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PRACTICE

GUIDELINES

Parkinson's disease: summary of updated NICE guidance

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Parkinson's disease is one of the most common neurological conditions, estimated to affect around 250 people per 100 000 in the UK.[1] People with Parkinson's disease classically present with motor symptoms including bradykinesia, rigidity, rest tremor, and postural instability; however, non-motor symptoms may also be prominent, including depression, cognitive impairment, and autonomic disturbances.

This article summarises the most recent update to the National Institute for Health and Care Excellence (NICE) guideline for the diagnosis and management of Parkinson's disease in adults.[2] This NICE guideline provides an update on most aspects of managing Parkinson's disease, incorporating knowledge generated by a series of recent, large scale, independently funded, randomised trials in Parkinson's therapy, and replaces guidance published in 2006. The update reflects emerging experience in areas such as impulse control disorders that may coexist with Parkinson's disease and provides recommendations on the use of treatments that may provide some relief from the distressing symptoms of advanced Parkinson's disease. The guideline update has not changed the suggested approach to the diagnosis of Parkinson's disease, communication with people with Parkinson's disease and their carers, pharmacological neuroprotective therapy, and interventions by Parkinson's disease nurse specialists. Recommendations, full details of evidence, and the NICE pathway are available via the NICE website (www.nice.org.uk/guidance/ng71).

Recommendations

NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are given in italic in square brackets.

Diagnosis

Parkinson's disease remains a clinical diagnosis based on the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for Parkinson's disease[3] (see box 1).

Pharmacological management of motor symptoms

Involve the person with Parkinson's disease and family members and carers (as appropriate) in all decisions. Take account of their clinical and lifestyle circumstances, their preferences, needs and goals, and how they view the potential benefits and harms of different drug classes.

First line treatment

Oral levodopa remains the preferred first line medicine for people with troublesome motor symptoms. When starting treatment, give information about adverse events. For dopamine therapy, these adverse events may include impulse control disorders (particularly dopamine agonists), excessive sleepiness, and hallucinations and delusions (all Parkinson's disease treatments but particularly dopamine agonists). Table 1⇓ lists the benefits and harms from first line drugs, and the infographic outlines the general strategy for managing Parkinson's disease symptoms.

- Offer levodopa to people with early Parkinson's disease whose motor symptoms affect their quality of life. [*Based on moderate quality evidence from randomised controlled trials (RCTs)*]
- Consider a choice of dopamine agonists, levodopa, or monoamine oxidase B inhibitors for people with early

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What you need to know

- Impulse control disorders can develop in a person with Parkinson's disease who is receiving any dopaminergic therapy at any stage in the disease
- A wide range of non-motor symptoms are common in Parkinson's disease, which may have modifiable causes (including antiparkinsonian medicines) and may be amenable to non-pharmacological management as well as some medicines
- Offer all people with Parkinson's disease access to the services provided by Parkinson's disease specialist nurses
- Offer access to specialist physiotherapy, occupational therapy, speech and language therapy, and cognitive behavioural therapy when relevant symptoms develop

What's new in this guidance

- Updated recommendations on the pharmacological management of Parkinson's disease, including first line and adjuvant pharmacotherapy of motor symptoms and medicines for non-motor complications
- Recommendations on the recognition and management of impulse control disorders, which may be caused by dopaminergic therapy
- Guidance for advanced Parkinson's disease, recommending deep brain stimulation (but not levodopa-carbidopa intestinal gel) for people whose symptoms are not adequately controlled by best medical therapy

Box 1: Parkinson's Disease Society Brain Bank diagnostic criteria for Parkinson's disease[3]

Step 1. Diagnosis of a parkinsonian syndrome

- Bradykinesia and at least one of the following:
  - Muscular rigidity
  - Rest tremor (4-6 Hz)
  - Postural instability unrelated to primary visual, cerebellar, vestibular, or proprioceptive dysfunction

Step 2. Exclusion criteria for Parkinson's disease

History of:

