

Management of Parkinson's Disease A Review of Current and New Therapies

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ABSTRACT: The management of Parkinson's disease has undergone recent changes with the advent of new therapies, both pharmacotherapy and surgery. Available interventions are discussed. Levodopa remains the mainstay of therapy. New drugs include the dopamine agonists and COMT inhibitors. New dopamine agonists which may have a levodopa "sparing effect;" it has been suggested that some of the drugs should be considered as first line treatments for newly diagnosed Parkinson's disease patients. We review roles of these drugs. The concept of neuroprotection in neurodegenerative disorders such as Parkinson's disease became popular in the mid 1980s and it is hoped that eventually therapy will be directed at slowing progression of the disease. A great deal more work needs to be done before a suitable agent is identified as being neuroprotective. Potential neuroprotective agents are reviewed. Surgical therapies for Parkinson's disease consisting of various forms of lesion surgery as well as stimulation procedures are reviewed. Complications of drug therapy include motor problems such as motor response fluctuations, as well as psychiatric complications including levodopa-induced psychosis. Atypical neuroleptic agents and ECT for psychiatric syndromes associated with Parkinson's disease are discussed. Algorithms for the management of early disease as well as the management of psychosis in Parkinson's disease are included. Treatment options for advanced disease are tabulated.

RÉSUMÉ: Le traitement de la maladie de Parkinson: revue des thérapies actuelles et des nouvelles options thérapeutiques. Le traitement de la maladie de Parkinson a subi plusieurs changements récemment avec l'arrivée de nouvelles options thérapeutiques tant pharmacologiques que chirurgicales. Dans cet article, nous discutons des modes de traitement qui sont disponibles actuellement. La lévodopa demeure la pierre angulaire du traitement de la maladie de Parkinson. Cependant, plusieurs agents pharmacologiques nouveaux ont été développés, dont les agonistes de la dopamine et les inhibiteurs de la COMT. Avec la venue de nouveaux agonistes de la dopamine qui pourraient avoir un effet d'épargne de la lévodopa, on a suggéré que certains médicaments devraient être considérés comme traitement de première ligne chez les patients dont le diagnostic est récent. Nous revoyons en détail le rôle de ces médicaments. Le concept de la neuroprotection dans les maladies neurodégénératives comme la maladie de Parkinson s'est popularisé au milieu des années 80 et on espère qu'éventuellement le traitement pourra ralentir la progression de la maladie. Il reste beaucoup de travail à faire avant qu'on puisse identifier un agent susceptible d'être neuroprotecteur dans la maladie de Parkinson. Dans cet article, nous revoyons les agents neuroprotecteurs potentiels. Il y a un regain d'intérêt pour les traitements chirurgicaux de la maladie de Parkinson et nous revoyons les différentes formes de traitements chirurgicaux par lésion ainsi que les procédures de stimulation. Les problèmes moteurs, tels les fluctuations de la réponse motrice, et les complications psychiatriques dont la psychose induite par la lévodopa, sont des complications du traitement médicamenteux. Nous revoyons plusieurs interventions utilisées dans ce contexte dont les agents neuroleptiques atypiques et les ETC, dans le contexte des syndromes psychiatriques associés à la maladie de Parkinson. Nous proposons des algorithmes pour le traitement de la maladie de Parkinson au début ainsi que pour la prise en charge de la psychose associée à cette maladie et nous présentons un inventaire des différentes options thérapeutiques dans la maladie de Parkinson en phase avancée. Il y a de plus en plus d'options thérapeutiques dans la maladie de Parkinson et le traitement de ses complications. Il existe des traitements pharmacologiques et chirurgicaux, et, pour la prise en charge des complications psychiatriques, des thérapies psychiatriques. Nous revoyons ces options dans cet article.

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The major goal of treatment in neurodegenerative disorders such as Parkinson's disease is improving quality of life. A successful therapy must maximize improvement in function and produce relatively few side-effects. A variety of newer therapies as well as established treatments are available. Ideal therapy would be directed at arresting or slowing progression of the disease. Although a few tentative steps have been taken recently in developing drugs with neuroprotective effects, future studies may more clearly identify such agents.

In this review, the range of anti-Parkinsonian agents and treatments will be discussed, including medications and non-pharma-

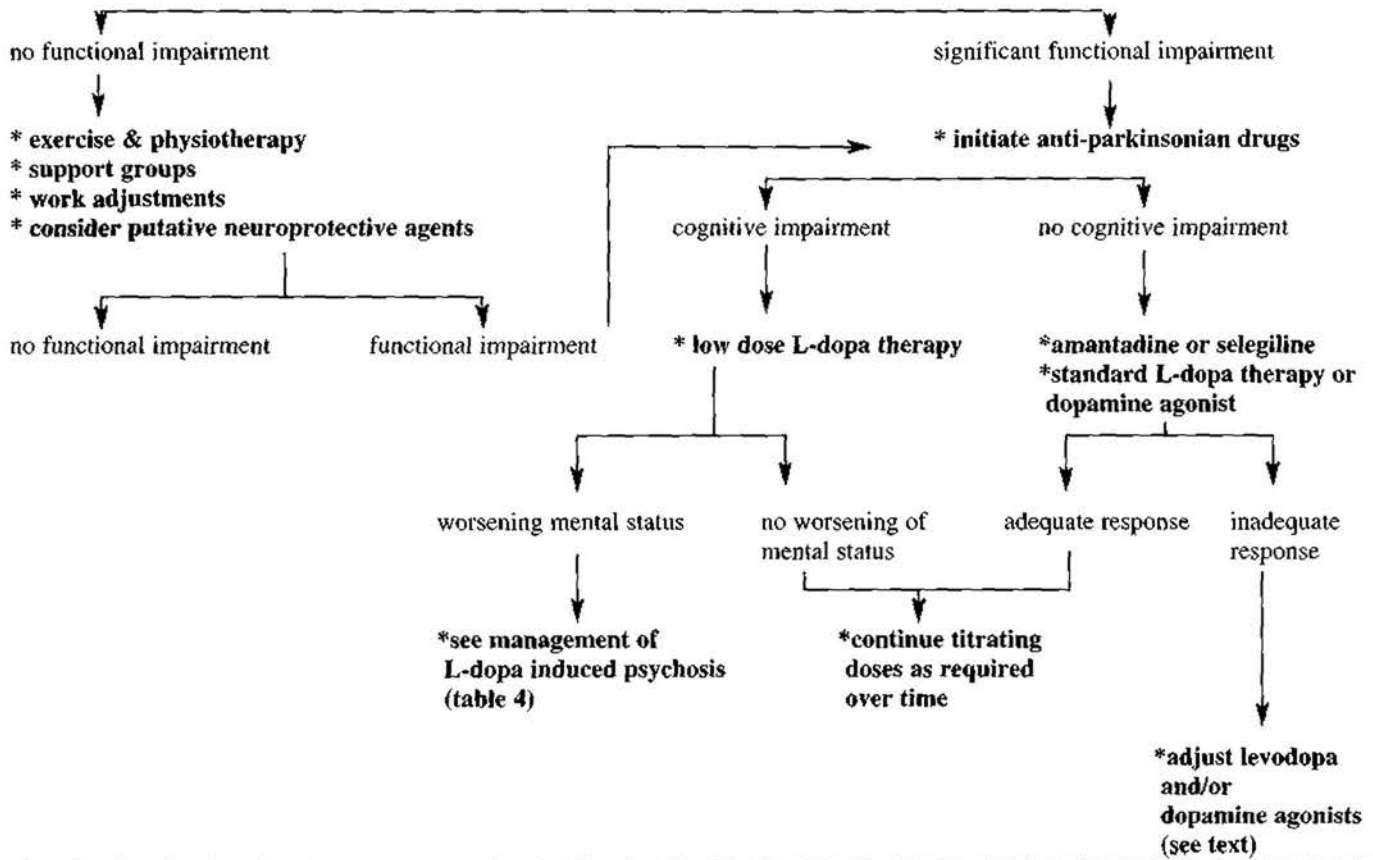
logical interventions such as surgery and electroconvulsive therapy. In addition, since symptoms as well as complications of therapy change with the duration of illness, disease management will be addressed in the context of early- versus late-stage disease. Management in early stages of Parkinson's disease includes

