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Diagnosis and pharmacological management of Parkinson's disease

A national clinical guideline



January 2010

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

1 ⁺⁺	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1 ⁺	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 ⁻	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2 ⁺⁺	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2 ⁺	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 ⁻	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A	At least one meta-analysis, systematic review, or RCT rated as 1 ⁺⁺ , and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1 ⁺ , directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2 ⁺⁺ , directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1 ⁺⁺ or 1 ⁺
C	A body of evidence including studies rated as 2 ⁺ , directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2 ⁺⁺
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2 ⁺

GOOD PRACTICE POINTS

- | | |
|-------------------------------------|--|
| <input checked="" type="checkbox"/> | Recommended best practice based on the clinical experience of the guideline development group. |
|-------------------------------------|--|

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Scottish Intercollegiate Guidelines Network

**Diagnosis and pharmacological management of
Parkinson's disease**

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purpose of implementation in NHSScotland

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1 Introduction

1.1 THE NEED FOR A GUIDELINE

Parkinson's disease (PD) is a common neurodegenerative disorder with a cumulative effect on patients, their families and the healthcare and social care systems. In Scotland, there are between 120 and 230 patients with PD per 100,000 people.¹⁻³ While the population of Scotland remains stable, the age related incidence of PD means that the number of cases will increase by 25–30% over the next 25 years.⁴

There are a wide range of drug treatments for Parkinson's disease. However, it is not always clear which is the most appropriate treatment for the patient and whether the choice should be affected by age, clinical condition, or other factors. As the disease progresses, combination therapy is usually prescribed but there are gaps in clinical knowledge about when this should be initiated and what combinations of therapies are most effective.

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

Parkinson's disease is a complex neurological disorder which can affect many aspects of the patient's health and daily life. Ongoing rehabilitation in a patient with a progressive disease such as PD is best approached by a multidisciplinary team, which comprises several different professionals and services.

This guideline provides recommendations based on current evidence for best practice in the diagnosis and pharmacological management of PD. It includes comparisons of the accuracy of diagnoses carried out by different healthcare professionals, and the value of different diagnostic tests for differentiating PD from other associated conditions. It includes a comprehensive assessment of pharmacological management of motor and non-motor symptoms associated with PD. It also includes a narrative review of qualitative evidence describing the attitudes, beliefs and opinions of patients with PD across six themes. The role of the allied health professionals and the benefits of neurosurgical management of Parkinson's disease, such as deep brain stimulation, have not been covered. The management of some non-motor symptoms is not included in this guideline as in many cases their management is not significantly different from that in people without Parkinson's disease.

1.2.2 TARGET USERS OF THE GUIDELINE

The management of patients with Parkinson's disease covers a wide range of specialities, and this guideline will be of interest to general practitioners (GPs), neurologists, physicians, geriatricians, nurses working in hospitals, the community and care homes, pharmacists, psychologists, psychiatrists, patients, their carers and members of the voluntary sector. A wide range of medical disciplines is involved in routine management reflecting the fact that Parkinson's disease is much more than simply a disorder of physical movement, and that the neurological involvement frequently causes symptoms across many different functional areas, such as mental health, bowel, bladder and blood pressure.

1.3 DEFINITIONS

Parkinsonism is a clinical syndrome involving bradykinesia, plus at least one of the following three features: tremor, rigidity and postural instability. Parkinsonism is a broader, less specific, term than Parkinson's disease, and is used as an umbrella term to describe the clinical profile without being specific as to the cause. All patients with Parkinson's disease have parkinsonism (or sometimes monosymptomatic tremor), but not all patients with parkinsonism have PD.

Vascular parkinsonism describes parkinsonism caused by cerebrovascular disease. This may be small vessel disease in the subcortical areas and/or brainstem, and/or in association with larger artery occlusion.

Idiopathic Parkinson's disease. A description of the classic parkinsonian syndrome described by James Parkinson (see Annex 2).

Parkinson's plus is a collective term for degenerative parkinsonian syndromes that involve a wider area of the nervous system than idiopathic PD. For example, multiple system atrophy includes parkinsonism, cerebellar, and autonomic degeneration.

Bradykinesia is slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions.

Dementia is the progressive decline in cognitive function due to damage or disease in the brain beyond what might be expected from normal ageing.

Dyskinesia is involuntary movement with a rotatory, writhing appearance, which can affect the limbs, trunk and face, and occurs as Parkinson's disease progresses. Dyskinesia is one form of motor fluctuation.

'On' and 'off' states. With the use of levodopa for several years, many patients will develop fluctuating responses to the drug which can be divided into 'on and off' motor states. 'On' is used to describe when a person is responding optimally to their medications (primarily a response to levodopa). During 'on' periods, a person can move about and perform activities of daily living with relative ease, often with less tremor and rigidity. Some individuals can experience involuntary writhing movements as the medication effect reaches its peak; this is referred to as 'on with dyskinesias'.

'Off' is most frequently used to describe the period of time when a person with PD is having more difficulty with movement. Walking, eating, bathing and even speaking may be more impaired during an 'off' period and there may be non-motor manifestations such as low mood or fatigue. The most common time for a patient to experience an 'off' episode is when their medication is losing its effect prior to the time for the next dose. This is referred to as 'wearing off'.

Gait freezing is a motor block during walking, whereby the patient tries to take a step but is unable to do so. The freezing often occurs at the beginning of walking (start hesitation/gait initiation failure) but can also occur when the patient turns, confronts obstacles or distractions such as narrow doorways, or during normal walking. The individual episodes of freezing are usually brief (lasting seconds) and are not associated with worsening upper limb parkinsonism unlike 'on-off' fluctuations, with which they are often confused.

Sensitivity is the ability of the test to identify correctly those who have the disease. It is the number of subjects with a positive test who have disease divided by all subjects who have the disease. A test with high sensitivity has few false negative results.

Specificity is the ability of the test to identify correctly those who do not have the disease. It is the number of subjects who have a negative test and do not have the disease divided by the number of subjects who do not have the disease. A test with high specificity has few false positive results.

Positive likelihood ratio (LR+) is a measure of diagnostic accuracy calculated as sensitivity/(1-specificity). If a test is positive, the pre-test odds of having the condition can be multiplied by the LR+ to give the post-test odds of having the condition. An LR+ of between 3 and 10 implies a moderately useful test, whereas an LR+ ≥ 10 implies a positive test can be used to rule in the condition.

Negative likelihood ratio (LR-) is a measure of diagnostic accuracy calculated as specificity/(1-sensitivity). If a test is negative, the pre-test odds of having the condition can be multiplied by the LR- to give the post-test odds of having the condition. An LR- of between 0.1 and 0.3 implies a moderately useful test, whereas an LR- ≤ 0.1 implies a negative test can be used to rule out the condition.

1.4 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

1.4.1 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (product licence). This is known as "off label" use. It is not unusual for medicines to be prescribed outwith their product licence and this can be necessary for a variety of reasons.

Generally the unlicensed use of medicines becomes necessary if the clinical need cannot be met by licensed medicines; such use should be supported by appropriate evidence and experience.⁵

Medicines may be prescribed outwith their product licence in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose.

'Prescribing medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines.'⁵

Any practitioner following a SIGN recommendation and prescribing a licensed medicine outwith the product licence needs to be aware that they are responsible for this decision, and in the event of adverse outcomes, may be required to justify the actions that they have taken.

Prior to prescribing, the licensing status of a medication should be checked in the current version of the British National Formulary (BNF).

1.4.2 ADDITIONAL ADVICE TO NHSSCOTLAND FROM NHS QUALITY IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

NHS QIS processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Clinical Excellence (NICE) in England and Wales.

The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

SMC advice and NHS QIS validated NICE MTAs relevant to this guideline are summarised in the section on implementation.

2 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation. The grade of recommendation relates to the strength of the supporting evidence on which the evidence is based. It does not reflect the clinical importance of the recommendation.

2.1 DIAGNOSIS

2.1.1 CLINICAL DIAGNOSIS COMPARED WITH PATHOLOGICAL CONFIRMATION

C Clinicians should be aware of the poor specificity of a clinical diagnosis of Parkinson's disease in the early stages of the disease, and consider this uncertainty when giving information to the patient and planning management.

2.1.2 WHO SHOULD MAKE THE DIAGNOSIS?

C Patients with suspected Parkinson's disease should be referred untreated to a hospital clinician with sufficient expertise in movement disorders to make the diagnosis.

2.2 PHARMACOLOGICAL MANAGEMENT

2.2.1 DRUG EFFICACY IN EARLY DISEASE

A Patients with early Parkinson's disease and motor symptoms may be considered for treatment with levodopa in combination with a dopa decarboxylase inhibitor.

A Patients with early Parkinson's disease and motor symptoms may be considered for treatment with oral/transdermal dopamine agonists.

A Patients with early Parkinson's disease and motor symptoms may be considered for treatment with monoamine oxidase B inhibitors.

B Anticholinergic drugs should not be used as first line treatment in patients with Parkinson's disease.

ADVERSE EFFECTS ASSOCIATED WITH DOPAMINE AGONISTS

B Ergot derived dopamine agonists should not be used as first line treatment for Parkinson's disease.

A Patients should be warned about the potential for dopamine agonists to cause impulse control disorders and excessive daytime somnolence and be informed of the implications for driving/operating machinery.

2.2.2 PHARMACOLOGICAL MANAGEMENT OF MOTOR COMPLICATIONS

A Dopamine agonists (*oral or transdermal*) may be considered for the management of motor complications in patients with advanced Parkinson's disease. The non-ergot agonists (*ropinirole, pramipexole, and rotigotine*) are preferable to the ergot agonists.

A Monoamine oxidase B inhibitors may be considered for the treatment of motor complications in patients with advanced Parkinson's disease.

A Catechol-o-methyl transferase inhibitors may be considered for the reduction in 'off' time in patients with advanced Parkinson's disease who have motor fluctuations.

3 Narrative review of publications describing patient issues

3.1 CONTENT OF NARRATIVE REVIEW

A narrative review of the qualitative literature was conducted to identify issues of concern to patients with PD. The search strategy is outlined in section 8.1

The narrative review identified six themes that arose either from incidental findings from other research or as primary topics in their own right. These were:

- communication
- attitudes to drug therapy
- information needs
- family/carer needs
- non-motor symptoms
- multidisciplinary team working.

These topics reflect the most frequently cited issues and are not a comprehensive list of insights generated by qualitative researchers. These topics are not discrete, they overlap and are inter-related. For example, one study highlights the communication implications of non-motor symptoms, such as diminished attention span.

Much of the literature identified was limited by the methodological quality of the studies (see *supplementary material on SIGN website for further details of the methodological analyses undertaken*).

3.2 COMMUNICATION

The ability to communicate is a vital part of normal life and deficits in communication can have a devastating effect. Good communications are very important for people with PD, both at the initial diagnostic stage and also as the condition progresses. Studies have suggested that this must be a three-way process between the person with PD, their carers and the appropriate professionals. A sharing of information with family members was perceived to be vital for each person to understand their individual situation. A deterioration in the quality of speech of a person with PD, in parallel with disease progression, has a significant negative impact on the communication process. One person stated "...my voice doesn't come out correctly".⁶ This also made it difficult for him to express emotion. In addition, interruption, or the finishing of sentences by others, was highlighted as impacting on a person's ability to interact in a social context. This particularly occurs when a person gets slightly confused in mid-sentence. This may lead to social isolation as the person may be embarrassed by their disease and its symptoms.

The effect of altered emotions during the communication process was also highlighted. One person said: "I don't have the ability to control my emotion".⁷ People felt unable to tell others about their PD, especially at the early stages as they were unsure about the potential reaction. One person said "the people you work with do not understand when I have to ask to leave early on Tuesday to go to [my] appointment".⁸

3.3 ATTITUDES TO DRUG THERAPY

Although people with PD are likely to react in a range of different ways when they start drug therapy, there are few studies which describe this from the patient's perspective. The main issue identified was the importance of information provision at the time of diagnosis about the condition, therapy and progression. One factor that impacted on the experience of taking medication was for people to realise that they were not alone. Meeting with other people with PD reassured them that others also had to take different medication, frequently with unwanted

side effects. In this way, support groups were felt to be helpful and reassuring.⁹ People with PD do not always appreciate the importance of medication timing, possibly due to a lack of information provision at the time of prescription. One person with PD who missed his medication stated: "I just kind of froze up...you have to find out the hard way [that that's] what the medication is doing to you".⁹ This study was carried out in the USA where people with PD do not necessarily have access to specialist PD nursing support. Nevertheless, it gives an indication of the level of distress that can follow from an information deficit.

3.4 INFORMATION NEEDS

Information about Parkinson's disease is a primary element in assisting people to come to terms with the condition and the impact it will have on their future as it progresses. It is important the information is appropriately targeted and at the correct educational level to ensure complete understanding. A particularly important time for giving information and education is at the time of diagnosis. Some skill has to be exercised in determining the amount of information imparted at diagnosis, steering between too little - "I was shocked in maybe 12 minutes of his total time seeing me, he diagnosed me with an illness and gave me no hope and told me to take some medicine, period. And then he dismissed me"¹⁰ - and too much "knowing all the facts would probably have finished me off".¹¹

It is important that clinicians make patients feel well supported. They should also make sure that patients are aware of the potential risks arising from unreliable, inaccurate and unregulated sources of information about their condition such as the Internet and newspapers. This could lead to possible negative impact on the maintenance and strength of relationships with their clinical advisors - "when I was diagnosed, I remember just kind of crying that day and coming home and looking up that word in the dictionary and it was like, well, I'm going to die with this disease".⁹ Some patients reported the need to lie to or "cheat" their healthcare providers by hiding experiential knowledge gained from experimenting with drug dosing or diet.¹⁰

As in other areas, self help groups are identified as being associated with both positive and negative consequences. Many patients reported them useful for reinforcing such factors as medicines management or dietary requirements, but a number used coping strategies which centred upon maintaining as normal a life as possible and found the self help group a source of some discomfort - "I have seen the future in the eyes, faces and activities, or inactivities, of my fellow Parkinson sufferers".¹¹ See section 6.1 for sources of further information for people with Parkinson's disease.

3.5 NEEDS OF THE FAMILY/CARER

The role of carers looking after those with chronic conditions is multifaceted. Carers have unique and individualised coping strategies for dealing with the daily pressures of care. Many carers report the difficulty in adopting the twin roles of therapist and friend. The evidence reports that spouses often found great difficulty in watching their partner struggle and can be frustrated by the illness without promoting dependency but helping when necessary. Studies acknowledge that not only does the person with PD have a change in lifestyle, so does the carer.

For example, in one paper, a carer acknowledged that "sometimes I feel a little guilty because I don't do something for him; maybe I force him to be more independent. But it's because I want him to be able to do it. Sometimes I haven't come to grips with it because I think I should have done it rather than him because it was hard on him. But then I think he did it and he was able to do so."¹²

Among the range of coping strategies identified in the literature, one paper identified spirituality as a major factor.¹³

The qualitative literature used was from American sources and, as such, may not be wholly representative of provision in NHSScotland. This highlights the need for more appropriate qualitative research from the UK in this area.

3.6 NON-MOTOR SYMPTOMS

Despite the perception of the severity of non-motor symptoms for people with PD, little evidence on patients' experiences was identified. In two studies carried out by the same researchers the main impact of non-motor symptoms was perceived to be psychosocial - "embarrassed people just keep staring at you when you cannot get your words out... so I just avoid people".⁶ In the case of swallowing - "he doesn't want to face people when he is eating as he slavers, you see".¹⁴

Coupled with manifestations such as tremor and falls, non-motor symptoms contributed to a very significant curtailment of social activity, "sitting in the subway is a problem because everybody looks at you. You're the centre of attraction."¹⁵

A second theme arising was that in both speech and swallowing, the impact of the problem on the patient was significant even early on in the disease. In speech, in contrast to straightforward articulation difficulties, patients identified issues such as distractibility, diminished attention span, and difficulty finding words and formulating ideas - "It's difficult to keep my attention going, I drift away...".⁶ In the case of swallowing, coping strategies used to overcome difficulties with food were perceived as putting significant stress on to carers who had to spend more time in food preparation and the feeding process itself - "...didn't affect me, affected my wife".¹⁴ Attitudes of others, particularly identified in conversation with partners, were identified as a significant contributor to the frustration felt by sufferers - "By the time you've finished the subject has changed and they haven't waited for your answer to come out".⁶ Non-motor symptoms may be recorded with a standard questionnaire (see Annex 3).

3.7 MULTIDISCIPLINARY TEAM WORKING

There is a perception among healthcare professionals and client groups that a multidisciplinary team with specialist knowledge and skills specific to the management of Parkinson's disease is best practice and is the preferred choice of patients and professionals alike.¹⁶ There is no good quality qualitative research to support this view and this lack of evidence highlights the need for work in this area.