- Repeated strokes with stepwise progression
- Repeated head injury
- Antipsychotic or dopamine-depleting drugs
- Definite encephalitis or oculogyric crises on no drug treatment
- More than one affected relative
- Sustained remission
- Negative response to large doses of levodopa (if malabsorption excluded)
- Strictly unilateral features after 3 years
- Other neurological features: supranuclear gaze palsy, cerebellar signs, early severe autonomic involvement, Babinski sign, early severe dementia with disturbances of language, memory, or praxis
- Exposure to known neurotoxin
- Presence of cerebral tumour or communicating hydrocephalus on neuroimaging

Step 3. Supportive criteria for Parkinson's disease

Three or more required for diagnosis of definite Parkinson's disease:

- Unilateral onset
- Excellent response to levodopa
- Rest tremor present
- Severe levodopa-induced chorea
- Progressive disorder
- Levodopa response for over 5 years
- Persistent asymmetry affecting the side of onset most
- Clinical course of over 10 years.

Parkinson's disease whose motor symptoms do not affect their quality of life (see table 1⇓). [*Based on low and moderate quality evidence from RCTs*]

Adjuvant treatment of motor symptoms

When a person with Parkinson's disease develops dyskinesia or motor fluctuations (including "wearing off" episodes when effects of medication start to wear off in between medication doses) adjuvant therapy may be added, on advice from a healthcare professional with specialist expertise in Parkinson's disease. Table 2⇓ lists the benefits and harms of adjuvant drugs, and the infographic outlines the general strategy for managing Parkinson's disease symptoms.

- Offer a choice of dopamine agonists, monoamine oxidase B inhibitors, or catechol-O-methyl transferase inhibitors as an adjunct to levodopa for people with Parkinson's disease who have developed dyskinesia or motor fluctuations despite optimal levodopa therapy (see table 2⇓). [*Based on low and moderate quality evidence from RCTs*]
- If dyskinesia is not adequately managed by modifying existing therapy, consider amantadine. [*Based on the*

experience and opinion of the Guideline Development Group (GDG)]

Impulse control disorders as an adverse effect of dopaminergic therapy

People with impulse control disorders (ICDs) fail to resist the temptation to perform an act harmful to themselves or others such as compulsive gambling, hypersexuality, binge eating, and obsessive shopping. They are a recognised adverse effect of dopamine-replacement therapies, and occur in 14-24% of patients with Parkinson's disease who are taking these medications. ICD behaviours can cause distress for patients and carers, financial difficulties, and even criminal convictions. They may be difficult to recognise, particularly if patients conceal their behaviour from carers and family. ICD behaviours can develop in a person with Parkinson's disease who is taking any dopaminergic therapy, particularly dopamine agonists, at any stage in the disease. They are also associated with previous impulsive behaviours and a history of alcohol consumption or smoking.

- When starting dopamine agonist therapy, give people and their family members and carers (as appropriate) oral and written information about the following, and record that the discussion has taken place:
  - The increased risk of developing ICD behaviours when taking dopamine agonist therapy, and that these behaviours may be concealed by the person affected
  - The different types of behaviour (such as compulsive gambling, hypersexuality, binge eating, and obsessive shopping)
  - Who to contact if ICD behaviours develop.

  [*Based on low to moderate quality observational studies and the experience and opinion of the GDG*]
- If a person with Parkinson's disease has developed a problematic ICD behaviour, discuss the following with the person and family members and carers (as appropriate):
  - How the impulse control disorder is affecting their life
  - Possible treatments, such as reducing or stopping dopaminergic therapy
  - The benefits and disadvantages of reducing or stopping dopaminergic therapy.

  [*Based on the experience and opinion of the GDG*]
- When managing ICD behaviours, modify dopaminergic therapy by gradually reducing any dopamine agonist. Monitor whether the impulse control disorder improves and whether the person has any symptoms of dopamine agonist withdrawal. [*Based on low quality observational studies and the experience and opinion of the GDG*]
- Offer specialist cognitive behavioural therapy targeted at ICD behaviours if modification of dopaminergic therapy is not effective. [*Based on high quality evidence from a single RCT*]

Management of non-motor symptoms

Rule out possible pharmacological and physical causes of any new non-motor symptoms, and think about non-pharmacological treatments (for example, speech and language therapy for saliva management) before prescribing medicines.