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Table 1: Management of early Parkinson's disease



reaching an accurate diagnosis and deciding when treatment should be initiated. As the disease progresses, motor problems take on different forms, including some which are treatment-induced. Since there are now several drugs available for the treatment of PD, there are different opinions on how they should be used. Suggested approaches (Tables 1 and 2) reflect our own clinical practice. Surgical intervention is growing in importance in later stages of the disease and is reviewed in detail.

ANTI-PARKINSONIAN AGENTS

Anti-cholinergic agents

Anticholinergic drugs have largely become agents of historical interest. It was first recognized that these agents had antiparkinsonian properties in the latter part of the nineteenth century. At that time belladonna alkaloids were used without knowledge of their mechanisms of action. It later became established that central cholinergic receptors were predominantly of the muscarinic type and these were the site of action of the synthetic anticholinergic drugs, such as trihexyphenidyl, benzotropine and diphenhydramine. Newer nicotinic agonists are currently being considered. A Canadian, Andre Barbeau, is credited for the explanation that these agents partially restore the dopaminergic-cholinergic balance in the striatum, in which the primary deficit of a decrease of dopamine leads to a relative cholinergic hyperactivity.²

The clinical trials of the late fifties and early sixties³ as well as clinical experience confirmed the lasting symptomatic effects of anticholinergic agents. These are still used as initial therapy by some neurologists in young (less than 60) patients with rest tremor as the predominant symptom.

Amantadine

The antiparkinsonian properties of amantadine were discovered fortuitously by Schwab et al in 1969.⁴ Clinical trials confirmed the symptomatic value of amantadine in doses of 100 to 300 mg daily^{5,6} alone or with levodopa. The therapeutic profile was considered to be better than placebo^{6,7} at the current optimal dose of 200 mg daily. The most common side-effect is ankle edema, with livedo reticularis being less frequent. A liquid formulation offers the possibility of smaller 25-50 mg doses in older and frail Parkinsonian patients who tolerate little else. The pharmacological mechanisms of action of amantadine have been suggested as release of dopamine from neuronal storage sites in the peripheral⁸ and the central⁹ nervous systems. No anticholinergic effects could be demonstrated in animals⁸ and very little in man.¹⁰ The primary mode of action maybe an amphetamine-like effect.¹¹ Amantadine and related drugs are also potent antagonists at the N-methyl-D-aspartate (NMDA) receptor.¹² A possible neuroprotective effect has been proposed, based on this antagonism, and could explain the improved survival noted with the use of amantadine in one study.¹³ An anti-dyskinetic effect

has also been noted with this drug. The algorithm for the management of Parkinson's disease¹⁴ recommends the introduction of amantadine in young (less than 60) and old patients with mild symptoms as first line symptomatic monotherapy.

Levodopa

Levodopa was introduced in the 1960s^{15,16,17} and rapidly established itself as the most effective agent for symptomatic treatment of Parkinson's disease. Levodopa is generally combined with a peripheral decarboxylase inhibitor (carbidopa in Sinemet and benserazide in Prolopa) to prevent its conversion to dopamine peripherally, thus reducing some of its side effects, such as those involving the gastro-intestinal system. Although in the early stages of the disease there is a stable response to levodopa therapy, prolonged use is associated with potential complications. As the disease progresses, the clinical response to a dose of levodopa becomes shorter. This short duration of action may result, in part, from ongoing degeneration of the nigrostriatal dopamine system and a reduced capacity to store dopamine. Post-synaptic changes may also play a role in producing such changes.

Sustained-release preparations of levodopa, such as Sinemet CR, (and Madopar HBS in Europe), have been developed to counteract this effect. Standard Sinemet is almost completely absorbed in three hours, while with Sinemet CR, levodopa absorption is sustained over a 4-6 hour period. A change to this preparation may be considered in the case of a patient who has been on regular levodopa and begins to notice a loss of effect towards the end of the dose. Patients who need to take levodopa more than three times per day might also be considered for a change to Sinemet CR. The bioavailability of Sinemet CR at 71% is less than that of standard Sinemet at 99%, but the Sinemet CR formulation has been shown to produce more sustained levodopa plasma levels.¹⁸ Thus when converting from a standard preparation to an equivalent dose of the CR form, a dose increase of approximately 25-30% is required, but the frequency of dosing may be reduced. Patients converted from regular levodopa preparations to Sinemet CR show a reduction in "off" time ranging from a mean of 1.4 hours for all converted patients to 2.7 hours for those with severe fluctuations.¹⁹ In a study involving 306 parkinsonian patients initiated on Sinemet CR, symptomatic relief was noted in a majority, regardless of the stage of disease. Patient preference for the CR preparation was also noted. The most common causes for this preference were smoother effect, longer duration of action, convenience, predictability and better sleep.¹⁹

Another motor complication of long-term levodopa therapy is the development of drug-induced dyskinesias. These usually consist of a combination of choreo-athetoid and dystonic movements, and have been thought to occur in up to 50% of patients after five years of sustained levodopa therapy.^{20,21} Dyskinesias are a major factor in limiting doses of anti-PD medications. Two patterns of dyskinesias have been described.²² The most common is the IDI response (Improvement-Dyskinesia-Improvement), characterized by a single phase of dystonia or choreiform movement which occurs at the peak of plasma dopa concentrations. Involuntary movements may also develop as biphasic dyskinesias or the DID response (Dyskinesia-Improvement-Dyskinesia), which occur during both the rise and fall of the plasma levodopa concentration time curve usually in younger patients.^{22,23} In this

case, involuntary movements occur when the concentration of plasma levodopa passes through a critical, but relatively low level, and remain absent as long as the concentration of levodopa remains above that level.²²

Does levodopa therapy result in these fluctuations? Animal experiments suggest that motor fluctuations are dependent on two factors: 1) integrity of the nigrostriatal system and 2) intermittent dopaminergic therapy. Thus in the presence of denervation within the nigrostriatal system, intermittent non-physiologic administration of dopaminergic drugs may result in changes which lead to motor fluctuations.²⁴ It has been suggested that the early use of controlled-release levodopa preparations might delay the onset of motor response fluctuations.²⁵ The five-year CR FIRST study compared regular Sinemet to Sinemet CR in patients who were being started on therapy, and who had not received levodopa or dopamine agonists previously. This study failed to show any significant difference between the two groups in terms of motor fluctuations.²⁶ Interestingly, the study showed a lower than expected rate of motor fluctuations and dyskinesias associated with levodopa therapy (20.6% in the Sinemet group and 21.8% in the Sinemet CR group). This probably reflects the fact that low doses of levodopa were used to initiate therapy by the clinicians involved in the study. This practice is in contrast to previous approaches which used higher doses and a more rapid rate of escalation in *de novo* patients, leading to the higher rate of motor complications reported in other studies.²⁷ Other methods of continuous delivery, such as intravenous levodopa infusion therapy²⁸ and continuous intraduodenal infusions of levodopa have been shown to produce steady plasma levels as well as a reduction in motor fluctuations.^{29,30} These approaches have obvious practical restrictions and need refinement before they can be adopted in clinical practice.

