consequence is the current near standstill of clinical drug research in PD.

Dilemma of Negative Clinical Outcomes

One must crucially scrutinize whether the past focus on neuropathological findings with Lewy body accumulation, misfolded α-synuclein enrichment or oxidative stress increase is so important [5, 8, 33]. For example, free radical occurrence may also be influenced by the available chronic symptomatic treatments, i.e. L-dopa. Environmental, genetic and further still to be discovered pathways probably complement each other in PD onset. PD appears to be the final clinical disease consequence of various pathways to disease onset. The smouldering PD manifestation is followed by an individually differing, non-linear progression. The academic claim to identify and define an interval before onset of motor symptoms is difficult in real-world clinical practice. Easy to manage, cheap and simple to perform biomarkers or predisposing gene analysis are currently discussed. Determination of α-synuclein in body fluids or skin is proposed and validated, but its value as a screening method in the general population is questionable [43]. However even healthy individuals are not always interested in receiving some information on the likelihood of getting a chronic neurodegenerative disease, as shown in Huntington's disease [44]. The main reason is the currently missing availability of a therapeutic prevention or disease modification. Additionally such an intervention should be safe and well tolerated during long-term application. Therefore one may assume that onset of motor symptoms, such as tremor, will still remain the main diagnostic feature in real life in the next few years and not the so-called premotor PD interval [13]. Clinicians often see an individual different sensitivity for initial impairment of motor behaviour in patients with PD. A wide range from total symptom neglect to hypochondria is common. Accordingly disease severity even in cohorts with previously untreated patients with PD is highly variable. This is in contrast to the experimental investigations on therapeutic disease modification in animal PD models with their more uniform deterioration of motor behaviour. Documentation of drug safety and tolerability is also important during performance of clinical studies in contrast to preclinical research in experimental PD models. Moreover in PD trials on disease modification, coexisting disorders, if not excluded in the inclusion criteria, may further impact diversity of PD participants. These different trial conditions may also contribute for the failed translation of promising experimental

results into positive clinical research outcomes [1].

Assessment Problem Past clinical studies mainly employed changes of rating scale scores as endpoints. They are additionally biased by symptomatic treatment effects. Thus trials equated symptomatic improvement (e.g. in UPDRS scores) with disease modification. This is further complicated by the lack of a reliable biomarker allowing the monitoring of disease progression. Moreover the estimate that most dopaminergic neurons are already lost at the moment of diagnosis in clinical practice contributes to the failed approaches in the translational studies on disease course modification. A more clinically relevant primary objective may be the need for dopamine substitution, calculated as L-dopa/DDI equivalents [45]. To date, no new real alternatives to clinical rating have been accepted. An easy to perform, cheap and reliable convincing objective assessment model is not available. Even instrumental monitoring of motor activity interferes with the symptomatic dopamine substitution therapies. Instead L-dopa or L-dopa equivalent-sparing effects with the main criterion of diverging curves, i.e. of rating scores, as the main study objective may be employed to compare the effect of a tested compound against placebo [29]. Moreover trials over several years are warranted to demonstrate drug safety and long-term tolerability of the investigated treatments and to avoid negative consequences, as shown, for example, in the case of iron chelation.

FUTURE

Personalised treatment regimes for patients with PD with an individual dosing of compounds and repeated adaptation of a patient-tailored combination drug regimen will gain more importance again throughout the whole PD course. This was and will be an essential precondition to achieve an optimum therapeutic outcome and quality of life for patients with PD. One will realize that overly strict dosing ranges and regimen embedded in increasingly standardised treatment guidelines are counterproductive for the daily practice [46, 47].

Possible Future Pharmacologic Developments

One may consider to develop centrally acting COMT inhibitors [48]. They may have an impact on central glial dopamine metabolism, but may enhance central glial oxidative stress. Therefore they should always be combined with MAO-B inhibitors [49]. Central COMT constraint will probably lower centrally elevated homocysteine levels in patients with PD similar to the already demonstrated effects in plasma [50, 51]. Clinically these COMT inhibitors will probably improve certain non-motor symptoms, such as depression, cognition, learning and apathy. This effect also results from higher concentrations of biogenic amines in the mesolimbic system. It resembles the consequences of the mode of action of noradrenergic and serotonergic reuptake inhibitors. A future study programme should focus on these non-motor symptoms in addition to the well-known effect on OFF time reduction. One may consider self-rating by patients combined with additional external rating by physicians, i.e. as already done in a trial with tolcapone on non-motor symptoms [52, 53].

A further pharmacological principle may be peripheral inhibition of tyrosinase, i.e. with resveratrol [54]. This enzyme oxidizes L-dopa to dopaquinone. This pathway is not considered as major. Dopaquinones are oxidation intermediates. They lead to a multitude of different products. Their amino group can attack the electrophilic quinone ring to form the cyclic aminochrome. It tautomerizes to 5,6-dihydroxyindole, which is a precursor for the neuronal pigment neuromelanin. In the presence of iron, DA-quinone can react further to form the neurotoxin 6-hydroxydopamine. DA-quinones are also precursors for the enzymatic formation of tetrahydroisoquinolines like salsolinol. Particularly N-methylation of salsolinol forms an endogenous neurotoxin. It causes oxidative stress and mitochondrial damage by inhibition of the electron transport chain. Additionally, salsolinol

can heavily disturb metabolism of catechols by inhibition of tyrosine hydroxylase, dopamine-β-hydroxylase, COMT and MAO. Dual peripheral inhibition of COMT and dopa decarboxylase as a standard treatment approach nowadays may enhance L-dopa metabolism via tyrosinase in the periphery. Combined central inhibition of catechol-*O*-methyltransferase, MAO-B and tyrosinase should be mandatory in L-dopa-treated patients, if tolerated. This approach may hypothetically protect against toxins resulting from catecholamine metabolism [54–56].

