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Emerging Therapies in the Pharmacological Treatment of Parkinson's Disease

Amos D. Korczyn and *Miri Nussbaum*

Department of Neurology, Sackler School of Medicine, Tel-Aviv University Medical School, Ramat-Aviv, Israel

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Abstract

The pharmacological management of Parkinson's disease is a complex and dynamic task; there is no one 'right' strategy indicating which drugs should be used at a particular stage of the disease. There are now many different drugs belonging to several classes that may be effective, and there are still differences of opinion among leading clinicians about the best course of treatment.

This review focuses on drug therapy for the motor impairment in Parkinson's disease. Current and future research directions are summarised by taking inventory of recent and innovative areas of development in the field, representing each category with at least one of its featured treatments.

The main research efforts are being directed towards delaying the use of levodopa or finding therapies to be used as adjunct to it, in order to postpone motor complications and, in particular, dyskinesias. One of the recent trends is early employment of dopamine agonists. Additional efforts are being directed towards

protecting and restoring dopamine neurons. Novel therapies acting on non-dopaminergic systems are also being researched.

On March 20, 2000, after several months of conferencing and almost endless discussions involving US government officials, university-based scientists, drug industry representatives and Parkinson's disease patient advocates, the US National Institutes of Health sent to Congress a 5-year plan to spend close to $US1 billion in new funds for research to combat and conquer Parkinson's disease. This document is possibly unprecedented in its focus on a single neurological condition. This ambitious plan not only delineates the scope of research for the next 5 years, but also emphasises the utmost priority that is given to Parkinson's disease research. Captured in the investigative spotlight were all of the principal areas of basic and applied research, including genetic and environmental studies of the causes of Parkinson's disease, and the development of new therapies, both pharmacological and surgical.

One section of the report calls for increased attention to the development of new tools and techniques for use in the research process itself, including finding new cellular, molecular and animal models of Parkinson's disease, and developing new biomarkers and neuroimaging techniques. Another recommendation is to address such topics as genetics, epidemiology, the 'life and death' of neurons, and the neural circuits involved in Parkinson's disease. Yet another recommended focus is on treatment strategies, including new drugs, deep-brain stimulation, cell implantation, gene therapy and rehabilitation. Although active research is already on its way in all these disciplines, undoubtedly the coming years will see great advances in current trends along with the breakthrough of innovative treatments.

Levodopa remains the 'gold standard' of Parkinson's disease therapy. It is the most potent antiparkinsonian drug available.[1,2] However, long-term use of levodopa therapy often leads to complications later in the disease, such as wearing-off, dyskinesias, freezing episodes, and the unpredictable 'on-off' fluctuations which is the most problematic.[3-7] The pathogenesis and pathophysiology underlying these complications are unclear; altered pharmacokinetic and pharmacodynamic factors as the disease progresses may be major contributors. In addition, it has been speculated that the complications may derive, at least partly, from toxic effects of levodopa or dopamine oxidative metabolites.[8] Alternatives that delay or reduce the exposure to levodopa have been explored; this trend will probably continue in the future. Another focus of research efforts will be improving patient quality of life by treating adverse effects and complications of current therapies.

Since levodopa treats the symptoms of the disease, accurate assessment of the patient's real condition and monitoring the disease progression are problematic issues. At present, the only way to assess progression or deterioration is by withdrawing levodopa for a period exceeding 2 weeks. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) markers are being developed and have shown significant correlations between global severity of Parkinson's disease and functional imaging.[9-11] These methods will undoubtedly be used in future research as surrogate markers for disease progression.

Several therapeutic approaches for Parkinson's disease are now being explored:

- Compensating for the main deficiency in Parkinson's disease, the decreased levels of dopamine in the brain. This objective can be achieved in several ways: direct stimulation of the remaining dopaminergic receptors (using dopamine agonists) as well as increasing the level of available dopamine in the synaptic clefts by inhibiting either its breakdown [catechol O-methyltransferase (COMT) or monoamine oxidase B (MAO-B) inhibitors] or its reuptake (reuptake inhibitors). Therapies based on these approaches are already being extensively used, but newer, more specific treatments with better

efficacy and tolerability profiles are being developed.
- Manipulation of other neurotransmitter systems that possibly interact with the dopamine system.
- Protecting dopamine neurons and other neuronal populations which degenerate in the brains of patients with Parkinson's disease.
- Restoring neuronal systems involved in Parkinson's disease.