Some concern has been expressed as to the likelihood of levodopa being toxic to remaining cells in the substantia nigra. This theory is based on the observation that dopamine metabolism results in the formation of oxygen free radicals, which may damage neurons.³¹ The damage may be more evident when dopamine turnover is elevated, as with the administration of levodopa.³² This theory has led to the view that levodopa therapy should be delayed, and anti-PD therapy should be initiated with other compounds. Much of the evidence supporting the theory of toxicity, is based on studies of postmortem brain tissue. Levodopa can be toxic when present in high doses in vitro or in the absence of glial cells which probably have a protective role in the cellular environment.³³ More recent clinically based studies indicate that levodopa therapy is not as potentially toxic as previously feared. Indeed, it has been observed that life expectancy for PD patients increased significantly since the widespread use of levodopa. The beneficial effect on survival is evident only if levodopa is introduced prior to Hoehn and Yahr stage 2.5.³⁴ The issue of which drug should be used in initiating therapy is discussed further in the next section. However, current thinking is that levodopa remains the most effective treatment in PD, and that questions related to timing have more to do with reversible effects on cell dysfunction, rather than any permanent toxic effect.³³

Dopamine agonists

Dopamine agonists by binding directly to the post-synaptic receptors, bypass the nigrostriatal system. Numerous studies have shown their effectiveness in improving function in patients

Table 2: Treatment Options with Advancing Parkinson's Disease

Motor difficulties	Treatment Options
* 'wearing off' of levodopa despite good response at peak dose	* change to controlled-release preparations of levodopa * increase dosing frequency * add dopamine agonist * add COMT-inhibitor * add selegiline, amantadine or anticholinergic agents (the latter only in patients who are not cognitively impaired)
* inadequate response at peak dose	* increase dose of levodopa * add dopamine agonist * add other anti-parkinsonian drugs (amantadine, selegiline or anticholinergics)
* unpredictable 'on-off' (ie. not related to timing of levodopa dose)	* add dopamine agonist * apomorphine * physiotherapy/gait training * low protein diet * surgical options
Dyskinesias - chorea (with or without dystonia)	* reduce individual doses of levodopa * more frequent levodopa dosing * add dopamine agonist * liquid levodopa preparation * early morning dose of levodopa * controlled release levodopa at bedtime * add dopamine agonist * see management of "wearing-off" * reduction in individual doses of levodopa
* improvement-dyskinesia-improvement pattern * dyskinesia-improvement-dyskinesia pattern	* surgical options for better control of dyskinesias
Dyskinesias - pure dystonia	* physiotherapy and gait training * check for postural hypotension and treat
* morning dystonia * dystonia as part of 'wearing off' * peak dose dystonia	
* postural instability and gait problems	

on levodopa.^{35,36} Until recently, the dopamine agonists available in Canada were two ergot-derived compounds, bromocriptine and pergolide. Because of potential side effects, in particular, nausea, it is recommended treatment should be started at low doses (0.05 mg OD of pergolide or 1.25 mg of bromocriptine) and increased very gradually, with the medication taken on a full stomach. Usually, the therapeutic benefit is not seen until a minimum daily dose of 15 mg of bromocriptine or 1.5 mg of pergolide is achieved. With disease progression, daily doses can be increased to 30 mg daily of bromocriptine or 3 mg of pergolide. However, these should not be regarded as absolute maximums as higher doses of both drugs have been used.

Monotherapy with either of these drugs has not proven very effective in North America, although it has been used in Europe. One recent study using pergolide in *de novo* patients has shown that up to 70% of patients do reasonably well for up to two years before requiring addition of levodopa.³⁵ In advanced patients, it is frequently possible to decrease levodopa dose, improving dyskinesias.

Common side effects of dopamine agonists include nausea/vomiting, orthostatic hypotension, nightmares, psychosis and confusion. Concomitant use of domperidone may be help-

ful in relieving gastrointestinal symptoms. Pergolide may allow for somewhat faster titration and result in fewer side effects than bromocriptine.³⁶ An important but uncommon side effect of these ergot derivatives, is pleuropulmonary and/or retroperitoneal fibrosis^{37,38} which typically occurs at high doses. However, one case was reported in a patient taking a fairly low dose of pergolide (1 mg per day). Yearly chest x-rays for anyone on high-dose dopamine agonist therapy is recommended.

Two new dopamine agonists have recently made their way to the market. Ropinirole is a highly selective non-ergoline D2 agonist. Initial studies have shown beneficial effects in both *de novo* patients as monotherapy^{39,40} and as adjunctive treatment.⁴¹ The starting dose, 0.25 mg tid, is usually taken with meals, and titrated weekly to a minimum therapeutic dose of 3 mg daily. Dosing up to 24 mg per day has been shown to be safe and effective. As it is metabolized by the cytochrome P450 system, and excreted in urine, use is restricted in hepatic and renal failure.⁴²

Pramipexole, also a non-ergoline agonist, is highly selective for D2 family, specifically the D3 receptors. Effectiveness has been shown in both *de novo*⁴³ and advanced patients.^{44,45} The minimum effective therapeutic dose is 1.5 mg per day, with initiation at 0.125 mg tid. Maximum effective dose is 4.5 mg od.

Pramipexole has low protein binding and is excreted in urine. The dose should be modified in renal failure.⁴⁶

Side effects of these two drugs are similar to those expected with other dopamine agonists. However, pleuro-pulmonary and retroperitoneal fibrosis are not expected with ropinirole and pramipexole as they are not ergot-derived.

Relative efficacy between older and new dopamine agonists is still unclear. One study comparing bromocriptine to pramipexole suggests that 30 mg of bromocriptine is equivalent to 4.5 mg of pramipexole with pramipexole showing a tendency towards improved efficacy.⁴⁵ Another study, comparing ropinirole to bromocriptine suggests similar efficacy between the two, with equivalency of 17 mg of bromocriptine to 8 mg of ropinirole.⁴⁷

A third dopamine agonist, cabergoline, was released in Europe earlier last year. Its advantages are its long half life, and once daily dosing.⁴⁸ Unfortunately, there are no plans to release it in North America at this time for treatment of PD.

