NEUROLOGICAL DILEMMAS

First-line treatment in Parkinson's disease

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Parkinson's disease is a common neurodegenerative condition with a prevalence of about 160/100 000 in Western Europe rising to as high as 2% of the population over 80 years old (Mutch *et al.* 1986). The disease has a major socio-economic impact. The annual direct cost of care per patient is about £6000, while the indirect costs and the burden of the disease on patients and their carers are incalculable (Findley *et al.* 2003). Furthermore, a move from home to residential care is associated with an approximately 500% cost increase. Therefore, the management of Parkinson's disease is likely to prove an increasingly important and challenging aspect of medical practice as the population ages.

Therapeutic strategies have for the large part focused on pharmacological agents, and there has also been an increasing trend towards specialist Parkinson's disease clinics run by physicians with a specific interest in the disease. Such clinics often provide better integrated care with a specialist Parkinson's nurse and allied health specialists. However, the prevalence of the condition is such that the vast majority of neurologists will still have to be involved in the regular care of Parkinson's disease patients. In many cases this will be from shortly after symptom onset and often it is the neurologist who makes the diagnosis. Consequently, it is frequently the neurologist who will discuss the condition with the patient and his or her family as well as the issues around the initiation of treatment. This article focuses on the options a general neurologist might consider as first-line treatment for a newly diagnosed patient.

IS TREATMENT NECESSARY AT THE TIME OF DIAGNOSIS?

The timing of the introduction of drug treatment is important but can be difficult to decide. On the one hand, the neurologist may feel that the symptoms and signs of the disease are unequivocal and would clearly benefit from medication. Furthermore, the neurologist may consider that certain treatments offer the potential for 'neuroprotection' and that the earlier treatment can be implemented the greater the likelihood of slowing neurodegeneration and disease progression. On the other hand, this decision must be made in the context of the patient and their individual circumstances, and with their full and informed consent. Many patients need time to come to terms with, and to accept the diagnosis, and do not necessarily want to begin treatment immediately. Indeed, a period

of time without treatment is often reasonable unless there are clear problems with maintaining independence, or the symptoms are interfering significantly with employment or social activities. But any delay in treatment must be balanced against the *theoretical* possibility that early restoration of a more normal pattern of basal ganglia physiology might have long-term benefits.

WHICH DRUG FIRST?

Assuming the diagnosis of Parkinson's disease is secure and the patient has enough functional disability to merit drug treatment, how does one decide on first-line therapy? This decision will be based on the age of the patient, the likelihood of proper adherence, the presence of any cognitive impairment, any additional medical conditions, and the wishes of the patient. Treatment in the initial stage is to alleviate symptoms, so allowing the individual to be fully independent and to carry out their normal daily activities. It is of course vital that any treatment is well tolerated. The use of a single drug, or drug combination in a single capsule or tablet, is usually desirable to maximize adherence. If patients can remain on treatment with minimal or no adverse effects, with a satisfactory reduction of symptoms and a feeling of well-being that allows them to live independently and productively, then the introduction of treatment will clearly have been worthwhile.

NEUROPROTECTION

The ideal is to slow the progression of neuronal loss (neuroprotection) and additionally to restore function to neurons that have been damaged but may still have the capacity for recovery. The concept of neurorestoration, whereby one brings about an increase of functional neurones either by transplantation or the use of trophic factors, is of great interest but is unlikely to be considered as first-line treatment in the near future. The issue of 'neuroprotection' merits more consideration. The premise that a first-line treatment is neuroprotective is clearly attractive but unfortunately difficult to prove. This is perhaps best illustrated by the DATATOP (Deprenyl and Tocopherol Antioxidant Therapy of PD) trial assessing selegiline, a monoamine oxidase type B inhibitor (Parkinson Study Group 1989). This study tried to test an effect on the natural history of the disease by assessing the delay before levodopa therapy was required. However, the results were confounded by the *symptomatic*

