

# DIAGNOSIS AND MANAGEMENT OF PARKINSON'S DISEASE

## KEY POINTS

- 1. The diagnosis of Parkinson's disease is still based on careful history taking and clinical examination, despite ongoing advances in neuro-imaging and laboratory testing.***
- 2. One of the first challenges is to differentiate between Parkinson's disease and Parkinsonism – any group of nervous system disorders characterised by muscular rigidity, tremor and impaired motor control.***
- 3. Management of Parkinson's disease and co-existent health problems is a long journey, requiring a multidisciplinary team approach.***
- 4. Initiation of drug treatment for early Parkinson's disease is usually delayed until functional problems develop.***
- 5. Levodopa is the drug of choice for Parkinson's disease but approximately half of patients will experience fluctuations in motor control after 5 to 10 years of treatment.***
- 6. Long-term management of Parkinson's disease involves careful adjustment of medications and their doses along with other strategies such as education, exercise, speech therapy and nutrition.***

**Key Adviser:** Dr Wendy Busby - Consultant Geriatrician,  
University of Otago

**Reviewer:** Dr Alistair Dunn - GP, Whangarei

***Parkinson's disease is one of the most common neurodegenerative diseases, with prevalence ranging from 100–180 per 100,000 population and an incidence of 4–20 cases per 100,000. There is a male to female predominance of 1.3:1. It typically presents in those over 60 years and the prevalence will increase with the ageing population.***

While most cases of Parkinson's disease are thought to be sporadic in onset, mutations in six nuclear genes have been associated with autosomal dominant or recessive Parkinson's disease. A number of aetiologic factors have been considered including infections, toxins, head trauma, coffee and alcohol consumption. The strongest association is that non smokers are at greater risk of developing Parkinson's disease.

The diagnosis of Parkinson's disease is based upon careful history taking and examination, despite ongoing advances in neuro-imaging and laboratory testing. Computerised tomography (CT) and Magnetic Resonance Imaging show no specific changes but may help to exclude other conditions. Positron emission tomography and single photon emission CT may help in diagnosis but are not routinely available.

Ideally, patients should be managed jointly with GP, specialist and other health professionals including nurse specialist, physiotherapists, occupational therapists, social workers, speech-language therapists and the Parkinson's Society field worker. Effective communication and team work are paramount for optimal management.

This is often a long journey which also requires the management of co-existent health problems and may culminate in end stage Parkinson's disease and palliative care.

## **MAKING THE DIAGNOSIS**

Getting the diagnosis correct underpins the best management of patients and a specialist opinion is usually helpful, ideally before starting any medications.

Careful history taking is essential and often provides a clear guide to the diagnosis. The duration of symptoms is important, as is any family history of either Parkinson's disease or tremor.

The error rate in diagnosing idiopathic Parkinson's disease has been reported as around 50% in general practice, 25% in general specialist clinics and 8% in specialised Parkinson's disease clinics.<sup>1</sup>

### **Differentiating Parkinson's disease from Parkinsonism**

One of the first challenges is differentiating Parkinson's disease from Parkinsonism as the management is usually quite different.

Parkinsonism is any of a group of nervous system disorders with symptoms similar to Parkinson's disease, characterised by muscular rigidity, tremor, and impaired motor control. There is often a specific cause, such as the use of certain drugs or frequent exposure to toxic chemicals.

It is essential to check for medications which interfere with dopamine release in the brain and hence cause Parkinsonism (neuroleptics, metoclopramide, prochlorperazine).

### **Features of Parkinson's disease**

**Tremor:** (Table 1) The most common presenting symptom is tremor, although the majority of those with tremor do not have Parkinson's disease. Tremor in Parkinson's disease usually presents as a unilateral, pill rolling hand tremor. It may affect other limbs and the head. Always query the diagnosis if tremor is absent.

The pattern of any tremor should be clarified, for example, whether it is worse on activity or at rest or if there are any relieving factors. Past medical history may indicate other diseases. A careful medication history is essential to exclude drug induced tremor.

- Essential tremor is relatively common, affecting 0.4 to 4% of the population and approximately 2.5% of those over 60 years. It is often bilateral, progressive and not associated with other extrapyramidal signs.
- Cerebellar tremor may be unilateral or bilateral depending upon its aetiology. It is worse on movement, often with a stuttering or saccadic character and worse at the beginning and end of movement. There may be other cerebellar signs including nystagmus and ataxia.