Both ropinirole and pramipexole have been postulated to have neuroprotective effects.^{49,50} For this reason, as well as potential 'levodopa sparing effect', it has been suggested that they should be started as monotherapy in *de novo* patients, particularly, with onset prior to 60 years of age.⁵¹

The question of when to initiate dopamine agonist therapy rather than levodopa in *de novo* patients remains controversial. Some studies support the notion that the early use of these agents as a levodopa-sparing strategy delays the long term complications of levodopa, such as motor fluctuations and dyskinesias.^{51,52} Other recent reports suggest that as there is no evidence for levodopa toxicity, levodopa use should not be delayed.⁵³ Long term studies comparing levodopa to either pramipexole or ropinirole in *de novo* PD patients are ongoing to answer this important clinical question. Both studies are coupled with neuroimaging (using either PET or SPECT) to assess progression of nigrostriatal damage, and results should be available in the next 2-3 years.

Lastly, a brief word about apomorphine, the oldest of the dopamine agonists. Its advantage is that it has a rapid onset of action, but unfortunately effects are of short duration. Although it has been used in the past as a challenge test in an attempt to establish the diagnosis and to predict responsiveness to dopaminergic therapy, this compound has not been commonly considered for use as a therapeutic agent until relatively recently. The initial oral formulation was discontinued on account of drug-related nephrotoxicity with azotemia and efforts have been made to develop alternate routes of administration. Subcutaneous administration, intermittently or by continuous infusion, has been shown to reduce daily off time by about 50%,⁵³⁻⁵⁷ and some patients find it helpful when trying to come out of a sudden "off" state. Since apomorphine administration is frequently accompanied by nausea, vomiting and orthostatic hypotension, concomitant treatment with domperidone is usually required. Patients often find repeated injections intolerable, limiting the practical applications of this approach. Rectal and sublingual administration have been studied, and a nasal spray has also been used with some success.⁵⁷ Apomorphine can be useful for managing patients in the perioperative state in which oral medications cannot be taken.⁵⁸ Although apomorphine may have a role in advanced disease with rapid on-off fluctuations it is currently only available for compassionate use through the distributor in Canada.

Monoamine oxidase (MAO) inhibitors

The enzyme, monoamine oxidase is present in two forms, MAO-A and MAO-B. The striatal terminals of the dopaminergic neurons in the substantia nigra contain MAO-B in sufficient quantities to account for up to 25% of the deamination of dopamine. The most widely used drug in this category is selegiline (deprenyl, Edepryl) a non-reversible MAO-B inhibitor. A reversible MAO-B inhibitor lazabemide has just been released for the treatment of Alzheimer's disease. It should also be effective in PD, but no formal studies have been performed on levodopa treated patients. One study on *de novo* PD patients showed no symptomatic benefit.⁵⁹ As these drugs selectively inhibit MAO-B, they do not cause the 'cheese effect' (including hypertensive crisis) which results from the ingestion of tyramine rich foods; a special diet is not required when prescribing these agents.

There is some evidence to suggest that selegiline may act through mechanisms other than MAO inhibition, resulting in increased neuronal survival. This led to the DATATOP study (Deprenyl and Tocopherol Antioxidative Therapy of Parkinson's Disease) which was designed to examine the potential neuroprotective effects of selegiline.⁶⁰ Since both extrinsic and intrinsic oxidative-mediated mechanisms may be at play in the neuronal loss associated with Parkinson's disease, it was logical to use selegiline and tocopherol, a natural antioxidant. The DATATOP study showed that selegiline 5 mg twice a day considerably delayed the need for levodopa therapy, whereas tocopherol had no effects. It was later determined that a small but clinically detectable and statistically significant symptomatic effect can be seen with selegiline.⁶¹ This finding together with a waning of the benefit of selegiline in delaying the end-point after the first year has suggested that the effects of selegiline is symptomatic rather than neuroprotective.^{62,63} Although some have continued to infer a protective effect,⁶⁴ the majority of movement disorder neurologists feel that the postulated neuroprotective effect of selegiline remains unlikely.

With respect to symptomatic therapy, selegiline may be used as one of the first-line interventions for the early management of PD symptoms. In later stages, selegiline can be continued once levodopa has been started, as it prolongs the action of levodopa, although it may also worsen dyskinesia.⁶³ One recent study suggesting a detrimental effect of this combination over five to six years, especially in terms of increased mortality⁶⁵ has not been supported by other studies.⁶⁶

Catechol-O-methyltransferase (COMT) inhibitors

Catechol-O-methyltransferase (COMT) is an enzyme present both peripherally and in the central nervous system. Its main function is to convert levodopa to 3-O methyl-dopa (3-O MD) peripherally and dopamine to homovanillic acid (HVA) centrally. Thus levodopa, administered as Sinemet or Prolopa, is broken down into inactive forms through the activity of this enzyme. Inhibition of COMT would allow for increased bioavailability and longer duration of action, both of levodopa and dopamine.

Tolcapone, the first COMT inhibitor to be released, is theoretically active both peripherally and centrally, as it crosses the blood/brain barrier. However, the peripheral effect appears to be clinically the prominent one.⁶⁷ Preliminary studies using

tolcapone added to Sinemet⁶⁸ or Prolopa⁶⁹ in patients have shown benefit with a significant increase in 'on' time due to a prolongation of action of levodopa. There is no increase in C max or T max, and benefit has been shown in both early and late PD patients.^{70,71} An increase in the duration of dyskinesias can be seen in advanced patients, but this may be balanced by a reduction in the dose of levodopa. Side effects are uncommon, the most uncomfortable being diarrhea, leading to discontinuation in 5-10% of patients. A rare but important one is liver dysfunction leading to fulminant hepatic necrosis.⁷² This has resulted in withdrawal of this drug from general availability in Canada and Europe. It still may be obtained through compassionate use where other available medications are ineffective.

Dosing of 100 mg tid, taken every six hours is recommended. Liver function tests must be monitored every two weeks in the first 12 months of therapy, and monthly for the duration of treatment.

A second COMT inhibitor, entacapone, which is only active peripherally, is under development and should be released soon.⁷³ Entacapone needs to be administered at a dose of 200 mg together with each dose of levodopa. Side effects are similar to that seen with tolcapone; however no liver problems have been reported to date. All trials suggest that COMT inhibitors will be useful as adjunctive treatment in PD patients.

Neuroprotective agents

The concept of neuroprotection in Parkinson's disease gained popularity in the mid-1980s with studies such as DATATOP, testing the feasibility of delaying the need for symptomatic therapy. The hypothesis was that an intervention that protects the valuable neurons of the substantia nigra would retard the functional decline seen in Parkinson's disease.^{74,75}

While it appears that neither selegiline nor vitamin E have a significant role to play in neuronal protection or rescue^{62,63} other strategies are currently being tested. Other agents which may have potential neuroprotective effects include dopaminergic agonists, such as pergolide,³⁵ pramipexole⁴⁹ and ropinirole.⁵¹ Glutamate agonists, particularly those acting on the N-methyl-D-aspartate (NMDA) receptor, are also being tested in this context. Remacemide and amantadine may have an effect through this mechanism.⁷⁶ At this time, until the studies are completed, no specific recommendations with respect to neuroprotection can be given.

SURGICAL ADVANCES

There has been a resurgence of interest in surgical therapies for PD in the past few years. Surgical treatment has a long history with the first known interventions dating back to the 1930s.⁷⁷ The introduction of levodopa therapy resulted in a pronounced decline in the need for neurosurgical interventions except in rare patients with disabling, refractory tremors. However, recognition of the shortcomings of late-stage levodopa therapy has combined with a number of other factors to stimulate renewed interest in neurosurgical therapies.

