EDITORIAL

Dopamine agonists: their role in the treatment of Parkinson's disease

Parkinson's disease is a chronic and disabling illness. There is still some uncertainty in its diagnosis, particularly in the early stages, as some other neurological conditions present with similar clinical features. There has been wide variation in the management of Parkinson's disease due to a lack of consensus on the best approach. Recently, United Kingdom specific guidelines for the management of Parkinson's disease have been produced[1] which provide, where possible, evidence based recommendations and the collective opinion of a Parkinson's Disease Consensus Working Group, whose members have substantial experience in managing patients with the disease.

Current drug therapy in Parkinson's disease is symptomatic and primarily aimed at restoring dopaminergic function in the striatum. Levodopa, in combination with a peripheral decarboxylase inhibitor, is still the most effective symptomatic treatment.[2] Levodopa enters dopaminergic neurons where it is metabolised to dopamine, replacing the depleted endogenous neurotransmitter. Along with its proved efficacy, levodopa is well tolerated, easy to administer, and relatively inexpensive.[3] However, long term use is associated with disabling complications such as fluctuating motor responses and dyskinesias[4–6] and narrowing of the therapeutic window.[7] In addition, levodopa is toxic in vitro to dopaminergic neurons[8] and in vivo its use could lead to formation of cytotoxic free radicals when exogenous dopamine is decarboxylated; these would cause damage to surviving dopaminergic neurons and potentially exacerbate the disease.[9 10]

In the light of these complications, the United Kingdom guidelines suggest that pharmacological intervention should be delayed until a diagnosis of Parkinson's disease has been confirmed by a specialist in movement disorders and the symptoms start to interfere with daily life.[1] In addition, the United Kingdom guidelines recommend that treatment with levodopa should be delayed for as long as possible providing alternative drugs, such as dopamine agonists, can achieve adequate symptom control.

The role of dopamine agonists

DEFINITION
Dopamine agonists exert their antiparkinsonian effects by acting directly on dopamine receptors and mimicking the endogenous neurotransmitter.[11] There are two subclasses of dopamine agonists: ergoline and non-ergoline agonists. Both of these subclasses target dopamine D_2-type receptors. The ergoline dopamine agonists include bromocriptine, pergolide, lisuride, and cabergoline, whereas rop-

inirole and pramipexole are non-ergoline agonists. Apomorphine, one of the first dopamine agonists shown to improve parkinsonian symptoms, is a combined D_1 and D_2 agonist but has to be administered subcutaneously. Its use has been well documented and will not be discussed in this review.[12–14]

Rationale for use
Dopamine agonists have proved antiparkinsonian activity.[15] Initially, they were introduced as an adjunct to levodopa treatment in patients exhibiting fluctuating motor responses and dyskinesias associated with its chronic use.[15–17] Addition of agonists to these patients' regimes allows around a 20%-30% reduction in the dose of levodopa in practice and leads to improvement in the disabling complications. Dopamine agonists have also been successfully used as monotherapy in de novo patients with the intention of delaying treatment with levodopa and consequently deferring the onset of complications.[18–21]

Dopamine agonists are not metabolised by oxidative pathways and so do not lead to the cytotoxic free radical formation that may be associated with metabolism of dopamine. By suppressing endogenous dopamine release it is also conceivable that they may protect dopaminergic neurons from injury, a theoretical concern if high concentrations of exogenous dopamine are present. The reason why motor complications are less often encountered with dopamine agonists than with levodopa is not fully understood. It may be related to the longer half life of dopamine agonists and differences in receptor selectivity.[22] Chase (1998) has suggested that pulsatile use of levodopa leads to an imbalance of basal ganglia opioid concentrations and resetting of voltage gated channels in *N*-methyl-D-aspartate (NMDA) receptors.[23] The de novo use of dopamine agonists may help to avoid these downstream pharmacological changes in the striatum and pallidum.[24]

Various therapeutic strategies may be adopted when starting treatment of Parkinson's disease in an attempt to delay and minimise the long term complications associated with levodopa. One approach is to start treatment with low dose levodopa and, if the efficacy declines, to add a dopamine agonist instead of increasing the levodopa dose.[19] Conversely, treatment may be started with a dopamine agonist or alternative symptomatic agent and low dose levodopa added later if required. Finally, it has been suggested that treatment should be initiated with a combination of low doses of levodopa and a dopamine agonist.[25]

Summary of key characteristics for dopamine agonists (data adapted from Utti and Ahlskog)[15]

