7 Management of Parkinson's Disease

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This review is based on the National Institute for Health and Care Excellence (NICE) guideline on the diagnosis and management of Parkinson's disease.[1,2]

When to Start Treatment in Parkinson's Disease

Once Parkinson's disease has been diagnosed, any therapy which can slow or halt progression should be commenced immediately. Such neuroprotective or disease modifying therapy does not exist at present. Many agents have been investigated for neuroprotective properties in vitro and in vivo without success.[3] The future for disease modification in Parkinson's disease is more promising with the discovery that alpha-synuclein may act as a prion-like particle spreading through the central and enteric nervous systems.[4]

Most clinicians delay the introduction of symptomatic treatment until the patient has significant functional disability, i.e. when it is interfering with activities of daily living. Symptomatic therapy is unlikely to be effective for mild symptoms which are not interfering with life. Indeed, many patients report little change in symptoms when therapy is commenced, even though motor scores improve.

Initial Management of Parkinson's Disease

The 2017 update of the NICE guidelines states that levodopa is more effective than MAO-B inhibitors and dopamine agonists in all aspects of symptomatic control, but particularly in controlling motor symptoms, in both short-term and long-term trials up to 7 years (table 1).[2] In the long-term pragmatic UK trial (PD MED) comparing initial therapy with levodopa, dopamine agonists and MAO-B inhibitors,[5] there were long-term quality of life gains associated with initial levodopa therapy (which included the long-term disutility of dyskinesia), implying that for this population the balance of benefits and harms favours initial treatment with levodopa. NICE concluded with the recommendation: "Offer levodopa to people in the early stages of Parkinson's disease whose motor symptoms impact on their quality of life".[2]

Table 1 Potential benefits and harms of dopamine agonists, levodopa and MAO-B inhibitors[2]

	Levodopa	***Dopamine agonists***	***MAO-B inhibitors***
Motor symptoms	More improvement in motor symptoms	Less improvement in motor symptoms	Less improvement in motor symptoms
Activities of daily living	More improvement in activities of daily living	Less improvement in activities of daily living	Less improvement in activities of daily living
Motor complications	More motor complications	Fewer motor complications	Fewer motor complications
Adverse events	Fewer specified adverse events*	More specified adverse events*	Fewer specified adverse events*

Abbreviation: MAO-B - Monoamine oxidase B.

* Excessive sleepiness, hallucinations and impulse control disorders (see the summary of product characteristics for full information on individual medicines).

With disease progression, the levodopa dose needs to be steadily increased, but the dose should be restricted as dyskinesia is dose-dependent.[6-8] For patients with an average body weight, the initial dose of levodopa will be 100 mg tds (with meals) which can be increased to 100 mg five times per day (additional doses with mid-morning and mid-afternoon drinks) and finally 600 mg per day (8-9 mg/kg body weight) with a double dose with breakfast. Thereafter, dyskinesias and/or wearing off will require adjuvant therapy.

Adjuvant Therapy to Levodopa

Once motor complications have developed, or when patients have progressed on 600 mg/d of levodopa, adjuvant therapy is required with a dopamine agonist, MAOB inhibitor or catechol-O-methyl transferase (COMT) inhibitor (Table 2).[1]

Table 2 Potential benefits and harms of dopamine agonists, MAO-B inhibitors, COMT inhibitors and amantadine[2]

	Dopamine agonists	***MAO-B inhibitors***	***COMT inhibitors***	***Amantadine***
Motor symptoms	Improvement in motor symptoms	Improvement in motor symptoms	Improvement in motor symptoms	No evidence of improvement in motor symptoms
Activities of daily living	Improvement in activities of daily living	Improvement in activities of daily living	Improvement in activities of daily living	No evidence of improvement in activities of daily living
Off time	More off-time reduction	Off-time reduction	Off-time reduction	No studies reporting this outcome
Adverse events	Intermediate risk of adverse events	Fewer adverse events	More adverse events	No studies reporting this outcome
Hallucinations	More risk of hallucinations	Lower risk of hallucinations	Lower risk of hallucinations	No studies reporting this

Abbreviations: MAO-B, monoamine oxidase B; COMT, catechol-O-methyl transferase.