4 Diagnosis

Parkinson's disease is a lifelong chronic progressive neurodegenerative condition. Accurate diagnosis underpins its management but this is not always easy. Whilst Parkinson's disease is the commonest cause of a parkinsonian syndrome, there are several other degenerative and non-degenerative diseases that can mimic it (see *Table 1*). It is important to distinguish these mimics because many do not respond to the treatment used for PD and they have a different prognosis from PD. Accurate diagnosis is essential to ensure that patients receive the correct information and treatment.

Table 1: Common mimics of Parkinson's disease

Degenerative disorders	Non-degenerative disorders
Multiple system atrophy	Essential tremor
Progressive supranuclear palsy	Dystonic tremor
Corticobasal degeneration	Cerebrovascular disease
Dementia with Lewy bodies	Drug-induced parkinsonism
Alzheimer's disease	

4.1 CLINICAL DIAGNOSIS COMPARED WITH PATHOLOGICAL CONFIRMATION

The diagnosis of Parkinson's disease is largely clinical and depends on the presence of a specific set of symptoms and signs (the initial core features being bradykinesia, rigidity, rest tremor and postural instability), the absence of atypical features, a slowly progressive course, and a response to drug therapy. This diagnosis requires clinical skill but is open to a degree of subjectivity and error. It is important to consider the accuracy of the clinical diagnosis against a suitable reference standard, which for almost all cases of Parkinson's disease remains neuropathological confirmation at post mortem (a very small percentage of cases can be diagnosed genetically, see *section 4.5*). Given that the signs of PD and many of the other conditions that mimic it develop gradually and evolve over many years (mean survival is over 10 years), it is likely that, for individual patients, the diagnostic accuracy may improve over the course of the disease. Thus, it is important to consider the accuracy of the clinical diagnosis both in the early stage of the disease when decisions about initiating treatment will be made and also later in the disease.

4.1.1 CLINICAL EXPERT DIAGNOSIS COMPARED WITH DIAGNOSIS BY POST MORTEM REFERENCE STANDARD

Only five studies (n = 507) assessed the accuracy of an expert clinical diagnosis (mostly made by neurologists) against post mortem confirmation: two assessed the initial clinical diagnosis^{17,18} and five assessed the final clinical diagnosis before death.¹⁷⁻²¹ All the studies had significant flaws which may have introduced bias and which affect generalisability. These flaws included: the reference standard was only available in a limited spectrum of patients that did not reflect the types of patients seen in most clinical settings, particularly in the initial stages of the disease;¹⁸⁻²¹ the patients included were younger (mean age 53-65 years) with longer disease duration than seen in many clinical settings; details of how the clinical diagnosis was made were not available; the clinicians were often highly specialised movement disorder experts;¹⁹ clinical diagnoses were identified by retrospective review of the case notes after death, which may have reduced accuracy;^{18,19} and one study did not blind the clinical diagnosis to the pathological diagnosis.¹⁹

2+

In the early stages of the disease, expert clinicians had good sensitivity (consistently about 0.90) but poor specificity (range 0.42 to 0.77) in diagnosing PD compared to post mortem confirmation. This results in a significant number of false positive diagnoses. The sensitivity and especially specificity of expert clinical diagnosis increased with follow up and the final clinical diagnosis had a good sensitivity (range 0.91 to 0.94) and better specificity (range 0.62 to 0.98), which was highest in highly specialist centres of excellence.¹⁹ Studies from the UK Parkinson's Disease Society Brain Bank showed that the proportion of those carrying a clinical diagnosis of PD at death who were confirmed to have PD at post mortem improved from 0.75 in the late 1980s to 0.90 in the late 1990s.^{20,21}

2+

C Clinicians should be aware of the poor specificity of a clinical diagnosis of Parkinson's disease in the early stages of the disease, and consider this uncertainty when giving information to the patient and when planning management.

Patients should be offered long term, regular, follow up to review the diagnosis of Parkinson's disease. This should include a review of the ongoing benefits in those started on dopamine replacement therapy.

Patients initially considered to have a possible diagnosis of Parkinson's disease may benefit from a trial of dopamine replacement therapy to assist with an accurate diagnosis.

4.1.2 DIAGNOSIS USING SPECIFIC RESEARCH CRITERIA COMPARED WITH DIAGNOSIS BY POST MORTEM REFERENCE STANDARD

The clinical diagnosis of Parkinson's disease may be improved by applying strict criteria such as those used in research settings. There are two commonly used research criteria, the UK Parkinson's Disease Society Brain Bank criteria²² and the Gelb criteria²³ (see Annex 2). Improved diagnostic accuracy would be most useful early in the course of parkinsonian disorders when clinical diagnosis is most inaccurate and important management decisions must be made. Unfortunately, no studies have addressed the diagnostic accuracy of research criteria applied early in the course of Parkinson's disease. Moreover, some of the criteria are difficult to apply in early disease. For example, only two of the supportive criteria in the UK Brain Bank criteria (unilateral onset and rest tremor) can be applied in the initial phase of the condition because the rest require prolonged follow up. The Gelb criteria for probable Parkinson's disease require at least three years follow up from symptom onset.

Only one small study (n = 100) from the UK has assessed the accuracy of using the UK Brain Bank and Gelb criteria late in the disease compared to neuropathological confirmation of the diagnosis.²¹ This study only included patients whose final clinical diagnosis before death was Parkinson's disease with the result that other parkinsonian syndromes may be under-represented compared to normal clinical practice. A direct comparison found that the UK Brain Bank criteria and the Gelb criteria for both possible and probable PD all had poor specificity (0.30-0.40) resulting in significant numbers of false positive diagnoses. The UK Brain Bank (0.90) and the Gelb criteria for possible PD (0.87) had better sensitivity than the Gelb criteria for probable Parkinson's disease (0.72). No direct comparison of research criteria versus expert clinical diagnosis was possible apart from the positive predictive value, which was similar (0.90 to 0.93) for all diagnostic criteria. Indirect comparison with studies that compared the final expert clinical diagnosis with post mortem diagnosis suggests that expert clinical diagnosis has a higher specificity than research criteria. Although clinicians do not formally apply these research criteria in making a diagnosis, they will take many of the features outlined in the criteria into account.

2+

D Formal research criteria should not be used in isolation for diagnosing Parkinson's disease in a clinical setting but clinicians should take them into account when making a clinical diagnosis.

4.2 WHO SHOULD MAKE THE DIAGNOSIS?

In Scotland, some patients with Parkinson's disease are diagnosed and managed by general hospital physicians who are not specialists in PD, and around 15% are diagnosed and managed solely by general practitioners without referral to secondary care.²⁴ A GP with an average list size of about 1,500 will see only one new case of PD every 3.3 years which makes it difficult to develop and maintain expertise.

4

4.2.1 BENEFITS OF SPECIALIST DIAGNOSIS

Two studies were identified which assessed the accuracy of a diagnosis of PD made by a GP or hospital non-specialist compared to review by a movement disorder specialist applying UK Brain Bank research criteria.^{25,26} No studies were identified which compared clinical diagnosis alone made by GPs, non-specialist hospital physicians and hospital PD specialists with a reference standard of post mortem confirmed diagnosis. Only one study could be used to derive diagnostic sensitivity and specificity values but this study did not make a distinction between hospital physicians with and without a specific interest in PD. Nor did it specify whether the diagnosis was made early or later in the disease course.

General practitioners had only moderate sensitivity (0.74) and specificity (0.79) in diagnosing PD when compared to a movement disorder specialist applying research criteria.²⁶ Non-specialist hospital physicians had good sensitivity (0.93) but poor specificity (0.65). Hospital physicians made more false positive diagnoses of PD whereas GPs had more false negatives. General practitioners made more diagnostic errors overall. A misdiagnosis (either false positive or false negative) of PD is important because it will result in patients being given misinformation about their prognosis and can also have an impact on clinical management.

2+

It is more important not to confuse PD with a non-parkinsonian condition (such as essential tremor) or drug-induced parkinsonism where the treatment is clearly different than it is to differentiate PD from other degenerative or vascular parkinsonian conditions which may respond to some degree to dopaminergic treatment. GPs have been shown to make more important errors (ie confusing PD with essential tremor) than hospital physicians who tend to misdiagnose PD as another degenerative parkinsonian condition.^{25,26}

Despite the limited evidence, clinical common sense would imply that patients should be seen and diagnosed by clinicians who have specific expertise and interest in the condition. How such expertise is defined and maintained is beyond the scope of this guideline. Treatment for PD can mask some or all of the important signs and hence it is desirable that patients should be referred before treatment is initiated.

C Patients with suspected Parkinson's disease should be referred untreated to a hospital clinician with sufficient expertise in movement disorders to make the diagnosis.

4.3 DIAGNOSTIC TOOLS

The diagnosis of PD is traditionally a clinical one. Recent brain imaging techniques are generally categorised as structural (magnetic resonance imaging, MRI; computed tomography, CT) and functional (positron emission tomography, PET; single photon emission computed tomography, SPECT). There are several studies of structural and functional imaging, but they are mainly conducted at single centres and case numbers are generally small.²⁷⁻³¹ A recurrent difficulty with study design is the validation of the reference standard which is usually achieved by prolonged clinical follow up and/or blinded clinician review. There are a small amount of data relating functional imaging results to post mortem confirmation, in the area of dementia with Lewy bodies versus Alzheimer's disease,³² but otherwise there is no published work comparing functional imaging results with post mortem results.

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4.3.1 FUNCTIONAL IMAGING

Functional imaging of the presynaptic dopaminergic system is sensitive to the presence of dopamine deficiency in the early stages of degenerative parkinsonism (including idiopathic Parkinson's disease), because at least 50% of dopamine activity is lost before the first symptoms of the condition emerge. This means that such techniques offer the potential for confirming or refuting the clinical diagnosis at an early stage of clinical presentation.

In the clinical trial setting, between 11 and 15% of patients considered clinically to have a diagnosis of early PD have tested normal with functional brain imaging.^{33,34} It is likely that these patients have an alternative non-degenerative parkinsonism/tremor disorder, such as essential tremor, dystonic tremor, vascular parkinsonism or drug-induced parkinsonism.³⁵

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The differentiation of idiopathic PD from other degenerative forms of parkinsonism through the use of functional imaging is much more difficult and is generally of limited benefit, especially at the earlier clinical stages. The other conditions under consideration include progressive supranuclear palsy, multiple system atrophy, dementia with Lewy bodies and corticobasal degeneration. Although many small studies report differences between groups of patients with these diagnoses, such testing has generally been conducted at a later disease stage when clinical features are more developed.^{27,28,30}

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Cerebrovascular disease may cause direct basal ganglia damage (pre- and postsynaptic neurones affected), or affect the presynaptic dopaminergic neurones along the nigrostriatal pathway.³⁵ Functional imaging of the presynaptic system may show evidence of resulting focal damage, but the pattern differs from that of idiopathic PD and other forms of degenerative parkinsonism (which are non-focal, and progress asymmetrically from putamen to caudate). Interpretation of functional imaging of the dopaminergic system in patients with vascular risk factors and/or structural imaging evidence of cerebrovascular disease should consider the possibility that focal deficits are due to vascular insults (eg small vessel disease, focal infarction, and, more rarely, haemorrhage) rather than being caused by degenerative change.

SPECT

Differentiating idiopathic PD from non-degenerative disorders with parkinsonism/tremor is possible using functional imaging such as ¹²³I-FP-CIT SPECT (N-ω-fluoropropyl-2β-carboxymethoxy-3β-(4-iodophenyl)tropane). In a study of 38 patients with probable early PD, 24 with uncertain parkinsonism and 14 volunteers, ¹²³I-FP-CIT SPECT was compared with clinical diagnosis giving a sensitivity in detecting degenerative parkinsonism of 100% for ¹²³I-FP-CIT (95% confidence interval (CI), 87 to 100%), specificity 73.6% (48.6 to 89.9%), a positive predictive value of 86.8% and a likelihood ratio of 3.8.²⁹

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PET

The main radioisotope used is ¹⁸F Fluorodopa, which images the presynaptic dopamine system. There is no evidence that PET scanning has a superior ability to diagnose Parkinson's disease and differentiate it from non-Parkinson disorders, compared to SPECT. One study of 32 subjects found a sensitivity of 95.8% for ¹⁸F-PET in the differentiation of PD from multiple system atrophy (MSA), but included only eight patients with PD.³¹

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PET scanning is not recommended as part of the diagnostic work-up of parkinsonian syndromes, except within a research framework.

B ¹²³I-FP-CIT SPECT scanning should be considered as an aid to clinical diagnosis in patients where there is uncertainty between Parkinson's disease and non-degenerative parkinsonism/tremor disorders.

C Routine use of functional imaging is not recommended for the differential diagnosis of Parkinson's disease and Parkinson's plus disorders such as progressive supranuclear palsy and multiple system atrophy.

4.3.2 STRUCTURAL IMAGING

Patients presenting with parkinsonism/tremor may show structural abnormalities on CT or MRI scanning. Often such findings are incidental, for example, basal ganglia calcification was found in 0.6% of 7,000 patients, with no relationship to parkinsonism.³⁶ It is rare to find a causative structural lesion such as an arteriovenous malformation, tumour, or hydrocephalus and only isolated cases are reported.^{37,38}

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Transcranial ultrasound records the echo signal returned from the basal ganglia and has been studied in patients with Parkinson's disease, other forms of degenerative parkinsonism, and tremor disorders. Acquisition and interpretation of the images is operator-dependent and reported studies are small with limited longer term clinical follow up.³⁹ Transcranial ultrasound has shown some ability to differentiate PD from other degenerative parkinsonism such as progressive supranuclear palsy and multiple system atrophy. In 38 patients with diagnostic uncertainty at baseline, the sensitivity of transcranial ultrasound was 90.7% and specificity 82.4%.³⁹

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Structural imaging of the brain with CT or MRI scanning does not differentiate idiopathic Parkinson's disease from other forms of degenerative and non-degenerative parkinsonism.^{40,41} Although one study suggested that measurement of brain volume in areas such as midbrain and pons could differentiate progressive supranuclear palsy (PSP) on the one hand from PD and MSA on the other, cut-off values were derived within the study and differed according to the clinical diagnosis; it is unclear whether the results could be replicated in another study.⁴²

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There are three situations in which structural imaging supports or clarifies the clinical diagnosis:

- the presence and extent of cerebrovascular changes can give an indication of the contribution of cerebrovascular disease to clinical features of parkinsonism and thereby support or refute a clinical diagnosis of probable vascular parkinsonism. As imaging evidence of small vessel cerebrovascular disease becomes more common with increasing age, these changes may be coincidental, rather than causative of a parkinsonian presentation. The presence of basal ganglia and/or thalamic infarcts increases the likelihood of a causative relationship.³⁵
- the presence of a particular pattern of brain atrophy or gliosis may help define a Parkinson's plus syndrome rather than idiopathic PD.⁴¹ For example, midbrain atrophy may suggest progressive supranuclear palsy whilst cerebellar or brainstem atrophy or gliosis is more suggestive of multiple system atrophy.⁴¹
- identification of structural abnormalities, eg hydrocephalus, arteriovenous malformation, brain tumour, which can present with parkinsonism and/or tremor.^{37,38}

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C Transcranial ultrasound should not be undertaken in the differential diagnosis of idiopathic Parkinson's disease from other associated conditions, except within defined research protocols.

C Computed tomography or magnetic resonance imaging brain scanning should not be routinely applied in the diagnosis of idiopathic Parkinson's disease.

D Magnetic resonance imaging brain scanning is recommended in patients where it would be clinically helpful to identify:

- the degree and extent of cerebrovascular disease, in particular in subcortical brain areas including the basal ganglia, to differentiate idiopathic Parkinson's disease from vascular parkinsonism
- the degree and distribution of brain atrophy, in patients with features suggesting a Parkinson's plus disorder.

D Computed tomography or magnetic resonance imaging brain scanning is recommended in patients where it would be clinically helpful to identify:

- the presence of a structural lesion or lesions which may cause or contribute to parkinsonism/gait disorder/tremor.

4.3.3 ACUTE DOPAMINERGIC TESTING AND CHRONIC LEVODOPA RESPONSE

Acute challenge testing with either levodopa plus dopa decarboxylase inhibitor (DDI) or apomorphine has been suggested as helpful in discriminating PD from other parkinsonian syndromes or mimics.

One systematic review was identified which compared chronic trials of treatment, defined as up to 1,000 mg levodopa/day for at least one month, with acute dopaminergic challenges.⁴³ Acute challenge testing is similar to, but no better than, chronic levodopa treatment in terms of diagnostic accuracy (see Table 2). Given that most patients with suspected PD will be treated with dopaminergic therapy at some stage, there is no additional benefit with acute challenge testing, but such challenges are associated with adverse effects and extra costs. An adequate chronic levodopa challenge should be regarded as 1,000 mg/day for at least one month. Patients whose rigidity/bradykinesia fails to improve despite such a challenge may be considered levodopa unresponsive and treatment should be tapered to discontinuation.