	B	Pe	L	C	R	Pr
Receptor activity: agonist (antagonist)	D_2 (D_1)	D_2, D_1	D_2 (D_1)	D_2	D_2	D_2, D_1
Pharmacological properties	Ergot	Ergot	Ergot	Long acting ergot	Non-ergot	Non-ergot
Plasma half life (hours)	3–8	16	1–7	65	6	7–9
Time to peak plasma concentration (hours)	1–2	1.5	1	0.5–4	1.5	2
Administration (max dosage, UK, ABPI data)	Oral (10–40 mg/daily)	Oral (<5 mg/day)*	Oral, subcutaneous (<5 mg/day)	Oral (20 mg/day)	Oral (<24 mg/day)	NA

B=bromocriptine; Pe=pergolide; L=lisuride; C=cabergoline; R=ropinirole; Pr=pramipexole; NA=not available.
*Some clinics exceed this; the highest daily dose prescribed for several patients with refractory Parkinson's disease has exceeded 30 mg.

In the absence of clear evidence that any particular agent has an advantage in slowing or preventing progression of Parkinson's disease, the United Kingdom guidelines recommended that the choice of first line symptomatic therapy be made on an individual patient basis. Various interrelated factors should be borne in mind, including age, severity of disease, cognitive impairment, and intercurrent illness.[26] For advanced Parkinson's disease, and in elderly patients, levodopa was thought to be the agent of choice because of its clinical potency and convenience. However, in younger patients with mild to moderate symptoms, de novo use of dopamine agonists was suggested to be a more appropriate first line option,[1] as they seem to be as effective as levodopa in early disease and delay its use,[21 22 27] thus minimising the long term problems associated with levodopa. A summary of the key characteristics of dopamine agonists is shown in the table.

ERGOT-DERIVED DOPAMINE AGONISTS
The early oral dopamine agonists were ergot derivatives acting primarily on the D_2-like (D_2, D_3 and D_4) dopamine receptors (although pergolide has weak D_1 agonist activity and bromocriptine has D_1 antagonist activity). Examples of this type of dopamine agonist are bromocriptine, pergolide, lisuride, and the long acting ergoline, cabergoline.

Bromocriptine
Bromocriptine has been in regular use as adjunct therapy in patients receiving levodopa to allow lower doses of levodopa to be used and to improve "end of dose" motor fluctuations.[28] Use of bromocriptine as monotherapy in de novo patients has been shown to delay the need for levodopa treatment and the occurrence of motor complications.[19] Generally a three times daily regime has been employed.

Pergolide
Pergolide has similarly been shown to improve symptoms of Parkinson's disease both when used as monotherapy and in combination with levodopa. Treatment with pergolide monotherapy over 6 months in de novo patients has been shown to provide similar symptomatic efficacy and incidence of adverse events as levodopa.[29] As adjunct medication it allows a 20%-30% reduction in the dose of levodopa.[30 31] Again a three times daily regime has usually been employed. Clinical data have suggested that pergolide may be more effective than bromocriptine both as adjunct treatment with levodopa and as monotherapy in de novo patients.[32–34] The greater benefit found with pergolide could reflect its action on both D_1 and D_2-like receptors, in comparison with bromocriptine, which stimulates D_2-like receptors and is a weak antagonist at D_1 sites.[34] In some patients with complicated Parkinson's disease, high (4 mg) doses of pergolide have been shown to reduce motor fluctuations and achieve good control of parkinsonian signs and symptoms without the need for concomitant levodopa treatment.[35]

Lisuride
Lisuride, like bromocriptine, stimulates D_2-like dopamine receptors. Lisuride is as effective and well tolerated as bromocriptine when used in combination with levodopa in patients with advanced Parkinson's disease experiencing a deteriorating response to levodopa and motor fluctuations.[36] In an open non-randomised study, combination therapy with lisuride and levodopa, over 10 years, has been shown to decrease and delay the development of motor fluctuations and dyskinesias in patients with early disease compared with therapy with levodopa alone while maintaining an equivalent therapeutic response.[37] Trials have also shown that lisuride provides effective monotherapy and, when used in conjunction with levodopa, permits reduction of levodopa dose.[37 38]

Cabergoline
Cabergoline is a long acting ergoline dopamine agonist with selective affinity for D_2-like dopamine receptors and a long plasma half life of 65 hours.[3] Once daily cabergoline has been shown to be effective as monotherapy in de novo patients, reducing the Unified Parkinson's Disease Rating Scale (UPDRS) motor score by up to 30% and the time in "off" by up to 60%. It is also effective as adjunct therapy to levodopa in patients with advanced Parkinson's disease.[27] Cabergoline monotherapy for up to 1 year has been shown to be only slightly less effective than levodopa treatment. Rinne *et al* found that more than 60% of de novo patients could be managed on cabergoline alone for at least a period of 1 year.[3] Recent reports have also confirmed the efficacy of cabergoline in delaying motor complications.[25 39]