Anatomical localization has been improved with the introduction of MRI and microrecording techniques. Non-human primate MPTP-induced parkinsonism has provided an extremely good animal model of Parkinson's disease. Studies in these animals have given important insights into the pathophysiological

changes which occur in the parkinsonian basal ganglia, most notably that dopamine deficiency results in overactivity of the principle output station of the basal ganglia, the internal segment of the globus pallidus (GPi).⁷⁸ This overactivity is in part due to excessive stimulation from excitatory glutamatergic input from the subthalamic nucleus (STN).⁷⁹ The output of the GPi modulates normal movement through its inhibition of the thalamus (which in turn excites motor cortical areas). Overactivity of the GPi thus excessively inhibits normal thalamic activation of cortex. Animal studies have also provided a greater understanding of the neuroanatomical makeup of the basal ganglia. This includes the recognition of several segregated functional "loops" including one principally involved in motor control which maintains distinct somatotopic representation in every component of the loop (cortex, striatum, external and internal pallidum, subthalamic nucleus, thalamus and premotor and supplementary motor areas of the frontal lobes).⁸⁰

Two other sources of impetus for the current activity in neurosurgical therapies for PD are the major developments that have occurred in the burgeoning sciences of neuro-transplantation and neuroregeneration and the recognition that high frequency stimulation can provide a safer alternative to irreversible ablative electrocoagulation lesioning. Although it has been suggested that the gamma knife could be used successfully in functional neurosurgery of movement disorders,⁸¹ most investigators believe that the absence of any physiological correlation of lesion location adds more risk to this approach.

Thalamic Surgery

Vim thalamotomy results in a pronounced reduction in tremor in 80-90% of patients.⁸² The benefit is sustained over many years of follow-up.^{83,84} Levodopa-induced dyskinesias also may be improved.⁸⁵ Side effects are not uncommon, including paraesthesiae, dystonia, dysmetria, gait disturbances, disequilibrium and dysarthria. The common occurrence of speech and swallowing dysfunction with bilateral procedures accounts for the infrequency of this approach in current practice.

High frequency deep brain stimulation (DBS) of the Vim thalamus provides an alternative which seems to have equal efficacy to ablation but fewer irreversible side effects.^{86,87} This is typically accomplished using a 4-contact electrode attached either to an implanted externally programable stimulator or a radio-frequency receiver with an external stimulator. Electrode combinations and stimulation parameters can be chosen to optimize clinical benefit and minimize adverse effects. Complications are essentially the same as for thalamotomy, but, with the exception of those related to intracerebral hemorrhage occurring during the procedure, they are reversible and resolve when the stimulator is turned off. Problems unique to this approach include the need for a second procedure to implant the stimulator and complications of having a device similar to a cardiac pacemaker *in situ* (e.g., a greater risk of infection, electrode fracture and the need for stimulator replacement with battery wear, usually three to four years).

The mechanism of action of high frequency stimulation is not fully established. Considerations include direct depolarization blockade of neuronal activity in the vicinity of the electrode (unlikely), stimulation of white matter afferent connections to the Vim thalamus and stimulation of inhibitory connections within the thalamus (e.g., the reticular nucleus of the thalamus).⁸⁸

Although implantation of the electrode can entail some permanent lesioning effect ("microthalamotomy"), this is usually transient and a recent postmortem study of a patient implanted 43 months before death revealed only minimal evidence of tissue disruption and gliosis at the site of the electrode contacts.⁸⁹ One of the principle advantages to the reversibility of the effects of DBS is its potential use when bilateral procedures are required.

Pallidotomy and Pallidal Stimulation

Initial attempts to lesion the globus pallidus were directed predominantly at the anterodorsal GPi. Inconsistent results with this technique and the greater efficacy of thalamotomy for tremor resulted in most surgeons abandoning the pallidum as a primary stereotactic target. Leksell and his colleagues, however, reported significant benefit from lesions placed in the posteroventrolateral GPi.⁹⁰ It is now recognized that this is the site of the pallidal neurons involved in the "motor" cortico-striato-pallido-thalamo-cortical loop.⁹¹ It is believed that benefit is obtained through the resultant reduction of the excessive suppression of the VA/VL thalamus by pathologically overactive GPi neurons. In support of this mechanism, positron emission tomography studies have demonstrated normalization of cortical metabolic activity in several frontal motor cortical areas following pallidotomy.^{92,93} Laitinen et al⁹⁴ renewed modern interest in this technique reporting improvement in all aspects of parkinsonism including bradykinesia and gait, two features which may be worsened by thalamotomy. A small number of recent studies have confirmed the significant benefit obtained with respect to "off"-period parkinsonian disability and "on"-period levodopa-induced dyskinesias, especially, but not exclusively, on the side of the body contralateral to the surgery.⁹⁵⁻¹⁰⁶ Experience at The Toronto Hospital using blinded evaluation of videotaped examinations and open-assessments has demonstrated a 30-40% reduction in "off"-period parkinsonism and an almost complete elimination of contralateral dyskinesias with an additional significant reduction in ipsilateral dyskinesias.¹⁰⁷ Improvements in total "off" scores, scores for contralateral "off" rigidity, tremor and bradykinesia and "on" period dyskinesias are sustained for two years.¹⁰⁸ Ipsilateral dyskinesias tend to worsen again after the first year and improvements in gait and other axial symptoms are not sustained beyond six months. Mixed results have been obtained with bilateral procedures^{106,109,110} and we have seen significant cognitive decline even in two of four patients undergoing stage procedures. Neuropsychological and behavioral changes have been variably noted following pallidotomy.^{98,102,111-114} Many groups reporting benefit have utilized microrecording to define the appropriate target as well as the critical neighboring structures to avoid (optic tract, internal capsule).^{98,115} Others have obtained good results using somewhat faster macrorecording and stimulation.¹⁰⁰ The relative safety and efficacy of these approaches requires further study.

High frequency DBS of the pallidum may be an alternative to ablation. Preliminary reports have described substantial benefit in patients undergoing bilateral pallidal stimulation.¹¹⁶⁻¹¹⁹ We (AEL) have had promising preliminary experience with unilateral pallidal stimulation both as the sole procedure and in patients who had undergone previous contralateral ablative pallidotomy.¹²⁰ Response to pallidal stimulation is complex. There may be varied response depending upon which part of the nucleus is stimulated. Stimulation of the dorsal part may give good anti-

parkinsonian effects, but induces dyskinesias, while ventral stimulation suppresses dyskinesias but may have a prokinetic effect.¹²¹⁻¹²³

Subthalamic Nucleus

The STN projects an excitatory glutamatergic pathway to the two segments of the globus pallidus and the substantia nigra reticulata. The finding of a marked increase in tonic neuronal activity of the STN in MPTP-treated parkinsonian monkeys encouraged De Long's group to lesion this structure with a resultant marked improvement in all features of parkinsonism in these animals.¹²⁴ Similar improvement has been seen in rare human parkinsonian patients with spontaneous STN lesions.¹²⁵ Concern about the development of persistent hemichorea/hemiballism has limited the application of this approach to human PD,¹²⁶ however, bilateral high frequency stimulation of the STN has been reported to markedly improve "off"-period parkinsonism in a small number of patients.^{117,127,128} The benefit of STN stimulation closely mimics that obtained with maximally effective doses of levodopa.¹¹⁷ Our experience¹²⁹ has confirmed benefit to "off"-period disability as well as refractory tremor.¹³⁰ Dyskinesias induced by STN stimulation may be managed by reducing anti-parkinsonian drug doses.^{129,131} The respective roles of thalamic, pallidal and STN stimulation are currently under study.

