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Parkinson's disease: aetiology, diagnosis, and management

帕金遜病的病因、診斷及治療

Objective. To review the aetiology, diagnosis, and management of Parkinson's disease, with a local perspective.

Data sources. Medline from 1966 onwards, and all major neurological journals and movement disorder journals were searched for evidence on the aetiology, diagnosis, and management of Parkinson's disease.

Study selection. Key words for the literature search were "Parkinson's disease" and "Chinese" or "Hong Kong".

Data extraction. All relevant articles in English were reviewed.

Data synthesis. The number of promising genes for familial Parkinson's disease is still expanding rapidly and there has been a wealth of studies on susceptibility genes for Parkinson's disease. Potential treatment choices include the use of agents thought to be neuroprotective, symptomatic treatment with drugs or surgery, and non-pharmacological treatments. Pharmacological treatment using a dopa-sparing strategy and continuous dopaminergic stimulation is now gaining support to address the issue of long-term motor complications. Surgical treatment with deep brain stimulation is safe and effective for refractory cases and has been increasingly utilised locally.

Conclusions. Medical therapy remains the mainstay of treatment and newer agents and treatment approaches are emerging, which will hopefully address the issue of neuroprotection and provide symptomatic treatment with fewer motor complications.

目的：以本地角度檢討帕金遜病的病因、診斷及治療。

資料來源：應用MEDLINE檢索自1966年起所有神經病學及活動失調的文獻，以搜集關於帕金遜病病因、診斷及治療的資料。

研究選取：以'Parkinson's Disease'加'Chinese'或'Hong Kong'作為檢索的關鍵詞。

資料選取：所有有關的英文文章。

資料綜合：家族性帕金遜病的高預兆性基因數量仍急速膨脹，並且有大量關於易感性基因與帕金遜病的研究。可選擇的治療方法包括使用相信對神經系統有保護作用的藥物、藥物或手術的對症療法和非藥物治療。藥物療法如多巴節約法和多巴胺持續刺激法，在針對長期運動神經併發症個案時逐漸獲得重視。深腦刺激療法的手術屬安全的治療法，它對難治病例有效，並逐漸為本地醫院所使用。

結論：藥物治療仍是主要治療方法，而新的藥物和治療方法亦不斷出現，有望針對神經系統作出保護，並提供引致較少運動神經併發症的對症療法。

Key words:
Chinese;
Hong Kong;
Parkinson disease

關鍵詞：
中國人；
香港；
帕金遜病

Hong Kong Med J 2005;11:476-89

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Introduction

Idiopathic Parkinson's disease (PD) is an insidious and slowly progressive neurodegenerative disease. A recent explosion of knowledge in the

understanding of its pathological processes and of clinical trial data has afforded treatment options at various stages of the disease. This paper provides a review of current knowledge on this neurological condition. We searched the literature from 1966 onwards, using Medline, major neurological journals, and movement disorder journals for evidence on the aetiology, diagnosis, and management of PD. Relevant studies conducted among the Chinese population were particularly noted.

Genetics and environmental factors

The pathological hallmark of PD is the cell death of dopaminergic neurons in the pars compacta of the substantia nigra and the appearance of Lewy bodies in surviving neurons. There is an increased incidence of PD in the elderly population, although the regional distribution of cell loss and the speed of cell death in normal ageing are considered different. In the GenePD study,[1] PD was found to aggregate among biological relatives more frequently than in married couples. However, data from another study showed concordance in monozygotic twins was only present in young-onset PD.[2] Rekindled interest in familial PD has led to the discovery of genetic loci, namely PARK 1 to PARK 11.[3] Five proteins implicated are alpha-synuclein, parkin, DJ1, PINK1, and UCH-L1. The alpha-synuclein gene mutations, most of which being point mutations, were found in autosomal dominant PD patients of Italian, German, or Spanish ancestry and they were usually fully penetrant.[4] When alpha-synuclein was shown to be a major component of Lewy bodies, interest in the role of genetics in PD was given new impetus. However, alpha-synuclein gene mutations were not found in a study of PD in a Chinese population.[5] The parkin gene mutation, on the other hand, was first described in Japanese patients with autosomal recessive juvenile PD and subsequently found in Chinese and other ethnic groups.[6] Although Lewy bodies were not observed in these patients, the accumulation of parkin substrates within nigral neurons was thought to contribute to the pathological process.

The number of promising genes for familial PD is still expanding rapidly and there has been a wealth of studies on 'susceptibility genes' for PD. In a recent study, heterozygosity of mutation of a glucocerebrosidase gene was found to predispose Ashkenazi Jews to PD.[7] More specifically for the Chinese population, multidrug transporter gene *MDR1* haplotypes have been suggested as protective against PD,[8] whereas the slow-acetylator genotype *NAT2* is associated with PD.[9] However, the majority of sporadic cases still cannot be easily explained by a simple genetic paradigm, and the environmental causative theory continues to serve as a default answer.