The efficacy of cabergoline as adjunct therapy to levodopa in patients with advanced Parkinson's disease and motor complications has been investigated in studies totalling more than 1500 patients.[39] Cabergoline treatment allowed the levodopa dose to be significantly reduced when compared with placebo (18% *v* 3%). The activities of daily living (ADL) score was also improved by cabergoline treatment (23%) compared with placebo (4%). Comparisons of cabergoline with bromocriptine have shown cabergoline to be as effective and well tolerated as bromocriptine, with the added advantage of once daily administration and improved patient compliance. The long half life of cabergoline may make it an appropriate choice for the treatment of nocturnal akinesia.

Side effects of ergot-derived dopamine agonists
Although the ergot-derived dopamine agonists have proved to be successful agents in the management of Parkinson's disease, there are side effects associated with their use. Some of these adverse effects are also associated with levodopa use and include nausea, vomiting, orthostatic hypotension,[40] hallucinations, and delusions[41 42] and, when used as an adjunct to levodopa, exacerbation of dyskinesias. These side effects are, therefore, likely to be dopaminergic in origin.

Nausea is caused by stimulation of the vomiting centre in the area postrema of the medulla which functionally lies

outside the blood-brain barrier. Transient use of the peripherally acting dopamine antagonist, domperidone, is effective in reducing nausea without blocking central dopamine receptors.[11][15] Orthostatic hypotension may be reduced by supplementing the diet with salt, increasing fluid intake, and administering fludrocortisone.[15] Raising the head of the bed and wearing elastic stockings may also help. Recently, there have been reports that the serotonin reuptake inhibitor, fluoxetine, may be effective in combatting orthostatic hypotension in patients with Parkinson's disease.[43]

Side effects, which are rare but seem to be specific to the use of ergot dopamine agonists, are vasospasm, erythromelalgia, and pleuropulmonary or retroperitoneal fibrosis.

NON-ERGOLINE DOPAMINE AGONISTS
These new dopamine agonists include ropinirole and pramipexole.

Ropinirole
Ropinirole is a potent and selective dopamine D_2-type receptor agonist and was the first available non-ergoline orally active dopamine agonist. Studies have shown that ropinirole is effective when used as monotherapy in early Parkinson's disease, providing symptomatic relief for up to 5 years.[21][44-46] It is also effective as adjunct therapy in patients with motor fluctuations: 65% of patients taking ropinirole with levodopa had a 30% increase in "on" time compared with 39% in the placebo group ($p<0.077$).[47] A recent 6 month study in patients with motor fluctuations showed that the use of ropinirole permits a >20% reduction in levodopa dose, while significantly reducing the time spent "off" compared with placebo (35% v 13%; $p=0.003$).[48]

The results of a 5 year, double blind, randomised trial comparing ropinirole with levodopa plus benserazide in the treatment of 268 patients with early Parkinson's disease have been recently presented.[21][22] Forty seven per cent of ropinirole patients and 51% of levodopa patients completed the 5 year study; of these, 34% of patients on ropinirole did so on monotherapy. In those patients on ropinirole who were given levodopa supplements, a lower dose of levodopa was required compared with patients on levodopa alone (427 mg/day v 753 mg/day respectively). Similar clinical efficacy of treatment in the ropinirole and levodopa groups was demonstrated throughout the study (assessed by change in ADL score). Ropinirole monotherapy was also found to be associated with a significantly lower incidence of dyskinesia than levodopa monotherapy (5% v 36% respectively; $p<0.0001$). In the intention to treat ropinirole arm of the study (including levodopa rescued patients), the incidence of dyskinesia was still significantly reduced (20% for ropinirole v 46% for levodopa; $p<0.001$). Adverse experiences, typical for dopaminergic agents, caused 27% of ropinirole patients and 29% of levodopa patients to withdraw from the study prematurely (not significantly different).

A 3 year, randomised, double blind study comparing the actions of ropinirole and bromocriptine in 335 patients with early Parkinson's disease has also just been completed.[18] Patients initially received either ropinirole (n=168), or bromocriptine (n=167) as monotherapy. Where insufficient relief from symptoms was achieved, supplementary levodopa was added and the study allowed to continue. In patients completing the study, both agonists were found to be effective for giving symptomatic relief; however, patients maintained a significantly better functional status on ropinirole than on bromocriptine. This

suggested an increased efficacy of the non-ergoline agonist for treatment of early Parkinson's disease over this 3 year period.