**Table 1: Characteristics of Tremor**

<b>Tremor</b>	<b>Character</b>	<b>Tone</b>	<b>Reflexes</b>
Extrapyramidal	Resting	Cogwheel/ Lead pipe	Normal range
Cerebellar	Action, Past pointing	Hypotonic	Pendular
Essential	Action	Normal	Normal
Action	Action	Normal	Normal

**Rigidity and Bradykinesia:** Bradykinesia and rigidity, micrographia, stiffness and slowness, may be features of other conditions including ageing, depression, dementia, arthropathies, polymyalgia rheumatica, and hypothyroidism, as well as Parkinson's disease.

At first presentation of Parkinson's disease, patients may complain of a general slowing up and stiffness which can be attributed to ageing or osteoarthritis. There may be difficulties in turning over in bed, which may contribute to sleep disturbance. Speech may be slower, quieter and more monotonous. Patients may have expressionless faces and be less spontaneous.

The increased tone is classically present throughout movement (lead pipe) or has a cog-wheeling component to it. This can be thought of as the additive effects of tremor upon the lead pipe rigidity.

**Gait disorder, postural changes and falls:** These occur later in the disease course and if present early, should alert the clinician to an alternative diagnosis.

In Parkinson's disease, the characteristic features usually begin with unilateral loss of arm swing and it is often helpful to watch the patient walk along a corridor. The gait is typically small-stepped and shuffling, described as festinating. The posture becomes stooped, and arms flexed. Patients turn en bloc, shuffling around on the spot. Postural stability becomes impaired and the risk of falling increases. Postural hypotension as a result of autonomic dysfunction and/or medication can contribute to falls.

## Examination

Assessment should include:

- Anaemia
- Cognitive function
- Gait
- Lying and standing blood pressure
- Musculoskeletal conditions
- Thyroid disease
- Weight

Neurological assessment should include checking for red flags for alternative diagnoses.

## Red Flags

There are some “red flags” (Table 2) which should always alert the clinician to an alternative diagnosis (Table 3).

**Table 2: Red Flag alerting clinicians to an alternative diagnosis**

No tremor at time of diagnosis
Bilateral signs at onset
Dementia or hallucinations early in the disease course
Early onset of postural hypotension and autonomic failure
Reduced range of eye movements at diagnosis
Falls or drop attacks early in history
Up-going plantar reflex
No response to levodopa

## Parkinsonian Syndromes

**Include the following:**

**Progressive Supra-nuclear palsy** is a rare neurodegenerative condition, usually presenting after the age of 40 years. It is characterised by vertical gaze paralysis, truncal and neck rigidity, postural instability and unexplained falls. Tremor is rare.

**Dementia with Lewy bodies** is characterised by sudden falls or dropping to the ground associated with cognitive deficits in attention, visual spatial and loss of executive function, insight and judgment. Hallucinations occur relatively early in the disease course and patients often have marked intolerance to neuroleptic agents.

**Normal pressure hydrocephalus** is associated with the triad of an ataxic gait, urinary incontinence and cognitive loss.

**Vascular Parkinsonism** is often distinguishable from the history and accompanying cognitive loss. Tremor is not usually present. Examination of the patient and a CT headscan should help to confirm the diagnosis. The use of levodopa does not improve symptoms and may exacerbate cognitive problems. Unilateral Parkinsonism may be difficult to distinguish from a CVA.

**Multi-systems atrophy** includes the conditions known as olivopontocerebellar atrophy, nigrostriatal degeneration and Shy-Drager syndrome which often presents with early and severe autonomic dysfunction including postural hypotension. There may be a combination of extra-pyramidal signs without tremor, pyramidal and cerebellar signs.

**Table 3: Parkinsonian Syndromes**

Drug Induced Parkinsonism
Alzheimer's Disease or Vascular Dementia
Dementia with Lewy Bodies
Multiple Systems Atrophy/ Shy Drager Syndrome
Corticobasal degeneration
Progressive Supra-nuclear Palsy
Normal Pressure Hydrocephalus
Vascular Parkinsonism

See opposite panel for more details

## NATURAL HISTORY

By the time symptoms of Parkinson's disease appear, approximately 70–80% of the dopamine is lost from the substantia nigra indicating a substantial sub-clinical period. While dopamine is the primary neuro-transmitter involved in the pathology of Parkinson's disease it is clear that others are involved including acetylcholine, noradrenaline, adenosine, glutamate and GABA.