In addition, novel delivery systems are being tested, in order to overcome the devastating 'on-off' fluctuations and dyskinesias, such as implanted pumps that release a continuous supply of levodopa.[12]

1. Increase Dopaminergic Stimulation

1.1 Dopamine Agonists

Dopamine agonists are at present the most widely used adjunct therapies to levodopa.[13] Similarly to levodopa, they stimulate dopamine receptors, albeit with variations in their affinity towards receptor subtypes. Consequently, they can be used as adjunct therapy to reduce levodopa dose, or to replace levodopa altogether, thereby limiting or abolishing its unwanted effects.[14,15] Indeed, there is a heated controversy regarding the preferred initial therapy; the use of a dopamine agonists as monotherapy as first line therapy for Parkinson's disease is increasingly advocated, sparing levodopa for later stages of the disease.[16-19]

Apomorphine is the most potent dopamine agonist and the only one that stimulates effectively both dopamine D_1 and D_2 receptors (as does dopamine itself). However, its therapeutic effect is hampered by its complex interindividual pharmacokinetics and pharmacodynamic variability and its narrow therapeutic range.

In order to overcome these difficulties, several attempts to create individualised controlled delivery systems for apomorphine are being explored, such as transdermal iontophoresis[20] and sublingual delivery of apomorphine, for a fast effect to control fluctuations.[21,22] In a recent study, carboxymethyl cellulose powder of apomorphine was tested as an intranasal sustained-release formulation.[23] These newer delivery systems will hopefully enhance the use of apomorphine as a rescue medication in patients with severe symptoms.[22,24]

Currently used dopamine agonists include the 'ergot-derived' or 'ergoline' agents: bromocriptine, cabergoline, lisuride, and pergolide, with chemical structures based on ergot, a plant alkaloid. The newer, 'non-ergoline' dopamine agonist synthetic medications: pramipexole and ropinirole (chemically unrelated to ergot) are being promoted vigorously.

Adverse effects typical of all dopamine agonists as well as levodopa include nausea, vomiting, dizziness, and orthostatic hypotension.[25,26] At higher doses, dopamine agonists may induce confusion, hallucinations or psychosis.[27-29] Sedation and insomnia are other reported adverse effects of some dopamine agonists, as well as of levodopa,[30,31] and are probably not associated with any specific agonist. Episodes of a compelling urge to sleep (so called 'sleep attacks') have been observed in patients treated with dopamine agonists.[32-34] This is a serious adverse effect that may results in driving accidents.

Some of the adverse effects specifically linked to the ergot derivatives include digital or coronary vasospasm, as well as pleuropulmonary and retroperitoneal fibrosis.[35] These are not associated with the newer and safer 'non-ergoline' dopamine agonists, ropinirole and pramipexole.[36]

A transdermal formulation of the experimental D_2-receptor selective agonist rotigotine (N-0923) is being developed.[37] It was found to reduce daily levodopa doses by 30% in a multicentre phase IIb trial in patients with mild to severe Parkinson's disease. A phase II efficacy trial also gave encouraging results.[38] Levodopa methylesther and levodopa ethylester - new, highly soluble prodrugs of levodopa, are being evaluated in clinical trials as rescue therapies for severe fluctuations in patients with advanced Parkinson's disease.[39,40]

The efficacy of the dopamine agonists is primarily attributed to their interaction with the D_2 subtype dopamine receptors, and less, if at all, to D_1

receptor stimulation. Nevertheless, some interest in pure D_1-receptor agonists still exists, for example in adrogolide (ABT-431),[41] BAM-1110,[42] and dinapsoline.[43,44] The investigational results may direct future research efforts towards developing a combination of D_1- and D_2-receptor agonists.