Peripheral consumption of L-dopa metabolism enzyme activity by certain nutrients may also be interesting, when they undergo metabolic decarboxylation [57, 58]. L-Dopa alone is mainly decarboxylated to dopamine in the periphery. This reaction limits the therapeutic L-dopa efficacy on motor impairment in PD. Therefore L-dopa is applied with a DDI. Inhibition of decarboxylation is induced by DDIs like carbidopa and benserazide. They work to an individual but only certain and probably constant extent. Continuous dosing of nutrients, such as short fatty acids, which undergo decarboxylation, consumes enzyme activity. It results in an overall impaired decarboxylation capacity. Accordingly the efficacy of the applied DDI goes up. As a result, L-dopa is less metabolised. L-Dopa's half-life and its plasma bioavailability are elevated. More L-dopa is transported across the blood–brain barrier and converted to dopamine by dopa decarboxylase in presynaptic nigrostriatal dopamine-synthesizing neurons. The therapeutic efficacy of each L-dopa/DDI formulation administration increases. This principle works. A similar effect was observed by an elevated carbidopa dosing. Administration of 65 or 105 mg carbidopa instead of the EU conventionally applied 25 mg carbidopa improved symptoms in L-dopa/entacapone-treated patients with PD [59].

From Transplantation to Repair

Experimental researchers still mainly focus on substitution of dopamine-generating neurons in their uniform PD models. They observe benefits on motor behaviour. However the translation into clinically reliable and positive outcomes faces serious problems, i.e. due to the heterogeneity of patients with PD [60]. Transplantation of dopamine-synthesizing cells had negative results in controlled clinical trials. Conversion of neural or non-neural lineage cells into functional neurons may be promising. This approach may overcome disadvantages of neural stem cell therapy. Many strategies were developed to transform astrocytes, fibroblasts and glial cells into mature and functional neurons. Further approaches were the regulation of transcription factors or application of small chemical molecules, secretomes and exosomes. Experimental researchers administered these therapies [61, 62]. However it is also important to address the safety, efficacy, ethical, cost and regulatory concerns before scaling these treatments to clinical use [63]. In view of these past failed translations into clinical trials, experimental research has already provided a promising alternative. The concept is to stimulate an existing, endogenous regeneration pathway in the peripheral and central nervous system [64, 65]. This is now a more general treatment concept in chronic neurodegeneration (Fig. 2).

Regeneration by Repair

Evidence accumulates that repulsive guidance molecule A (RGMa) accelerates neuronal death as a more general principle, i.e. via apoptosis as

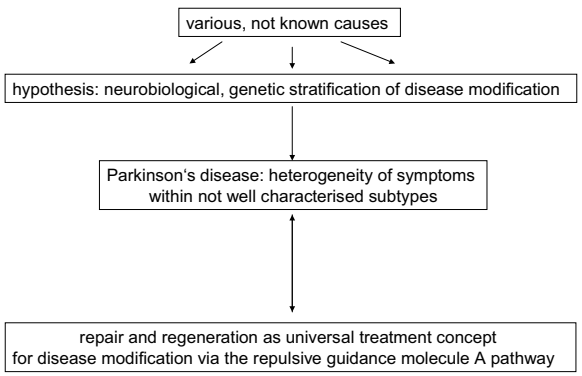

Fig. 2 Repair and regeneration in the peripheral and central nervous system via the repulsive guidance molecule A pathway blocking

suicidal cell death mechanism. RGMa inhibits growth of axons and regulates cell death. RGMa levels increase after acute and chronic neuronal injury. RGMa concentrations are elevated in chronic neurodegenerative diseases [64, 65]. Antagonism of RGMa function has the potential to initiate neuroregeneration (Fig. 2). The RGMa antibody elezanumab was efficacious in models of optic nerve crush and optic neuritis. It enhanced axon regeneration and prevented retinal degeneration. Elezanumab was also efficacious in multiple sclerosis models [66, 67]. RGMa antagonism covers the peripheral and central nervous system. Therapeutic decrease of the physiologic effects of RGMa contributes to regeneration of neurons in the long term. It performs repair and weakens the consequences of toxin exposure. A complementary approach is the additional neoginin blockade, which supports cell survival and axonal regeneration together with RGMa blocking. Prior experimental findings provided a compelling rationale for the clinical development of the RGMa antibody elezanumb in chronic neurodegeneration, like PD. A RGMa increase was also found in the substantia nigra of patients with PD [64]. One cannot be sure that this outcome may partially be induced by L-dopa/DDI administration with concomitant L-dopa-induced generation of free radicals [16, 68, 69]. RGMa antagonism represents a more general but promising repairing treatment approach compared with substitution of dopamine-generating cells, application of stem cells and of associated cell exosomes or secretomes. It is a more uniform treatment for the various nervous system diseases. To date no therapies exist that promote recovery of function following lesions in the central nervous system in the clinic [1]. In PD, an appropriate moment for this kind of therapeutic repair approach will initially be after diagnosis to modify progression with subsequent support of endogenous, probably continuous neuronal and glial repair with blood–brain barrier-crossing small molecules.

Author Contribution. Thomas Müller is the author solely. He is responsible for conception, design and writing of this review.

Funding. No funding or sponsorship was received for this study or publication of this article.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Thomas Müller is an Editorial Board member of Neurology and Therapy. Thomas Müller was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by the authors.

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