The occurrence of parkinsonism in drug users exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) highlights that environmental agents are capable of causing PD. Farming and rural living have been regarded as risk factors in westernised countries. In Asia, one Taiwanese study[10] lent support for this but conversely, one completed in Mainland China[11] did not. Chan et al[12] pointed out that pesticide and herbicide usage may be the key to this difference, as there was low usage of pesticides, at least in the past, in Mainland China. The consumption of tea among Chinese and that of coffee among Caucasians have been found to be protective against PD. However, the type of tea or coffee and its additional content are also important in determining the association and, in fact, caffeine, present in both tea and coffee, has been shown to be protective for PD only in laboratory studies.[13] An inverse relationship between smoking and PD has also been observed but cigarettes cannot be recommended as a protective agent as the harm obviously outweighs the benefit.[12] Whatever the cause of PD, the final pathway for nigral degeneration is thought to involve mitochondrial dysfunction, oxidative stress, excitotoxins, inflammatory responses, and apoptosis. Central to this is the failure of the ubiquitin proteasome system.[14]

Prevalence

The age-specific prevalence of PD has been found to be 5 to 10 fold lower in Mainland China compared with Europe in the past epidemiological studies.[15] The rates in the more developed ethnic Chinese regions are considered to lie between those of Europe and Mainland China. A study in 1989[16] showed that the prevalence of PD in Hong Kong was 3.4% among residents of homes for the elderly, aged 60 to 103 years. A more recent, door-to-door survey in the community in Hong Kong revealed a prevalence rate of 188 per 100 000 (including both institutional and community dwellers).[17] The prevalence for Taiwan has been reported as between 119 and 367 per 100 000.[15] The prevalence in some regional Chinese populations in the Mainland has been said to be increasing.[12] In Singapore, a recent study reported the prevalence as comparable with that of western countries.[18]

Diagnosis

There is currently no biological marker for PD and

Clinical diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank[19]

Step 1. Diagnosis of parkinsonism

Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) and at least one of the following:
(a) muscular rigidity
(b) 4-6 Hz resting tremor
(c) postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction

Step 2. Exclusion criteria for Parkinson's disease

History of repeated strokes with stepwise progression of parkinsonian features
History of repeated head injury
History of definite encephalitis
Oculogyric crises
Neuroleptic treatment at onset of symptoms
More than one affected relatives
Sustained remission
Strictly unilateral features after 3 years
Supranuclear gaze palsy
Cerebellar signs
Early severe autonomic involvement
Early severe dementia with disturbances of memory, language, and praxis
Babinski's sign
Presence of a cerebral tumour or communicating hydrocephalus on computed tomographic scan
Negative response to large doses of levodopa (if malabsorption excluded)
Exposure of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine)

Step 3. Supportive prospective positive criteria for Parkinson's disease (three or more required for diagnosis of definite Parkinson's disease)

Unilateral onset
Rest tremor present
Progressive disorder
Persistent asymmetry affecting the side of onset most
Excellent response (70-100%) to levodopa
Severe levodopa-induced chorea
Levodopa response for 5 years or more
Clinical course of 10 years or more

the pathological diagnosis can only be achieved by autopsy analyses. Making a clinical diagnosis during life is therefore the sole responsibility of the clinician. Many diagnostic criteria have been proposed. Clinical diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank provide some of the most stringent criteria for diagnosis (Box[19]). Hughes et al[20] concluded that an accuracy of up to 90% can be expected when using these diagnostic criteria. The list of differential diagnoses is long and one would normally exclude other syndromes such as essential tremor, vascular parkinsonism, normal pressure hydrocephalus, progressive supranuclear palsy, multi-system atrophy, corticobasal degeneration, anergic depression, and drug-induced parkinsonism. For those patients in whom the clinical diagnosis is still in doubt after thorough history taking, examination, and investigations, ongoing observations and follow-up may ultimately delineate the disease entity. The use of a dopa challenge may aid diagnosis but remains controversial.

From a local point of view, a recent registry detailing 1091 patients with PD in Hong Kong[21] showed that tremor was the most common presenting symptom (77.3%), followed by slowness (48.7%), and stiffness (37.8%). Slightly more patients initially presented with symptoms on the right side (47.5%), and the majority (75.9%) were considered to have mild-to-moderate disease. As many as 22.9% of patients experienced falls, among whom 20.4% had fractures. It was also noted that women with PD were more likely to fall and to sustain fractures. The reason for the association between female sex and fall is unknown, although a propensity to fractures is known to be related to postmenopausal hormonal changes. For those with young-onset (<50 years) PD, in whom two family members (including the proband) are affected, referral to specialists for possible genetic testing can be considered, although it raises many issues for patients and their family.[3]