Table I summarises the status of dopamine agonists currently under development along with other novel Parkinson's disease therapies.

1.2 Catechol O-methyltransferase (COMT) Inhibitors

Catechol O-methyltrasferase (COMT) is an enzyme that breaks down levodopa, before it can be converted to dopamine, as well as dopamine itself. COMT inhibitors prolong the availability of a single dose of levodopa, without delaying the onset of its effects, frequently reducing the total amount of levodopa needed. The present indication for COMT inhibition is as adjunct therapy to levodopa in patients with advanced Parkinson's disease who have developed wearing off or 'on-off' fluctuations.[45] However, treatment of earlier stages of the disease may also be worthwhile by preventing or delaying these motor complications. COMT inhibition as a new treatment strategy for Parkinson's disease has been recently comprehensively reviewed in this journal and elsewhere.[45-48]

Two COMT inhibitors, tolcapone and entacapone, have been widely tested so far. Although

Table I. Drugs in clinical development for the treatment of Parkinson's disease

Drug	Phase	Originator
Apomorphine sublingual	Phase III	
CHF 1301 (levodopa ethylester, levodopa prodrug)	Registered in Italy	Chiesi
Efilevodopa [TV 1203] (levodopa ethylester dopamine agonist, levodopa pro drug)	Phase III	Teva Pharmaceuticals
Rotigotine [N-0923] (trans-dermal formulation; D_2 agonist)	Phase III	Discovery Therapeutics/ Schwarz Pharma
Sumanirole [PNU-95666] (D_2 agonist)	Phase II	Pharmacia Corporation
Entacapone (an improved formulation)	Phase III	Novartis Comtan
SPD-473 [BTS-74 398] (dopamine re-uptake inhibitor)	Phase II	Knoll
Brasofensine (dopamine re-uptake inhibitor)	Phase II	NeuroSearch
Memantine (NMDA channel antagonist)	Phase III	Merz & Co
Remacemide (NMDA channel antagonist)	Phase III	AstraZeneca
Riluzole (Na^+ channel blocker)	Phase III	Aventis
Rasagiline (MAO-B inhibitor)	Phase III	Teva Pharmaceuticals/ Lundbeck
NW-1048 (reversible MAO-B inhibitor)	Preclinical	Newron
Safinamide [NW-1015] (MAO-B inhibitor)	Phase II	Newron
SL-251131 (reversible non-specific MAO inhibitor)	Preclinical	Sanofi-Synthelabo
Talipexol (α_2-adrenoreceptor agonist, D_2 receptor agonist)	Launched in Japan	Boehringer Ingelheim
KW-6002 (adenosine A_2 receptor antagonist)	Phase III	Kyowa Hakko
KF-17837 (adenosine A_2 receptor antagonist)	Preclinical	Kyowa Hakko
SCH-58261 (adenosine A_2 receptor antagonist)	Preclinical	Schering Plough
Zelapar (improved formulation of selegiline)	Phase II	Elan Pharmaceuticals
Altinicline [SIB-1508Y] (adenosine A_2 receptor antagonist)	Phase II	SIBIA Neuroscience
Leteprinim potassium (hypoxanthine analogue)	Phase II	NeoTherapeutics
GPI-1046 (immunophillin ligand)	Phase I	Guilford Pharmaceuticals
V-10367 (neuroimmunophilin ligand)	Preclinical	Vertex
NIL-Aneuroimmunophilin ligand	Phase II	Amgen/Guilford Pharmaceuticals
Spheramine (cell transplant therapy)	Phase I	Titan Pharmaceuticals
DU-127090	Phase I/II	Solvay
NeuroCell (cell transplant Therapy)	Phase III	Diacrin/Genzyme

MAO = monoamine oxidase; **NMDA** = *N*-methyl-D-aspartate.

motor fluctuations such as 'off' periods are frequently reduced or eliminated,[49-52] peak dose dyskinesias are sometimes precipitated, requiring a reduction of the individual doses of levodopa. Both drugs were shown to improve the quality of life of the patient. Tolcapone was recently removed from the market in Europe, and its use restricted in the US, because of presumed hepatic toxicity. However, the exact relationship to the drug exposure is still ambiguous. On the basis of the rarity of these adverse events, some practitioners believe that its withdrawal might have been premature, arguing that the drug is possibly superior to entacapone (although a direct comparison has not been performed).