We reserve these surgical treatments for patients experiencing significant disability despite the use of optimal drug therapy. Therefore, this decision should be made by a team that includes a neurologist who is experienced in all facets of drug therapy for Parkinson's disease. Generally, symptoms unresponsive to levodopa, with the exception of tremor, do not respond to pallidotomy or pallidal or STN stimulation. Optimal patients for these procedures are relatively young ("physiological age" is more important than chronological age) and otherwise healthy, who obtain an excellent response to levodopa with respect to all features of Parkinson's disease but in whom this response is compromised by disabling fluctuations or dyskinesias. Patients who remain disabled at the peak benefit of levodopa, primarily by such symptoms as on-period freezing and severe postural instability and falls, will not be helped by these interventions. Similarly, patients with other levodopa resistant forms of parkinsonism such as multiple system atrophy and progressive supranuclear palsy, do not benefit. Cognitive dysfunction is an important factor to consider in defining surgical candidacy. Even the mildest degree of dementia should serve as a relative contraindication and patients with moderate to severe dementia should not undergo these procedures.

Considerably more research is required in the evaluation of ablative and stimulation therapies for Parkinson's disease. It is not absolutely certain which type of symptoms optimally respond and which symptoms are resistant to these techniques. It is not known how long the benefit of pallidotomy is sustained, what constitutes an absolute contraindication to the procedure (e.g., dementia) and how safe and efficacious are bilateral pallidotomies. The efficacy, safety and advantages over ablative surgeries of DBS in various sites require further assessment. The role of combined ablative and DBS procedures or the combination of DBS in different sites tailored to the nature of the predominant symptomatology also remain to be studied. One important concern, particularly regarding ablative surgeries is the

potential adverse effect that these procedures might have upon the future response to newer experimental therapies such as selective glutamate antagonists and neuronal transplantation.

Tissue Transplantation

This treatment is based on the theory that implanting dopamine-producing cells into the striatum can compensate for degenerating nigral cells. Laboratory experiments using 6-hydroxy-dopamine-treated rodents and MPTP-treated non-human primates have demonstrated that implanted fetal nigral cells will survive, extend processes, form connections with host neurons, produce dopamine and improve motor disturbances. Initially, clinical studies were performed using adrenal medullary grafts.¹³² Up to six months later, an increase in "on" time and mild improvement in motor functioning during "off" periods were reported.¹³³⁻¹³⁶ However, benefits were lost by 18 months¹³⁷ and complications were considerable. It has been suggested that these results could be improved by cografing the adrenal medullary tissue with some source of trophic stimulation (e.g., peripheral nerve).¹³⁸

Human fetal nigral grafting has been performed on a small scale with varying success.¹³⁹⁻¹⁴³ No controlled studies have been reported to date, thus a placebo effect cannot be ruled out. Some ongoing trials have taken this confounding factor into account with the addition of a control arm using a sham procedure (e.g., a twist drill). It is also possible that striatal lesioning at the time of transplantation confers a beneficial effect. Studies using fluorodopa positron emission tomography have demonstrated that transplants survive and function.^{143,144} A marked improvement in dyskinesias have been reported even when levodopa therapy is maintained.¹⁴³ This is associated with an improvement of 30% in total UPDRS scores and a 50% reduction in "off" time. Almost all patients have continued to require ongoing levodopa therapy although dosage requirements may be lessened. One recent postmortem study performed 18 months after bilateral striatal implantation revealed large numbers of surviving graft neurons extensively innervating the host striatum.¹⁴⁵

Issues that need to be resolved include, among others, the optimal number and locations of the graft tracts, as well as the number of fetal donors required for optimal reinnervation of the striatum, the optimal age range of the donors, and whether the graft tissue should take the form of cell suspensions or solid grafts. There are also unresolved ethical and logistic issues pertaining to the widespread application of this technique. This has led to the search for alternative graft sources such as nigral xenografts or cell lines genetically modified to produce dopamine or trophic factors. This technology, however, requires further development before its application becomes feasible in human patients.

MANAGEMENT OF PSYCHIATRIC PROBLEMS IN PARKINSON'S DISEASE

Although PD is usually thought of as a movement disorder, it is increasingly recognized that associated behavioral changes may occur. Some of these result in psychiatric illnesses such as major depression, drug-induced-psychosis and dementia. However, more subtle behavioral difficulties may manifest themselves as conditions which may not be severe enough to be classifiable as psychiatric disorders. Such conditions include early

cognitive changes (not meeting current criteria for dementia), non-motor fluctuations resulting in mood changes and mild perceptual problems.

Depression

Depression is the commonest psychiatric problem associated with PD.^{146,147} It has been estimated that between 40% and 50% of PD suffer from major depression.¹⁴⁸ Prevalence rates vary widely, mainly because of differences in definitions and because symptoms of depression and those of PD overlap. Both conditions may give rise to motor slowing, sleep disturbance and loss of energy, making it difficult to distinguish PD in the early stages, from major depression. There has been a debate in the literature, as to whether the mood changes are a result of a reaction to a chronic debilitating illness or due to neurochemical changes. It is more realistic to understand depression as a complex interaction between physical and psychological factors.¹⁴⁹ Neurotransmitter disturbances play an important role in producing depression in PD, with good evidence that Serotonin depletion is a major factor.^{150,151} Risk factors for developing depression with PD include right-sided hemi-parkinsonism, akinesia, increased severity of disability, anxiety and psychosis.¹⁵²

A survey of anti-depressant use amongst investigators caring for approximately 23,410 PD patients indicates that selective serotonin reuptake inhibitors (SSRIs) are used as first line therapy 51% of the time, tricyclic antidepressants 41% of the time and other agents 8% of the time.¹⁵³ However, there are concerns that the SSRIs may have a dopamine antagonist effect, and there are case reports of worsening motor symptoms in patients exposed to these drugs. The use of SSRIs is further limited in PD patients who are on selegiline. The concurrent use of selegiline with this group of drugs is not recommended because of the possibility of interactions, which include the serotonin syndrome¹⁵⁴ even though this syndrome has not commonly been reported. The tricyclic antidepressants can be used with relative safety in treating depression in PD, although elderly patients may experience unpleasant side effects, including dry mouth, blurred vision and memory problems. Some of the newer antidepressants such as venlafaxine have a weak dopaminergic effect and may be useful in treating depression in PD, without causing a deterioration in motor status. Bupropion is a non-tricyclic, non-SSRI which also has dopaminergic effects, but has had mixed results in treating PD patients. At this time, there is a lack of adequate controlled trials which will assist the clinician in determining the most appropriate drug for treating depression in this group of patients.

Mood changes sometimes accompany motor fluctuations and may manifest themselves as off-period dysphoria. Treatment is that of the underlying fluctuations rather than the accompanying psychiatric symptoms. In this context, it may be more appropriate to choose one of the antiparkinsonian agents used to reduce fluctuations rather than an antidepressant.