Pramipexole
In vitro electrophysiological studies suggest that pramipexole has greater potency for stimulating dopamine receptors than the ergoline agonists.[49] Pramipexole stimulates D_2-like receptors, with highest affinity for D_3 receptors. The efficacy of pramipexole in patients with Parkinson's disease has been demonstrated in some short term, placebo controlled trials.[50-52]

Use of pramipexole as adjunct therapy to levodopa has been investigated in advanced Parkinson's disease.[50][52] A three times daily regime has generally been employed. In one study,[50] 12 patients with motor fluctuations received adjunct pramipexole in an 11 week prospective, single blind, parallel group, placebo controlled trial. In this trial pramipexole significantly improved ADL assessed with UPDRS ($p<0.05$). Use of pramipexole allowed a reduction in levodopa dose of up to 30% ($p<0.05$).

In another trial conducted in 26 centres across the United States and Canada, 181 patients with advanced Parkinson's disease treated with levodopa were randomly scheduled to receive adjunctive therapy with either pramipexole or placebo for 32 weeks.[52] This trial found that pramipexole decreased time in "off" by 31% ($p=0.0006$) and permitted a 27% decrease in levodopa dose ($p=0.0001$). A double blind, placebo controlled study of adjunct use of pramipexole and bromocriptine in 247 patients showed a trend towards pramipexole being more effective than bromocriptine in patients with advanced Parkinson's disease and motor fluctuations.[51] Adjunct use of pramipexole improved the ADL and motor sections of the UPDRS by 27% and 34% although at the expense of increased dyskinesias and nausea.

The efficacy, safety, and tolerability of pramipexole as an add on drug has also been examined in an 11 week, double blind, placebo controlled, randomised trial in 78 patients with advanced disease and motor fluctuations.[53] Pramipexole or placebo was given, as add on therapy, to patients who had been previously stabilised on antiparkinsonian medication. The mean UPDRS total score was reduced by 37.3% under pramipexole compared with 12.2% under placebo ($p<0.001$). Patients who received pramipexole also reported a 12% reduction in "off" periods compared with a 2% increase with placebo.

The efficacy of pramipexole has been assessed over 9 weeks in 55 patients with de novo Parkinson's disease.[54] Compared with placebo, those patients receiving pramipexole showed a 40% improvement in ADL ($p=0.002$) and a 44% improvement in the motor score of the UPDRS ($p=0.10$). In a follow up study by the Parkinson Study Group, 264 patients with early Parkinson's disease were randomised to either pramipexole or placebo for 10 weeks. Pramipexole led to a 20% improvement in total UPDRS score and was well tolerated. Nausea and somnolence were the most common adverse events.[55]

Side effects of non-ergoline dopamine agonists
The non-ergoline dopamine agonists ropinirole and pramipexole seem to be well tolerated although they are still associated with the usual dopaminergic side effects; nausea, hypotension, somnolence, and exacerbation of dyskinesias. Disappointingly, both can cause confusion and hallucinations when used as adjunct medication. To date, ropinirole and pramipexole do not seem to cause side effects specific to ergots such as skin inflammation, digital vasospasm, and paraesthesias, pleural effusion, pulmonary infiltrates, or erythromelalgia.[56][57]

Addendum

Since this review was first submitted an article has appeared[61] detailing the case reports of nine patients taking non-ergot agonists who had sudden sleep attacks while driving, resulting in accidents. Eight of these patients were taking pramipexole and one was taking ropinirole at the time of the event and none experienced prodromal drowsiness or had had previous sleep attacks or somnolence. Six of these nine cases were also taking levodopa/carbidopa preparations and a seventh was taking pergolide. After their accidents six patients discontinued pramipexole and another two reduced the dosage and no further sleep attacks occurred. Since that publication SmthKline Beecham have reported 17 episodes of sleep attacks associated with the use of ropinirole, five occuring in the same patient. Some of these attacks were associated with prior somnolence. This is in the context of 68 200 patient-years of exposure.

As a result of these reports, the Committee for Proprietary Medicinal Products (CPMP) has recommended adjustments to the summary of product characteristics (SmPC) for pramipexole and ropinirole. In the SmPCs patients are advised not to drive when taking either of these dopamine agonists and to avoid other dangerous activities. Those patients experienceing sudden onset of sleep should consider drug reduction or withdrawal.