Neuroimaging in Parkinson's disease

The reduction in putaminal uptake of specific radioligands in PD patients has been considered to have a diagnostic role. 18-F-dopa positron emission tomography (PET) is a marker of dopa transport into dopamine terminals, its decarboxylation by dopa decarboxylase and terminal dopamine storage capacity. Similarly, 123-I-beta-CIT single photon emission computed tomography (SPECT) [Dopascan; Guildford Pharmaceuticals, Maryland, US] is a marker of dopamine transporter density. These imaging techniques raised the hope of detecting 'preclinical' PD which would have clinical utility should neuroprotective agents become available. However, the role of adding a scan to a clinically uncertain diagnosis still remains controversial. The use of image surrogate markers in monitoring disease progression has shown good promise, as evidenced by recent dopamine agonist trials using these modalities.[22-24] There has been considerable debate as to whether the pharmacology of dopaminergic therapy may alter the imaging target or the metabolism and transport of the radioligands. This in turn would influence the utility of image surrogate markers in the assessment of new drugs for neuroprotection.

Rating scales and qualitative assessment

Assessment of patients, both initially at diagnosis and during follow-up, constitutes a large part of the clinical workload and to this end, a number of clinical rating scales have been developed. The most commonly used is the Unified Parkinson's Disease Rating Scale (UPDRS), which assesses 42 items, scored from 0 to 4, to establish the patient's mental status, activities of daily living, motor function, and complications of therapy.[25] In current clinical practice, the UPDRS is typically used with the Schwab and England Activities of Daily Living Scale,[26] and Hoehn and Yahr Staging.[27]

The question of neuroprotection

Any agent able to protect or rescue nigral neurons would be considered to be neuroprotective. Vitamin E in doses of 2000 IU per day was tested in the DATATOP study but no delay in disease progression was detected.[28] Selegiline, a monoamine oxidase inhibitor (MAOI), on theoretical grounds could block oxidation of MPTP to the toxin MPP (1-methyl-4-phenylpyridinium) and was the other drug tested in the DATATOP study. Initial results showed a delay in the emergence of disability and progression of motor signs and symptoms compared with placebo. This finding was criticised on the basis that selegiline can induce symptomatic effects to account for some or all of the benefits seen. Other controversies soon followed when the Parkinson Disease Research Group of the United Kingdom reported increased mortality in patients who were treated with selegiline and levodopa compared with levodopa alone[29] but this study was also criticised heavily for methodological and statistical flaws. As yet it is not possible to state conclusively whether selegiline has a neuroprotective effect in patients with PD. One recent sub-analysis of the previous DATATOP study data[30] has suggested that selegiline may be useful in the prevention of freezing of gait.

Rasagiline, another MAOI, unlike selegiline, does not produce the metabolite methamphetamine. In the TEMPO study[31] in which rasagiline was used as monotherapy, the placebo group included a delayed-start analysis. This showed that patients receiving rasagiline for 12 months had less functional decline than patients whose treatment was delayed for 6 months, supporting a possible neuroprotective effect.

Dopamine agonists as a group offer the hope for neuroprotection on the basis of numerous in-vitro and in-vivo studies.[14] The imaging components of the dopamine agonist monotherapy trials using SPECT (CALM PD study, pramipexole[23]) and PET (REAL-PET study, ropinirole[22]) highlighted the slower rate of disease progression by way of surrogate markers. The significance of this has remained controversial. Coenzyme Q10 was shown in one randomised study[32] to slow the worsening of PD as measured by the total UPDRS score, with the greatest effect in the activity of daily living scores. However, the time to disability requiring treatment with levodopa was not significantly delayed. Minocycline has been suggested as a neuroprotective agent but research is still in the experimental stages.[33] Riluzole has been tested for use in early disease in small patient samples but the results have not been encouraging.[34]

Management

Potential treatment choices discussed in a recent evidence-based review include the use of agents thought to be neuroprotective, symptomatic treatment with drugs or surgery (Table 1), and non-pharmacological treatments.[35] From a practical point of view, a treatment algorithm such as that proposed by Olanow et al[36] is useful, in which symptomatic treatment is given when the patient becomes functionally impaired. This dopa-sparing strategy is believed to delay the onset of motor complications and has been employed by most centres. Using any agent with a more extended half-life is now part of the concept of continuous dopaminergic stimulation. It goes without saying that each patient's treatment should be individualised and that all patients should be encouraged to be mobile and active. In refractory cases, liquid preparations of levodopa and surgical options can be considered.

Levodopa

Levodopa is an amine precursor of dopamine which is active orally and absorbed in the small intestines but subject to metabolism in the periphery by dopa-decarboxylase and catechol-O-methyltransferase (COMT). Levodopa is now routinely administered together with a dopa-decarboxylase inhibitor (carbidopa or benserazide). There is no doubt about the clinical benefit of levodopa as an effective symptomatic treatment to ameliorate bradykinesia, rigidity, and tremor. In fact, all patients with PD eventually require levodopa treatment.