Anxiety disorders

Anxiety and panic attacks occur in approximately 40% of PD patients. It is unclear if this is a result of biochemical changes or if it is associated with an emotional response to the disease. In clinical practice, some patients appear to experience attacks of severe anxiety, together with somatic and autonomic symptoms during the "off" period. In these patients, therapy needs to be directed at reducing "off" time, by adjusting anti-PD medications.

Other patients, who suffer from chronic anxiety disorders may need anxiolytic agents such as the benzodiazepine drugs. Low dose tricyclic antidepressants with low anticholinergic effects (eg nortriptyline, desipramine or imipramine) may be useful in those patients who do not respond to benzodiazepines.¹⁵⁷ The SSRIs have been used in managing anxiety disorders but, as indicated earlier, may potentially aggravate motor symptoms. Further studies are needed to evaluate the role of these drugs in the Parkinsonian population. In our experience, moclobemide is an useful agent in treating anxiety disorders, either as an isolated phenomenon, or in association with depression.

Electro-convulsive therapy (ECT)

ECT has been utilized in the treatment of psychiatric syndromes associated with Parkinson's disease. While severe depression has been the main indication for ECT, it has also been tried in the management of drug-induced psychosis.¹⁵⁸ Besides exerting a therapeutic effect on psychiatric symptoms, improvements in motor status have been noted as well.^{159,160} The benefits of ECT have usually been found to be transient. However, one study, which involved a long-term follow-up of six PD patients treated with ECT, demonstrated an improvement in both depression and parkinsonism, with the improvement being maintained in four patients after three to eight years.¹⁶¹ It has been suggested that in order for the treatment to be effective in the long term, ECT should be used as a "maintenance" therapy.¹⁶² Post-ECT confusion and memory loss are the main adverse effects associated with ECT and are drawbacks when considering maintenance treatments.

The specific therapeutic action of ECT has not been well explained, possibly because multiple changes occur in the brain following this procedure. These include an initial increase in prolactin release, which is subsequently diminished with successive seizures. There is also an increase in permeability of the blood-brain barrier¹⁶³ which has been invoked as a possible reason for the effectiveness of ECT. More recent explanations include the observation that chronic ECT results in a relatively selective enhancement of the D1 receptor of the dopaminergic system, presumably associated with enhanced nigrostriatal function and an improvement in parkinsonism. Although it has also been suggested that ECT-activated pineal melatonin release may account for the clinical improvements seen, commonly,¹⁶⁴ there is little evidence to support this theory. The GABA system is also changed by ECT, raising the possibility that an interaction between the dopaminergic and GABA systems may play a role in producing anti-parkinsonian effects. Thus, while the mechanism of action is unclear, clinical benefits have been observed in some parkinsonian patients. Further prospective studies are clearly needed before the position of ECT as a treatment alternative in parkinsonism is established.

Drug-induced psychosis

Treatment-induced psychotic symptoms are among the most disruptive complications of pharmacological therapy in Parkinson's disease. These can range from vivid dreams or nightmares to more disturbing symptoms such as hallucinations or delusions. These symptoms occur in up to 13% of parkinsonian patients¹⁶⁵ and are the most important risk factors for nursing home placement.¹⁶⁶ Sometimes alluded to as the levodopa psychoses, such psychotic symptoms can be produced by virtually

any of the anti-parkinsonian agents in current use.¹⁶⁷ Several different mechanisms have been proposed, including both dopaminergic and serotonergic hypotheses. Since dopamine is differentially distributed in the brain,¹⁶⁸ dopamine replacement may result in different effects on the cortex and the basal ganglia. Excessive stimulation of dopamine receptors in the mesolimbic/mesocortical pathways may lead to the development of psychotic symptoms similar to those seen in schizophrenia.¹⁶⁹ Alternatively, chronic levodopa therapy may cause changes in receptors, leading to hypersensitivity of a progressively larger group of neurons.^{168,170} The serotonergic mechanism suggests that levodopa-induced elevations of serotonin release may result in overstimulation of cortico-limbic serotonergic receptors.¹⁷¹ Based on these competing theories, different anti-psychotic agents have been used.

Although most standard neuroleptic agents worsen parkinsonian symptoms, thioridazine used in low doses may permit a compromise between reduced mobility and the control of psychosis.¹⁷² In our experience, doses of 10 to 50 mg may be used, with regular monitoring visits.

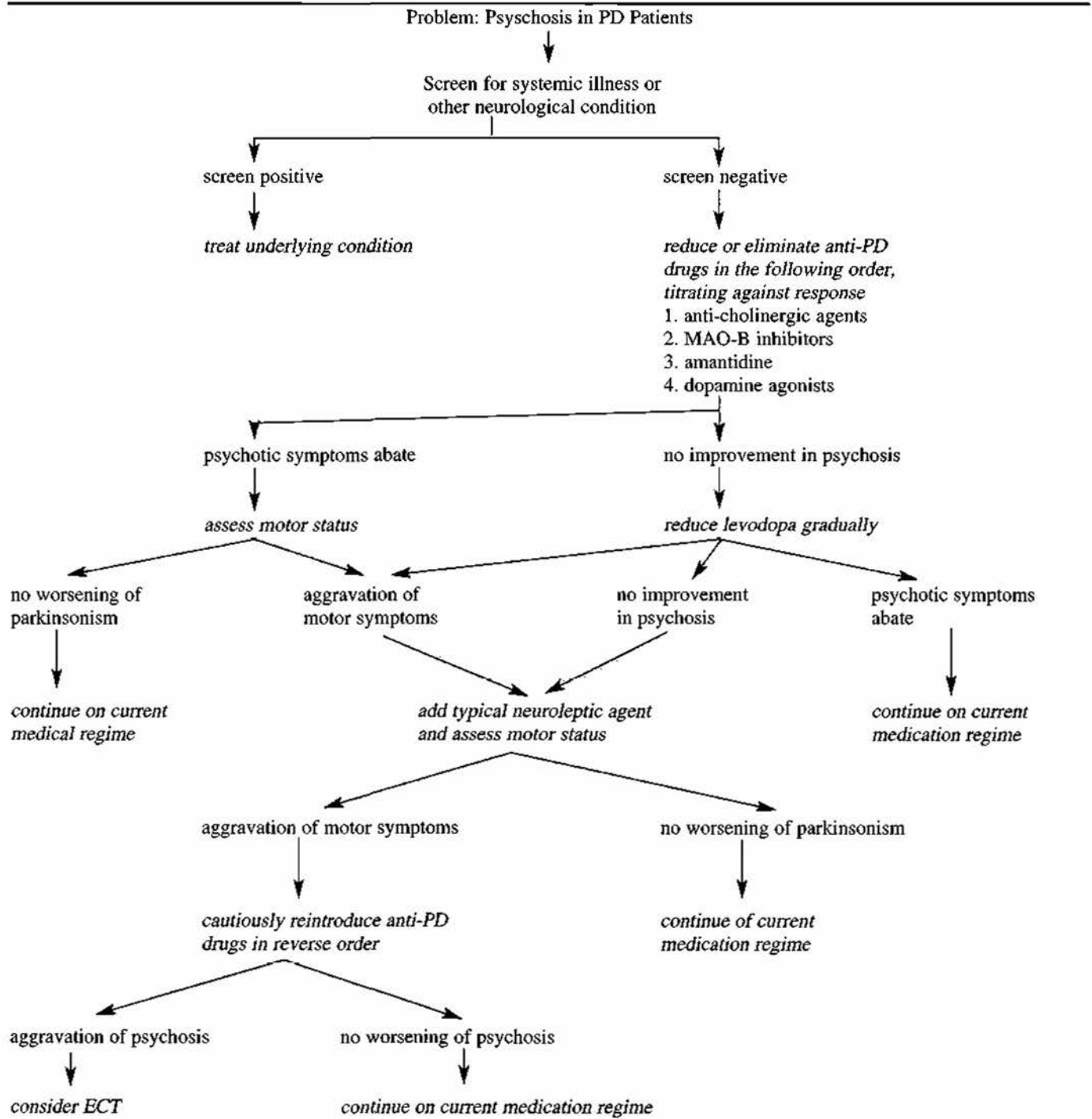
Atypical neuroleptic agents include clozapine, which has been the most widely accepted in treating psychosis in Parkinson's disease.¹⁷³ With its predilection for dopamine receptors in the limbic as compared with the striatal system,¹⁷⁴ it has little potential for worsening parkinsonian symptoms, and improvements in both parkinsonian tremor¹⁷⁵ and levodopa-induced dyskinesias¹⁷⁶ have been reported. The most serious side-effect with this drug is agranulocytosis. This complication occurs in approximately 2% of patients and is not dose-related. However, regular monitoring of blood counts is a safe way to avoid major reductions in the white blood count. Olanzapine, another new atypical neuroleptic agent, does not require blood monitoring, and may be used in small doses. Its effectiveness and the risk of worsening motor symptoms need to be evaluated in controlled studies. Risperidone, a compound with central 5HT₂ and D₂ antagonistic effects, has been used in low doses (up to 1.5 mg) without apparent worsening of parkinsonian symptoms.¹⁷⁷ In higher doses, however, motor deterioration has been described.¹⁷⁸ Ondansetron, a 5HT₃ receptor antagonist used as an anti-emetic in cancer patients, has been found, in a few non-blinded, non-comparative clinical trials, to be effective in controlling hallucinations without aggravating parkinsonian symptomatology.¹⁷⁹ Quetiapine, the newest atypical neuroleptic, has also been used to successfully control psychotic symptoms without worsening motor disability, in a small open-label study.¹⁸⁰

