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THERAPEUTICS

Initial drug treatment in Parkinson's disease

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A 69 year old retired bus driver with no medical history of note presented to the outpatients department with a three year history of progressive tremor of the right hand; slowness of movement; and difficulty turning in bed at night, buttoning shirts, and using cutlery. He is keen to know what is wrong and whether it can be treated.

What drugs are available for initial treatment of Parkinson's disease?

Parkinson's disease is a progressive neurodegenerative disorder characterised by tremor, rigidity, bradykinesia, and a wide spectrum of non-motor symptoms including sleep disorders, hyposmia, bladder and bowel dysfunction, fatigue, dementia, and other neuropsychiatric symptoms.[1]

Although the disease has no cure, available treatments effectively control motor symptoms and improve quality of life.[2 3] Several drug classes are licensed for use as monotherapy in early Parkinson's disease and adjuvant therapy in later disease:

- Levodopa is the main precursor in dopamine synthesis and has been the mainstay of treatment for decades
- Dopamine agonists simulate dopamine by binding directly to post-synaptic dopamine receptors in the striatum.[4] They include:
  - Non-ergot dopamine agonists (oral pramipexole and ropinirole, and transdermal rotigotine)
  - Ergot derived dopamine agonists (cabergoline, bromocriptine, and pergolide): their use requires frequent monitoring for complications of heart valve and retroperitoneal fibrosis, so the National Institute for Health and Care Excellence guidelines recommend non-ergot dopamine agonists instead[5]
- Monoamine oxidase B inhibitors (rasagiline and selegiline) selectively inhibit monoamine oxidase type B enzyme, which metabolises dopamine, increasing dopamine availability.[4]

THE BOTTOM LINE

- First line treatments for Parkinson's disease include levodopa, non-ergot dopamine agonists, and monoamine oxidase B inhibitors
- Consider starting levodopa treatment in all (except young) patients, especially those with serious motor impairment (because it has greater motor benefits than other drugs) or cognitive impairment (because it has fewer neuropsychiatric complications than dopamine agonists)
- Monitor for motor complications (dyskinesias, motor fluctuations) and impulsivity and adjust doses accordingly
- Do not stop treatment abruptly because this may cause malignant hyperthermia (Parkinson hyperpyrexia syndrome)

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THE ARTICLE

We thank Sue McLoughlin and Wendy Williams from the Birmingham Parkinson's Disease Patients and Public Involvement Panel who commented on the draft manuscript. They asked us to clarify when levodopa should be taken in relation to meals and to include carers in the "tips for patients" box because "carers are more likely to notice impulse control disorders"

How well do they work?

Levodopa

Levodopa provides superior benefits in motor function, activities of daily living, and quality of life compared with other drug classes.[2 3 6] In a randomised controlled trial of 361 untreated patients given levodopa (150 mg, 300 mg, 600 mg daily) or placebo for 40 weeks, total UPDRS (unified Parkinson's disease rating scale; standard measure used in trials) scores in the levodopa treated groups were significantly better than in those taking placebo: (1.9 (standard deviation 6.0), 1.9 (6.9), and 1.4 (6.9) for levodopa groups, respectively, and 7.8 (9) for placebo; P<0.001).[7] A more recent large open label randomised trial (PD MED) in early Parkinson's disease demonstrated a small benefit of levodopa in patient rated quality of life over dopamine agonists and monoamine oxidase B inhibitors (PDQ-39 mobility score mean difference 1.8, 95% confidence interval 0.5 to 3.0; EuroQol EQ-5D mean difference 0.03, 0.01 to 0.05). Although this did not reach a predefined minimum clinically important difference (six points in the PDQ-39 mobility section), the small benefits from levodopa were still seen at seven years' follow-up.[8] Furthermore, those taking dopamine agonists or monoamine oxidase B inhibitor therapy were more likely to need add on treatment than those on levodopa only at two years (40%, 64%, and 20%, respectively; P<0.0001).[8]