There has been concern about the theoretical consequences of levodopa producing neurotoxic metabolites, such as hydrogen peroxide, on

Table 1. Commonly used symptomatic interventions for Parkinson's disease

	Remarks
Medical therapy *Drug (brand names/sub-categories)*	
Levodopa/carbidopa (Sinemet) Levodopa/benserazide (Madopar) Levodopa/carbidopa, controlled-release (Sinemet CR) Levodopa/benserazide, controlled-release (Madopar HBS) Dispersible levodopa/benserazide (Madopar dispersible)	Half-life of standard release preparation: 1-1.5 hours; half-life of controlled-release preparation: 2-3.5 hours
Bromocriptine (Parlodel) Lisuride (Dopergin) Pergolide (Permax) Cabergoline (Cabaser, Dostinex)	Ergot-derived dopamine agonists
Pramipexole (Mirapex) Ropinirole (Requip) Apomorphine, subcutaneous (Apomine) Piribedil (Trivastal, Circularina) Rotigotine (Transdermal patch)	Non-ergot–derived dopamine agonists (the conversion factor between pramipexole and ropinirole is 1:4)
Entacapone (Comtan) Tolcapone (Tasmar)	COMT (catechol-O-methyltransferase) inhibitors have half-lives of 2 hours
Trihexyphenidyl (Artane)	Anticholinergic
Amantadine (Symmetrel)	Antiviral agent, with anticholinergic and possible dopaminergic and antiglutaminergic effects
Selegiline (Deprenyl) Rasagiline (Azilect)	Monoamine oxidase-B inhibitors
Surgical therapy *Intervention*	
Pallidotomy	Mainly for patients with severe dyskinesia although the operation may lead to partial improvement in other parkinsonian features. Concerns about visual impairment and transient facial weakness
Thalamotomy	Effective for tremor. Concerns about hemiparesis and seizure
Deep brain stimulation of ventral intermediate thalamus	Suppression of tremor only
Deep brain stimulation of globus pallidus	Direct antidyskinetic effect but overall less efficacious than stimulation of subthalamic nucleus
Deep brain stimulation of subthalamic nucleus	Improvement in most cardinal signs, although indirect antidyskinetic effect shown (needing levodopa-dose reduction)

dopaminergic neurons. In a clinical study aimed to test this hypothesis, the ELLDOPA study,[37] 360 patients with no previous exposure to levodopa were randomised to 40 weeks of treatment with either placebo or carbidopa/levodopa. Patients were evaluated using the UPDRS motor score at baseline and after a 2-week washout period at the end of the treatment period. The study found no evidence that levodopa had any deleterious effect on disease progression and the concept of levodopa neurotoxicity was thereby not supported. Strangely, the rate of decline of an imaging surrogate marker of nigrostriatal function was greater in the levodopa group.[38] In spite of this, most specialists on PD would agree that levodopa is not harmful to nigrostriatal neurons in PD and that it should not be withheld for this reason.

Long-term administration of levodopa is associated with motor complications, including dyskinesia and motor fluctuations. Motor fluctuations and dyskinesia have been reported to occur in 30% to 50% of patients after 2 to 5 years of treatment, and in an alarming 80% to 100% after 10 years of treatment, with a propensity to affect the young-onset patients.[39] Table 2 summarises various strategies employed for treating motor complications. In early disease, despite an approximately 60% to 80% loss of nigral neurons, the delivery of dopamine from the presynaptic to the postsynaptic receptor is still maintained by the storage capacity of surviving neurons. A dose of levodopa thus can provide a smooth antiparkinsonian response, even if dosing intervals are infrequent. When the storage capacity fails, due to ongoing loss of neurons, 'wearing-off' effects become apparent and the synaptic dopamine concentration depends on plasma levodopa levels. The clinical response is

Table 2. Strategies for treating motor complications

Motor complication	Strategy employed	Caution
'Wearing-off' phenomenon	Adding selegiline	Beware confusion, psychosis, and dyskinesia
	Controlled-release levodopa	Total daily dose may need to be adjusted upwards
	Adding COMT (catechol-O-methyltransferase) inhibitors	Dyskinesia may develop necessitating reduction of levodopa dose
	Giving levodopa doses closer together	Beware overlapping with meal time and dose failures
	Adding dopamine agonist	May induce dyskinesia
'Sudden-off' phenomenon	Switching to liquid levodopa	Apomorphine not available locally
	Adding dopamine agonist	
	Other rescue therapy if available	
Dose failure	Rearranging timing of levodopa dose	
	Switching to liquid levodopa	
'Delayed-on' phenomenon	Higher dose of standard formulation levodopa as first dose	
	Dispersible/liquid levodopa	
Freezing (off-freezing)	Same as treating 'wearing-off' phenomenon	
(on-freezing)	Reducing dose of levodopa	
Peak-dose dyskinesia	Reducing dose of levodopa	May need to increase dose frequency
	Adding dopamine agonist while reducing dose of levodopa	
	Controlled-release levodopa	Danger of increased dyskinesia at the end of the day when blood levels sustained
	Adding high-dose amantadine	
Diphasic dyskinesia	Dopamine agonist	Notoriously difficult to treat
	Liquid levodopa	
Off dystonia	Same as treating 'wearing-off' phenomenon	