Entacapone received an EU approval in September 1999. It has a brief duration of action of approximately 2 hours, that is, it has to be consumed with each levodopa dose (or even more frequently). Future preparations containing levodopa, entacapone and a decarboxylase inhibitor in a single tablet or capsule could be beneficial, especially for patients who are receiving other drugs as well. Long acting derivatives or sustained release formulations of entacapone could also be advantageous.

1.3 Dopamine Re-Uptake Inhibitors

Inactivation of released dopamine is mainly by reuptake of the unbound molecules in the synaptic clefts into the nerve terminals through specific carrier molecules. These so-called dopamine transporters can be blocked by drugs, thereby enhancing the action of the endogenously released dopamine. The two most potent blockers of dopamine transporters are amphetamine and cocaine. However, due to severe adverse effects, particularly their abuse potential, they are not used as treatments for Parkinson's disease. Attempts to synthesise safer drugs are in progress.

Brasofensine is an investigational molecule representative of this class of drugs.[53] Phase II investigations of brasofensine indicated that it is metabolised differently in humans than in animals, imposing further toxicology studies. In addition, clinical results did not show any significant improvement at several dose levels. Nevertheless, phase II trials are ongoing in several European countries.

2. Modulating Non-Dopaminergic Systems

Because of the complex neuronal interactions and the delicate balance between several neurotransmitter systems in Parkinson's disease, non-dopaminergic modulation is an alternative direction for regulating the effects of endogenous or exogenous dopamine.[54]

Noradrenaline/dopamine interactions have been demonstrated in behavioural, biochemical, physiological and anatomical studies. The α_2-adrenoreceptor antagonist idazoxan was tested in animal models (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPTP). Idazoxan had demonstrated some antiparkinsonian effects and was developed as a potential adjunct therapy to levodopa.[55-57] However, its development was terminated, possibly due to recently published results suggesting that it did not ameliorate levodopa-induced dyskinesias.[58]

Adenosine receptors are present in high concentrations in the striatum. The receptors are localised on neurons containing γ-aminobutyric acid (GABA) and enkephalin, which also have dopamine receptors. Adenosine stimulation has a negative effect on motor function, whereas antagonists (such as caffeine) can increase locomotor activity, particularly when dopamine receptors are decreased or blocked. Interestingly, it has recently been demonstrated that caffeine consumption apparently prevents the development of Parkinson's disease.[59] Thus, adenosine antagonists may present a new treatment for Parkinson's disease if their efficacy and safety are proven.[60,61] The compound KF-17837, an investigational adenosine receptor antagonist, showed a significant reduction in parkinsonian symptoms in MPTP-treated marmosets.[61,62] SCH-58261, an adenosine A_2-receptor antagonist is being developed as a potential neuroprotecting agent, still at a pre-clinical stage.[63] KW-6002, an-

other drug of this class, has reached phase II clinical trials.

The novel compound altinicline (SIB-1508Y), which is a subtype-specific nicotinic agonist, has also reached phase II clinical trials. In preliminary studies, the drug was shown to regulate the release of dopamine and acetylcholine levels in the brain.[64] The balance between these two neurotransmitters is believed to play a crucial role in controlling movement and possibly cognition. Combination therapy with altinicline and sub-therapeutic doses of levodopa/benserazide improved both motor and cognitive functions in MPTP-treated monkeys.[65]

3. Neuroprotection

An intriguing therapeutic attitude in the treatment of Parkinson's disease is to slow down the disease progression by salvaging or protecting neurons from ongoing degeneration.