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Clinicians should be aware that some patients, particularly the elderly or those with cognitive dysfunction, may be unable to tolerate high doses of levodopa, usually because of significant neuropsychiatric effects or postural hypotension.

Table 2: Diagnostic accuracy of challenge testing in patients with established Parkinson's disease

Test regimen	Sensitivity	Specificity
acute apomorphine (0.7–10 mg)	0.86 (95% CI 0.78 to 0.94)	0.85 (95% CI 0.74 to 0.96)
acute levodopa (275 mg)	0.75 (95% CI 0.64 to 0.85)	0.87 (95% CI 0.77 to 0.97)
chronic levodopa (< 1,000 mg)	0.91 (95% CI 0.85 to 0.99)	0.77 (95% CI 0.61 to 0.93)

- A**
 - **Acute challenge testing is not recommended in the diagnosis of Parkinson's disease.**
 - **Patients with suspected Parkinson's disease should be considered for a trial of chronic levodopa treatment.**
- Patients whose rigidity/bradykinesia fails to improve despite such a challenge may be considered levodopa unresponsive and treatment should be gradually withdrawn.
- Levodopa, as part of a challenge test, should be titrated slowly with clinical monitoring, until patients respond, become intolerant, or achieve a daily dose of 1,000 mg/day without response.

4.3.4 OLFACTORY TESTING

Olfactory function is impaired in most patients clinically diagnosed with PD but is normal or less impaired in patients with atypical syndromes and other imitators. Anosmia and hyposmia are found more frequently in patients with PD than in controls or patients with conditions which may imitate PD such as vascular parkinsonism, progressive supranuclear palsy (PSP), Alzheimer's disease and essential tremor.

The American Academy of Neurology has suggested that olfactory testing should be considered in distinguishing PD from PSP and corticobasal degeneration but not multiple system atrophy (MSA).⁴⁴

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A systematic review of olfactory testing in PD described two studies which used two objective smell tests, the University of Pennsylvania Smell Identification Test (UPSIT) and 'Sniffin Sticks'.⁴⁵

The UPSIT produced moderate sensitivity (77%, LR- 0.27) and specificity (85%, LR+ 4.9) for differentiating PD from other parkinsonian syndromes, but was less specific (62%, LR+ 2) for differentiating PD from MSA. Methodological issues such as small sample size, lack of blinding and the use of clinical examination or imaging techniques rather than a pathological diagnosis as the gold standard reference are likely to reduce the true diagnostic accuracy of olfactory testing.

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The diagnostic accuracy of olfactory testing for differentiating idiopathic PD from other disorders is insufficient to justify its routine clinical use.

B Objective olfactory testing is not recommended in the diagnosis of Parkinson's disease.

4.4 DIAGNOSING DEPRESSION IN PATIENTS WITH PARKINSON'S DISEASE

Mood disorders including depression are common in PD, although reported prevalence rates have varied widely. A systematic review concluded that the prevalence of major depressive disorder was 17% in patients with PD, that of minor depression 22% and dysthymia 13%. Clinically significant depressive symptoms, irrespective of the presence of a depressive disorder defined by Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, were present in 35% of patients with PD.⁴⁶ Accurate recognition, diagnosis and formulation of such disorders is vital, though the process is not straightforward because of the overlap between the cognitive and somatic symptoms of PD and those associated with depression. This may lead to inaccurate diagnosis with some patients with PD being misdiagnosed as depressed when symptoms are caused directly by the PD. In other patients a genuine mood disorder may be missed as symptoms of depression may be wrongly assumed to be caused by the underlying PD.

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4.4.1 DIAGNOSTIC CRITERIA

Many studies have examined the effectiveness of various tools used in the assessment of depression in PD.^{47,48} These measures, primarily self report questionnaires or clinician rating scales, were not typically developed for use in PD but for use in general adult mental health settings. Given the issue of symptom overlap between depression and PD it is important that the effectiveness of these measures in assessing depression in PD is tested.

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Two systematic reviews and a further six studies provide evidence of the effectiveness of a wide range of assessment tools.^{47,49-55} These studies consistently show that a number of assessment scales are useful but that there are weaknesses in most and no single scale that stands out above the rest.

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The Hamilton Depression Rating Scale (Ham-D) and the Montgomery-Asberg Depression Rating Scale (MADRS) are clinician-rated scales that can be used in the assessment of depression in patients with PD.^{47,49,50} There is substantially more research evaluating the Ham-D than the MADRS. For self rating scales the Beck Depression Inventory (BDI), the Geriatric Depression Scale (GDS) and Hospital Anxiety and Depression Scale (HADS) can be used.^{47,51-55}

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Expert opinion suggests that, at an individual case level, a diagnosis of depression should not be made on the basis of rating scale score alone because of the possibility that scores will be inflated by ratings of somatic/cognitive symptoms arising directly from the PD.⁵⁶ A structured interview remains the gold standard method of assessment. Problems have been noted in the use of diagnostic classifications, especially DSM criteria, for depression in PD. It has been suggested that the DSM exclusion criterion ("due to the effects of a general medical condition") be eliminated and the anhedonia/loss of interest criterion be modified to clarify whether any reduction of activity is caused by loss of interest (arising from difficulties engaging in activities as a result of disability) rather than loss of pleasure.⁵⁷ Emphasis should be placed on assessing whether mood disturbance is linked to fluctuations in motor symptoms. It is also suggested that relatives or carers who know the patient well are used to supplement information. This is particularly important in the context of people with cognitive impairment.

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C Self-rating or clinician-rated scales may be used to screen for depression in patients with Parkinson's disease.

When clinician-rated assessment is possible, the Hamilton Depression Rating Scale or the Montgomery-Asberg Depression Rating Scale should be used to establish the severity of depressive symptoms.

- Diagnosis of depression should not be made on the basis of rating scale score alone.
- Assessment/formulation of depression should be carried out via clinical interview, with a focus on low mood, and with due caution in relation to interpretation of cognitive/somatic symptoms that may be symptoms of Parkinson's disease rather than depression.
- Relatives or carers who know the patient well should be invited to provide supplementary information to assist the diagnosis, particularly in the context of cognitive impairment.

4.5 GENETIC TESTING

Most classical PD is considered to arise sporadically, although several genetic susceptibility factors may be pertinent.⁵⁸ A number of monogenic causes of PD have now been identified, and up to 20% of patients with PD have a family history of PD in first degree relatives.⁵⁹ Mutations in five causative genes may account for around 2-3% of all cases of PD with clinical features similar to classical disease.⁶⁰ The best studied of these are leucine-rich repeat kinase 2 (LRRK2, autosomal dominant pattern), and parkin (autosomal recessive pattern).

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4.5.1 LEUCINE-RICH REPEAT KINASE 2 MUTATIONS

Worldwide, LRRK2 mutations have been found in 5% to 8% of patients with PD with a first degree relative with PD and in 0.4% to 1.6% of patients with apparently sporadic PD, making this the commonest known monogenic cause of PD.^{59, 61, 62} The commonest mutation is G2019S, which has a UK prevalence of 0.4%.⁶² The penetrance of this mutation is age dependent, increasing from 17% at age 50 years to 85% at age 70 years. The variation in penetrance prevents the provision of any appropriate advice on prognosis for affected individuals.

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4.5.2 PARKIN MUTATIONS

Parkin mutations appear to be associated with young onset PD. In one large study of families (including UK families) with at least one of the affected siblings with early onset PD (onset under 46 years of age) nearly 50% had parkin mutations, with age of onset ranging from 7 to 58 years.⁶³ In patients with sporadic PD the prevalence was 77% in those with an age of onset of 20 years or younger, but only 3% in those with an age of onset of 30 years or older.

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Despite increasing commercial availability of genetic testing there is no evidence of benefit for routine testing of affected individuals or asymptomatic family members. There are no discriminating clinical features of parkinsonism that would permit targeting of genetic testing for specific genes in affected individuals. Interpretation of tests remains difficult because of issues related to variable penetrance, variable disease expression, inconclusive tests and the uncertain influence of heterozygous mutations in recessive and susceptibility genes.

There is no evidence for a different therapeutic approach in an individual with a positively identified genetic parkinsonism and no therapies available which would modify or prevent disease in asymptomatic identified family members.

- Genetic testing for monogenic parkinsonism is not recommended in routine clinical practice.
- Patients who request genetic testing, particularly those with young onset parkinsonism, should be assessed in a specialist movement disorders clinic for consideration of counselling and testing.

5 Pharmacological management

Parkinson's disease mostly affects movement (motor symptoms) but can also affect, for example, mood, behaviour, thinking, and sensation (non-motor symptoms). Control of symptoms is the goal of pharmacological management in PD.

The basic efficacy of the various classes of drugs for symptomatic control in people with PD is well described in clinical guidelines.⁶⁴⁻⁶⁶ These guidelines also provide a comparison of effect in both early and late PD. Drug efficacy and symptom control are often measured in clinical trials by improvements in validated rating scales, eg the Unified Parkinson's Disease Rating Scale (UPDRS), the Hoehn and Yahr scale and the Schwab and England scale.

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The choice of agent depends on a combination of factors including the relative effectiveness and adverse effect profile of the drugs, patient comorbidities, patients' employment status, clinician experience and patient preference. The choice should be made following individual assessment and discussion. The timing of when to start treatment will also be governed by the patient's individual circumstances.

5.1 DRUG EFFICACY IN EARLY DISEASE

Early disease is classed as the stage at which the diagnosis of idiopathic PD has been made and a clinical decision has been made to commence treatment. Five classes (or individual) drugs have been reviewed for efficacy in the management of symptoms of early PD. Sufficient evidence was available to recommend the use of three of these drug types (see sections 5.1.1 to 5.1.3). Claims that certain drug treatments are neuroprotective and may be started prior to the development of disabling symptoms are not supported by clear clinical evidence.

5.1.1 LEVODOPA

Levodopa, the precursor of dopamine, has been used as the mainstay of treatment for Parkinson's disease since the early 1970s. It is given with a dopa decarboxylase inhibitor (DDI) to reduce the peripheral availability of levodopa and thereby reduce the adverse effects associated with treatment. Such combinations are often still described as levodopa monotherapy. Two levodopa/DDI combinations are widely available, co-beneldopa, which combines levodopa with benserazide, and co-careldopa, which combines levodopa with carbidopa.

The ELLDOPA trial compared the use of three doses of an immediate release carbidopa/levodopa combination (in a 1:4 ratio) and placebo over 40 weeks in 361 drug naïve patients with early PD.⁶⁷ There was an improvement in motor symptoms (measured by total UPDRS score, $p=0.001$) in all the levodopa treatment groups. Adverse effects (dyskinesia $p<0.001$, hypertonia $p=0.03$, infection $p=0.01$, nausea $p=0.001$, headache $p=0.03$) were increasingly associated with high-dose treatment and longer duration of treatment.

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The PDRG-UK trial recruited 782 patients with early disease. Duration of follow up at final assessment was 14 years in the 166 surviving participants.⁶⁸ Patients were randomised to the combination of DDI (benserazide) plus immediate release levodopa, DDI/levodopa (immediate release) plus selegiline or bromocriptine alone. The primary outcomes were mortality and motor disability. For the final follow up, health related quality of life and mental function were also assessed. After initial treatment for PD for 14 years patients commenced on levodopa appeared to have a sustained improvement in motor function (disability scores $p=0.05$, physical functioning $p<0.001$) compared with the dopamine agonist (DA) bromocriptine. Differences in mortality rates and prevalence of dyskinesias, motor fluctuations and dementia were not significantly different. The limitation in this trial was the loss of participants for the final analysis which included only 21% of the study total.

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Although the relative prevalence of dyskinesias with long term levodopa therapy may resemble that of dopamine agonists,⁶⁸ there is evidence that patients treated with levodopa therapy for four to six years have approximately a 40% likelihood of experiencing motor fluctuations and a 40% risk of dyskinesias.⁶⁹ Alternative therapeutic agents are often employed as first line treatment to delay starting levodopa and thereby reduce the onset of disabling dyskinesias. 1+ 3

Nausea and vomiting, common adverse effects of levodopa and DAs (see Annex 4), can be treated with domperidone, a peripheral D2 antagonist in a dose of 10-20 mg three times daily.⁷⁰ 1+

A Patients with early Parkinson's disease and motor symptoms may be considered for treatment with levodopa in combination with a dopa decarboxylase inhibitor.

- The lowest effective dose of levodopa should be used to minimise the incidence of adverse effects.

Impulse control disorders (ICDs) are uncommon with levodopa monotherapy. Pathological gambling and other ICDs may occur with dopamine dysregulation syndrome (DDS) where patients self escalate doses of levodopa and/or apomorphine to levels above those required to control motor symptoms and patients with DDS often exhibit severe dyskinesia and 'off' period dysphoria.⁷¹ 3

- Surveillance for dopamine dysregulation syndrome should be undertaken in patients receiving levodopa or intermittent apomorphine.

5.1.2 DOPAMINE AGONISTS

One meta-analysis, two systematic reviews and a number of RCTs have looked at the efficacy of DAs in early PD. Overall, dopamine agonists improve the motor symptoms in early disease with significant improvements in UPDRS total, motor, and activities of daily living (ADL) scores.

Randomised trials comparing the effectiveness of dopamine agonists with placebo in patients with early PD have shown a significant improvement in UPDRS scores for agonist-treated patients, in particular for part III motor examination scores.⁷²⁻⁷⁷ 1+ 1++

A meta-analysis of DA therapy in patients with early PD included 29 RCTs involving 5,247 participants.⁷⁸ Dopamine agonists were associated with fewer motor complications compared to levodopa but other important side effects were increased and people treated with agonists were more likely to discontinue treatment due to adverse events (odds ratio OR 2.49, 95% CI 2.08 to 2.98; p<0.00001). People randomised to a dopamine agonist were less likely to develop dyskinesia (odds ratio (OR) 0.51, 95% CI 0.43 to 0.59; p<0.00001), dystonia (OR 0.64, 95% CI 0.51 to 0.81; p=0.0002) and motor fluctuations (OR 0.75, 95% CI 0.63 to 0.90; p=0.002) compared with people treated with levodopa. The study suggested that motor symptom control was initially better with levodopa than dopamine agonists alone but direct comparison of the symptomatic effect on Parkinson's disease was difficult as data were inconsistent and incomplete. 1++

Two systematic reviews were identified. One compared bromocriptine to levodopa in patients with early PD⁷⁹ and the second compared a bromocriptine/levodopa combination to levodopa used alone in patients with early PD.⁸⁰ In both reviews the RCTs examined varied widely in terms of outcome measures, the methodology was inadequate in many studies and it was not possible to draw any firm conclusion from this body of evidence. 1+

The PDRG-UK trial which followed 166 surviving patients (21% of the original recruits) over a median of 14 years found that initial DA treatment provided no disease-modifying benefit when compared with levodopa and the reduced frequency in motor complications seen in the early stages of treatment was not sustained.⁶⁸ 1+

Rotigotine is available as a patch and this transdermal delivery system offers potential applications for people for whom the oral route is inappropriate. One RCT examined the efficacy of transdermal rotigotine in four treatment doses (ranging from 4.5 mg to 18 mg) compared with placebo in 242 people with early PD.⁸¹ Significant dose-related improvements in the motor and ADL UPDRS score between baseline and week 11 were found in the group treated with 13.5 mg ($p=0.001$) and 18 mg ($p<0.001$). Local skin reactions have been reported with this route of administration ($p=0.03$).⁸¹

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A Patients with early Parkinson's disease and motor symptoms may be considered for treatment with oral/transdermal dopamine agonists.

Adverse effects associated with dopamine agonists

Dopamine agonists may be classified as ergot derived (bromocriptine, pergolide and cabergoline) or non-ergot derived (apomorphine, pramipexole, ropinirole and rotigotine).

Ergot derived agonists are associated with a risk of:

- moderate to severe cardiac valvulopathy.⁸²⁻⁸⁴
- serosal fibrosis (pleural, pericardial and retroperitoneal).^{85,86}

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Ergot and non-ergot derived dopamine agonists are associated with an increased risk of:

- impulse control disorders including pathological gambling, binge eating and hypersexuality.^{71,87} One survey reported a lifetime risk of 13.7% for impulse control disorders in patients on dopamine agonists.⁸⁸ Young males and those with a history of mood disorder, alcohol abuse or obsessive compulsive disorder are particularly vulnerable.⁸⁹ There is no good evidence that ergot and non-ergot DAs differ in this regard nor that any individual agent carries a higher risk; therefore switching between agonists to control ICDs is not generally recommended.
- daytime somnolence compared to both placebo (relative risk, RR 4.98, 95% CI 1.79 to 13.89) and levodopa (2.06, 95% CI 1.47 to 2.88).⁹⁰ There is no strong evidence that ergot based agonists differ from non-ergots in this respect.⁹¹
- peripheral oedema compared with levodopa monotherapy in RCTs (pramipexole, OR 3.44 (95% CI 2.21 to 5.33); pergolide, OR 4.92 (95% CI 1.31 to 18.49); cabergoline, OR 4.22 (95% CI 2.22 to 8.04).⁷⁸
- other significant adverse symptoms including⁷⁸
 - nausea (OR 1.32, 95% CI 1.05 to 1.66, $p=0.02$)
 - dizziness (OR 1.45, 95% CI 1.09 to 1.92, $p=0.01$)
 - hallucinations (OR 1.69 95% CI 1.13 to 2.52, $p=0.01$)
 - constipation (OR 1.59, 95% CI 1.11 to 2.28, $p=0.01$).