Non-pharmacological management

Consider referral for assessment and advice from specialist physiotherapists, occupational therapists, speech and language therapists, and dietitians early in the disease. Always offer these therapies under the following circumstances:

- Offer Parkinson's disease-specific physiotherapy for people who are experiencing balance or motor function problems. [*Based on very low to moderate quality evidence from RCTs*]
- Offer disease-specific occupational therapy for people who are having difficulties with daily living activities. [*Based on moderate to high quality evidence from a single RCT*]
- Offer speech and language therapy for people with Parkinson's disease who are experiencing problems with communication, swallowing, or salivation. [*Based on very low to high quality evidence from RCTs*]

NICE has not updated its guidance that people with Parkinson's disease should have regular access to the services provided by a Parkinson's disease nurse specialist.

Pharmacological management

Box 2 summarises the medicines recommended for persistent symptoms. Some of these recommendations represent off-label use of the medicine in question; follow GMC advice when prescribing.[4]

Management of advanced Parkinson's disease

Deep brain stimulation may be considered for people with advanced Parkinson's disease, but only when symptoms are not controlled with best medical therapy (which may include intermittent apomorphine injection or continuous subcutaneous apomorphine infusion). Analysis undertaken for the guideline showed that levodopa-carbidopa intestinal gel is not cost effective in people with advanced Parkinson's disease; therefore, the guideline recommends that NHS England reviews its current specialised commissioning policy[6] in the light of this information.

- Consider referring people at any stage of Parkinson's disease to the palliative care team to give them and their family members or carers (as appropriate) the opportunity to discuss palliative care and care at the end of life. [*Based on the experience and opinion of the GDG*]

Implementation

The guidance recommends specialist care—including physiotherapy, occupational therapy, and cognitive behavioural therapy specifically for Parkinson's disease—after reviewing evidence demonstrating its effectiveness and considering its costs. However, the Guideline Development Group recognised that access to some or all of these services is limited in some areas. Similarly, provision of Parkinson's disease specialist nurses remains patchy, although NICE has recommended the services they provide for over a decade. The Department of Health has asked NICE to prepare quality standards for Parkinson's disease; we hope that these will provide additional impetus for access to these effective therapies.

The members of the Guideline Development Group were Paul Cooper (chair), Janine Barnes, Ivan Bennett, Angela Birleson (co-opted member until June 2015), Alistair Church, Debbie Davies, Julian Evans (co-opted member), Robin Fackrell, Richard Grunewald, Clare Johnson (co-opted member), Graham Lennox, Fiona Lindop, Jane Little, Nicholas Miller

Box 2: Recommended pharmacological management of non-motor symptoms of Parkinson's disease

When modifiable causes and non-pharmacological treatments have been ruled out:

- *Excessive daytime sleepiness*—Consider modafinil [*Based on low quality evidence from 4 RCTs*]
- *Rapid eye movement sleep behaviour disorder*—Consider clonazepam* or melatonin*
- *Nocturnal akinesia*—Consider levodopa or oral dopamine agonists [*Based on experience and opinion of the GDG*]
  - If neither is effective, consider rotigotine [*Based on high quality evidence from 1 RCT*]
- *Orthostatic hypotension*—Consider midodrine (taking into account the contraindications and monitoring requirements) [*Based on low quality evidence from 2 RCTs*]
  - If midodrine is contraindicated, not tolerated, or ineffective, consider fludrocortisone* (taking into account its safety profile and potential interactions with other medicines) [*Based on very lowquality evidence from 1 RCT and the experience and opinion of the GDG*]
- *Depression*—Identify and manage in accordance with NICE guideline on depression in adults with a chronic physical health problem[5]
- *Hallucinations and delusions*—Do not treat if well tolerated [*Based on experience and opinion of the GDG*]
  - Consider quetiapine* in people without cognitive impairment [*Based on low to moderate quality evidence from network meta-analysis of 3-8 RCTs*]
  - If standard treatment is not effective, offer clozapine in people without cognitive impairment (registration with a patient monitoring service is needed) [*Based on low to moderate quality evidence from network meta-analysis of 3-8 RCTs*]
  - Lower doses of quetiapine and clozapine are needed for people with Parkinson's disease than in other indications [*Based on experience and opinion of the GDG*]
  - Do not offer olanzapine [*Based on low to moderate quality evidence from network meta-analysis of 3-8 RCTs*]
- *Dementia*—Offer a cholinesterase inhibitor for mild or moderate dementia (rivastigmine, donepezil,* or galantamine* capsules or rivastigmine patches*) [*Based on high quality evidence from network meta-analysis of 7-10 RCTs*]
  - Consider a cholinesterase inhibitor* for severe dementia [*Based on experience and opinion of the GDG*]
  - Consider memantine* if cholinesterase inhibitors are not tolerated or contraindicated [*Based on low to moderate quality evidence from 3 RCTs*]
- *Drooling*—Consider glycopyrronium bromide* [*Based on very low to moderate quality evidence from 3 RCTs*]
  - If glycopyrronium bromide is not effective, not tolerated or contraindicated, consider referral to a specialist service for botulinum toxin A* [*Based on very low to moderate quality evidence from 10 RCTs*]
  - Consider anticholinergic medicines other than glycopyrronium bromide only if the person's risk of cognitive adverse effects is thought to be minimal [*Based on experience and opinion of the GDG*]