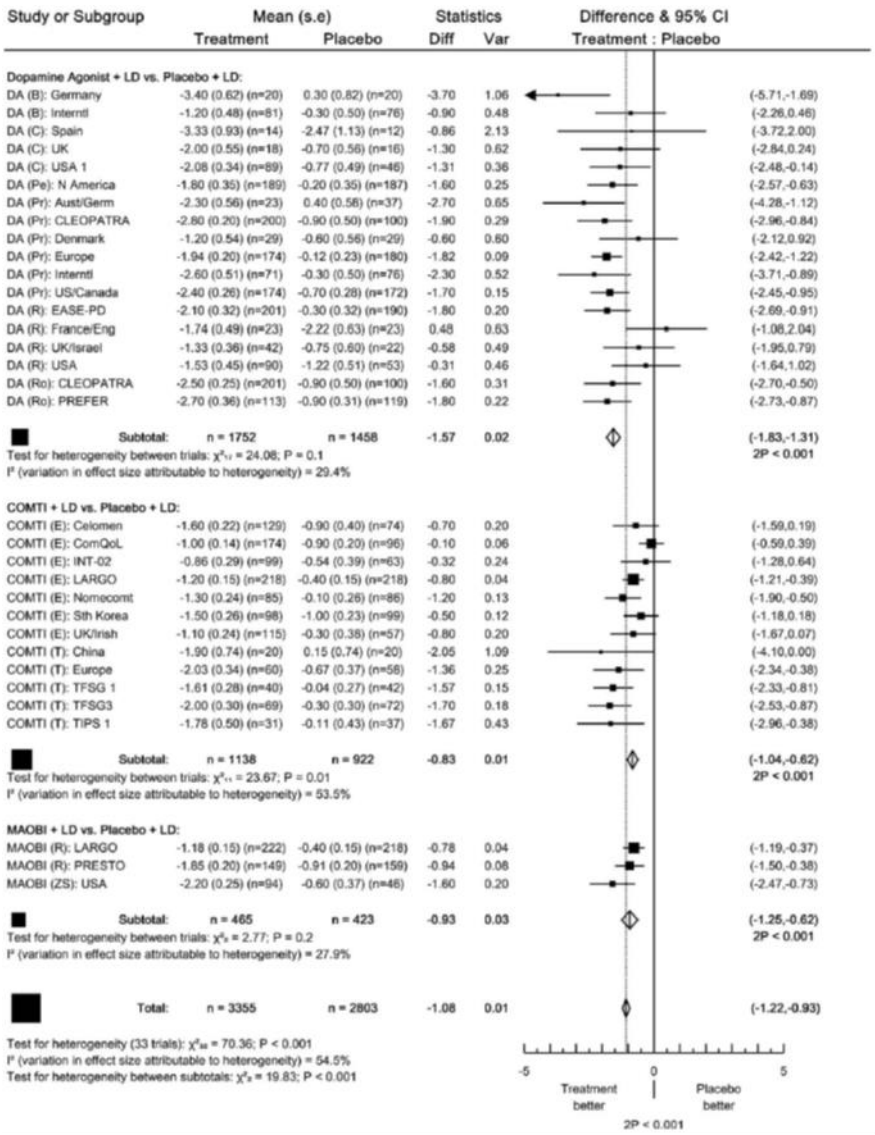
A systematic review of all placebo controlled trials with these three drug classes suggested that the dopamine agonists and tolcapone were more effective than entacapone and MAOB inhibitors at reducing off time and levodopa dose without an excess of side effects (Figure 1).[9,10] However, this was based on indirect comparisons and in a predominantly younger patient population, so the results may not be generalisable to all patients. Further evidence from head-to-head trials is required.

The PD MED LATER trial randomised patients on levodopa with motor complications to any dopamine agonist, MAOB inhibitor or COMT inhibitor.[11] The key finding was the large drug withdrawal rate due to adverse effects which was similar with all three drug classes. After one year of treatment, around 33% had stopped the allocated treatment, rising to 50% withdrawal after two years. There was no benefit in quality of life in using a dopamine agonist compared with a MAOB inhibitor or COMT inhibitor. However, there was weak evidence that quality of life is inferior with entacapone compared with MAOB inhibitors and dopamine agonists, in keeping with the systematic review of placebo-controlled trials.[9]

These results suggest that many patients will only be able to tolerate levodopa therapy and that attempts to introduce adjuvant agents should not be made. Further work from PD MED LATER should clarify which patients should avoid add-on therapy, but initial results suggest the only predictor of withdrawal was older age, probably due to the onset of cognitive decline.