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Transdermal dopamine agonist therapy (rotigotine) is associated with:⁸¹

- nausea ($p<0.001$)
- application site reactions ($p=0.03$)
- somnolence ($p=0.005$)
- fatigue ($p=0.01$).

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B Ergot derived dopamine agonists should not be used as first line treatment for Parkinson's disease.

- ☑ When an ergot derived dopamine agonist is used patients should undergo:
 - baseline echocardiographic screening and regular follow-up scans to identify cardiac abnormalities
 - baseline laboratory (eg erythrocyte sedimentation rate, serum creatinine) and radiological (eg chest X-ray) investigations with regular follow-up surveillance to identify serosal fibrosis.

A Patients should be warned about the potential for dopamine agonists to cause impulse control disorders and excessive daytime somnolence and be informed of the implications for driving/operating machinery.

Healthcare professionals should discuss impulse control disorders with patients with Parkinson's disease who are taking dopamine agonists.

5.1.3 MONOAMINE OXIDASE B INHIBITORS

Two meta-analyses^{92, 93} and two subsequent RCTs^{94, 95} addressed the effectiveness of monoamine oxidase B (MAO-B) inhibitors in treating people with early PD. Both meta-analyses showed a significant improvement in UPDRS scores in MAO-B inhibitor-treated patients.

A meta-analysis of 17 randomised controlled trials involving 3,525 patients compared the efficacy of MAO-B inhibitors and placebo or levodopa in the treatment of patients with early PD.⁹² MAO-B inhibitors provided a significant beneficial symptomatic effect compared with placebo. Early use of the MAO-B inhibitor, selegiline, delayed the need for levodopa compared with placebo (0.57, 95% CI 0.48 to 0.67; $p < 0.00001$). Selegiline also had a significant levodopa sparing effect when given simultaneously with levodopa. Motor fluctuations were less frequent in the MAO-B inhibitor group (0.75, 95% CI 0.59 to 0.95; $p = 0.02$). Withdrawal from treatment due to adverse events was significantly more common in the MAO-B inhibitor treated patients (2.16, 95% CI 1.44 to 3.23; $p = 0.0002$). 1++

In a second meta-analysis of 10 RCTs involving 2,422 people⁹³ MAO-B inhibitors did not delay disease progression in patients with early PD. A levodopa sparing effect (OR 0.53, 95% CI 0.36 to 0.79; $p = 0.01$) associated with a significant reduction in motor fluctuations but not dyskinesias was demonstrated (dyskinesia OR 0.98, 95% CI 0.76 to 1.26). There were significantly more withdrawals due to adverse events with MAO-B inhibitors (OR 2.36, 95% CI 1.32 to 4.20; $p = 0.004$). 1++

One RCT published after the meta-analyses, studied 56 patients with rasagiline as monotherapy compared with placebo.⁹⁴ No evidence of drug effect was noted with respect to the Clinical Global Impression of change scale (CGI), Hoehn and Yahr scale, Schwab and England ADL scale or BDI. No statistically significant differences were found in adverse effects between treatment and placebo groups. 1++

In a further double blind delayed start RCT (n = 404) patients were randomised to rasagiline 1 mg v rasagiline 2 mg for one year v matching placebo for six months followed by rasagiline 2 mg/day for six months.⁹⁵ People treated with rasagiline for 12 months showed less functional decline than those whose treatment was delayed for six months (total UPDRS score -2.29 units, 95% CI -4.11 to 0.48 units; $p = 0.01$). 1+

A Patients with early Parkinson's disease and motor symptoms may be considered for treatment with monoamine oxidase B inhibitors.

5.1.4 ANTICHOLINERGICS

A pooled analysis of effect could not be calculated from a systematic review of 221 patients in nine randomised trials comparing efficacy and tolerability of anticholinergics in the symptomatic treatment of patients with PD (compared to placebo or no treatment) due to variations in trial methodology and outcome measures.⁹⁶ The review suggested that anticholinergics were more effective than placebo in improving motor function in PD when used as monotherapy, or as an adjunct to other antiparkinsonian drugs but at the expense of neuropsychiatric and cognitive adverse events. 1+

Anticholinergics were associated with an increased frequency of neuropsychiatric and cognitive adverse events in comparison with placebo and should be used with caution particularly in those prone to cognitive impairment.⁹⁶ | 1+

B Anticholinergic drugs should not be used as first line treatment in patients with Parkinson's disease.

Anticholinergics should not be given to patients with comorbidities such as cognitive impairment or clinically significant psychiatric illness.

5.1.5 AMANTADINE

One systematic review was identified that included six RCTs involving 215 patients.⁹⁷ The included trials were small and some poorly conducted and the dose and frequency of amantadine used varied between studies. No evidence for the efficacy of amantadine in patients with early PD could be derived. | 1+

There is insufficient evidence to support the use of amantadine in the treatment of patients with early Parkinson's disease.

5.2 IMPACT OF AGE ON DRUG EFFICACY

Parkinson's disease predominantly affects older adults. The prevalence and incidence of idiopathic Parkinson's disease are both age related. The majority of those affected are aged over 65 at the time of diagnosis and up to 2% of people aged 80 and over have PD.⁹⁸ As people get older there is an increased likelihood of having concurrent comorbidities and receiving medications other than to treat their Parkinson's disease. | 3

The evidence for the relative efficacy of the various classes of antiparkinsonian drugs (MAO-B inhibitors, dopamine agonists, catechol-o-methyl transferase (COMT) inhibitors, amantadine and anticholinergics) between younger (<75 years at diagnosis) and older (≥75 years at diagnosis) patients with PD was examined. The extent to which comorbidity influenced treatment and outcome was also considered. In practice, the majority of RCTs did not differentiate effects between different age groups.

One study differentiated between patients under or over 70 years. This trial randomised 687 patients with PD and motor fluctuations who were on optimal levodopa treatment (± a dopamine agonist) to receive adjuvant therapy with the MAO-B inhibitor rasagiline (1 mg/day), the COMT inhibitor entacapone (200 mg with every dose of levodopa) or placebo.⁹⁹ Rasagiline reduced mean daily 'off' time (p=0.0001) and improved symptom control (p<0.0001) compared to baseline. The beneficial effect was not dependent on age (p=0.961) and not dependent on adjuvant use of dopamine agonists (p=0.852). | 1+

An RCT comparing cabergoline with levodopa examined adverse effects in those aged <65 years and those ≥65 years.¹⁰⁰ Adverse effects tended to occur with a higher frequency in the elderly (>65 years) than in the younger adults (aged <65 years) with the exception of headache and migraine. With cabergoline, certain adverse events (sleep disorder, somnolence and insomnia) tended to occur with a higher frequency in the older age group whilst the opposite was apparent for levodopa. Hallucinations occurred more frequently in the elderly in both cabergoline and levodopa groups. | 1+

The BNF notes that "antiparkinsonian drugs can cause confusion in the elderly. It is particularly important to initiate treatment with low doses and to increase the dose gradually"⁵ but the efficacy of the various treatments within different age groups is unclear. | 4

The relative efficacy of various antiparkinsonian drug groups should be studied in different age cohorts before a firm recommendation can be made.

5.3 IMPACT OF COMORBIDITIES ON DRUG EFFICACY

Some trials of drug therapy in patients with PD allowed concomitant treatment with stable dosages of antiparkinsonian treatment but little mention was made of concomitant illnesses or medications for other conditions. Patients with significant comorbidities are often excluded from drug trials. It is unclear to what extent existing comorbidities influence the effectiveness of different classes of drugs in the treatment of symptomatic PD.

5.4 TRIGGERS FOR INITIATING ADJUNCTIVE THERAPY

Many trials have looked at the addition of second line drugs in patients with PD. The majority of this evidence relates to commencing second therapies in those already on levodopa to treat levodopa-induced dyskinesias and motor fluctuations (see *section 5.5*). Some studies examine the effectiveness of combination therapy with levodopa against levodopa monotherapy to assess whether the levodopa-sparing potential of the combinations reduced the risk of subsequent motor complications. The newer dopamine agonists were initially licensed for adjunctive therapy to levodopa, and so much of the newer research focuses on this use.

Frequently the reason for initiating a second drug is unclear. There is no evidence to identify robust clinical indicators such as significant changes in symptoms, or changes in validated scores that could be used to help decide at what point those already commenced on non-levodopa treatment should start second line therapy.

Within a study, clinical experience is often used to decide when a patient's symptoms have worsened or that the effect of treatment has decreased so that they require adjunctive treatment. For example:

- in the TEMPO study "in making the determination of the need for levodopa the investigator was asked to consider the impact of PD symptoms on the ability of the research participant to remain employed, manage finances, carry out domestic responsibilities, and perform ADL".¹⁰¹
- in the DATATOP trial the authors reported adding further treatment "when, in the judgement of the enrolling investigator a subject reached a level of functional disability sufficient to warrant" the initiation of levodopa therapy.¹⁰²

Some studies use an arbitrary cut-off point of a 20% increase or decrease in UPDRS scores to assess failure or success of treatment, but in clinical practice the UPDRS would rarely be routinely scored, and would not necessarily be the most appropriate method of making treatment decisions.

There is no evidence on which to base a recommendation as to when to commence a second agent in patients already commenced on non-levodopa monotherapy.

- ☑ The decision to add levodopa to non-levodopa monotherapy should be taken on an individual basis, taking into account the patient's overall level of symptoms, both motor and non-motor, and the risk of adverse effects. An informed discussion with the patient is essential and with the carer and Parkinson's disease specialist nurse with experience of managing the patient is desirable.

5.5 PHARMACOLOGICAL MANAGEMENT OF MOTOR COMPLICATIONS

Almost all patients with PD, if treated with levodopa long enough, will develop loss of smooth motor control. A systematic review of case series reports that patients treated with levodopa therapy for four to six years have approximately a 40% likelihood of experiencing motor complications.⁶⁹ These range in severity from mild and non-disabling, to severely incapacitating. Early features are end of dose wearing off and levodopa-induced dyskinesias and may deteriorate to random fluctuations between the 'off' state (usually without dyskinesias) to the 'on' state complicated by dyskinesias.

There are three main strategies when managing motor complications:

- manipulation of oral/topical drug therapy
- more invasive drug treatments (such as apomorphine infusion or intraduodenal levodopa)
- neurosurgery, most commonly deep brain stimulation.

Only the first two approaches are within the remit of this guideline.

A variety of drug treatments have been suggested as helpful in managing motor complications. Much of the evidence is derived from carefully selected patient populations, and the results may not be easily generalised to the average 'real life' clinic population. Non-motor features, particularly psychiatric and cognitive problems, often limit the therapeutic options available, and patients are often susceptible to deterioration following even minor changes in their medications. Most of the trials followed patients for very short time periods.

As the disease advances, the management of patients (and their families) becomes increasingly complex, and may involve many different healthcare workers. The importance of good communication in such complex management cannot be overemphasised.

- ☑ Patients with complex and disabling motor complications should be assessed regularly by Parkinson's disease/movement disorder specialists. In the later stages of PD, as non-motor symptoms begin to dominate quality of life, the withdrawal of some drugs is often appropriate. These decisions should be made by specialists in combination with the patient and their carers.

5.5.1 MONOAMINE OXIDASE B INHIBITORS

Two MAO-B inhibitors are available, selegiline and rasagiline. A systematic review concluded that the use of MAO-B inhibitors in patients with motor fluctuations led to statistically significant reductions in UPDRS total scores compared to placebo (weighted mean difference, WMD -5.03, 95% CI -7.38 to -2.68; $p < 0.0001$).¹⁰³ Patients receiving MAO-B inhibitors also had greater reductions in UPDRS motor scores than those taking placebo (WMD -3.19, 95% CI -4.57 to -1.80; $p < 0.0001$). There was no significant difference in withdrawals due to adverse drug reactions between patients receiving MAO-B inhibitors and placebo, although the former group was reported as experiencing more dyskinesias (OR 1.84, 95% CI 1.17 to 2.89; $p < 0.0001$); Despite the statistical significance of the UPDRS score reductions, there is uncertainty regarding the clinical significance of the modest improvements recorded.

1++

Only one trial in this systematic review reported changes in 'on' time, favouring MAO-B inhibitors (mean difference (MD) 0.82, 95% CI 0.35 to 1.29; $p < 0.0001$, average improvement without troublesome dyskinesias 0.85 hour compared to placebo). Two trials reported changes in 'off' time, favouring MAO-B inhibitors with a statistically significant reduction compared to placebo (WMD 1.10, 95% CI 1.88 to 0.31; $p = 0.006$).

- A** Monoamine oxidase B inhibitors may be considered for the treatment of motor complications in patients with advanced Parkinson's disease.

Rasagiline is not recommended by the SMC for use within NHSScotland as adjuvant therapy (with levodopa) in PD patients with motor fluctuations, as there are no comparative data with selegiline which is less expensive, and thus the economic case has not been demonstrated.

5.5.2 ORAL AND TRANSDERMAL DOPAMINE AGONISTS

There is evidence from systematic reviews that the oral agonists cabergoline,¹⁰⁴ pramipexole¹⁰⁵ and pergolide¹⁰⁶ are modestly effective (reductions in daily 'off' times of between one to two hours) in the treatment of motor complications. There is insufficient evidence to support the use of bromocriptine.¹⁰⁷

1++

A systematic review concluded that ropinirole has similar effects to bromocriptine in the management of motor complications, but these trials did not include placebo arms.¹⁰⁸ A prolonged release preparation of ropinirole is also available, with evidence from one RCT that it may reduce daily 'off' time by almost two hours.¹⁰⁹ The use of ergot dopamine agonists (cabergoline, pergolide, bromocriptine) is complicated by concerns regarding fibrotic adverse effects and valvulopathies (see section 5.1.2).

1++

Transdermal rotigotine is effective in reducing daily 'off' time by almost two hours in patients with advanced PD.¹¹⁰ There is further evidence that rotigotine is as effective as oral pramipexole in the management of advanced PD, and both were significantly more effective than placebo in reducing daily 'off' time by one to two hours.¹¹¹

1+

In some of these studies there is a trend for more adverse events in the patients treated with agonists, and an increase in dyskinesias although data are inconsistent.

A Dopamine agonists (oral or transdermal) may be considered for the management of complications in patients with advanced Parkinson's disease. The non-ergot agonists (ropinirole, pramipexole, and rotigotine) are preferable to the ergot agonists.

5.5.3 APOMORPHINE

Apomorphine is a non-ergot dopamine agonist which is delivered subcutaneously.

A systematic review of RCTs indicated that intermittent subcutaneous apomorphine (dose range 2 to 6 mg), provides rapid and consistent rescue from 'off' episodes. The duration of effect is relatively short (up to 100 minutes).¹¹²

1+

No RCTs of continuous subcutaneous infusions were identified but a number of small, non-randomised, mainly retrospective studies indicated that continuous apomorphine infusions may reduce dyskinesias and increase 'on' time in patients with severe motor fluctuations. Infusion therapy is associated with a risk of serious adverse events and requires adequate back-up resources.¹¹³⁻¹²¹

3

A Intermittent subcutaneous apomorphine may be considered for the reduction in 'off' time in patients with advanced Parkinson's disease.

D Subcutaneous apomorphine infusions may be considered for the management of severe motor complications, but should only be provided in units with sufficient experience and resources.

5.5.4 CATECHOL-O-METHYL TRANSFERASE INHIBITORS

A systematic review of COMT inhibitors concluded that both entacapone and tolcapone are associated with statistically significant improvements in the UPDRS, compared to placebo in patients with advanced PD; however, there were uncertainties regarding the clinical relevance of the modest improvements recorded, and adverse effects (most commonly dyskinesias) led to more patients withdrawing than with placebo.¹⁰³ An earlier systematic review concluded that entacapone or tolcapone provide modest benefits for patients experiencing end of dose wearing off and fluctuating motor control, reducing daily 'off' time by about 1.5 hours.¹²² Tolcapone has been associated with fatal hepatic toxicity, and has strict licensing criteria and requires frequent blood monitoring.¹²²

1++

There are few trials that directly compare different medications to treat motor fluctuations but one trial that compared a COMT inhibitor with an MAO-B inhibitor found no difference between entacapone and rasagiline in the reduction in 'off' time.⁹⁹ | 1+

A Catechol-o-methyl transferase inhibitors may be considered for the reduction in 'off' time in patients with advanced Parkinson's disease who have motor fluctuations.