Parkinson's disease is one of several late-onset neurodegenerative diseases (among others are Alzheimer's disease and amyotrophic lateral sclerosis) in which specific neurons of the central nervous system are affected. The pathological mechanisms underlying these diseases, such as apoptosis and oxidative stress are not yet understood and are subject to intensive research. Major practical constraints on possible pharmaceutical interventions are the timing along the disease course at which therapy will still be effective and the complete characterisation of the pathological findings. Recently caspase 1 and 3 were shown to be activated in degenerating neurons in Parkinson's disease, although it is unclear at what stage of the disease this activation takes place.[66,67]

3.1 Antioxidants

Selective degeneration of dopamine neurons in Parkinson's disease may be caused by an imbalance between the oxidation of dopamine and the availability of antioxidant defences.[68,69] Vitamin E is in wide clinical use today, even though data concerning its efficacy in Parkinson's disease are controversial,[70,71] probably due to its poor penetration of the blood-brain-barrier. Nevertheless, some promising results were recently obtained from clinical trials in patients with Alzheimer's disease.[72]

3.2 Monoamine Oxidase (MAO)-B Inhibitors

The efficacy of selegiline in the treatment of Parkinson's disease is based on the assumption that inhibition of the MAO-B enzyme may prevent dopaminergic neurotoxicity.[73,74] The extensive DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) study demonstrated its safety and beneficial symptomatic effects in early Parkinson's disease, although not its neuroprotective effect. Consequently, several drugs of this class are at various stages of development. Currently in development is a new formulation of selegiline which dissolves instantly in the mouth, eliminating the first pass effect in the liver, so that therapeutic concentrations are reached at one-eighth of the daily regular dose of selegiline. This reduces the concentrations of amphetamine, the unwanted metabolite of selegiline[75] that otherwise limits the maximal tolerated dose. It is possible that at higher therapeutic doses, MAO-B inhibitors will not only ameliorate disease symptoms, but could also provide neuroprotection, which has been demonstrated *in vitro* with equivalent drug concentrations.

Rasagiline, another MAO-B inhibitor, is presently being evaluated in clinical trials in the USA, Europe and Israel. At doses up to 4 mg/day, rasagiline showed good safety and tolerability.[76] It has a similar pharmacological profile to selegiline, but without amphetamine as a metabolite.[77,78]

Lazabemide, another potent and selective MAO-B inhibitor, was under development for Parkinson's disease. Although the results of large-scale clinical trials in patients with early stage Parkinson's disease (and in Alzheimer's disease) suggested attenuation of disease progression,[79] its further development in most countries has been discontinued.[80]

SL-251131, a member of the new generation of reversible MAO-B inhibitors, has also been discontinued from further development.[81]

3.3 N-Methyl-D-Aspartate (NMDA) Antagonists

Accumulating evidence suggests that excessive glutamatergic stimulation could be one mechanism underlying neurodegeneration in Parkinson's disease, as well as in other neurodegenerative diseases.[82] Accordingly, blockers of glutamate release or of glutamate receptors [specifically N-methyl-D-aspartate (NMDA) receptors] have attracted considerable interest as potential neuroprotective agents. The clinical testing program with the NMDA antagonist eliprodil has been recently aborted, following extensive clinical trials, for failing to demonstrate efficacy.

Another experimental drug of this class is the low-affinity NMDA channel blocker remacemide, approved for the treatment of epilepsy. Preliminary studies have demonstrated that the drug could be effective for Parkinson's disease when administered with dopaminergic agents, such as levodopa.[83] Moreover, encouraging results regarding its safety and tolerability (although not efficacy) were recently obtained from a multicentre study in patients with Parkinson's disease, where remacemide was used as a monotherapy for 5 weeks.[84] However, higher dosages or longer treatment periods could produce more benefits.

Amantadine has been used for the treatment of Parkinson's disease for several decades, even though its mechanism of action was obscure.[85,86] Recently, it was shown to function by inhibiting NMDA receptors and found to be effective in reducing dyskinesias.[87,88] Memantine, a related drug, also functions as a neuroprotective agent through this mechanism. Memantine is used in Germany as an antispastic drug and also to treat dementia, and is presently being evaluated for its effectiveness in Parkinson's disease, based on preliminary results.[89] The antiglutamatergic effect of amantadine and memantine could also suggest a neuro-protective action.