Prior to the use of atypical neuroleptic agents, the clinician was left with the option of reducing or systematically eliminating anti-parkinsonian drugs,¹⁷⁶ or else further compromising motor functions with the addition of standard neuroleptic agents. With the advent of these new agents, however, it is possible to control drug-induced psychiatric side-effects, while continuing anti-parkinsonian agents to alleviate disabling motor symptoms. A step-wise approach to the PD patient with psychosis is outlined in Table 4 and includes the withdrawal of drugs with low efficacy and a tendency to produce toxicity. These include anti-cholinergics, MAO-B inhibitors, amantidine and, in some cases, dopamine agonists.

Dementia

Cognitive impairment is increasingly being recognized as a

Table 3: Approach to PD Patients with Psychosis



From: Drug-induced Psychosis in Mohr. CNS Drugs 1996;5(3):166-174.

complicating factor in PD. Prevalance rates of dementia have been estimated to be between 20% and 30%.¹⁸¹ In other patients, milder forms of cognitive impairment may occur, and result in executive function deficits, memory and visuospatial problems.¹⁸² When dementia occurs, it most often manifests as frontal-subcortical changes, resulting in the typical parkinsonian dementia. However, Alzheimer's disease may occur as a concur-

rent illness with PD and give rise to a predominantly cortical type dementia. Other neurological conditions, such as diffuse Lewy body disease may cause dementia together with parkinsonian motor symptoms. Although there is no specific treatment, donepezil, an acetylcholinesterase inhibitor, used in the treatment of Alzheimer's disease, may have a role in stabilizing cognitive decline.¹⁸³ However, it remains to be seen if this group of

drugs has a potential for worsening motor function. In the future, the new nicotinic acetylcholine receptor agonists and other drugs being evaluated in the treatment of dementia may have a role in the management of this group of patients.

OTHER INTERVENTIONS

Autonomic dysfunction.

As the disease progresses, autonomic system dysfunction becomes a prominent problem.¹⁸⁴ Postural hypotension is common, due to both the disease process and anti-parkinsonian medications. All Parkinson's patients should be asked about postural symptoms, and have blood pressure checked lying and after 2-3 minutes of standing. Frequently, older people will decrease salt intake (sometimes as a result of a spouse with heart disease or hypertension) and counselling to increase salt and fluid intake may solve the problem. If postural symptoms persist, addition of fludrocortisone or midodrine is helpful as well as decreasing or discontinuing concomitant diuretics and anti-hypertensives.

Constipation is a frequent problem and, in addition to usual management with bran and stool softeners, cisapride may be effective in increasing bowel motility. Bladder function exhibits the opposite problem, that of urgency and frequency. Nocturia can be particularly distressing and disruptive to a good night's sleep. Low dose amitriptyline or anti-cholinergics at bedtime can be used. Occasionally, intranasal DDAVP is helpful.¹⁸⁵ Other autonomic problems include sleep abnormalities (usually insomnia), increased sweating, dysphagia, painful limbs, drooling and seborrhea. Probably the least discussed problem is sexual dysfunction resulting in impotence which can be quite distressing to male patients. Referral to a urologist may be helpful for discussion of possible therapies. Alternatively, counselling by a sexual psychologist can help in accepting limitations. At this time, sildenafil would not be recommended, due to the potential side effect of postural hypotension.

Supportive therapies

Physiotherapy and exercise are useful in keeping patients mobile and in good general health. Patient education is an important part of management, and the various Parkinson's disease societies that exist world wide can be extremely helpful by disseminating information through meetings and newsletters. Support groups are available in many larger centres, and allow patients and caregivers to ventilate their anxieties and frustrations, be aware of problems which may not have been attributed to the disease before, and also create an awareness of the various services available. In selected cases, individual or family counselling may be indicated, and is best performed by a therapist who is familiar with the disease. Less commonly, a referral to a psychiatrist may be necessary. Indications for such a referral include resistant depression or psychosis. Other medical specialists who are frequently consulted include orthopedic surgeons for back and posture problems, urologists of problems relating to urinary incontinence and impotence, and rehabilitation specialists for advice regarding ambulation and other issues pertaining to daily activities. Speech therapists at many centres have specialized in the management of difficulties in communication and swallowing in parkinsonian patients. Nutritionists may be helpful in assessing the diets of these patients, in the case of patients

who are losing weight rapidly, or who may benefit from the use of a protein modified diet in the case of major motor fluctuations.

Lastly, it is important not to forget to provide support and counselling to the primary caregiver, usually the spouse, who may develop significant medical and/or psychological problems themselves dealing with a patient with PD.¹⁸⁶

CONCLUSIONS

Advances in the treatment of Parkinson's disease are taking place with considerable rapidity. Recent developments include a renewed interest in surgical approaches, the development of new drugs, including long-acting preparations, and the possibility of finding effective neuroprotective agents in the future. Treatment-related complications are being managed and prevented more effectively. As the psychiatric and neurological complications of treatment with dopaminergic agents are reduced, therapeutic options for patients with more advanced disease are increased. The potential contribution of other disciplines should be borne in mind, as the quality of life of many of these patients can be enhanced.

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