dictated by peripheral pharmacokinetics, such as gastric emptying and competition with the neutral amino acid carrier system. In the later stages of the disease, where interaction between dopamine and the striatal receptors is altered, 'sudden-off' phenomena can develop. Intermittent stimulation of these receptors with standard-dose levodopa brings about changes in receptor sensitivity and motor fluctuations, including peak-dose dyskinesia.

Another issue relating to levodopa use is that levodopa can elevate plasma homocysteine levels. It is currently contentious as to whether a high plasma homocysteine level increases the risk of cardiovascular events and cognitive impairment.[40]

Manipulation of the absorption kinetics of levodopa

Controlled-release levodopa has been manufactured to address the 'wearing-off' phenomenon. However, two trials failed to support the use of controlled-release levodopa in delaying the onset of motor fluctuation or dyskinesia.[41,42] Owing to the reduced and sometimes erratic absorption of the drug, the overall dosage may need to increase by 30% when patients are changed from immediate-release to controlled-release preparations. Dispersible levodopa addresses the 'delayed-on' issue, with its theoretical advantage of reducing gastric transit time. However, it only shortens the time to peak plasma level, without affecting 'on-time' duration.[43] Liquefying levodopa offers the advantage of fine adjustment of the levodopa dose, in addition to bypassing the gastric emptying effect, making it an option for patients with severe motor complications. However, liquid levodopa needs to be prepared afresh almost every day, using ascorbic acid as the stabilising agent. Ten tablets of Sinemet 100/25 may be dissolved in 1 L of water with ascorbic acid 2000 mg to give a concentration of 1 mg/mL for frequent dosing, such as an hourly intake. Chemical modification of levodopa to make water-soluble derivatives has produced limited clinical data thus far.

Table 3. Evidence supporting the use of dopamine agonist therapy[22-24,44-78]

Dopamine agonist	Study evidence	Details
Studies which showed that dopamine agonists produce symptomatic benefits		
Bromocriptine	Ramaker and van Hilten,[44] 2000	Adjuvant therapy of bromocriptine to levodopa gives better impairment scores
Pergolide	Kulisevsky et al,[45] 1998; Barone et al,[46] 1999	Monotherapy with pergolide provides a significant reduction in UPDRS* scores compared with placebo
	LeWitt et al,[47] 1983; Pezzoli et al,[48] 1994; Mizuno et al,[49] 1995	Comparator trials of pergolide with bromocriptine showed similar efficacy or slightly better improvement in motor scores
Pramipexole	Molho et al,[50] 1995; Lieberman et al,[51] 1997; Wermuth,[52] 1998; Pinter et al,[53] 1999; Mizuno et al,[54] 2003	Pramipexole was superior to placebo as adjuvant therapy to levodopa in terms of improvement on specific parts of the UPDRS score
	Shannon et al,[55] 1997	Pramipexole used in early Parkinson's disease has good symptomatic effect
	Pogarell et al,[56] 2002	Pramipexole demonstrated to alleviate drug-resistant tremor
	Wong et al,[57] 2003	Pramipexole led to improvement in part II, III or combined UPDRS scores in Chinese patients whether or not they were taking levodopa
Ropinirole	Brunt et al,[58] 2002; Brooks et al,[59] 1998; Adler et al,[60] 1997; Im et al,[61] 2003; Mungersdorf et al,[62] 2001; Clarke and Deane,[63] 2000	Improvement in motor function. Ropinirole has similar efficacy to bromocriptine and was better than placebo
	Schrag et al,[64] 2002	Improvement in resting tremor
	Korczyn et al,[65] 1999	Ropinirole treatment resulted in better functional status than bromocriptine in addition to improvement in motor scores
Rotigotine	The Parkinson Study Group,[66] 2003	Monotherapy improved UPDRS scores
Studies which showed that dopamine agonists assist in management of motor complications after their onset		
Cabergoline	Clarke and Deane,[67] 2001	Cabergoline produced similar benefits to bromocriptine in off-time reduction, motor impairment and disability ratings, and levodopa dose reduction over the first 3 months of therapy. Cabergoline produced slightly more dyskinesia compared with bromocriptine
Pergolide	Olanow et al,[68] 1994; Clarke and Speller,[69] 2000	Pergolide as adjuvant therapy reduced off time and levodopa dosage
Pramipexole	Guttman,[70] 1997; Clarke et al,[71] 2000	There was a larger reduction in off time with adjuvant pramipexole compared with bromocriptine but similar effects in terms of reduction of levodopa dosage
	Pinter et al,[72] 2000	Improvement in UPDRS part IV score when pramipexole was used as adjuvant therapy
Ropinirole	Cristina et al,[73] 2003; Im et al,[61] 2003; Lieberman et al,[74] 1998	Adjuvant therapy with ropinirole led to a reduction in off time and levodopa dosage
	Cristina et al,[73] 2003	Adjuvant therapy with ropinirole led to improvement on a dyskinesia rating scale
	Mungersdorf et al,[62] 2001	Duration of dyskinesia was reduced
Rotigotine	Hutton et al,[75] 2001; Metman et al,[76] 2001	Rotigotine as adjuvant therapy led to less off time and reduction in levodopa dose compared with placebo
Studies which showed that dopamine agonists can delay motor complications before their onset†		
Cabergoline	Rinne et al,[77] 1998	Cabergoline delayed onset of motor complications
Pergolide	Oertel,[24] 2001 (PELMOPET study)	Pergolide delayed onset of motor complications
Pramipexole	Parkinson Study Group,[23] 2000	Pramipexole improved UPDRS scores and delayed onset of motor complications
Ropinirole	Rascol et al,[78] 1998 (056 Study Group); Whone et al,[22] 2003 (REAL-PET study)	Ropinirole delayed onset of motor complications

