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Advances in the treatment of the motor symptoms of Parkinson's disease

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ABSTRACT Parkinson's disease is a chronic progressive neurodegenerative condition. It damages central nervous system dopaminergic but also serotonergic and noradrenergic pathways. There is no known cure, and no existing therapy has been proven to slow or reverse progress of the disease. Treatment aims to alleviate symptoms and preserve functional independence while minimising adverse affects.

KEYWORDS Dopaminergic stimulation, motor symptoms, neuroprotection, neuroregeneration, Parkinson's disease

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WHICH DRUG?

The National Institute for Health and Clinical Excellence's (NICE) guidelines recommend that once motor symptoms interfere with daily function, treatment should be commenced using a first-line agent (levodopa, dopamine agonists or monoamine-oxidase-B inhibitors). Evidence from randomised controlled trials and systematic reviews has confirmed the effectiveness of these medications for controlling motor symptoms in early Parkinson's disease (PD) (i.e. for patients without motor complications).[1] However, which class is superior in any particular clinical situation remains unclear and is the subject of the ongoing PD MED trial (http://www.pdmed.bham.ac.uk). A similar lack of head-to-head efficacy evidence exists in advanced PD (i.e. for patients with motor complications). The second part of the PD MED trial aims to address this uncertainty.

Levodopa

Levodopa has been the mainstay of PD treatment for the past 30 years and remains the most effective for controlling motor symptoms.[1] The treatment is given with a peripheral dopa-decarboxylase inhibitor to reduce peripheral metabolism of levodopa, which allows a higher percentage of ingested levodopa to cross the blood-brain barrier and be decarboxylated to dopamine in the nigrostriatal pathways.

Initially, patients have a good symptomatic response to relatively small doses of levodopa. Disease progression leads to motor complications in virtually all patients. These comprise dyskinesias (dystonia and athetosis) and motor fluctuations during which patients may experience a 'wearing off' of levodopa's beneficial effects, predictably related to dopamine blood levels after each dose of levodopa and/or unpredictable 'on' and 'off' periods.[1] Many clinicians have adopted treatment strategies, using dopamine agonists and MAO-B inhibitors in early PD with the aim of delaying the need for levodopa (especially in younger patients who are more prone to developing motor complications). However, these drugs are less effective in controlling motor symptoms and have common and sometimes severe adverse affects.[1–3]

Recently, a novel preperation of levodopa consisting of a continuous infusion of levodopa gel (Duodopa) directly into the jejunum has been licensed for the management of severe motor complications. In small trials, monotherapy with Duodopa has been shown to reduce 'off' periods and improve motor function and quality of life compared with conventional multidrug regimes.[4] The use of this preparation is likely to be limited by its cost (£30,000 a year) and the need for gastrostomy tube insertion.

Dopamine agonists

Dopamine agonists fall into two groups: ergot-related (bromocriptine, cabergoline, lisuride and pergolide) and non-ergot-related (ropinirole, pramipexole and rotigotine). The latter are generally considered first line due to the occurrence of serious fibrotic and serosal inflammatory disorders (including cardiac valvulopathies, pleural, pericardial and retroperitoneal fibrosis and effusions) seen with the former.[1]

Dopamine agonists may be used as monotherapy in early PD or as combination therapy in advanced stages. In early PD, dopamine agonists are effective in controlling motor symptoms (though less so than levodopa) and are associated with significantly fewer motor complications than levodopa.[1,2] However, dopamine agonists are associated with more severe non-motor side effects (see Table 1), which result in poor tolerability when compared with levodopa.[1,2]

In advanced PD with motor complications, adjuvant dopamine agonist therapy improves motor symptoms and reduces both 'off' time and the required levodopa dose. However, adjunctive use of agonists increases the risk of dopaminergic adverse events, including dyskinesia, hallucinations and postural hypotension.[1,5,6]