Entacapone should be used in preference to tolcapone.

5.5.5 AMANTADINE

A systematic review concluded there were insufficient data to confirm whether amantadine was helpful in the management of motor complications, particularly dyskinesias.¹²³ | 1++

Subsequently, two small RCTs have suggested a very modest, short-lasting effect on dyskinesias.^{124,125} | 1+

5.5.6 INTRADUODENAL GEL LEVODOPA

One crossover design, single blinded RCT comparing best oral medical treatment and gel levodopa delivered via infusion to the duodenum suggested better results with the infusion.¹²⁶ The study was small, only six weeks long and used non-standardised outcome measures. | 1-

A number of uncontrolled case series indicated reductions in 'off' time and better 'on' time, and that the delivery mechanism was safe and tolerable for most patients.¹²⁷⁻¹²⁹ | 3

There is insufficient evidence to support the routine use of intraduodenal levodopa. Intraduodenal levodopa is not recommended for use by the SMC.

5.5.7 ATYPICAL ANTIPSYCHOTICS

One RCT showed that clozapine reduced dyskinesias in patients with advanced PD. Clozapine is not licensed for this indication.¹³⁰ Low-dose (25 mg) quetiapine did not reduce dyskinesias in patients with PD.¹³¹ There is currently insufficient evidence to support the use of clozapine or quetiapine in the management of dyskinesias. | 1+

Patients who have impaired quality of life due to motor fluctuations, and who are not responding to alterations in their oral medication should be considered for their suitability for other therapies, such as apomorphine, intraduodenal levodopa, or surgery.

5.6 MANAGEMENT OF DAYTIME SLEEPINESS

Excessive daytime sleepiness (EDS) is common in patients with Parkinson's disease with prevalence rates ranging from 15% to 54%.¹³²⁻¹³⁴ | 3

The aetiology of daytime sleepiness and sleep attacks in Parkinson's disease is likely to be multifactorial with dopaminergic cell death, altered night-time sleep architecture and the effect of antiparkinsonian medication all thought to be associated.^{135,136} Increasing age is also associated with an increased risk of EDS.¹³³ | 3
4

Treatment of excessive daytime sleepiness should centre on finding a reversible cause such as depression, poor sleep hygiene, and drugs associated with altered sleep pattern. Dopaminergic drugs, and dopamine agonists in particular, have been associated with increased sleepiness in some patients.^{135,137} | 4

Five RCTs were examined which looked at the role of modafinil, a stimulant wake-promoting agent, (three studies) or melatonin, a hormone produced from the pineal gland, (two studies) in the treatment of daytime sleepiness.

One RCT examined the effect of modafinil (200-400 mg/day) over seven weeks in 20 patients with PD and found no significant improvement in EDS in PD compared with controls.¹³⁸ 1++

A second RCT looked at doses of 100 mg and 200 mg of modafinil in 12 patients with EDS. Although there was an improvement in the subjective Epworth Sleepiness Scale (ESS) in the treatment group compared with placebo (ESS of 3.42 ± 3.9 versus 0.83 ± 1.99), there was no change in the objective polygraphic maintenance of wakefulness test ($p=0.14$). This study contained small numbers (12 patients completed) and was of short duration (two 2-week blocks).¹³⁹ 1+

The third RCT used a treatment dose of modafinil 200 mg daily and examined 21 PD patients over a three-week treatment period. The ESS scores for the placebo group worsened from 16.0 ± 4.2 (mean \pm standard deviation) to 17.0 ± 5.1 and for the modafinil group improved from 17.8 ± 4.2 to 14.4 ± 5.7 ($p=0.039$). 1-

There was no significant difference in Clinical Global Impression of change.¹⁴⁰

Two RCTs assessed the role of melatonin. One crossover RCT assessed the effect of melatonin (5 mg and 50 mg doses) in 40 subjects with idiopathic PD and sleep disturbance over a 10-week period (two 2-week treatment periods). Although there was an improvement in the daytime sleepiness subscale of the General Sleep Disturbance Scale (GSDS) in those treated with 5 mg melatonin ($p<0.05$) there was no measurable change in other scales examined (ESS and Stanford Sleepiness Scale (SSS)).¹⁴¹ 1++

The second RCT assessed the effect of melatonin 3 mg *nocte* in 20 patients. This was a small study of short duration and there was no effect of the drug on daytime sleepiness.¹⁴² 1-

Management of excessive daytime sleepiness should centre on finding a reversible cause such as depression, poor sleep hygiene, and drugs associated with altered sleep pattern.

A Modafinil and melatonin are not recommended for the management of excessive daytime sleepiness associated with Parkinson's disease.

5.7 ORAL SUPPLEMENTS

Many patients seek alternative therapies as adjuvants to conventional treatment. As these are available without prescription and may be expensive it is important to establish the level of benefit or harm that these might confer. Coenzyme Q10 has been suggested to have neuroprotective properties which may delay or slow PD progression. Antioxidant therapies such as tocopherol (vitamin E) are proposed to offer protective benefit against free radical generation and possibly delay the progression of Parkinson's disease.

5.7.1 COENZYME Q10

Coenzyme Q10 is an essential co-factor in the electron transport chain and is a potent antioxidant in both mitochondria and lipid membranes.

One RCT studied the effects of coenzyme Q10 100 mg three times daily or placebo for a period of three months. It measured the symptomatic effects via changes of the sum score of the UPDRS parts 2 and 3 between the baseline and three months in 131 patients (all already receiving antiparkinsonian drugs).¹⁴³ There was no significant difference between groups ($p=0.82$). Reported adverse effects with coenzyme Q10 were not significantly different from that in the placebo group ($p=0.44$). The most frequently reported adverse effects in both placebo and coenzyme Q10 groups were viral infection, diarrhoea, acute hearing loss, night sweats, nausea and bronchitis. 1+

One small study of 80 patients examined coenzyme Q10 at doses of 300 mg, 600 mg and 1,200 mg against placebo.¹⁴⁴ The trial measured total change in the UPDRS score from the baseline to the last visit or until the patient needed treatment with levodopa. The primary analysis was a test for a trend between dosage and mean change in UPDRS score and was significant ($p=0.09$) according to prespecified criteria. A secondary outcome was comparison of each treatment group with placebo. The difference was significant for the 1,200 mg group ($p=0.04$), but not for the 300 mg or 600 mg groups.

1+

There is insufficient evidence to recommend treatment with coenzyme Q10 for patients with early PD.

5.7.2 TOCOPHEROL (VITAMIN E)

Tocopherol is a biologically active component of vitamin E that attenuates the effects of lipid peroxidation by trapping free radicals.

A large placebo controlled trial ($n=800$) investigated the effect of selegiline or tocopherol on slowing functional decline in patients with early, untreated Parkinson's disease.¹⁰² The primary end point was the onset of disability prompting the clinical decision to begin administering levodopa.

1++

Tocopherol treatment (regardless of selegiline administration) did not reduce the probability of reaching the end point (hazard ratio, HR 0.91, 95% CI 0.74 to 1.12, $p=0.35$). Tocopherol alone did not significantly reduce the risk of reaching the end point as compared with placebo (HR 0.92, 95% CI 0.70 to 1.22, $p=0.57$). There were no significant differences in the rate of change in secondary response variables between subjects assigned to tocopherol and those not assigned to tocopherol.

The trial revealed no evidence of any beneficial effects of tocopherol (2,000 iu/day) in either slowing functional decline or ameliorating the clinical features of Parkinson's disease.

A Tocopherol is not recommended for neuroprotection in patients with early Parkinson's disease.

5.8 TREATMENTS FOR ORTHOSTATIC HYPOTENSION

Orthostatic (postural) hypotension (OH) is the most frequently reported autonomic finding in idiopathic PD with an estimated prevalence of 20%.¹⁴⁵ Orthostatic hypotension is defined as a fall in blood pressure (BP) of at least 20 mm Hg systolic and 10 mm Hg diastolic within three minutes in the upright position. Characteristic symptoms of OH include light-headedness, visual blurring, dizziness, generalised weakness, fatigue, cognitive slowing, leg buckling and gradual or sudden loss of consciousness.

Patients with PD experiencing OH symptoms can suffer seriously compromised quality of life. Consequences of OH include increased cognitive decline, increased cardiovascular mortality and increased rates of overall mortality.¹⁴⁶

4

The evidence for pharmacological treatment of OH is drawn from a variety of diagnoses (not solely PD), eg multiple system atrophy (MSA), autoimmune autonomic neuropathy, diabetic autonomic neuropathy and pure autonomic failure. There is no specific scale for PD patients with orthostatic hypotension but the orthostatic domain of the Composite Autonomic Symptom Scale (COMPASS-OD), postural blood pressure testing and CGI were used as end points in the studies evaluated.

5.8.1 DOMPERIDONE

Domperidone antagonises peripheral D2 receptors and has been proposed as a treatment for OH. One small RCT (n = 13) investigated the use of domperidone and fludrocortisone.¹⁴⁷ Patients were randomly allocated to receive either domperidone 10 mg three times daily or fludrocortisone 0.1 mg in the morning and two placebo tablets at lunch and supper. Patients were crossed over to the alternative therapy after three weeks with one week washout period. Patients taking domperidone 10 mg three times a day demonstrated a significant change in the COMPASS-OD score (median score 6 [mean 7 ± SD 2]) compared with non-pharmacological therapy, (median score 9 [mean 9 ± SD 3]; p = 0.04).

1+

5.8.2 FLUDROCORTISONE

Fludrocortisone is a synthetic mineralcorticoid with minimal glucocorticoid effects. It increases renal sodium reabsorption and expands plasma volume through the renin aldosterone system. One small RCT (n = 13) investigated the use of fludrocortisone 0.1 mg/day and domperidone 10 mg three times a day.¹⁴⁷ Patients were randomly allocated to receive either fludrocortisone 0.1 mg in the morning and two placebo tablets at lunch and supper or domperidone 10 mg three times daily. Patients were crossed over to the alternative therapy after three weeks with one week washout period. Fludrocortisone 0.1 mg/day demonstrated a significant change in the COMPASS-OD score, (median score 6 [mean 6 ± SD 3]) compared with non-pharmacological therapy, (median score 9 [mean 9 ± SD 3]; p = 0.02).

1+

5.8.3 MIDODRINE

Midodrine is a vasopressor with antihypotensive properties. One RCT (n = 171) showed that 10 mg of midodrine three times daily significantly elevates the upright systolic BP in patients with OH compared with placebo (p < 0.001).¹⁴⁸ This is associated with an improvement in orthostatic light-headedness (p = 0.001). The midodrine group experienced adverse events (mostly pilomotor reactions, pruritis, paraesthesia, urinary retention and supine hypertension) more frequently than the placebo group (p = 0.001). The study duration was short (six weeks).

1+

Another RCT (n = 97) showed that 10 mg midodrine increased standing systolic blood pressure by 22 mm Hg compared with placebo (28%, p < 0.001).¹⁴⁹ Midodrine improved the following symptoms of OH compared to placebo: dizziness/light-headedness, weakness/fatigue, syncope, low energy level, impaired ability to stand and feelings of depression (p < 0.05). Adverse effects (mostly pruritis/tingling of the scalp) were reported by 22% of the placebo group versus 27% of the midodrine treatment groups. Supine hypertension was reported for 8% of the midodrine treated patients versus 1% for the patients taking placebo. The study duration was short (four weeks).

1+

5.8.4 PYRIDOSTIGMINE

Pyridostigmine is a cholinesterase inhibitor which enhances sympathetic activity by increasing acetylcholine in sympathetic synapses thus enhancing baroreflex mediated increases in systemic resistance.

One RCT (n = 58) evaluated the efficacy of a single 60 mg dose of pyridostigmine alone or in combination with 2.5 and 5 mg of midodrine compared with placebo.¹⁵⁰ It is not clear whether any of the subjects in the study had PD, however 17 patients had MSA. The primary end point of the fall in standing diastolic BP was significantly reduced with treatment compared to placebo (p = 0.02). There was a significant reduction in the fall in diastolic BP by pyridostigmine alone (BP fall of 27.6 mm Hg v 34.0 mm Hg with placebo; p = 0.04) and by pyridostigmine with 5 mg of midodrine hydrochloride (BP fall of 27.2 mm Hg v 34.0 mm Hg with placebo; p = 0.002). No significant differences were seen in the supine BP measures, either systolic (p = 0.36) or diastolic (p = 0.85) indicating that pyridostigmine did not increase supine BP.

1+

5.8.5 SUMMARY

There is insufficient evidence (due to a small number of studies, small sample sizes and short study duration) to make a recommendation on the use of domperidone, fludrocortisone, midodrine or pyridostigmine for the treatment of OH. Midodrine is an unlicensed drug and domperidone, fludrocortisone and pyridostigmine are used 'off label' in this indication.

5.9 GAIT DISORDERS

Bradykinesia, tremor and rigidity are the commonly recognised features of PD but, particularly later in the course of the disease, there are often other motor symptoms affecting mobility, notably freezing of gait (FOG), postural instability and falls (see *section 1.3*).

Falls are usually multifactorial (eg involving gait freezing, postural instability, postural hypotension, polypharmacy, poor vision, environmental factors, and cognitive impairment) and require a multidisciplinary approach in assessment and treatment.¹⁵¹

4

A systematic review of prospective studies involving falls estimated that 46% of PD patients fell over a three-month period.¹⁵² Falls have a high morbidity (physical and psychological), mortality, and social and financial cost.¹⁵¹

2++
4

Postural instability occurs later in PD, is usually not improved with additional dopamine replacement therapy and leads to an increased risk of falls.¹⁵³

4

5.9.1 TREATMENTS FOR GAIT DISORDERS

The mainstay of treatment for gait disorders is input from Parkinson's disease nurse specialists and allied health professionals such as physiotherapists, occupational therapists and podiatrists. These interventions are beyond the remit of this guideline but are covered in the NICE guideline on Parkinson's Disease.⁶⁶

4

Evidence for the pharmacological treatment of gait disorders is limited to interventions in gait freezing.

Gait freezing that occurs when a patient's parkinsonism is undertreated (so called 'off' freezing, ie in the presence of significant residual tremor, rigidity, or bradykinesia) may respond to an increase in dopaminergic replacement therapy.^{154,155} Gait freezing that occurs when the patient's parkinsonism is well controlled ('on' freezing) is difficult to treat and may be worsened by increasing dopamine replacement therapy.¹⁵⁵

1-
4

It has been suggested that MAO-B inhibitors prevent or improve gait freezing. A post hoc analysis of the DATATOP trial showed that after a mean follow up of 14 months patients who were randomised to selegiline had a 50% reduction in the relative risk of developing gait freezing compared to placebo.¹⁵⁶ This may not have been a specific effect of selegiline but rather a general effect of dopamine replacement therapy delaying 'off' freezing.

2+

Similarly, a post hoc analysis of the LARGO trial suggested that rasagiline but not entacapone produced a small (0.16 point in UPDRS gait freezing question) improvement in established gait freezing compared to placebo but this is unlikely to be clinically significant.⁹⁹

No published trials were identified that specifically addressed whether MAO-B inhibitors prevent gait freezing or improve established gait freezing. A prespecified substudy within a larger trial did analyse changes in the Freezing of Gait Questionnaire (FOG-Q) but has only been published in abstract form.¹⁵⁷ Both rasagiline and entacapone resulted in a statistically significant one point improvement in the FOG-Q compared to placebo but this is unlikely to be clinically significant and may be due to a reduction in 'off' gait freezing rather than a specific effect.

Trials of interventions to improve established gait freezing are restricted to L threo 3,4-dihydroxyphenylserine (L DOPS) and botulinum toxin. Two uncontrolled case series from Japan suggested that L DOPS, a precursor of noradrenaline, may improve gait freezing in parkinsonian patients.^{158,159} However, a small crossover trial in six people with gait freezing and parkinsonism showed no benefit of L DOPS over placebo although this study has only been published in abstract form.¹⁶⁰ No subsequent RCTs were identified.

3

Three very small short term randomised trials were identified (n = 38) which assessed the benefit of injecting botulinum toxin (A or B) into the calf muscles of one or both legs of PD patients with gait freezing.¹⁶¹⁻¹⁶³ None of the trials showed any clinically or statistically significant benefits with botulinum toxin in terms of severity of gait freezing, walking speed, UPDRS or quality of life and one was stopped early because those given the toxin appeared to have more falls.

1+

B Injection of botulinum toxin into the calf muscles of people with Parkinson's disease who have significant gait freezing is not recommended.

5.10 PHARMACOLOGICAL TREATMENT OF MENTAL HEALTH DISORDERS

Parkinson's disease is principally defined as a movement disorder. Non-motor deficits are also a significant part of the syndrome and contribute to the functional consequences of PD. Dementia, depression and psychosis can all develop in Parkinson's disease. This section considers the evidence relating to the pharmacological treatment of these mental health disorders.