Dopamine agonists

The effectiveness of these drugs in ameliorating motor symptoms has been reported in randomised controlled trials and in a systematic review comparing dopamine agonists with placebo.[6 9-11] In a randomised double blind placebo controlled trial in early disease, the non-ergot dopamine agonist pramipexole (immediate and extended release formulations) significantly reduced the mean adjusted UPDRS motor and activities of daily living scores more than placebo: 8.8, −8.6, and −3.8, respectively, (P<0.0001) at 33 weeks.[9] In a multicentre extension study of a randomised controlled trial, more ropinirole treated patients completed the 12 month study period on monotherapy without requiring additional levodopa compared with the placebo group (44% *v* 22.4%; P<0.001; number needed to treat over 12 months to prevent levodopa use was 5) and their mean UPDRS scores were lower.[10] In another randomised controlled trial, there were more responders (defined as 20% improvement in UPDRS

Box 1 | Common adverse effects of first line treatments in Parkinson's disease

Levodopa

Sedation, nausea, and vomiting can occur but are rarely dose limiting[14]

Dyskinesias and motor fluctuations (including the wearing off phenomenon and unpredictable on/off fluctuations)[6] occur in about 40% of patients after five years of treatment.[15] Risk is higher for young onset Parkinson's disease (90% within five years), longer disease duration, and higher levodopa doses. Compared with placebo, the number needed to harm (NNH) over 42 weeks is 1380 for levodopa 150 mg, 94 for levodopa 300 mg, and 8 for levodopa 600 mg[16]

Impulse control disorders (hypersexuality, pathological gambling, excessive shopping, and excessive eating) can occur with levodopa use, especially when high doses are used[17]

Other impulse control behaviours include punding (1.4-14% of patients), where patients perform repeated pointless actions such as sorting or disassembling objects, and dopamine dysregulation syndrome—the compulsion to overuse dopaminergic drugs[18]

Dopamine agonists

Dopamine agonists compared with placebo or levodopa: nausea (NNH=9), somnolence (NNH=8), oedema, (NNH=9), dizziness (NNH=15), vomiting (NNH=34), hallucinations (NNH=22), and hypotension (NNH=48)[6]

Impulse control disorders: NNH 10 for patients taking dopamine agonists compared with those not taking dopamine agonists over six months[17]

Monoamine oxidase B inhibitors

Dopaminergic adverse effects, such as nausea and vomiting, are less common with these drugs than with dopamine agonists.[13]

scores) with rotigotine than placebo treatment (48% *v* 19%, 0.18 to 0.394).[11]

Monoamine oxidase B inhibitors

A systematic review of monoamine oxidase B inhibitors in early Parkinson's disease found a small but significant improvement in UPDRS motor scores with monoamine oxidase inhibitors compared with placebo (mean weighted decrease in UPDRS motor scores 3.79 points, −5.30 to −2.27).[12] However, in another systematic review, more participants taking monoamine oxidase inhibitors required add on therapy (odds ratio 12.02, 6.78 to 21.31) compared with those taking levodopa and dopamine agonists (odds ratio 2, 1.05 to 3.81).[13]

How do they compare with other drugs?

Amantadine, anticholinergics, and β blockers have been used in early disease in the past.[5] However, they are not recommended as first line treatment because more effective treatments are available.[5] In addition, anticholinergics can cause neuropsychiatric complications.[5] Treatment options in advanced Parkinson's disease when oral and transdermal therapies are exhausted include catechol-O-methyl transferase inhibitors, deep brain stimulation, apomorphine, and intrajejunal levodopa gel infusion, but these treatments are beyond the scope of this article.

How safe are these agents?

Box 1 outlines common adverse effects associated with these agents.

What are the precautions?