effect of the treatment and the long duration of response to treatment for weeks or months after withdrawal. More recently, the rate of change in ^{18}F fluorodopa uptake by dopaminergic neurons in the striatum using Positron Emission Tomography (PET) or beta-CIT, a radio-isotope that binds to the dopamine transporter on the presynaptic dopamine neuron so giving a presumed measure of the number of remaining dopamine neurones on single-photon emission computerized tomography (SPECT), have been used as surrogate outcomes for neuroprotection (Parkinson Study Group 2002a; Whone *et al.* 2003). Both imaging parameters demonstrated a significantly lower rate of decline in striatal signal in patients randomised to begin therapy with a dopamine agonist rather than levodopa. However, although this suggests a disease modifying

We tend to favour levodopa as first-line therapy in patients over the age of 75

effect, the studies provide only indirect evidence of neuroprotection and interpretation remains much debate (Schapira & Olanow 2004).

FIRST-LINE LEVODOPA TREATMENT?

For 40 years, levodopa, combined with a peripheral decarboxylase inhibitor, has been regarded as the gold standard for the treatment of Parkinson's disease. It still remains in many respects the most effective drug treatment. However, the benefits can come at a price. Levodopa-related adverse effects include postural hypotension, nausea, sedation, increasing confusion and hallucinations. Longer term therapy frequently leads to additional adverse effects – levodopa induced dyskinesias develop at an average rate of 10% per annum, a higher figure in younger onset patients. Motor complications, i.e. wearing off, freezing episodes and on–off fluctuations are most strongly related to disease duration and dose of levodopa exposure, while dyskinesias are predominantly related to the duration of levodopa treatment (Schrag & Quinn 2000). The development of drug-induced dyskinesias seems to be associated with intermittent stimulation of dopamine receptors, levodopa has a short half-life of 60–90 min, so pulsatile levodopa supply to a denervated striatum may be an important

aetiological factor. In addition, the more severe the nigral neuronal loss when levodopa is introduced, the sooner adverse features appear. This was particularly true in individuals exposed to the toxin MPTP who frequently developed violent dyskinesias within months of starting treatment.

Treatment of levodopa induced dyskinesias remains unsatisfactory. They can be very disabling and difficult to control in patients of all ages, and the onset of dyskinesias marks the beginning of the complex phase of Parkinson's disease management. Simply reducing the daily dose of levodopa generally renders the patients rigid and immobile. However, alteration of the delivery of levodopa, dopamine agonists, amantadine and functional surgery can all improve drug-induced dyskinesias.

We tend to favour levodopa as first-line therapy in patients over the age of 75. Elderly patients often have multiple comorbidities – including postural hypotension – which seem to be exacerbated to a greater extent by dopamine agonists. Furthermore, the relatively low risk of motor complications in elderly compared to younger (< 50 years) onset patients, together with the potential for disease related cognitive impairment, generally favours the use of levodopa over dopamine agonists in this elderly group.

FIRST-LINE DOPAMINE AGONIST TREATMENT?

There are six orally acting dopamine agonists. Four are ergot derivatives: bromocriptine, pergolide, cabergoline and lisuride; and two are non-ergot drugs, ropinirole and pramipexole. These drugs all work by stimulation of postsynaptic dopamine receptors. The dopamine agonists were initially licensed for use in conjunction with levodopa in patients with advanced disease. Their later introduction as first-line agents came about as a result of their efficacy in improving motor symptoms in addition to their ability to delay the introduction of levodopa and the subsequent development of levodopa complications. The adverse effect profile of the dopamine agonists is similar to levodopa but limb oedema, confusion and hallucinations are more frequent.