5.10.1 DEMENTIA

Dementia is a common feature of later disease, with estimates of prevalence of between 24-31%.¹⁶⁴ One longitudinal study of 126 patients with PD found that over a period of three to five years, 10% developed dementia, while a further 57% showed some degree of impairment on neuropsychological tests.¹⁶⁵

3

Some medications used in the treatment of motor symptoms may have deleterious effects on cognition because they have anticholinergic effects.^{166,167} No evidence was identified that specifically examined the effect of withdrawal of antiparkinsonian therapies on dementia, but good practice dictates that the first line of action in relation to treatment of dementia in patients with PD is to ensure that other causes of cognitive impairment are ruled out (infection, dehydration, electrolyte imbalance, or subdural haemorrhage).^{166,167} This is particularly relevant to patients presenting with delirium (sudden onset of confusion or symptoms of psychosis), but is also important in relation to any patient presenting with new symptoms of confusion.¹⁶⁷

4

One small RCT investigated the effect of withdrawal of dopaminergic medication in nursing home patients with advanced parkinsonism and concluded that dopaminergic medication withdrawal may be a feasible way to reduce polypharmacy and potential medication-related adverse effects with a minimal risk of worsening motor deterioration.¹⁶⁸ The small sample size and differences in baseline levels of dementia and motor dysfunction between the control and experimental groups limit the conclusions that can be drawn from this study.

1-

Consideration should be given to exclusion of any central nervous system (CNS)-acting non-parkinsonian drugs such as antidepressants with antimuscarinic properties (eg, tricyclic antidepressants) and benzodiazepines. The withdrawal of anticholinergic medication, amantadine, selegiline and dopamine agonists can also be considered along with the optimisation of levodopa therapy (without causing psychosis). The aim is to maximise motor control, but minimise impact on cognition.^{48,167}

4
2++

Although no studies are reported that specifically evaluate these first line approaches to treating dementia in PD the guideline development group considers them to reflect good clinical practice. In a proportion of patients these approaches will not substantially improve cognition.

5.10.2 CHOLINESTERASE INHIBITORS

There is evidence to suggest a correlation between pathological changes in the cholinergic neurotransmitter system in PD and the level of cognitive impairment or presence of dementia,¹⁶⁷ suggesting possible therapeutic benefit from the use of cholinesterase inhibitors.

Several cholinesterase inhibitors have been studied in patients with PD,^{48,166,167,169,170} although most studies have used the drug rivastigmine.

1++
4

Four reviews concluded that rivastigmine should be considered in patients with mild to moderate dementia (Mini-Mental State Examination MMSE 10-24) and Parkinson's disease, but note that the magnitude of benefit is modest and tremor may be exacerbated and vomiting increased.^{48,166,169,170}

The largest study of 541 patients found small, but statistically significant, increases in performance on the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog; $p < 0.001$) and on the Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change (ADCS-CGIC; $p = 0.007$).¹⁷¹ In terms of activities of daily living (ADL), the Alzheimer's Disease Cooperative Study-ADL scale, there was a significant benefit ($p = 0.02$) for the rivastigmine group, but the effect size was small/medium.

1++
4

Rivastigmine, which is available in both tablet and transdermal patch forms, is licensed for the treatment of patients with Parkinson's disease and dementia but in the absence of a submission from the holder of the marketing authorisation, SMC has not recommended this drug for use in NHSScotland for the indication of Parkinson's disease alone.

Three small RCTs have examined the effects of donepezil.¹⁷²⁻¹⁷⁴ Two^{172,174} reported statistically significant improvements on MMSE score ($p = 0.013$ and 0.0044 respectively), whilst one¹⁷³ found no statistical improvement in MMSE score (but a significant improvement on the Dementia Rating Scale). The studies varied in terms of frequency of adverse side effects of donepezil. Two trials^{172,174} concluded that donepezil was well tolerated and did not worsen PD symptoms, whilst one reported very poor tolerance.¹⁷³

1+
1-

There is insufficient evidence to determine the effectiveness of galantamine or any other cholinesterase drugs.

The SIGN guideline on management of patients with dementia discusses the use of cholinesterase inhibitors further.¹⁷⁵

In patients with Parkinson's disease and cognitive impairment treatable causes of dementia should be investigated and, if present, treated.

The exclusion of any other non-parkinsonian drugs which act on the central nervous system, withdrawal of anticholinergic medication, amantadine, selegiline and dopamine agonists should be considered.

5.10.3 DEPRESSION

Depression is commonly reported in patients with PD (see section 4.4). Mood disorders including depression are thought to affect up to 50% of patients.¹⁷⁶ There is significant overlap in the common symptoms of depression, cognitive impairment and Parkinson's disease including social withdrawal, flattened affect, lack of motivation and reduced motor activity making diagnosis of depression difficult in patients with PD.

3

In depressed patients with PD the underlying mechanism for development of symptoms is poorly understood, though thought to be related to similar changes in serotonergic, adrenergic and dopaminergic pathways found in major depression. It has been suggested that depression in patients with PD may be related more to the underlying pathology associated with Parkinson's disease itself rather than a behavioural response to the psychosocial aspects of the illness.⁴⁸

2++

Evidence of an effective treatment for depression in patients with PD is limited. Three systematic reviews of pharmacological therapy have been identified but no trials were identified in relation to psychotherapy.

One systematic review included six RCTs, three comparing active treatment to placebo and three comparing two active treatments.⁴⁸ The review concluded that amitriptyline was effective in treating depression in patients with PD although this had to be balanced against its anticholinergic side effects. There was insufficient evidence to support the efficacy or lack of efficacy of any other antidepressant.

1++

A meta-analysis included 11 trials of which only two were placebo controlled; a particular problem for depression in patients with PD due to the large placebo effect. Results indicated significant reductions in depression ratings following both antidepressant treatment and placebo administration. There was no significant difference between these reductions ($p=0.44$).¹⁷⁷ 1+

Another systematic review of treatments for depression in patients with PD identified only three RCTs involving antidepressant drug therapy and none involving behavioural therapies.¹⁷⁸ The studies were small and of moderate quality and the review concluded that there was insufficient evidence to make recommendations in relation to treatment with antidepressants. 1++

A subsequent RCT compared desipramine (a tricyclic antidepressant) or citalopram (a selective serotonin reuptake inhibitor) to placebo. After 14 days, desipramine prompted an improvement in the MADRS score, compared with citalopram and placebo. Both antidepressants produced significant improvements in the MADRS score after 30 days. Mild adverse events were twice as frequent in the desipramine group as in the other groups.¹⁷⁹ 1+

In clinical practice a wide range of antidepressant medication is available with an established evidence base for the efficacy in treatment of major depressive illness although this has not been replicated within the limited range of studies in patients with depression in Parkinson's disease. It is not possible to make a specific recommendation for pharmacological treatment of depression in patients with PD. Whilst there is some evidence for the effectiveness of tricyclic antidepressants (amitriptyline and desipramine), the importance of this is offset by adverse effects and the short term follow up in the relevant RCTs.

5.10.4 PSYCHOSIS

Psychosis is one of the key neuropsychiatric features of PD and is associated with a significant degree of disability.¹⁸⁰ Psychosis describes a wide range of symptoms including hallucinations, delusions and paranoid beliefs. In PD, visual hallucinations are the most prevalent manifestation occurring in between 30% to 40% of hospital based patients.¹⁶⁷ Many of the drug treatments for PD can exacerbate psychosis and antipsychotic medication might worsen motor symptoms, making clinical management problematic. 2++

Whilst the neuropathological changes resulting in psychosis in PD are not well understood the primary modality of psychosis is visual hallucinations. It has been suggested that decreased cerebral activation in both occipital temporal parietal regions and frontal eye fields may be involved in altering visual attentional pathways.¹⁶⁷ 2++

Two systematic reviews relating to the treatment of psychosis and reducing the risk of drug-induced hallucinations and psychosis in patients with PD were identified. One systematic review included seven RCTs involving 419 patients.¹⁸¹ The trials compared the antipsychotics clozapine, quetiapine or olanzapine versus placebo. One trial compared clozapine versus quetiapine. Patients receiving clozapine improved significantly more than the placebo groups on the CGI change scale (weighted mean difference WMD -1.1, 95% CI -1.24 to -0.97; $p < 0.0001$). Patients receiving quetiapine showed no significant difference to placebo groups, although it was not possible to include data from these trials in a meta-analysis. Patients receiving olanzapine showed no significant difference to placebo groups (WMD 0.13, 95% CI -0.27 to 0.53; $p=0.52$). In the head-to-head comparison no significant difference was recorded between patients receiving clozapine or quetiapine (WMD -0.20, 95% CI -0.57 to 0.1). 1++

The other systematic review was published before the above study and did not include any trials that were not included in the later publication.⁴⁸ Its conclusions were similar to the later review. 1++

One RCT not included in either systematic review was identified.¹⁸² This compared the efficacy of quetiapine versus clozapine for the treatment of psychosis in 27 patients with PD. Both drugs were effective in treating psychotic symptoms as measured by CGI scale ratings though clozapine produced more improvement on specific measures relating to frequency of hallucinations and delusions. 1-

Clozapine is associated with agranulocytosis and regular monitoring of total white blood cell count and absolute neutrophil count is necessary for patients treated with this drug.¹⁸³ 4

In summary, olanzapine is not helpful in improving psychosis in PD and worsens motor symptoms. Clozapine is effective in treatment of psychosis and also, in some cases, improved motor function. Quetiapine produced some improvement in psychotic symptoms with no benefit over clozapine. Quetiapine is not licensed for the treatment of patients with psychosis in Parkinson's disease, however clozapine is licensed for this indication. Where patients are not distressed by hallucinations, given the fact that antipsychotic medication might worsen the motor symptoms, a clinical decision may be made either not to treat symptoms or rationalise dopaminergic therapy.

Before considering use of antipsychotic medications, other treatable causes of psychosis should be excluded.

A Patients with psychosis in Parkinson's disease should be considered for treatment with low-dose clozapine and undergo weekly monitoring for the first 18 weeks of treatment followed by fortnightly monitoring for the first year and then monthly thereafter.

B Where weekly monitoring of blood is not possible on a consistent basis, low-dose quetiapine should be considered as an alternative antipsychotic for the treatment of patients with psychosis in Parkinson's disease.

6 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing Parkinson's disease with patients and carers and in guiding the production of locally produced information materials.

6.1 SOURCES OF FURTHER INFORMATION

NATIONAL ORGANISATIONS SPECIFIC TO PARKINSON'S DISEASE

Parkinson's Disease Society (Scottish Office)

Forsyth House, Lomond Court, Castle Business Park
Stirling FK9 4TU
Tel: 01786 433811 • Helpline: 0808 800 0303
Email: pds.scotland@parkinsons.org.uk
Website: www.parkinsons.org.uk/scotland

This UK charity supports people with Parkinson's disease and their families. The helpline is a confidential service staffed by registered nurses and advisors who offer advice, information and support to anyone affected by Parkinson's disease. The society provides a range of books, information sheets and DVDs. A number of local support groups throughout Scotland are available to help patients and their carers meet with people in a similar situation.

Younger Parkinson's Network

Tel: 01656 663 284
E-mail: alunmorgan@btinternet.com
Website: www.yap-web.net

This is a self-help group within the Parkinson's Disease Society which provides a focus for the needs of younger people with Parkinson's.

OTHER NATIONAL ORGANISATIONS

Alzheimer Scotland – Action on Dementia

22 Drumsheugh Gardens
Edinburgh EH3 7RN
Tel: 0131 243 1453 • 24 hour free helpline: 0808 808 3000
Email: alzheimer@alzscot.org
Website: www.alzscot.org.uk

Alzheimer Scotland provides people with dementia, carers and families with information and practical advice.

Alzheimer's Society

Devon House, 58 St Katherine's Way
London E1W 1JX
Tel: 020 7423 3500 • Helpline: 0845 300 0336
Website: www.alzheimers.org.uk

The Alzheimer's Society provides people with dementia and carers with information to help them cope with every aspect of living with dementia. It offers a range of factsheets and booklets.

Carers Scotland

The Cottage, 21 Pearce Street
Glasgow, G51 3UT
Phone: 0141 445 3070
Website: www.carerscotland.org
E-mail: info@carerscotland.org

Carers Scotland provides information and advice to carers on all aspects of caring.

Citizens' Advice Scotland

1st Floor, Spectrum House
2 Powderhall Road
Edinburgh EH7 4GB
Website: www.cas.org.uk

Citizens' Advice Bureaux (CABs) are local independent charities that provide free, confidential and impartial advice to people who need it. Citizens' Advice Scotland is the umbrella body that provides support to local CABs and maintains a list of local offices on its website.

Crossroads Scotland

24 George Square
Glasgow G2 1EN
Tel: 0141 226 3793
Website: www.crossroads-scotland.co.uk

Crossroads provides practical support to carers.

Department for Work and Pensions (DWP)

www.dwp.gov.uk

The DWP website can give you details on benefits to which people with Parkinson's disease may be entitled.

DVLA Drivers Group

DVLA, Swansea SA99 1TU
Tel: 0870 600 0301
Email: eftd@dvla.gsi.gov.uk
Website: www.direct.gov.uk

You can give DVLA information about your medical condition (or conditions) by post, phone or fax, or by email using a questionnaire available on the website.

Lewy Body Society

Hudson House, 8 Albany St
Edinburgh EH1 3QB
Tel: 0131 473 2385
Email: info:lewybody.org
Website: www.lewybody.org

The Lewy Body Society offers a range of information sources for people with lewy body dementia and their families.

National Tremor Foundation

Harold Wood Hospital, Gubbins Lane
Romford, Essex RM3 0BE
Tel: (freephone) 0800 3288046 • Tel: 01708 386 399
Website: www.tremor.org.uk

Offers a support and advice service to people of all ages who have been diagnosed with a tremor of all types.

NHS 24

Tel: 0854 24 24 24

NHS 24 is a 24 hour nurse-led helpline providing confidential health-care advice and information.

Princess Royal Trust for Carers

Charles Oakley House, 125 West Regent Street
Glasgow G2 2SD
Tel: 0141 221 5066
Email: infoscotland@carers.org
Website: www.carers.org.uk

The Princess Royal Trust for Carers provides information, advice and support to Scotland's carers and young carers.

PSP Association

PSP House, 167 Waitling Street West
Towcester, Northamptonshire NN12 6BX
Tel: 01327 322410 • Fax: 01327 322412
Email: psp@pspeur.org
Website: www.pspeur.org

The PSP Association provides information and support to people affected by Progressive Supranuclear Palsy and Cortico Basal Degeneration and their families.

Samaritans

The Upper Mill, Kingston Road
Ewell, Surrey KT17 2AF
Tel: 020 8394 8300 • Fax: 020 8394 8301
Email: admin@samaritans.org
Website: www.samaritans.org.uk
Helpline: 08457 90 90 90

Email: jo@samaritans.org

Write to:

Chris
PO Box 90, Stirling FK8 2SA.

Samaritans is available 24 hours a day to provide confidential and emotional support for people who are feeling despair and distress.

Sarah Matheson Trust for Multiple System Atrophy

Southbank House, Black Prince Road
London SE1 7SJ
Tel: 0207 9404666
Email: office@msaweb.co.uk
Website: www.msaweb.co.uk

The Sarah Matheson Trust provides information and support to people and carers affected by multiple system atrophy and other autonomic conditions.

6.2 CHECKLIST FOR PROVISION OF INFORMATION

This section explains what information a person with confirmed or possible Parkinson's disease and their carer can reasonably expect to be provided with at key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

Parkinson's disease can be very traumatic for those with the condition and their families, in terms of symptoms, progression and changing dynamics within the family. To help families cope, they need support and reassurance from healthcare professionals and other sources, where appropriate. Information should be offered continuously throughout the patient journey by the appropriate member of the multidisciplinary team. This information should balance the need for people to have adequate time to consider potential changes in the condition and/or its treatment before they happen with the need to avoid unnecessary concern. Healthcare professionals should use their judgement to assess the level and pace of information required at each stage. A narrative review which identifies some of the issues with which people with Parkinson's disease are concerned is included in section 3.

When Parkinson's disease is suspected

- Ensure the person with suspected Parkinson's disease understands the importance of being referred to a specialist before any treatment is started.
- Inform the person with possible Parkinson's disease of the difficulty of diagnosing the condition. Discuss parkinsonism with the person and their carer, advising them that their symptoms may also be symptoms of other disorders.

Diagnosis

- Emphasise to the person with a probable or confirmed diagnosis of Parkinson's disease that the condition affects individuals differently and not all patients will experience all symptoms.
- Remind the person with a probable diagnosis of Parkinson's disease of the difficulty of confirming the diagnosis. Discuss parkinsonism with the person and their carer, reminding them that their symptoms may also be symptoms of other disorders and that the diagnosis may change in future.
- Acknowledge the fear that the person and their carer may be experiencing and ensure they have a continuing point of contact for relevant sources of support, eg Parkinson's disease nurse specialist or voluntary organisations (listed in section 6.1)
- Address any misconceptions that the person and their carer may have and explore their understanding of the disease through targeted questioning, such as:
 - "What do you know about Parkinson's disease?"
 - "What do you want to know?"