* UPDRS Unified Parkinson's Disease Rating Scale

† In these trials, cabergoline, pergolide, pramipexole, or ropinirole was not as efficacious as levodopa

Evidence on dopamine agonists as treatment

Evidence from studies investigating the use of dopamine agonists in PD is summarised in Table 3.[22-24,44-78] Historically, dopamine agonists were used as adjuvant therapy with levodopa in the treatment of motor complications. The ergot derivatives include bromocriptine, cabergoline, lisuride, and pergolide. Non-ergot derivatives include apomorphine, piribedil, pramipexole, and ropinirole. These agents have direct action on dopamine receptors, without the need for metabolic conversion and theoretically produce fewer toxic metabolites. They offer the possibility of selective stimulation of dopamine receptor subsets, which may potentially avoid unwanted side-effects. Unlike levodopa, these agents are not subject to competition from circulatory amino acids for absorption. Furthermore, dopamine agonists have longer half-lives with better approximation to the idea of continuous dopaminergic stimulation and lastly, there is growing evidence that dopamine agonists may be neuroprotective, as discussed previously.

Bromocriptine may be useful as adjuvant therapy with levodopa, although a Cochrane review concluded that existing trial data were too heterogeneous to draw any firm conclusions on this matter.[79] Adjuvant therapy trials with other dopamine agonists using bromocriptine as a comparator have revealed that pergolide was more efficacious than bromocriptine. In comparator trials evaluating pergolide, pramipexole, ropinirole, and cabergoline, no clear superiority was demonstrated by any one agent over the others.[80] Trials performed more recently have been focused on the use of dopamine agonists in early disease. Landmark studies of levodopa-controlled monotherapy trials of pergolide (PELMOPET study[24]), cabergoline (PKDS009 study[77]), pramipexole (CALM PD study[23]) and ropinirole (056 study[78] and REAL-PET study[22]) have confirmed the use of these agents in delaying the onset of motor complications, although these agents were somewhat less efficacious than levodopa itself. Monotherapy trials comparing the newer agonists with the older agonists are few and far between, but indirect comparisons of existing data suggest that all agonists lead to a similar degree of improvement in UPDRS scores.

An East Asian collaboration has demonstrated the efficacy and tolerability of pramipexole in early and advanced disease in a randomised, placebo-controlled trial.[57] Both lisuride and apomorphine can be used as subcutaneous infusions, and there has been renewed interest in the use of apomorphine as rescue therapy. Neither of these agents is available in Hong Kong currently however.

The most common side-effects of dopamine agonists are nausea and dizziness, followed by dyskinesia, postural hypotension, and neuropsychiatric problems such as hallucinations. The occurrence of 'sleep attacks' with the newer agonists previously sparked attention, but it is now accepted that somnolence and sleep disturbance is equally applicable to all dopaminergic agents. In the year 2003 to 2004, at least three major journals published reports of valvular heart disease with pergolide use, illustrating the increasing scrutiny faced by ergot-derived dopamine agonists in relation to their potential to cause visceral fibrosis.[81-83]

The choice of dopamine agonist nowadays depends on the side-effect profile of the drug as much as its efficacy, and its ability to deliver continuous dopaminergic stimulation. One agent that holds new promise is the non-ergot–derived agonist rotigotine, which may be given as a transdermal patch, thus bypassing the gastric delaying effect.