There is still no evidence to direct the choice between adjuvant MAOB inhibitor and dopamine agonist therapy. Having chosen an MAOB inhibitor, there is no evidence comparing the efficacy and safety of selegiline with rasagiline or the relatively new agent safinamide. Selegiline should be tried first as it is less expensive, but switched to rasagiline if it is not tolerated. Beware the alerting effect of selegiline at night. There is some evidence to suggest that safinamide produces less dyskinesia, but this is not conclusive.[12]

Figure 1 Cochrane systematic review of placebo-controlled adjuvant trials in Parkinson's disease: Forest plot of off time reduction[9]



The non-ergot dopamine agonists (pramipexole, ropinirole and rotigotine) are now preferred to the ergot-derived dopamine agonists (bromocriptine, lisuride, pergolide and cabergoline) as the latter can cause pleural, pericardial and peritoneal effusions and fibrosis and cardiac valvulopathy. However, the non-ergot agonists cause impulse control disorders including pathological gambling, hypersexuality, punding (i.e. abnormal collecting and categorising behaviour), and hyperphagia. The DOMINION study found these in 14% of 3090 North American patients with Parkinson's disease.[13] It is important to warn patients and their carers about these problems before drug initiation and to monitor for their occurrence throughout treatment. The once daily prolonged-release versions of ropinirole and pramipexole or the rotigotine patch tend to be the preferred formulations.

Whilst entacapone is a relatively weak adjuvant therapy, and tolcapone tends to be avoided because of potential hepatic toxicity, the new COMT inhibitor opicapone is at least as effective as entacapone and may produce a greater increase in on time.[14]

With disease progression, adjuvant agents will be added successively, so in addition to levodopa many will take an MAOB inhibitor, a dopamine agonist, and a COMT inhibitor. This leads to what can be called ‘rational polypharmacy’.

Management of Advanced Parkinson's Disease

Three randomised controlled trials were included in a Cochrane review of amantadine used to treat dyskinesias in later Parkinson's disease.[15] Whilst the number of patients included was small (n=53) and the trials short, the NICE guidelines recommended that amantadine be used as an anti-dyskinesia agent.[2] It is best to start with just 100 mg once daily, titrating up through 100 mg bd, then 100 mg tds, and to warn patients about the rare side effects of livedo reticularis (i.e. mottled brown rash on the legs) and hallucinations.

The dopamine agonist apomorphine is not effective orally due to extensive first-pass metabolism in the liver. It was developed as intermittent bolus injections to rescue patients from severe off periods or as a subcutaneous infusion for patients with many off periods. Both uses require continuous treatment with the antiemetic domperidone in some patients to prevent nausea and vomiting. Three small trials (n=56) documented the efficacy and safety of intermittent injections of apomorphine and a larger randomised controlled trial of continuous apomorphine infusion will soon be published.[1] Nevertheless, the NICE guidelines approved both for use in treating motor complications which are intractable to changes in oral therapy.[1,2]

Trials showed that the continuous infusion of a levodopa gel directly into the jejunum (Duodopa®) reduces off time and improves motor function, activities of daily living, and quality of life.[16-18] However, its use is restricted by cost (£30,000 per annum for the drug alone) and the need for a jejunostomy in potentially ill patients. The NICE position on this therapy is ambiguous after a legal challenge to its initial rejection: "Levodopa–carbidopa intestinal gel is currently available through an NHS England clinical commissioning policy. It is recommended that this policy is reviewed in light of this guideline."[2]

In terms of which parenteral or surgical therapy to use in an individual patient, there are no head-to-head trials and few placebo controlled trials to guide such a choice.[19] Therefore, decisions tend to be pragmatic and based on patient preference and treatment availability and cost. Most patients elect for apomorphine infusion ahead of surgery, and in the NHS both must be considered before funding for levodopa gel infusion will be contemplated.

Surgery (see Chapter 9)

Improved understanding of the neural mechanism of Parkinson's disease showed that the subthalamic nucleus (STN) is overactive.[20] This led to the development of bilateral subthalamic (STN) stimulation surgery to switch off this nucleus. There have been many uncontrolled case series of STN stimulation, and now four randomised controlled trials (RCT)[21-23] including the UK PD SURG trial.[24] These showed that STN stimulation reduces off time and off time disability, so medication can be reduced, thereby reducing dyskinesia. Meta-analysis of the results of these RCTs shows a consistent improvement compared with deferred surgery at 6, 12 and 18 months of around 5 points in patient-rated quality of life (PDQ 39 summary index), a difference which has previously been shown to be clinically significant.[25]