Address any anxieties which patients and carers may have by providing information which addresses the following questions:

- "Why me?"
- "How will I cope?"
- "Will I be able to work?"
- "What will I tell my family and friends?"
- "What will the condition do to my relationships?"
- "Will I die because of the condition?"
- "Who will look after me if I can no longer look after myself?"
- Ensure that the person and their carer understand that Parkinson's disease is not contagious.
- Ensure that if the person and their carer are concerned about the risk of passing Parkinson's disease on, they have an understanding of the small number of cases that have genetic links. Offer reassurance that the probability of passing the disease on is very small.

The following carer issues should be discussed, as appropriate:

- expectations
 - impact on families and relationships
 - stress and coping abilities associated with changing/loss of roles
 - sources of support (see *section 6.1*)
 - availability and help offered by social services
 - availability of respite care.
- Ensure that driving issues such as insurance and the need to inform the DVLA are discussed.
- The following practical needs should also be discussed with the person and their carer:
 - financial issues and where to get advice (see *section 6.1*)
 - employment issues and the availability of Disability Employment Advisors.

Treatment

- Remind the person and their carer that everyone with Parkinson's disease will have different symptoms and that they may respond differently to treatment.
- Ensure that the person and their carer understand that Parkinson's disease is a progressive condition, that it does not have a cure and that the aim of treatment is to control symptoms/improve quality of life.
- Inform the person and their carer that they will receive ongoing treatment and that their condition and care will be regularly reviewed.
- Inform the person and their carer that their care will be delivered by a multidisciplinary team, in consultation with them and their carer.
- Discuss the treatment options and ensure that the person and their carer are involved in making decisions about their medication and other treatments.
- Ensure that the person and their carer are offered verbal and/or written information on drugs they are considering.
- Advise the person and their carer to be cautious when accessing internet sites for information and highlight the websites listed in *section 6.1*.
- Discuss adverse effects of medication and emphasise to the person and their carer that medication should not be stopped if adverse effects occur. Encourage the person and their carer to seek advice from their healthcare professional if adverse effects are experienced.
- Emphasise to the person and their carer the importance of informing their specialist of medication prescribed for other conditions, and any herbal or complementary treatments being used to avoid interactions with antiparkinsonian medication.
- Ensure that the person and their carer are fully aware of other options, eg physiotherapy, speech and language therapy and occupational therapy, and advise them of the referral process – eg self referral may be an option in some localities.
- Encourage the person and their carer to advise healthcare professionals of non-motor symptoms experienced, including mental health symptoms (eg depression, compulsive behaviours, hallucinations, etc). Highlight the availability of the non-motor symptoms questionnaire from the Parkinson's Disease Society's website which can help patients report symptoms to healthcare professionals. If patients ask for specific information on non-motor symptoms eg dementia, this should be offered.

Palliative Care

- Create awareness of palliative care teams and advise the person and their carer that they can self refer or be referred by a healthcare professional.
- Inform the person and their carer that the goal of palliative care is to achieve the best quality of life and that it seeks neither to shorten nor prolong life.
- Ensure that the person and their carer have the opportunity to discuss their feelings if they are moving from their own home to live in a care home or hospital, reassure them that they can still access the specialist Parkinson's disease team and give details about how to do this.
- The following issues should be addressed:
 - fear (for the person, their carer and family)
 - guilt
 - end of life issues, eg choice about where to live and die and decisions about treatment.

7 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

7.1 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

The guideline development group did not identify any significant resource implications associated with the key recommendations.

7.2 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The guideline development group has identified the following as key points to audit to assist with the implementation of this guideline:

Recommendation	Audit point	Options
C Patients with suspected Parkinson's disease should be referred untreated to a hospital clinician with sufficient expertise in movement disorders to make the diagnosis.	Was the patient referred untreated to a hospital clinician with sufficient expertise in movement disorders to make a diagnosis?	<i>Record drug class if treatment has already started</i>
A Patients with early Parkinson's disease and motor symptoms may be considered for treatment with levodopa in combination with a dopa decarboxylase inhibitor.	What drug classes were used to treat patients with motor symptoms in early disease?	<i>Recommended</i>
A Patients with early Parkinson's disease and motor symptoms may be considered for treatment with oral/transdermal dopamine agonists.		<ul style="list-style-type: none"> ▪ Levodopa (with DDI), ▪ Non-ergot dopamine agonists (oral or transdermal), ▪ MAO-B inhibitors
A Patients with early Parkinson's disease and motor symptoms may be considered for treatment with monoamine oxidase B inhibitors.		Not recommended
B Anticholinergic drugs should not be used as first line treatment in patients with Parkinson's disease		<ul style="list-style-type: none"> ▪ Anticholinergics ▪ Amantadine ▪ Ergot derived dopamine agonists
B Ergot derived dopamine agonists should not be used as first line treatment for Parkinson's disease.		

A	Patients should be warned about the potential for dopamine agonists to cause impulse control disorders, excessive daytime somnolence and the implications for driving/operating machinery.	Was appropriate information provided to patients prescribed dopamine agonists?	<i>Record provision of information:</i> <ul style="list-style-type: none"> ▪ Discussion with medical staff ▪ Discussion with nursing staff ▪ Written material ▪ Website ▪ Other
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7.3 ADVICE TO NHSSCOTLAND FROM THE SCOTTISH MEDICINES CONSORTIUM

The Scottish Medicines Consortium has issued guidance on the following medications.

Rasagiline is not recommended for use within NHSScotland for the treatment of idiopathic Parkinson's disease as adjunct therapy (with levodopa) in patients with end of dose fluctuations (November 2006). Rasagiline reduces 'off' time in patients with Parkinson's disease and end of dose fluctuations on levodopa, similar to reductions shown with the less effective of two currently marketed catechol-o-methyl transferase inhibitors. The economic case has not been demonstrated.¹⁸⁴

Ropinirole 2 mg, 4 mg, 8 mg prolonged-release tablets (Requip® XL) are accepted for use in NHSScotland for the treatment of idiopathic Parkinson's disease in patients already taking ropinirole immediate-release tablets and in whom adequate symptomatic control has been established (August 2008).¹⁸⁵

Levodopa, carbidopa and entacapone combination (Stalevo®) is accepted for use in NHSScotland for the treatment of patients with Parkinson's disease and end of dose motor fluctuations not stabilised on levodopa/dopa decarboxylase inhibitor treatment (January 2004).¹⁸⁶

Rivastigmine (Exelon) is not recommended for use within NHSScotland for the treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease (July 2006).¹⁸⁷ The holder of the marketing authorisation has not made a submission to SMC regarding this product in this indication.

Co-careldopa intestinal gel (Duodopa®) is not recommended for use within NHSScotland for the treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyperkinesia/dyskinesia when available combinations of medicinal products for Parkinson's disease have not given satisfactory results (September 2006).¹⁸⁸ In the pivotal study an increase in 'on' time was achieved compared with individually optimised conventional combinations of Parkinson's disease medication. However, the economic case has not been demonstrated.

Further information is available from the SMC website www.scottishmedicines.org.uk

8 The evidence base

8.1 SYSTEMATIC LITERATURE REVIEW

8.1.1 QUANTITATIVE SEARCH PARAMETERS

The literature review for this guideline addressed a set of key questions defined by the guideline development group. Searches were carried out for the period 1998-2008, with some covering the period 1980-2008. Databases used were the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, CINAHL, Embase, Medline and PsychINFO. A search of key terms and key sites was also carried out on the Internet. A copy of the Medline version of the main strategy will be included in the "supporting materials" section of the SIGN website after publication. Members of the guideline development group contributed additional literature.

The searches identified 2,448 papers of potential interest. Of these 640 were identified as having the potential to form part of the evidence base and were reviewed in detail.

8.1.2 IDENTIFYING QUALITATIVE EVIDENCE

A literature search was carried out covering the databases CINAHL, Embase, Medline, and PsychINFO for the period 1998-2008. This search focused on the identification of qualitative literature relevant to the following themes in Parkinson's disease: communication, information needs, family/carer needs, attitudes to drug therapy, non-motor symptoms and multidisciplinary team working. A copy of this search strategy is available on the SIGN website.

The initial result from this search was 597 references. An initial sift of the results aimed at removing clearly irrelevant papers and focusing on research journals reduced this number to 55 references.

Two pairs of reviewers independently reviewed this list of abstracts to identify relevant papers. At the end of this process, the number of papers considered to be of relevance was reduced to 10.

Each pair of reviewers was then asked to identify themes that emerged from the joint list of selected papers, and to pick out papers that they thought represented the key issues underlying each theme. These papers were reviewed for methodological quality using the Critical Appraisals Skills Programme (CASP) checklist developed by the Public Health Resource Unit, Oxford. At the conclusion of this process the papers included as evidence were split into six themes: communication, information needs, family/carer needs, attitudes to drug therapy, non-motor symptoms and multidisciplinary team working.

8.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline. The following areas for further research have been identified:

- identification of disease modifying treatments for PD.
- identification of more sensitive and specific investigations for the diagnosis of PD.
- characterisation of the monogenic forms of parkinsonism in more detail, specifically with regard to genetic counselling for families.
- are some monogenic forms of parkinsonism distinct from what is considered to be idiopathic PD?
- identification of more effective treatments for the management of motor complications and for cognitive/psychiatric/other non-motor symptoms.
- comparison of rasagline and selegiline in early and advanced PD.
- examination of the impact of age on efficacy of antiparkinsonian drugs.
- identification of better strategies for prognostic modelling to help inform patients and their carers.
- identification of the most efficient, and cost effective model of delivering health care to patients with PD in the UK.

9 Development of the guideline

9.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in “SIGN 50: A Guideline Developer’s Handbook”, available at www.sign.ac.uk

9.2 THE GUIDELINE DEVELOPMENT GROUP

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Dr Graeme Macphee (Secretary)	<i>Consultant in Medicine for the Elderly, Southern General Hospital, Glasgow</i>
Ms Juliet Brown	<i>Information Officer, SIGN</i>
Dr Carl Counsell	<i>Consultant Neurologist, University of Aberdeen</i>
Dr Richard Davenport	<i>Consultant Neurologist, Western General Hospital, Edinburgh</i>
Mr Phillip Dry	<i>Patient representative, Greenock</i>
Mr Alan Dunbar	<i>Patient representative, Edinburgh</i>
Professor Jonathan Evans	<i>Professor of Applied Neuropsychology, Gartnavel Hospital, Glasgow</i>
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Dr Graeme Simpson	<i>Consultant in Geriatric Medicine, Royal Alexandra Hospital, Paisley</i>
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Ms Carol Vennard	<i>Parkinson’s Disease Nurse Specialist, Southern General Hospital, Glasgow</i>

THE NARRATIVE REVIEW SUBGROUP

Dr Derek Jones (Co-Chair)	<i>Lecturer in Occupational Therapy, Queen Margaret University, Edinburgh</i>
Dr Moray Nairn (Co-Chair)	<i>Programme Manager, SIGN</i>
Dr Kieran Breen	<i>Director of Research and Development, Parkinson's Disease Society, London</i>
Mr Phillip Dry	<i>Patient representative, Greenock</i>
Mr Alan Dunbar	<i>Patient representative, Edinburgh</i>
Dr Edwin Robertson	<i>General Practitioner, Alexandria</i>
Ms Shona Scott	<i>Parkinson's disease Nurse Specialist, Royal Alexandra Hospital, Paisley</i>
Ms Carol Vennard	<i>Parkinson's disease Nurse Specialist, Southern General Hospital, Glasgow</i>

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive. Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive.

9.3 CONSULTATION AND PEER REVIEW**9.3.1 NATIONAL OPEN MEETING**

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held on 18 September 2008 and was attended by 131 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

9.3.2 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewer's comments.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Association of British
Neurologists, and
Royal College of Physicians,
London

Mrs Jean Ballantyne	<i>Scottish Council Chair, Parkinson's Disease Society, Fife</i>
Mrs Margo Biggs	<i>Volunteer member, Local Advisory Council, Falkirk</i>
Dr Richard Coleman	<i>Consultant Neurologist, Aberdeen Royal Infirmary</i>
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9.3.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows:

Dr Keith Brown	<i>Chair of SIGN; Co-Editor</i>
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Dr Rod Gibson	<i>Consultant Neuroradiologist, Western General Hospital, Edinburgh</i>
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Abbreviations

ADAS-cog	Alzheimer's Disease Assessment Scale-Cognitive
ADCS-CGIC	Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change
ADL	Activities of Daily Living
BDI	Beck Depression Inventory
BNF	British National Formulary
BP	blood pressure
CGI	Clinical Global Impression of change scale
CI	confidence interval
CNS	central nervous system
COMPASS-OD	Composite Autonomic Symptom Scale
COMT	catechol-o-methyl transferase
CT	computed tomography
DA	dopamine agonist
DATATOP	Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism trial
DDI	dopa decarboxylase inhibitor
DDS	dopamine dysregulation syndrome
DLB	dementia with Lewy bodies
DSM	Diagnostic and Statistical Manual of Mental Disorders
EDS	excessive daytime sleepiness
ELLDOPA	Earlier versus Later Levodopa Therapy in Parkinson Disease trial
ESS	Epworth Sleepiness Scale
FOG	freezing of gait
GDS	Geriatric Depression Scale
GP	general practitioner
GSDS	General Sleep Disturbance Scale
HADS	Hospital Anxiety and Depression Scale
Ham-D	The Hamilton Depression Rating Scale
ICD	impulse control disorder
¹²³I-FP-CIT	N- ω -fluoropropyl-2 β -carboxymethoxy-3 β -(4-iodophenyl)tropane
LARGO	Lasting effect in Adjunct therapy with Rasagiline Given Once daily trial
L DOPS	L threo 3,4,dihydroxyphenylserine
LID	levodopa induced dyskinesias
LR	likelihood ratio
LRRK2	leucine-rich repeat kinase 2

MADRS	Montgomery-Asberg Depression Rating Scale
MAO-B	monoamine oxidase B
MD	mean difference
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
MSA	multiple system atrophy
MTA	multiple technology appraisal
NHS QIS	NHS Quality Improvement Scotland
NICE	National Institute for Health and Clinical Excellence
OH	orthostatic (postural) hypotension
OR	odds ratio
PD	Parkinson's disease
PDRG-UK	Parkinson's Disease Research Group of the United Kingdom trial
PET	positron emission tomography
PSP	progressive supranuclear palsy
RCT	randomised controlled trial
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SPC	summary of product characteristics
SPECT	single photon emission computed tomography
SSS	Stanford Sleepiness Scale
TEMPO	Rasagiline Mesylate [TVP-1012] in Early Monotherapy for Parkinson's Disease Outpatients trial
UPDRS	Unified Parkinson's Disease Rating Scale
UPSIT	University of Pennsylvania Smell Identification Test
WMD	weighted mean difference

Annex 1

Key questions used to develop the guideline

DIAGNOSIS	
Key question	See guideline section
<p>1. In patients with suspected Parkinson's disease, what is the sensitivity and specificity of:</p> <ul style="list-style-type: none"> ▪ Clinical expert diagnosis in early and late stages of PD v post mortem reference standard? ▪ UK brain bank criteria in early and late stages of PD v post mortem reference standard? ▪ Gelb criteria in early and late stages of PD v post mortem reference standard? ▪ Clinical expert diagnosis v research criteria (UK Brain Bank or Gelb) in early and late stages of PD? 	4.1
<p>2. What is the diagnostic accuracy of diagnoses carried out by:</p> <ul style="list-style-type: none"> ▪ A generalist in a secondary care setting v a specialist? ▪ A general practitioner in a primary care setting v a specialist? 	4.2
<p>3. In patients with suspected parkinsonism, what is the diagnostic accuracy (sensitivity, specificity, likelihood ratios) of functional imaging (PET, SPECT, (using FP-CIT or TRODAT-1), fMRI) for the differential diagnosis of idiopathic PD from other conditions (drug-induced PD, degenerative PD, vascular PD, essential tremor, dementia with lewy bodies (DLB), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), dystonia or Wilson's disease)?</p>	4.3.1
<p>4. In patients with suspected parkinsonism, what is the diagnostic accuracy (sensitivity, specificity, likelihood ratios) of structural imaging of the brain (CT, MRI, transcranial ultrasound) for the differential diagnosis of idiopathic PD from other conditions (drug induced PD, degenerative PD, vascular PD, essential tremor, dementia with lewy bodies (DLB), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), dystonia or Wilson's disease)? (Consider: primary and secondary care)</p>	4.3.2
<p>5. In patients with suspected parkinsonism, what is the diagnostic accuracy (sensitivity, specificity, likelihood ratios) of:</p> <ul style="list-style-type: none"> ▪ acute dopaminergic challenge testing (1 dose only?) ▪ a trial of chronic dopaminergic testing (minimum period of trial?) <p>for the differential diagnosis of idiopathic PD from other conditions (drug induced PD, degenerative PD, vascular PD, essential tremor, dementia with lewy bodies (DLB), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), isolated gait disorder)?</p>	4.3.3