In the United Kingdom the Driving and Vehicle Licencing Authority (DVLA) has issued rather different advice. The DVLA has taken the view that the risk of somnolence with ropinirole is less than 2% and so its use should not result in automatic cessation of driving. Doctors should inform patients about the risk of somnolence and sleep attacks and should any such attacks occur the patient should cease driving until the dose is either withdrawn or the dose is reduced and symptoms have resolved.

The future role of dopamine agonists

Dopamine agonists provide an effective alternative to levodopa for the treatment of Parkinson's disease. They allow initiation of levodopa therapy to be delayed so deferring onset of levodopa associated treatment complications, a particular problem in younger patients. In addition, dopamine agonists provide benefits in more advanced disease by ameliorating fluctuating motor responses to levodopa.

The data currently available suggest that pergolide and the non-ergot agonists ropinirole and pramipexole are all more efficacious than bromocriptine when used in patients with de novo Parkinson's disease. This superior efficacy may be related to the absence of D_1 antagonist activity, which is a property of bromocriptine. There seems to be little difference in efficacy between the various agonists currently available when used as adjunct medication with levodopa, and so the choice is likely to depend on patient tolerability, dose regime, and cost. Cabergoline has the clear advantage that a once daily regime may be possible. Ropinirole and pramipexole need to be administered three times daily. However, they have the advantage that they are non-ergot and as such are unlikely to cause the peripheral vasospasm, erythromelalgia, and pleuropulmonary or retroperitoneal fibrosis occasionally associated with ergot derivatives.

New strategies to restore dopaminergic tone in Parkinson's disease have taken two approaches:[58] one avenue has been the development of new formulations of levodopa, and catechol-O-methyltransferase (COMT) inhibitors to overcome the effects of its short half life and short duration of action. New levodopa formulations include controlled release and dual release preparations.[59][60] The second avenue has been the development of improved dopamine agonists, with greater potency and fewer side effects, which can act independently of the degenerating neurons by stimulating post-synaptic dopaminergic receptors directly. Currently only D_2 stimulating agonists are available as oral preparations but in the future D_1 agonists are also likely to become available.

Whereas there is now clear evidence that dopamine agonists provide significant benefits in the treatment of Parkinson's disease, both as monotherapy and when used alongside levodopa, most studies with dopamine agonists have been relatively short term. However, results from a recently completed 5 year trial with the dopamine agonist ropinirole continue to support the efficacy, safety, and tolerability findings of earlier studies.[21] Further long term investigations are required to fully evaluate the efficacy and potential of dopamine agonists as monotherapy and neuroprotective agents. How dopamine agonists eventually fit into the treatment strategies for Parkinson's disease will depend ultimately on the results of these long term studies. With the exception of a recent trial which compared long term differences between bromocriptine and ropinirole[18] there has also been a lack of adequately designed trials to investigate whether there are significant differences in efficacy and tolerability between ergot or non-ergot dopamine agonists.

Finally, an exciting development is likely to be provided by patch formulations allowing continuous and stable agonist action for up to 24 hours. This could allow more effective control of both parkinsonism and nocturnal akinesia.

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EDITORIAL COMMENTARIES

Botulinum toxin in muscle spasticity

Botulinum toxin type A has been widely used in focal dystonias for more than 10 years, but it is also undoubtedly of benefit in the relief of spasticity,[1] a far commoner cause of motor impairment and neurological disability. The injection technique, by contrast with more traditional peripheral nerve blocks, requires little special equipment and can be learnt relatively easily. Thus it seems likely that botulinum toxin is destined to become much more widely used for this indication, although good evidence on which to base management decisions for busy clinicians is lacking.

There is uncertainty about the best delivery method regarding optimum dilution and the number of injection sites per muscle, but the toxin seems to diffuse adequately to produce dose dependent weakness. Dosage is usually estimated according to clinical judgement and the relative mass of the target muscle, but objective evaluation has always been difficult. In the paper by Hyman *et al* (this issue, pp 707–712) a careful attempt has been made to inform current, rather arbitrary, clinical practice with a properly controlled and randomised dose ranging study of hip adductor spasticity in multiple sclerosis.[2] These authors conclude that the optimal dose divided between both legs is around 500–1000 Units of the Dysport preparation, although evidence for a dose-response effect was not statistically significant.

Double blind studies often show less impressive effects than open label studies because of protocol constraints about which muscles to inject and doses to be used. The same is true of multicentre investigations using a very heterogeneous subject population. Nevertheless, it is salutary to note that the outcome measures improved in the placebo treated group almost as much as in those that received active treatment. Expressed differently, the effect size was relatively small and difficult to detect despite using a good range of appropriate measures.

Smaller doses injected into upper limb muscles are effective at relieving pain as well as spasticity after stroke