The NICE guidelines recommended STN stimulation for patients with motor complications refractory to best medical treatment, who are biologically fit with no clinically significant active co-morbidity, who are levodopa responsive and have no clinically significant active mental health problems (depression or dementia).[1,2]

Non-motor Features of Parkinson's Disease (see Chapters 4 and 8)

The motor features of Parkinson's disease can be controlled reasonably well in most patients with the measures outlined above. It is the non-motor features of the disorder which now present the greatest management challenge, including dementia, psychosis, imbalance and falls, autonomic dysfunction, sleep disorders, and pain. The NICE guidelines found a paucity of treatment trials for non-motor features.[1,2]

Nursing and Allied Health Professional Interventions

Three randomised controlled trials assessed the efficacy of Parkinson's Disease Nurse Specialists versus standard care.[1] The benefits of nurses related to the overall patient care experience and delivery of services rather than in outcome measures such as quality of life or health economics. Therefore, the NICE guidelines recommended Nurse Specialists for clinical monitoring and medication adjustment, a continuing point of contact for support, and a reliable source of information about clinical and social matters for patients and carers.[1,2]

The evidence for the use of physiotherapy, occupational therapy and speech and language therapy in Parkinson's disease is based on a small number of trials with few participants, but clinical experience suggests that they are valuable.[26-28]

The update of the NICE guidelines for physiotherapy and occupational therapy were heavily influenced by the UK PD REHAB trial. This was the largest pragmatic multicentre randomised controlled trial of combined occupational therapy and physiotherapy versus no therapy in patients with Parkinson's disease who reported limitations in activities of daily living.[29] Physiotherapy and occupational therapy did not produce immediate or medium-term clinically meaningful improvements in activities of daily living or quality of life. Given the varied experience levels of the therapists in the trial and the low dose of therapy, NICE concluded that specialists should only "consider" referring patients with early Parkinson's disease to physiotherapists and occupational therapists with experience in treating Parkinson's disease, whereas patients with balance or motor function problems should have referral "offered" to them.[2] The results of the UK PD SAFE trial are awaited, as this examined the effects of a more structured and intensive physical therapy programmes in Parkinson's disease patients with falls.

The recently published PD COMM pilot study was a randomised controlled trial to assess the feasibility of comparing Lee Silverman Voice Treatment (LSVT), traditional NHS speech and language therapy with no intervention in Parkinson's disease patients with communication problems.[30] 89 patients were recruited from 11 centres in the UK which provides the largest evidence base to date. There were trends for both forms of therapy being effective. The nationwide PD COMM trial is now recruiting 545 patients to provide more robust data.

Future Treatments

It is crucial that neuroprotective agents are found to slow or halt the progression of Parkinson's disease. There are fundamental questions about neuroprotection trial design, particularly delayed-start design trials[31,32] and futility studies.[33] There was also an over reliance on toxin-based models of Parkinson's disease (e.g. 6-hydroxydopamine rat and MPTP primate models) to develop potential disease modifying therapies. The alpha-synuclein prion-like model should lead to more promising targets in the future.[4]

Much effort has gone in to developing non-dopaminergic agents for parkinsonian symptoms and/or dyskinesias (e.g. adenosine A2A receptor antagonists[34]). However, many have proved disappointing in clinical trials because of lack of efficacy.

We require better agents to treat the non-motor manifestations of Parkinson's disease and more work is required to reduce the burden of hospitalisation.[35] More consideration should be given to end-of-life issues, particularly palliative care, as patients continue to die in excess of their peers.[36]

The prospect of neurorestoration with stem cell grafts continues to generate considerable attention.[37] However, two trials of foetal midbrain grafts found that, whilst beneficial effects occur, severe off period involuntary movements developed which necessitated pallidotomy in some cases.[38,39] There have also been recent post mortem results from these early grafting trials showing the development of Lewy bodies in the grafts which suggests the pathological process in Parkinson's disease continues throughout life.[40] It will be many years before stem cell implants are shown in large clinical trials to be free from tumour formation and capable of controlled dopamine release. In the meantime, various nerve growth factors may be shown to stimulate the development of remaining dopaminergic neurones, although initial results have been mixed.

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Further Reading

http://publications.nice.org.uk/parkinsons-disease-cg35 /
https://www.nice.org.uk/guidance/ng71/
http://www.cochranelibrary.com/cochrane-database-of-systematic-reviews/

Information Resources

http://www.parkinsons.org.uk/
http://www.cureparkinsons.org.uk/
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