Randomised trials have compared the various dopamine agonists with levodopa. The first, in the 1980s, showed a delay in onset of dyskinesias with bromocriptine monotherapy compared to levodopa but no effect on the onset of motor fluctuations (Ramaker & Van Hilten 2000) The

use of bromocriptine in conjunction with levodopa showed no additional benefit in terms of motor complications, motor impairment or disability. Randomised trials of the more recently introduced dopamine agonists have shown a significant delay in the development of motor complications in patients started on agonist monotherapy compared to levodopa (Parkinson Study Group 2000; Rascol *et al.* 2000).

A clinical rating scale which is widely used in treatment trials is the Unified Parkinson's Disease Rating Scale (UPDRS) (see Appendix). This allows longitudinal assessment of various domains including mentation and mood (Part 1), daily activities (Part 2) and motor function (Part 3). In the trials of ropinirole and pramipexole monotherapy, patients treated with levodopa showed improved UPDRS scores (parts II and III) compared to those on dopamine agonists, although during the trials, patient and physician assessments for the two arms were comparable. Quality of Life (QoL) outcome measures over the 4 years of the CALM-PD randomized study (Parkinson Study Group 2004a) were the same for the levodopa and pramipexole groups.

The dilemma of first-line treatment in Parkinson's disease is therefore this: dopamine agonists produce fewer motor complications and the same quality of life but the price is more frequent adverse effects and less symptom control. There has been a general belief that the potential for adverse effects with dopamine agonist monotherapy is much greater in elderly patients but studies with the newer agonists do not bear this out and these drugs can be well tolerated in patients over 75 years old (Shulman *et al.* 2000). However, as suggested above, particular caution is required when using agonists in the elderly.

WHICH DOPAMINE AGONIST?

A number of Cochrane reviews have compared bromocriptine with the newer dopamine agonists (Clarke & Speller 1998; Clarke & Dean 2000a; Clarke & Dean 2000b; Clarke *et al.* 2000). Although these reviews show little difference, many of the trials were underpowered to detect clinically meaningful differences. This leaves the decision on which dopamine agonist to initiate as rather empirical. However, there are some clinical features that may help. In a small trial, there was some evidence that pramipexole was more effective in the treatment of tremor though this benefit was at best mild (Pogarell *et al.* 2002). Another small trial of 30 patients showed a decrease in tremor in patients treated

Dopamine transporter (BetaCIT) binding in a healthy normal individual and patients with early, moderate and severe Parkinson's disease. Note the asymmetric loss particularly in the putamen in the early case and the progressive loss bilaterally in both putamen and caudate with disease progression. Picture courtesy of Dr Ken Marek and with permission from JAMA.

with either pergolide or pramipexole compared with placebo (Navan *et al.* 2003). Pramipexole has been shown to have a possible antidepressant action in a small study of 40 patients showing effect on one depression score, but not on another, in patients with mild and severe depression (Rektorova *et al.* 2003). Given the high prevalence of depression in Parkinson's disease, this may be an important consideration in choice of first-line treatment. Cabergoline has the longest half-life of the currently available dopamine agonists. In open-label trials, an evening dose of cabergoline had a beneficial effect on nocturnal motor symptoms with significantly reduced nocturnal akinesia (Chaudhuri *et al.* 1999). But with the long half-life, the dose has to be titrated up slowly. However, the once daily dosage is popular with patients and improves compliance.

There have been reports of noninflammatory fibrotic degeneration of cardiac valves with bromocriptine (Serratrice *et al.* 2002), pergolide (Van Camp *et al.* 2004) and cabergoline (Horvath *et al.* 2004). Although at first pericardial and pulmonary fibrosis occurred primarily with the ergot-derived agonists, recent data suggest that it occurs with both ergot and non-ergot agonists alike (Muller & Fritze 2003). At this stage, it is not possible to be certain that the

valvular fibrotic complications are exclusive or indeed more common with ergot as opposed to non-ergot agonists. Vigilance is clearly required – patients complaining of new cardio-pulmonary symptoms require careful examination and appropriate specialist investigation if appropriate.