Catechol-O-methyltransferase inhibitors

The inhibition of the enzyme responsible for the peripheral metabolism of levodopa brings about increased plasma half-lives and bioavailability of levodopa. Research has focused on adjuvant therapy with entacapone in patients who already had motor fluctuation. The amount of 'on' time was shown to be prolonged by roughly 1 hour in two large randomised controlled trials, the SEESAW study[84] and the NOMECOMT study.[85] The safety and tolerability of entacapone were also confirmed in their respective open-label extension studies, the SEESAFE and NOMESAFE study.[86] As entacapone 'smoothes out' the delivery of levodopa, it can more closely approximate continuous dopaminergic stimulation. A new three-in-one formulation of levodopa, carbidopa, and entacapone has already been marketed (Stalevo; Novartis, East Hanover, US). Whether early use of a COMT inhibitor can delay the onset of motor complications has yet to be clarified by clinical trials. The side-effects of COMT inhibitors are mainly nausea and worsening of dyskinesia, necessitating a reduction in levodopa dosage. Liver function derangement and fatal hepatotoxicity has been observed in tolcapone leading to its withdrawal in many countries, but these effects have not been reported with the use of entacapone.

Anticholinergic drugs

These agents have mild, beneficial effects on all the

cardinal features of PD and a possible role in tremor control which is controversial.[87] They are thought to antagonise the uninhibited striatal cholinergic neurons. Common side-effects include dry mouth, blurred vision, urinary retention, constipation, and a propensity to cause confusion in the elderly. A recent pathological study[88] has suggested that chronic use may be associated with irreversible Alzheimer's pathology. Anticholinergics should preferably be prescribed for younger patients as initial therapy for only a brief period.

Amantadine

Amantadine is an antiviral agent with anticholinergic and possibly dopaminergic and anti-glutaminergic effects. It has a mild symptomatic effect in PD and can be used before levodopa. In advanced-stage disease, it is antidyskinetic at high doses,[89] possibly due to its antagonistic function on N-methyl-D-aspartate receptors. The possibility that amantadine offers neuroprotection was extrapolated from one retrospective study in which patients on long-term amantadine had improved survival.[90] Amantadine therapy is often hampered by neuropsychiatric side-effects, including confusion, insomnia, hallucination, and nightmares. Livedo reticularis may also occur with amantadine treatment.

Monoamine oxidase-B inhibitors

Selegiline, despite its controversial role as a neuro-protector, can be used in both early disease as monotherapy and in later-stage disease as adjuvant treatment with levodopa. Rasagiline was shown in the TEMPO trial to improve UPDRS score in patients with early disease.[31]

Other novel symptomatic drug treatments

A host of new agents are currently under testing in clinical trials after encouraging animal models were elucidated. These include adenosine A2a receptor antagonists, alpha-2 noradrenergic receptor antagonists, GABAergic agents, serotoninergic agents, glutamate antagonists, cannabinoids, and opioid receptor agonists/antagonists. The clinical benefit of these agents remains to be established.[91] Riluzole, an agent used for amyotrophic lateral sclerosis, has not been shown to be of benefit for either early or late-stage PD in studies involving a small number of patients.[92]

Old and new surgical treatments

Long before the introduction of levodopa, lesion-producing procedures, such as pallidotomy, were used as a treatment for PD. With improving stereotactic techniques, there has been a resurgence in the use of surgical treatment. Such procedures are potentially irreversible however. Deep brain stimulation (DBS) has gained increasing support, particularly in treating refractory cases of severe motor complications.[93] Deep brain stimulation of the ventral intermediate thalamus (VIM), subthalamic nucleus (STN), and globus pallidus (Gpi) are all possible sites but the STN site appears to be the best location, producing improvement in all cardinal features of PD. At a cellular level, DBS can inhibit neuronal firing via activation of inhibitory GABAergic fibres. The anti-parkinsonian effect of inhibiting STN or Gpi by DBS may be explained by the current pathophysiological model of PD, in which abnormal firing of STN and Gpi nuclei are thought to contribute to motor features seen. According to the Hong Kong PD registry,[21] 39 of 1091 patients with PD underwent surgical treatment, of which 19 procedures were DBS (2 VIM, 1 Gpi, 16 STN). In another local series, 13 Chinese patients underwent DBS (2 VIM, 1 Gpi, 10 STN) and the effects were similar to those reported in other published series.[94] Serious adverse events, including intracranial haemorrhage or dementia, were in the order of 1%, although some recent data[95] have pointed towards weight gain as a side-effect. The selection of patients for surgery is individualised, but most authorities would consider only patients younger than 70 years with failed medical treatment, who continue to respond to levodopa and are without cognitive symptoms.

Another surgical endeavour is the transplantation of foetal dopamine neurons. In a randomised sham-controlled study[96] involving 40 patients, improvement in a global rating scale was seen only in younger patients. Even among this group of patients, dystonia and dyskinesia had developed in some patients at 3 years post-surgery, despite reduction or discontinuation of dopaminergic medication. Without further modification, the transplantation of foetal dopamine neurons cannot be recommended in clinical practice. Following the principles of transplantation, embryonic stem cell transplants and intracerebroventricular delivery of glial-derived neurotrophic factors have been investigated for future possible clinical use.