6. In patients with suspected parkinsonism, what is the diagnostic accuracy (sensitivity, specificity, likelihood ratios) of olfactory testing for the differential diagnosis of idiopathic PD from other conditions (essential tremor, vascular Parkinsonism, MSA)?	4.3.4
7a) What is the prevalence of monogenic forms of Parkinson's disease?	4.5
7b) What is the value of genetic testing to patients and relatives (positive consequences, eg certainty of diagnosis, reassurance if negative and negative consequences, eg guilt over risk to future generations, continued uncertainty if test negative, children living with risk if test positive)?	Referred to narrative review, but no evidence identified
8. In patients with Parkinson's disease, what are the diagnostic criteria for depression (positive/negative predictive values of rating scales compared to ICD criteria)?	4.4.1
PHARMACOLOGICAL MANAGEMENT	
Key question	<i>See guideline section</i>
9. What is the relative efficacy of various antiparkinsonian treatments (levodopa, dopamine agonists, anticholinergics, COMT inhibitors, MAO-B inhibitors and amantadine) for patients with Parkinson's disease in the following subgroups as measured by improvement in validated ratings scales: <ul style="list-style-type: none"> ▪ younger (< 75 at diagnosis) ▪ older (> 75 at diagnosis) What are the adverse effects associated with each?	5.1, 5.2 and 5.5
10. In patients with suspected PD what are the benefits and risks as measured by changes in validated ratings scales associated with instigating treatment with antiparkinsonian drugs (levodopa, dopamine agonists, anticholinergics, COMT inhibitors, MAO-B inhibitors and amantadine), at different time points: <ul style="list-style-type: none"> ▪ instigating treatment immediately (under 1 year from diagnosis)? ▪ waiting for one year or longer? ▪ delaying treatment until "functional impairment"? 	5.2
11. In patients with Parkinson's disease, what is the evidence for the benefit of oral nutritional supplements (eg vitamins, coenzyme Q10) – in terms of an improvement in validated ratings scales or reduction in symptom severity or reduction in dyskinesia?	5.7
12. In patients with Parkinson's disease what is the evidence of adverse effects associated with ergot (eg bromocriptine, pergolide, lisuride, and cabergoline) v non-ergot (eg ropinirole and pramipexole) dopamine agonists and levodopa; <ul style="list-style-type: none"> ▪ fibrotic effects ▪ impulse control disorders ▪ sleep disorder? 	5.1.2
13. In patients with Parkinson's disease on non-levodopa monotherapy early in the disease what symptoms prompt addition of second/rescue medication (levodopa)?	5.4

14. In patients with Parkinson's disease who have developed motor complications, what therapeutic strategies are effective in reducing these and dyskinesia, as measured by change in motor scores, and improving QoL?	5.5
15. What is the effectiveness of treatments for symptomatic postural hypotension in patients with Parkinson's disease: <ul style="list-style-type: none"> ▪ head up bed tilt ▪ fludrocortisone ▪ midodrine or other adrenergic drugs ▪ pyridostigmine ▪ domperidone 	5.8
16. Is there an effective pharmacological treatment for reducing daytime sleepiness in patients with Parkinson's disease? (eg modafanil, amantadine, selegiline?)	5.6
17. In patients with Parkinson's disease, is there any evidence for effective pharmacological treatment of gait disorders such as falls, freezing, gait initiation, hesitancy or postural instability?	5.9
18. In patients with Parkinson's disease developing early cognitive impairment, is there any evidence that either starting treatment with a cholinesterase inhibitor, or withdrawing dopaminergic therapy, leads to symptomatic improvement in cognitive function?	5.10.2
19. In patients with Parkinson's disease and depression, is there evidence that antidepressant therapy is superior to non-drug treatment in improving quality of life and/or depression scores?	5.10.3
20. In patients with Parkinson's disease with psychosis, is adding an atypical antipsychotic to antiparkinsonian medication better than reducing antiparkinsonian medication in terms of improving psychiatric symptoms without worsening motor symptoms?	5.10.4
21. How can the risk of drug induced hallucinations and psychosis be minimised in patients with Parkinson's disease?	5.10.4

Annex 2

Research criteria for diagnosis of Parkinson's disease

UK PARKINSON'S DISEASE SOCIETY BRAIN BANK CRITERIA

Step 1: Diagnosis of a parkinsonian syndrome

- Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
- And at least one of the following:
 - muscular rigidity
 - 4-6 Hz rest tremor
 - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.

Step 2: Exclusion criteria for Parkinson's disease. None of the following should be present:

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski's sign
- Presence of cerebral tumour or communicating hydrocephalus on CT scan
- Negative response to large doses of levodopa (if malabsorption excluded)
- MPTP exposure.

Step 3: Supportive criteria for Parkinson's disease (three or more required for diagnosis of definite Parkinson's disease)

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of 10 years or more

GELB CRITERIA

Group A features: characteristic of PD

- Resting tremor
- Bradykinesia
- Rigidity
- Asymmetric onset.

Group B features: suggestive of alternative diagnoses

- Features unusual early in the clinical course
 - Prominent postural instability in the first 3 years after symptom onset
 - Freezing phenomena in the first 3 years
 - Hallucinations unrelated to medications in the first 3 years
 - Dementia preceding motor symptoms or in the first year.
- Supranuclear gaze palsy (other than restriction of upward gaze) or slowing of vertical saccades
- Severe, symptomatic dysautonomia unrelated to medications
- Documentation of a condition known to cause parkinsonism and plausibly connected to the patient's symptoms (such as suitably located focal brain lesions or neuroleptic use within the past 6 months).

Criteria for POSSIBLE diagnosis of Parkinson's disease

At least 2 of the 4 features in Group A are present; at least 1 of these is tremor or bradykinesia

and;

either none of the features in Group B is present

or symptoms have been present for less than 3 years, and none of the features in Group B is present to date

and;

either substantial and sustained response to levodopa or a dopamine agonist has been documented

or patient has not had an adequate trial of levodopa or dopamine agonist.

Criteria for PROBABLE diagnosis of Parkinson's disease

At least 3 of the 4 features in Group A are present

and;

none of the features in Group B is present (note: symptom duration of at least 3 years is needed to meet this requirement)

and;

substantial and sustained response to levodopa or a dopamine agonist has been documented.

Criterion for DEFINITE diagnosis of Parkinson's disease

post mortem confirmation

Annex 3

Non-motor symptoms questionnaire



Parkinson's
Disease Society

Non-motor symptoms Questionnaire

Name: Date: Age:

Centre ID:

Male

Female

NON-MOVEMENT PROBLEMS IN PARKINSON'S

The movement symptoms of Parkinson's are well known. However, other problems can sometimes occur as part of the condition or its treatment. It is important that the doctor knows about these, particularly if they are troublesome for you.

A range of problems is listed below. Please tick the box 'Yes' if you have experienced it during the past month.

The doctor or nurse may ask you some questions to help decide. If you have not experienced the problem in the past month tick the 'No' box. You should answer 'No' even if you have had the problem in the past but not in the past month.

Have you experienced any of the following in the last month?

	Yes	No		Yes	No
1 Dribbling of saliva during the daytime.	<input type="checkbox"/>	<input type="checkbox"/>	16 Feeling sad, 'low' or 'blue'.	<input type="checkbox"/>	<input type="checkbox"/>
2 Loss or change in your ability to taste or smell.	<input type="checkbox"/>	<input type="checkbox"/>	17 Feeling anxious, frightened or panicky.	<input type="checkbox"/>	<input type="checkbox"/>
3 Difficulty swallowing food or drink or problems with choking.	<input type="checkbox"/>	<input type="checkbox"/>	18 Feeling less interested in sex or more interested in sex.	<input type="checkbox"/>	<input type="checkbox"/>
4 Vomiting or feelings of sickness (nausea).	<input type="checkbox"/>	<input type="checkbox"/>	19 Finding it difficult to have sex when you try.	<input type="checkbox"/>	<input type="checkbox"/>
5 Constipation (less than three bowel movements a week) or having to strain to pass a stool.	<input type="checkbox"/>	<input type="checkbox"/>	20 Feeling light-headed, dizzy or weak standing from sitting or lying.	<input type="checkbox"/>	<input type="checkbox"/>
6 Bowel (faecal) incontinence.	<input type="checkbox"/>	<input type="checkbox"/>	21 Falling.	<input type="checkbox"/>	<input type="checkbox"/>
7 Feeling that your bowel emptying is incomplete after having been to the toilet.	<input type="checkbox"/>	<input type="checkbox"/>	22 Finding it difficult to stay awake during activities such as working, driving or eating.	<input type="checkbox"/>	<input type="checkbox"/>
8 A sense of urgency to pass urine makes you rush to the toilet.	<input type="checkbox"/>	<input type="checkbox"/>	23 Difficulty getting to sleep at night or staying asleep at night.	<input type="checkbox"/>	<input type="checkbox"/>
9 Getting up regularly at night to pass urine.	<input type="checkbox"/>	<input type="checkbox"/>	24 Intense, vivid or frightening dreams.	<input type="checkbox"/>	<input type="checkbox"/>
10 Unexplained pains (not due to known conditions such as arthritis).	<input type="checkbox"/>	<input type="checkbox"/>	25 Talking or moving about in your sleep, as if you are 'acting out' a dream.	<input type="checkbox"/>	<input type="checkbox"/>
11 Unexplained change in weight (not due to change in diet).	<input type="checkbox"/>	<input type="checkbox"/>	26 Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move.	<input type="checkbox"/>	<input type="checkbox"/>
12 Problems remembering things that have happened recently or forgetting to do things.	<input type="checkbox"/>	<input type="checkbox"/>	27 Swelling of the legs.	<input type="checkbox"/>	<input type="checkbox"/>
13 Loss of interest in what is happening around you or in doing things.	<input type="checkbox"/>	<input type="checkbox"/>	28 Excessive sweating.	<input type="checkbox"/>	<input type="checkbox"/>
14 Seeing or hearing things that you know or are told are not there.	<input type="checkbox"/>	<input type="checkbox"/>	29 Double vision.	<input type="checkbox"/>	<input type="checkbox"/>
15 Difficulty concentrating or staying focussed.	<input type="checkbox"/>	<input type="checkbox"/>	30 Believing things are happening to you that other people say are not.	<input type="checkbox"/>	<input type="checkbox"/>

All the information you supply through this form will be treated with confidence and will only be used for the purpose for which it has been collected. Information supplied will be used for monitoring purposes. Your personal data will be processed and held in accordance with the Data Protection Act 1998. Developed and validated by the International PD Non Motor Group. For information contact: susanne.tluk@uhl.nhs.uk or alison.forbes@uhl.nhs.uk.

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Annex 4

Adverse events associated with drugs used in the management of Parkinson's disease

Parkinson's disease is usually managed with a combination of pharmaceutical agents, some of which are known to be associated with adverse effects. The range of drugs involved and the differences in severity and frequency of adverse reactions make it difficult to present universal advice for limiting harm across all potential combinations. To minimise adverse effects prescribers should initiate a low dose of drug, be aware of key effects and monitoring requirements and discuss possible side effects with patient and carer/family.

Some manufacturers rank adverse reactions under headings of frequency, the most frequent first, using the following convention: Very common ($> 1/10$ number of patients expected to experience the reaction); common ($> 1/100 < 1/10$); uncommon ($> 1/1,000 < 1/100$); rare ($> 1/10,000 < 1/1,000$); very rare ($< 1/10,000$) including isolated reports. The table below gives examples of very common and common adverse effects in placebo-controlled clinical trials versus monotherapy in Parkinson's disease or postmarketing experience for some commonly prescribed antiparkinsonian drugs as detailed in the Summaries of Product Characteristics (SPC) for each drug. Care must be taken to differentiate between symptoms which may be drug related or related to the disease or current comorbidities. This list does not distinguish between adverse effects at different stages of the disease process.

Class and name of Drug	Common and very common adverse effects. Incidence ($\geq 1/10$)
DOPAMINE AGONISTS	
Pramipexole* (Mirapexin)	Dizziness, dyskinesia, somnolence, hypotension, nausea, abnormal dreams, confusion, restlessness, hallucinations, insomnia, headache, constipation, vomiting, amnesia, fatigue, peripheral oedema, visual disturbance including blurred vision and reduced visual acuity, weight decrease
Ropinirole[†] (Requip)	Dyskinesia, somnolence, syncope, nausea, hallucinations, confusion, dizziness (including vertigo), syncope, postural hypotension, hypotension, abdominal pain, vomiting, dyspepsia, leg oedema
Rotigotine[‡] (Neupro)	Nausea, application site reactions, somnolence, dizziness, vomiting, dyspepsia, perception disturbances, hallucinations, confusion state, abnormal dreams, insomnia, dyskinesia, dizziness postural, headache, orthostatic hypotension, diarrhoea, constipation, dry mouth, dyspepsia, vomiting, hepatic enzyme increase, oedema, rash, erythema, pruritis, hyperhidrosis, peripheral asthenic conditions (including fatigue, asthenia, malaise), weight decreased, falls
Apomorphine (APO-go)	local induration and nodules at subcutaneous sites of injection (local subcutaneous effects can sometimes be reduced by rotation of injection sites or possibly by the use of ultrasound to areas of nodularity or induration). In patients on high doses of apomorphine these may persist and give rise to areas of erythema, tenderness and induration. Pruritis may occur at injection site, nausea and vomiting particularly when apomorphine treatment is first initiated usually as a result of the omission of domperidone, somnolence, transient sedation, neuropsychiatric disturbance including transient mild confusion and visual hallucinations
<p>◆ Uncommon impulse control responses to pramipexole include compulsive shopping, hypersexuality, libido disorder and pathological gambling.</p> <p>† Uncommon impulse control responses to ropinirole include pathological gambling, increased libido and hypersexuality (generally reversible upon reduction of the dose or treatment discontinuation).</p> <p>‡ Uncommon impulse control responses to rotigotine include pathological gambling, punting, increased libido (including hypersexuality)</p>	

COMT INHIBITORS	
Entacapone (Comtess)	Nausea, dyskinesia and urine discolouration, parkinsonism aggravated, dizziness, diarrhoea, vomiting, abdominal pain, constipation, dry mouth, dystonia, hyperkinesia, insomnia, hallucinations and confusion, paranoia, nightmares, agitation, fatigue, increased sweating, falls
MAO-B INHIBITORS	
Selegiline (Eldepryl)	nausea, dry mouth, abnormal movements such as dyskinesia, vertigo, postural hypotension, common sleeping disorders, confusion, hallucinations, transient rise in serum alanine aminotransferase
Rasagiline (Azilect)	Headache, flu syndrome, malaise, neck pain, dyspepsia, fever, arthralgia, depression, conjunctivitis, allergic reactions, angina pectoris, leucopenia, arthritis, rhinitis, postural hypotension, anorexia, vertigo, hallucinations, contact dermatitis, vesiculobullous rash, skin carcinoma, urinary urgency
GLUTAMATE ANTAGONISTS	
Amantadine (Symmetrel)	Oedema of ankles, livedo reticularis – usually after very high doses (exceeding 200 mg/day) or use over many months, anxiety, elevation of mood, light-headedness, headaches, lethargy, hallucinations, nightmares, ataxia, slurred speech, blurred vision, loss of concentration, nervousness, depression, insomnia, myalgia, palpitations, orthostatic hypotension, dry mouth, anorexia, nausea and vomiting, constipation, diaphoresis
ANTICHOLINERGICS	
Procyclidine [§] (Kemadrin)	blurred vision, dry mouth, constipation, urinary retention
Orphenadrine (Disipal)	dizziness, accommodation disorders, dry mouth, gastrointestinal disorders
COMBINATION PREPARATIONS	
For levodopa in combination with a dopa decarboxylase inhibitor (Madopar and Sinemet) the manufacturers do not rank adverse reactions under headings of frequency, however some adverse effects are listed below and full details can be obtained in each individual SPC: anorexia, nausea, vomiting, diarrhoea, gastrointestinal bleeding, somnolence, psychiatric disturbances (anxiety, agitation, insomnia, drowsiness, depression, aggression, delusions and hallucinations), dyskinesia and other involuntary movements.	
For the combination preparation levodopa, carbidopa and entacapone (Stalevo) side effects are listed above under each individual drug.	
For full details of all adverse effects of the above drugs and other antiparkinsonian drugs not listed consult the summary of product characteristics for each drug. ¹⁸⁹	
[§] With high doses of procyclidine dizziness, mental confusion, impaired cognition and memory, disorientation, anxiety, agitation and hallucinations may occur	

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