Newer glutamate antagonists in clinical development include L-701252, LY-235959 and WIN-634802. These agents are being tested in Alzheimer's disease, but none has yet reached phase III testing in Parkinson's disease. Also at various stages of developments are LIGA 20, LY-274614 and LY-354740.

Riluzole, previously thought to be an NMDA antagonist, but reclassified as a sodium channel inhibitor, is already in use for the treatment of amyotrophic lateral sclerosis. In a pilot study, riluzole appeared to be well tolerated by patients with Parkinson's disease.[90] A large multicentre study is currently evaluating patients at early stage of the disease, in order to test its restorative effect. Another study is evaluating the drug for patients with fluctuations and dyskinesias.[91]

4. Potential Therapies for Rescue of Dopaminergic Cells

While neuroprotection may be defined as preventing neuronal cell death and maintaining function without necessarily affecting the underlying biochemical mechanisms involved in pathogenesis, neurorescue could be considered a mechanism to reverse established metabolic abnormalities and restore normal neuronal function and survival. Clinically, this would result in an improvement in symptoms as well as a halt in the progress of the disease. Although there is inevitable overlap between neuroprotection and neurorescue, their relative benefits may vary according to the stage of the disease.

4.1 Anti Inflammatory Agents

Inflammatory reactions, such as activation of microglia (the brain equivalent of peripheral macrophages) are commonly seen in the brains of patients with Parkinson's disease.[92] However, it is unclear whether these reactions, presumably secondary responses to underlying disease pathology, are beneficial or detrimental. The role of anti-inflammatory agents has received considerable attention in Alzheimer's disease,[93] and clinical studies focusing on both the prevention and the slowing down of the disease are underway with the two recently launched selective cyclo-oxygenase (COX)-2 inhibitors, celecoxib and rofecoxib.[94] Research to examine their potential benefits in Par-

kinson's disease are likely to be initiated. Another potential approach involving inflammatory components in Parkinson's disease, which has already been proposed,[95] is to modulate cytokine actions.

4.2 Neurotrophic Growth Factors

Trophic factors are naturally occurring peptides that protect and support neurons.[96] These so-called growth factors are under investigation for treating Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and ischaemic injury. Glial cell line-derived neurotrophic factor (GDNF), one of these growth factors, was shown to actually protect midbrain dopaminergic neurons from toxic damage by iron and nitric oxide.[97] A major practical difficulty, however, is to ensure delivery of this large molecule across the blood-brain barrier and into the target neuronal population.

The sophisticated use of a lentiviral vector attached to GDNF to overcome these barriers was recently reported.[98] This elegant experiment was performed on rhesus monkeys by injecting the drug directly to the desired areas, using a magnetic resonance imaging (MRI)-guided technique. Apparently, this approach was able to save damaged midbrain dopaminergic neurons and their terminals in the caudate nucleus and putamen.

Leteprinim potassium (AIT-082), a hypoxanthine analogue, is an orally active drug that is believed to enhance the activity of several neurotrophic factors [nerve growth factor (NGF), ciliary neurotrophic factor and neurotrophin-3].[99] On the basis of the assumption that deficient neurotrophic stimulation is involved in neurodegeneration, leteprinim potassium, AK-30-NGF, brain-derived neurotrophic factor (BDNF), NBI-106 and recombinant human NGF itself are being evaluated in neurodegenerative diseases for their potential to attenuate the degenerative process.[99-102]

Although results of clinical testing in Parkinson's disease are still unavailable, this line of research is likely to be continued.