The table outlines common precautions, including drug interactions. Avoid abrupt withdrawal of dopaminergic agents, which can result in malignant hyperthermia (Parkinson's hyperpyrexia),[5] characterised by severe rigidity, fever, altered level of consciousness, and raised creatine kinase concentrations.[20] Close ophthalmological monitoring is needed when starting levodopa in patients with narrow angle glaucoma because of the potential risk of increasing intraocular pressure.[14] Melanoma cases have been reported with the use of levodopa and rasagiline.[21] A meta-analysis reported an association between Parkinson's disease and melanoma (odd ratio 2.1, 1.26 to 3.54), with cases of melanoma occurring before or after diagnosis of Parkinson's disease.[21] These findings suggest that factors other than these drugs explain the association between the two conditions.

Formulations and key precautions for first line drugs to treat Parkinson's disease[14]

Drug	Available formulations*	Potential drug interactions	Other precautions
Levodopa	Co-beneldopa capsules or co-careldopa tablets: start three times daily	Risk of hypotension when used at the same time as antihypertensives; consider adjusting the antihypertensive dose. If an antipsychotic is needed, prescribe clozapine or quetiapine instead of typical antipsychotics (which worsen Parkinson's disease symptoms)[4]	Avoid abrupt withdrawal, which can cause malignant hyperthermia (Parkinson's hyperpyrexia).† [5] Patients with narrow angle glaucoma require close initial ophthalmological monitoring[14]
Non-ergot dopamine agonists			
Ropinirole	Immediate release tablets: 3 times daily; modified release tablets: once daily	Do not co-prescribe metoclopramide or atypical antipsychotics because they reduce the effectiveness of dopamine agonists	Avoid abrupt withdrawal, which can result in malignant hyperthermia (Parkinson's hyperpyrexia)[5]
Pramipexole	Immediate release tablets: 3 times daily; modified release tablets: once daily	Precautions as for ropinirole	
Rotigotine	Transdermal patch once daily patch	Precautions as for ropinirole	
Monoamine oxidase B inhibitors			
Rasagiline	Tablets: once daily	Do not co-prescribe selective serotonin reuptake inhibitors or tricyclic antidepressants because this increases the risk of central nervous system toxicity, including serotonin syndrome. Mirtazapine, reboxetine, mianserin, and trazadone can be used.[19] Do not co-prescribe with other monoamine oxidase inhibitors because of the risk of hypertensive crisis	Monitor liver function in patients with hepatic impairment and cease if liver functions worsens. Avoid abrupt withdrawal, which can result in malignant hyperthermia (Parkinson's hyperpyrexia)[5]
Selegiline	Tablets: once daily	Precautions as for rasagiline; do not co-prescribe opioid analgesics because of the risk of hyperpyrexia and central nervous system toxicity	

*Doses and titration provided by the BNF.
†Severe rigidity, fever, altered level of consciousness, and raised creatine kinase concentrations.

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Pregnancy and breast feeding

Data on the safety of these agents are limited because Parkinson's disease mainly affects people above childbearing age. Dopamine agonists should be used in pregnancy only if the benefit outweighs the risk because data on safety are limited.[14] A case series reported three minor anomalies with levodopa use—persistent foramen ovale, talipes varus, and nose deformity.[22] Levodopa should therefore be used with caution in pregnancy.[14] Avoid breast feeding while taking levodopa and dopamine agonists, which inhibit lactation and are secreted in milk.[14] Avoid monoamine oxidase B inhibitors in pregnancy and breast feeding because safety data are limited.

How cost effective are these agents?

Box 2 describes studies comparing the cost effectiveness of levodopa, non-ergot dopamine agonists, and monoamine oxidase B inhibitors in early disease. However these studies were funded by drug companies and results may be biased. The use of different methods for ascertaining costs also makes comparisons between studies and populations difficult.[23]

How are dopaminergic drugs taken and monitored?

Take into account factors such as age, drug side effect profile, cognitive impairment, severity of motor disability, and patient preference when choosing initial treatment (see table for formulations).[4 5] Advise patients about adverse effects (especially motor complications and impulse control disorders) and monitor for these, adjusting doses accordingly (box 1). If nausea and vomiting are prominent, domperidone is the recommended antiemetic.