TABLE 1 Common adverse effects of agents used in PD

Drug	Main adverse effects and complications
Levodopa	Nausea, vomiting, taste disturbances, dry mouth, anorexia, arrhythmias, postural hypotension, syncope, drowsiness (including sudden onset of sleep), fatigue, psychoses, hallucinations, confusion, abnormal dreams, insomnia, depression,dizziness, dystonia, dyskinesia, chorea; neuroleptic malignant syndrome (associated with abrupt withdrawal)
Dopamine agonists	Nausea, constipation, postural hypotension, hypotension, headache, confusion, drowsiness (including sudden onset of sleep), fatigue, insomnia, dizziness, hallucinations, dyskinesia, peripheral oedema, psychosis, pathological gambling, hypersexuality and punding, fibrotic reactions with ergot-derived agonists
MAO-B inhibitors	Dry mouth, dyspepsia, constipation, angina, headache, depression, anorexia, weight loss, abnormal dreams, vertigo, hallucinations, influenza-like symptoms, urinary urgency, leucopenia, arthralgia, conjunctivitis, rash; rarely myocardial infarction and cerebrovascular accident. Interaction with SSRIs
COMT inhibitors	Nausea, vomiting, abdominal pain, diarrhoea, discolouration dry mouth,confusion, dizziness, abnormal dreams, fatigue, insomnia, dystonia, dyskinesia, hallucinations, increased sweating; rarely severe hepatotoxicity with tolcapone
Apomorphine	As per dopamine agonists plus injection-site reactions (including nodule formation and ulceration) and haemolysis when used with levodopa

Source: Joint Formulary Committee. *British National Formulary*. 56th ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2008.

Two once-daily dopamine agonist preparations are available, which aim to reduce the pulsatile dopaminergic stimulation thought to cause motor complications.[7] Rotigotine transdermal patches were launched in April 2006. Rotigotine is relatively well tolerated and effective when compared to placebo in both early and advanced PD, although recently there have been problems due to drug crystallisation in the patches.[7] Recently, once-daily ropinirole XL has been licensed for use in both early and advanced PD. This has been shown in a randomised controlled trial to reduce daily 'off' time in advanced PD, increase 'on' time without dyskinesia and allow a reduction in daily levodopa dose.[8]

MAO-B inhibitors

MAO-B inhibitors limit the central metabolism of dopamine, thereby increasing its central nervous system availability. Unlike MAO-A inhibitors, these drugs do not cause the hypertensive 'cheese reaction' when given with tyramine-rich foods; however, they may cause serotonin syndrome when combined with selective serotonin reuptake inhibitors commonly used for depression.

Two agents, selegiline and rasagiline, are available, and may be used for both early and advanced PD with motor fluctuations.[1] NICE advises that MAO-B inhibitors are effective in delaying the onset of motor complications but may be less effective than agonists in delaying the need for levodopa; trial data for these agents in early disease are limited.[1] Randomised controlled trials with buccal selegeline and rasagiline have confirmed the safety and efficacy of these drugs in advanced disease.[1]

Catechol-O-methyltransferase (COMT) inhibitors

Two COMT inhibitors are available: entacapone and tolcapone. These drugs inhibit the peripheral conversion of levodopa to 3-O-methyldopa by COMT and thus increase levodopa half-life (but not peak plasma concentrations), in turn increasing the effective period of each dose of levodopa and shortening 'off' periods.

Tolcapone was withdrawn in 1998 due to three cases of fatal hepatic toxicity. It is currently licensed for use with stringent liver function monitoring.[1] Consequently, entacapone is the first-line COMT inhibitor. NICE has advised that entacapone should be offered as a triple combination preparation of levodopa, carbidopa and entacapone (Stalevo), as this improves compliance.[1] Licensed for use in advanced PD, COMT inhibitors have been shown to reduce both 'off' time and levodopa dose, and modestly improve motor impairment and disability ratings.[1,9] The recent First Step trial has shown that Stalevo therapy is more effective than standard levodopa dopa-decarboxylase therapy in early PD.[10]