FIRST-LINE MONOAMINE OXIDASE (MAO) B INHIBITORS?

MAO-B inhibitors were widely used following the DATATOP study because of their efficacy in symptom improvement and presumed 'neuroprotective' effect. However, a study by the United Kingdom Parkinson's Disease Research Trial Group following over 700 patients with mild early disease appeared to show a significant increase in mortality in patients treated with selegiline and levodopa compared to levodopa alone or bromocriptine alone (The Parkinson's Disease Research Group 1995). This finding was not replicated in further studies, which in fact suggested the opposite, a possible reduction in mortality. A recent meta-analysis of 17 randomised trials involving a total of 3525 patients came to the conclusion that MAO-B inhibitors reduce disability (albeit by a small amount), the need for levodopa, and the risk of motor fluctuations but not dyskinesias, without substantial adverse effects or increased mortality (Ives *et al.* 2004). However, many of the trials were of short duration and had not compared selegiline to initial treatment with a dopamine agonist. Nonetheless, MAO-B inhibitors do have a potential role as first-line monotherapy, particularly in young patients with relatively mild symptoms. Studies using rasagiline, a novel MAO-B inhibitor, have demonstrated efficacy in early and advanced disease (Parkinson Study Group 2002b). The TEMPO wash-in trial gave results compatible with a disease modifying effect, although like the dopamine agonist studies cited above, additional work needs to be done to confirm any neuroprotective effect (Parkinson Study Group 2002).

FIRST-LINE ANTICHOLINERGIC TREATMENT?

Anticholinergic compounds with antimuscarinic action are the oldest available drugs for the treatment of Parkinson's disease. However, their use dwindled after the introduction of alternative and more effective therapies with a more tolerable adverse effect profile. Confu-

Figure 1 The early management of Parkinson's disease.

MAO-B inhibitors reduce disability (albeit by a small amount), the need for levodopa, and the risk of motor fluctuations but not dyskinesias, without substantial adverse effects or increased mortality

sion and psychosis induced by anticholinergics can be florid, particularly in older patients. For these reasons, and because of inconclusive efficacy (Katzenschlager *et al.* 2002), they are not generally recommended as first-line therapy. However, in younger patients with no cognitive impairment who have predominant rest tremor and little bradykinesia or rigidity they may occasionally be effective.

COMBINED LEVODOPA AND COMT INHIBITION AS FIRST-LINE TREATMENT?

In the UK entacapone, a selective catechol-O-methyltransferase (COMT) inhibitor is licensed for use with levodopa, and tolcapone has recently been reintroduced with special precautions (tolcapone was associated with fatal liver failure but there have been no such reports with entacapone). At present, entacapone is used to treat end of dose wearing off and so improve motor fluctuations. A combined preparation

(Stalevo) is now available and has the advantage of reducing the number of tablets taken daily, thus potentially improving compliance. It is also worth considering whether COMT inhibitors have a role in the treatment of newly diagnosed Parkinson's disease. Multiple-dosing studies have demonstrated that a COMT inhibitor is associated with more stable plasma levels of levodopa (Stocchi 1998). More stable drug concentrations provide enhanced and 'smoother' levodopa availability to the brain than when levodopa is administered alone. Avoiding fluctuating peak levodopa levels may in theory delay the development of motor complications though this is yet to be proven in humans. The addition of a COMT inhibitor when levodopa is first introduced might be expected to delay the onset of motor complications by two mechanisms. Firstly, by increasing the half-life of levodopa and secondly by reducing the fluctuations in peak levodopa levels which are likely to be important in the development of dyskinesias

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EDITORIAL COMMENT

Many clinicians in the UK are taking part in the PD MED trial comparing levodopa vs. a dopaminergic agonist of their choice vs. selegiline in early Parkinson's disease. Neurologists who are still uncertain which treatment to use first should consider joining this trial (<http://www.pdmed.bham.ac.uk>).