*Off-label use.

Guidelines into practice

- Do you provide oral and written information about adverse events including impulse control disorders when starting dopaminergic medicines?
- Do you refer people with Parkinson's disease for physiotherapy, occupational therapy, and speech and language therapy when they develop relevant symptoms?
- Have you discussed palliative care preferences with your Parkinson's disease patients?

Methods

The Guideline Development Group (GDG) comprised three consultant neurologists, two general practitioners, two consultant physicians, a Parkinson's disease specialist nurse, a Parkinson's disease nurse consultant, a specialist physiotherapist, a consultant neuropsychiatrist, a neurology specialist pharmacist, and two patient/carer members. Co-opted experts included two occupational therapists, a neurosurgeon, a speech and language therapist, and a specialist dietitian.

The guideline was developed using standard NICE guideline methodology (2012) (www.nice.org.uk/process/pmg6/chapter/introduction). The GDG developed clinical questions, collected and appraised clinical evidence, and evaluated the cost effectiveness of proposed interventions and management strategies through literature review and economic considerations where possible. Quality ratings of the evidence were based on GRADE methodology (www.gradeworkinggroup.org). These relate to the quality of the available evidence for assessed outcomes rather than the quality of the clinical study. Where standard methods could not be applied, a customised quality assessment was done. Stakeholder consultation was undertaken at both the scoping and development stages.

How patients were involved in the creation of this article

No patients were involved in the creation of this summary. However, committee members involved in this guideline included lay members who contributed to the formulation of the recommendations summarised here. The views of multiple patient organisations were sought for both the original scope of the guideline and its draft recommendations.

(co-opted member), Lynne Osborne, Beverly Sheaf (co-opted member), Paul Shotbolt, Matthew Sullivan, Richard Walker, Amanda Wardle (co-opted member).

The members of the NICE Centre for Guidelines team were Daniel Davies (from April 2016), Laura Downey (until October 2015), Sue Ellerby, Aimely Lee (from November 2015), Hugh McGuire (until December 2015), Sarah Mills (from January 2016 until April 2016), Stephanie Mills (until January 2016), Joshua Pink (from February 2016), Gabriel Rogers, Susan Spiers, Steven Ward (until April 2016).

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Tables

Table 1| Potential benefits and harms of first line medicines for management of Parkinson's disease motor symptoms

	Levodopa	Dopamine agonists	MAO-B inhibitors
Motor symptoms	Greater improvement	Less improvement	Less improvement
Activities of daily living	Greater improvement	Less improvement	Less improvement
Motor complications	More complications	Fewer complications	Fewer complications
Adverse events*	Fewer events	More events	Fewer events

MAO-B = monoamine oxidase B.

*Excessive sleepiness, hallucinations, and impulse control disorders.

Table 2| Potential benefits and harms of medicines used as adjuvants to levodopa for management of Parkinson's disease motor symptoms

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

COMT = catechol-O-methyl transferase. MAO-B = monoamine oxidase B.

*Periods of the day when levodopa is not working well, causing worsening of parkinsonian symptoms.