4.3 Neuroimmunophillins

Neuroprotection is perhaps best exemplified by strategies designed to prevent cells undergoing apoptosis. Upregulating apoptosis defence genes, such as *bcl 2*, or downregulating apoptosis promoting genes, such as *bax*, may be useful if effects can be targeted to nigral neurons. The role of mitochondria in the apoptotic pathway is also receiving attention as a possible target for neuroprotective agents.[103,104]

Neuroimmunophillins are ligands similar to the immunosuppressant drug cyclosporin, but lacking its effects on the immune system. In the early 1990s they were shown to possess neurotrophic activity, and since then were reported to increase neurite outgrowth *in vitro* and to have neuroprotective activity *in vitro* and *in vivo*.[105] GPI-1046, an immunophillin ligand, decreased signs of parkinsonism in animal models. Clinical trials with the drug were recently announced. Another agent of this class is tacrolimus (FK-506).[106]

4.4 Protein Antiaggregants

Deposition of proteinaceous aggregates inside neurons in the brain stem and elsewhere in parkinsonian patients is one of the hallmarks of the disease. The characteristic Lewy bodies contain several proteins, such as parkin, α-synuclein,[107] neurofilaments[108] and tubulin.[109] The deposition of parkin and synuclein has attracted a great deal of attention since mutations in these genes are associated with familial Parkinson's disease,[110,111] suggesting early involvement in neuronal degeneration. Analogous protein depositions – although different in their composition and the tissues involved – are found in other neurodegenerative diseases such as Alzheimer's disease, Creutzfeldt-Jakob's disease and Huntington's disease, suggesting related underlying pathological mechanisms. Thus, although at present the exact role of protein deposition in Parkinson's disease is unknown, they are serious candidates for research attempts to halt the aggregation processes (such as cross-bridging),

analogous to research attempts in other neurodegenerative diseases.

5. Genetic Factors and Gene Therapy

Until relatively recently, Parkinson's disease research was primarily focused on environmental risk factors such as viral infections or neurotoxins. However, a positive family history is gradually perceived to be a risk factor, a view supported recently when genes for Parkinson's disease were mapped to chromosomes 4 and 6.[110] Mutations in these genes have now been linked to several families with early onset Parkinson's disease.[111] Á-synuclein and parkin, the products of these genes, may be important targets for future therapies for Parkinson's disease.

Overwhelmed by the recent genome mapping accomplishment, one cannot overestimate the research potential for the future. As a chronic disease, the potential for gene therapy to provide long term correction of Parkinson's disease after just a single injection is extremely exciting. Currently, scientists are examining experimental animal models of the disease, where genes producing dopamine had been introduced.[112] Another promising approach may be use of implanted capsules containing genetically engineered, dopamine-producing cells.[113,114]

A related novel and exciting research trend that will flourish in the near future is 'genetic diagnosis' of many diseases, including Parkinson's disease. The first measures have already been taken. A group of neurologists from throughout the US and Canada, known as the Parkinson Study Group (PSG), has formed a collaborative effort with several research centres. The aim is to study genetic and other risk factors that may be important in the development of Parkinson's disease. This study, 'Parkinson's Research: The Organised Genetics Initiative', also known as PROGENI, is being sponsored by the National Institutes of Health and will involve 400 to 600 pairs of siblings who are affected, or possibly affected, with Parkinson's disease. DNA samples will be stored at a repository for future studies of genetic and environmental factors related to Parkinson's disease. These, in turn, will undoubtedly open many new opportunities for developing future drug therapies.

6. Conclusions

Being a chronic, progressive disease that affects one of every 100 people over the age of 60, and based on the fact that the prevalence of Parkinson's disease increases with age, this disease is a heavy and increasing social and healthcare burden. Obviously, it is attracting an overwhelming amount of research attention and efforts. Several new drugs are currently in the pipeline in clinical trials or awaiting approval by regulatory authorities.

Although our understanding of the underlying mechanisms of the disease is still limited, as more advanced techniques are at our disposal, newer, even more sophisticated approaches such as genetic engineering, are being put to the test.

Finally, in spite of all these new and exciting developments, almost half of patients with Parkinson's disease use some form of alternative medical therapy.[115] Thus, there is still a long way ahead of us to control, and hopefully to prevent, this chronic debilitating disease.

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Correspondence and offprints: Professor *Amos D. Korczyn*, Department of Neurology, Sackler School of Medicine, Tel-Aviv University Medical School, Ramat-Aviv 69978, Israel. E-mail: neuro13@post.tau.ac.il