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CONCLUSIONS

- This is a personal view of early Parkinson's disease treatment and we emphasize the need to consider each patient individually.
- We start with levodopa as first-line therapy in patients over the age of 75. Below this age, a dopamine agonist is our first-line treatment unless there is evidence of cognitive impairment.
- In most cases, there is insufficient comparative data between agonists to prefer one over another. However, the coexistence of depression may favour the use of pramipexole.
- MAO-B inhibitors may have a role as monotherapy. Indeed, there is the option to introduce a dopamine agonist followed by an MAO-B inhibitor, or vice versa, prior to the introduction of levodopa.
- Whatever the initial therapy, all patients will at some point require levodopa.
- The introduction of a single combination of levodopa, a peripheral decarboxylase inhibitor and a COMT inhibitor has the theoretical advantage of reducing the tendency towards motor fluctuations but cannot be recommended until there is robust evidence from randomized trials.

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APPENDIX

Unified Parkinson's Disease Rating Scale (UPDRS): Part 3 Motor sub-section

18. Speech
 - 0 = Normal.
 - 1 = Slight loss of expression, diction and/or volume.
 - 2 = Monotone, slurred but understandable; moderately impaired.
 - 3 = Marked impairment, difficult to understand.
 - 4 = Unintelligible.
19. Facial expression
 - 0 = Normal.
 - 1 = Minimal hypomimia, could be normal 'Poker Face'.
 - 2 = Slight but definitely abnormal diminution of facial expression.
 - 3 = Moderate hypomimia; lips parted some of the time.
 - 4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more. (head, upper and lower extremities)
20. Tremor at rest
 - (head, upper and lower extremities)
 - 0 = Absent.
 - 1 = Slight and infrequently present.
 - 2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
 - 3 = Moderate in amplitude and present most of the time.
 - 4 = Marked in amplitude and present most of the time.
21. Action or postural tremor of hands
 - 0 = Absent.
 - 1 = Slight; present with action.
 - 2 = Moderate in amplitude, present with action.
 - 3 = Moderate in amplitude with posture holding as well as action.
 - 4 = Marked in amplitude; interferes with feeding. (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)

22. Rigidity

(Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored)

0 = Absent.

1 = Slight or detectable only when activated by mirror or other movements.

2 = Mild to moderate.

3 = Marked, but full range of motion easily achieved.

4 = Severe, range of motion achieved with difficulty.

23. Finger taps

(Patient taps thumb with index finger in rapid succession.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

(Patient opens and closes hands in rapid succession.)

24. Hand movements

(Patient opens and closes hands in rapid succession)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

25. Rapid alternating movements of hands

(Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

26. Leg agility

(Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

27. Arising from chair

(Patient attempts to rise from a straightbacked chair, with arms folded across chest.)

0 = Normal.

1 = Slow; or may need more than one attempt.

2 = Pushes self up from arms of seat.

3 = Tends to fall back and may have to try more than one time, but can get up without help.

4 = Unable to arise without help.

28. Posture

0 = Normal erect.

1 = Not quite erect, slightly stooped posture; could be normal for older person.

2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.

3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.

4 = Marked flexion with extreme abnormality of posture.

29. Gait

0 = Normal.

1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.

2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.

3 = Severe disturbance of gait, requiring assistance.

4 = Cannot walk at all, even with assistance.

30. Postural stability

(Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)

0 = Normal.

1 = Retropulsion, but recovers unaided.

2 = Absence of postural response; would fall if not caught by examiner.

3 = Very unstable, tends to lose balance spontaneously.

4 = Unable to stand without assistance.

31. Body bradykinesia and hypokinesia

(Combining slowness, hesitancy, decreased arm swing, small amplitude, and poverty of movement in general.)

0 = None.

1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.

2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.

3 = Moderate slowness, poverty or small amplitude of movement.

4 = Marked slowness, poverty or small amplitude of movement.