Motor complications

Avoidance of motor complications requires the judicious use of agents as symptomatic treatment and individualised regimens (Table 2), with surgical treatment for refractory cases. Patients should be asked about a possible 'wearing-off' response or dyskinesia even in the early years of treatment, to facilitate timely detection of these signs. The spectrum of 'off' symptoms can range from recurring parkinsonism, dystonia,

Table 4. Treatment of non-motor complications in Parkinson's disease[99-109]

Non-motor complication	Strategy	Remarks
Cognitive impairment/dementia	Identify and treat underlying medical illness	
	Step-wise withdrawal of appropriate drugs	Useful order of withdrawal: anticholinergics, amantadine, selegiline, dopamine agonists and finally levodopa
	Donepezil	Aarsland et al,[99] 2002
	Rivastigmine	Giladi et al,[100] 2003; Emre et al,[101] 2004
Psychosis/hallucination	Identify and treat underlying medical illness	
	Stepwise withdrawal of appropriate drugs	Useful order of withdrawal same as above and consider discontinuing bladder antispasmodics or muscle relaxants
	Clozapine	The Parkinson Study Group,[102] 1999; The French Clozapine Parkinson Study Group,[103] 1999 Watch for agranulocytosis
	Olanzapine	Goetz et al,[104] 2000 Olanzapine may worsen motor symptoms
	Quetiapine	Gimenez-Roldan et al,[105] 2003; Juncos et al,[106] 2004; Mancini et al,[107] 2004
Depression	Alleviation of off states and other concurrent illness	
	Tricyclic antidepressants: trazodone	Fewer anticholinergic side-effects
	Selective serotonin re-uptake inhibitors	Serotonin syndrome may be precipitated by selegiline in 0.24% patients
Insomnia	Good sleep hygiene	
	Avoid excess caffeine and increase daytime physical activity	
	Set dose of amantadine/selegiline earlier in the day	
	Control of night-time motor symptoms	May need dopaminergic agents
	Treat nocturnal urinary symptoms	Restrict evening fluid intake or condom catheters; treat urological problems
Rapid eye movement behaviour disorder and vivid dreams	Reduce dose of levodopa	
	Clonazepam	
Restless leg syndrome	May need dopaminergic agents	
Daytime somnolence	Lower levodopa dose; switch to another dopamine agonist	
	Modafinil	Hauser et al,[108] 2000
Orthostatic hypotension	Increase intravascular volume and leg compressive stockings	
	Adjust dopaminergic medications (eg fludrocortisone)	
	Midodrine	Low et al,[109] 1997
Nausea and vomiting	Treat underlying illness	
	Additional carbidopa	
	Domperidone	
Constipation	High-fibre diet	
	Use suitable bulking agents and laxatives	
	Avoid anticholinergics	

through paraesthesia and pain, to psychiatric symptoms such as panic attacks, and autonomic manifestations, such as shortness of breath. There is now a growing belief that prevention of motor complications

is almost as important as treating them, but there remain unmet needs in those who have already developed complications.[97]

Data from the Hong Kong registry have shown that on-dyskinesia was significantly more common for patients who initially presented with signs on the left side of the body.[21] Female patients were significantly more likely to have off-dystonia and on-dyskinesia. An association was also observed between female patients with PD and falls, as well as fracture complications. Possibly these clinical stigmata should encourage clinicians to more meticulous attention to motor complications in these patient groups.

Non-motor complications

Many non-motor problems experienced by patients are disease-related, while others are treatment-related. The interplay between symptoms is complex and often treatment of one symptom may lead to the emergence of others. A fine balance between the various individual strategies is required. For instance, treatment of insomnia due to nocturnal motor symptoms with dopaminergic agents may lead to nightmares and vivid dreams which can then, of itself, cause insomnia. Treatment of orthostatic hypotension with increasing fluid intake may cause nocturia, thereby impairing sleep. Similarly, treatment with antispasmodics to alleviate urinary symptoms may lead to neuropsychiatric side-effects. Recently, the topic of sleep disorder in PD has received a lot of attention and now we have better tools for identification and better characterisation of disease sub-types.[98] Treatment of these will hopefully bring about a better quality of life for patients. Table 4[99-109] summarises treatments used in PD for non-motor problems. A holistic approach to treatment also includes physiotherapy, occupational therapy, speech therapy, and support groups for patients and their families.

Future directions

Ongoing research is needed to identify possible neuroprotective agents and to expand the current repertoire of symptomatic treatments, including surgical treatments. The concept of continuous dopaminergic stimulation may hopefully be approximated with novel agents such as the newer generation of dopamine agonists, monoamine oxidase-B inhibitors and levodopa/carbidopa/COMT inhibitor preparations.

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