Apomorphine

The potent dopamine agonist apomorphine is used to reduce 'off' periods and dyskinesia in patients with severe motor complications. It is ineffective orally due to extensive first-pass metabolism. It is a potent emetic, and pre-treatment with domperidone is essential. Currently, two apomorphine treatment strategies are used: intermittent subcutaneous rescue injections in those with fewer than six 'off' periods per day, and continuous infusions in those with more frequent episodes.[1]

The evidence for apomorphine treatment is limited. Three small randomised controlled trials (n=56) demonstrated the efficacy of intermittent injections, but only observational studies exist for the subcutaneous infusion.[1] Adverse reactions are listed in Table 1. Despite the limited evidence base, NICE recognises intermittent and continuous apomorphine regimes as useful treatment modalities for patients with intractable 'off' periods, noting that long-term, continuous apomorphine infusions may dramatically reduce both 'off' periods and sometimes dyskinesia.[1]

Surgery

Several sites and procedures have been identified as targets for neurosurgical intervention in advanced PD.[1] The most frequently performed procedure is bilateral subthalamic nucleus stimulation, which aims to 'switch off' the overactive

subthalamic nucleus. Numerous uncontrolled case series, but few randomised controlled trials, have been published examining the efficacy and safety of deep brain stimulation.[1,11] Adverse effects include a small but significant risk of permanent neurological disability related to the procedure and neuropsychiatric complications.[1]

NICE has recommended bilateral subthalamic stimulation for patients with refractory motor complications (on best medical treatment) who are biologically fit with no significant active comorbidities, are responsive to levodopa and have no clinically significant active mental health problems.[1] The long-term safety and cost-effectiveness of this expensive procedure (£19,500 per quality-adjusted life year in comparison to standard PD care) remains unclear.[1] The ongoing PD SURG trial (http://www.pdsurg.bham.ac.uk) aims to address these issues.

THE FUTURE

Neuroprotection refers to pharmacotherapy that slows the progressive loss of dopaminergic neurones seen in Parkinson's disease. To date, despite some encouraging (but inconsistent) results in small trials involving co-enzyme Q10, dopamine angonists and MAO-B inhibitors, no agent has clearly been shown to be clinically neuroprotective.[1] NICE has advised that no agent should be used for the purpose of neuroprotection outside of clinical trials.[1] The search for neuroprotective agents continues and further large trials with longer-term follow-up are required.

The prospect of neurorestoration (treatments to restore function to diseased neurones) attracts much interest. Stem cell transplantation has had enormous publicity in both the general and medical press. Two randomised trials (using donor fetal nigral cell grafts) demonstrated inconsistent motor benefits (which were restricted to younger patients) and a high incidence of severe dyskinesia, which persisted even when levodopa was withdrawn.[12,13] Post-mortem histology shows these allografts develop Lewy bodies in the transplanted cells, indicating PD is affecting the new cells. Especially in view of ongoing concerns over the safety of trials (concerns involving tumour formation, stem cell migration and, for xenografts at least, a risk of retrovirus infection),[14] it is likely to be years before transplanted stem cells are proven to be a safe and controllable source of dopaminergic stimulation. Gene therapy works by means of a virus vector, which inserts genes to produce glutamic acid decarboxylase; this in turn makes gamma amino butyric acid, a neurotransmitter which is deficient in the subthalamic nucleus of patients with PD. Gene therapy has proved effective in early research, but safety questions await the outcome of longer-term studies.[15]

In terms of symptomatic treatment, the pulsatile stimulation of dopamine receptors is thought to underlie the development of motor complications. Continuous dopaminergic stimulation may have the potential to reverse motor complications and improve nocturnal symptom control as well as daytime somnolence.[7] Newer agents and drug delivery systems, such as Duodopa, rotigotine and ropinirole XL, represent a significant step towards non-pulsatile dopaminergic administration and true continuous dopaminergic stimulation.[4,7,8]

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