Levodopa

Levodopa is the preferred drug for patients with severe motor impairment because it provides superior motor benefits compared with other treatments.[2 3] Levodopa is also the first line treatment in older patients (>60 years), particularly when there is cognitive impairment, because dopamine agonists increase the risk of neuropsychiatric complications.[4]

Start co-careldopa 25/100 tablets (mg carbidopa/mg levodopa) or co-beneldopa 25/100 capsules three times daily with meals.[14] Titrate the dose up every few years to 400-500 mg levodopa daily in divided doses, four or five times daily. Small levodopa doses may be taken at reduced intervals to reduce motor complications.[3] With disease progression, a double dose (200 mg levodopa) can be taken in the morning, with a total daily dose of 600 mg (8-9 mg/kg) levodopa per day. Controlled release levodopa is poorly absorbed and does not delay motor complications.[4] In later disease, adjuvant therapy with a dopamine agonist, monoamine oxidase B inhibitor, or catechol-O-methyl transferase inhibitor may be needed to reduce "off periods" (symptoms not controlled adequately).[3 5]

Dopamine agonists

These drugs can be used as initial therapy in young patients and those with mild symptoms to delay levodopa use and hence the onset of motor complications.[3 4] Long acting dopamine agonists provide more continuous dopaminergic stimulation and may be considered for patients with night-time or early morning off periods.[28] Transdermal rotigotine can be used when oral administration is not possible. Titrate doses against clinical response.[14] If there is inadequate symptom control despite dose titration, switch to another dopamine agonist or add a monoamine oxidase B inhibitor; eventually levodopa should be considered.[3]

Monoamine oxidase B inhibitors

These are recommended first line treatment (taken once daily) in those with mild symptoms[5] and in young patients. Monitor liver function in patients with hepatic impairment taking rasagiline. If hepatic function worsens, withdraw rasagiline.

Outcome

This patient was diagnosed clinically as having idiopathic Parkinson's disease. He started levodopa (co-careldopa 25/100) three times daily and reported greatly improved finger dexterity and overall movement when seen two months later.

Box 2 | Cost effectiveness studies for first line treatments in Parkinson's disease

Pramipexole *v* levodopa over two years (United States)[24]
Pramipexole was $2138 (£1388; €1893) more costly than levodopa; 45% of the total costs in the pramipexole arm and 32% in the levodopa group were due to drug costs

Pramipexole *v* levodopa over five years (US)[25]
Improvement in the cost effectiveness of pramipexole over time: incremental cost effectiveness ratio of $87 184 (at two years) and $42 989 (at four years) per quality adjusted life year (QALY; due to the effect of pramipexole on delaying motor complications and its potential antidepressive effect)

Ropinirole *v* levodopa over five years (Canada)[26]
Ropinirole was more costly than levodopa: net incremental costs of $C8071 (£3963; €5402; $6102) per patient for substituting levodopa with ropinirole. However, ropinirole was associated with $C3335 cost savings per patient over five years (lower incidence of dyskinesias *v* levodopa).

Rasagiline *v* pramipexole over five years (United Kingdom)[27]
Cost savings of £3931 per patient and 0.19 more QALYs gained when rasagiline was used as initial treatment

TIPS FOR PATIENTS AND CARERS

Do not stop Parkinson's disease drugs suddenly because this can result in life threatening complications

Inform your doctor if you develop excessive sleepiness when taking Parkinson's disease drugs. Refrain from driving or operating heavy machinery if symptoms are excessive

Inform your doctor if the drug's effects become unpredictable or do not last as long as expected, or if you develop abnormal body movements after taking drugs

Report to your doctor if you notice any of the following impulsive behaviours after starting treatment: inappropriate sexual impulses or excessive gambling, eating, or shopping