The factors which determine prognosis and disease progression in Parkinson's disease are not clearly established.

Initially, patients experience a prompt and even response to medication. Usually within two years, medication doses need to be increased and patients often take a combination of medications.

The lowest dose of medication needed should always be used. The progressive degeneration of dopamine terminals means the concentration of dopamine in the basal ganglia becomes more dependent upon plasma levels. These can fluctuate because of the 90 minute half life of levodopa and its unpredictable absorption. At this time, the consensus is that chronic administration of levodopa does not exacerbate the disease process.

***“One of the first challenges is differentiating Parkinson's disease from Parkinsonism”***

## MOTOR FLUCTUATIONS

Motor fluctuations occur in approximately half of patients after 5 to 10 years of treatment. These often are more severe in younger patients and are associated with the use of levodopa containing preparations. These include wearing off, dyskinesias and dystonias, and on-off episodes.

When the effect of levodopa wears off in less than four hours, this can initially be managed by increasing the dose of medication and/or shortening the dosing interval.

This can progress to on-off episodes (fluctuations between control and no control). Initially the pattern may be predictable with timing of medication and its effectiveness but it may become unpredictable. Patients may find themselves suddenly freezing, often when moving through doorways. Dyskinetic movements may occur typically when patients are in an “on” period. Dystonia, often painful, including dystonic inversion of the foot, may occur when the patient is either “on” or “off”

The treatment of such complications can be difficult and specialist help is usually required.

***“Fluctuations in motor control occur in approximately half of patients after 5 to 10 years of treatment with levodopa”***

# DRUG MANAGEMENT OF PARKINSON'S DISEASE

## SUMMARY POINTS

- Levodopa is the principal choice for initial treatment of Parkinson's disease but long term use is limited by motor complications and drug-induced dyskinesias.
- Dopamine agonists are also options for initial treatment and are not usually associated with motor complications. However they are inferior to levodopa in controlling motor symptoms.
- When levodopa related motor complications develop in advanced Parkinson's disease, the addition of a dopamine agonist, catechol-O-methyltransferase inhibitor (COMT) or monoamine oxidase-B inhibitor (MAOI-B) may be beneficial.
- Parkinson's disease is often associated with psychiatric illness such as dementia, depression and psychosis. Psychosis is often drug induced and can be managed by dose reduction of antiparkinsonism medication. Other conditions (e.g. depression) may require active drug management.
- Parkinson's disease is associated with a significant range of non-motor symptoms which should be identified and managed

## EARLY PARKINSON'S DISEASE

Early Parkinson's disease refers to people with mild symptoms or who have developed functional disability and who require symptomatic treatment. Late disease refers to people who are already taking levodopa and have developed motor complications.

Initiation of drug treatment for early Parkinson's disease is usually delayed until patients develop functional problems. As the benefit from medications reduces with time, some people prefer to delay initiation of treatment and the advantages and disadvantages should be discussed with the patient. Older patients may have greater disability at the time of onset of symptoms because of the compounding effects of other co-morbidities.

The Unified Parkinson's Disease Rating Scale (UPDRS), a standardized tool, can help in assessing and subsequent monitoring of disability and treatment response. It has four parts measuring;

- Activities of daily living
- Motor impairment
- Psychological/cognitive effects
- Treatment and disease complications

Available from <http://www.mdvu.org/pdf/updrs.pdf>

### ***Drug treatment in early Parkinson's disease***

Once functional impairment develops, drug treatment is usually required. There is no universal first-choice drug for those with early Parkinson's disease (see Table 4).

- Selegiline or an anticholinergic may improve mild symptoms, particularly in younger people, but most people usually require levodopa or a dopamine agonist
- Levodopa is better at improving motor disability and dopamine agonists cause less motor complications
- The long term use of levodopa is limited by motor complications and drug-induced dyskinesias
- Generally, a dopamine agonist is used in younger people with mild symptoms and levodopa used initially in older people with more severe motor symptoms
- Levodopa is the most effective treatment for bradykinesia and rigidity<sup>2,3</sup>

## NEUROPROTECTION

The use of neuroprotective agents such as vitamin E, monoamine oxidase inhibitors, co-enzyme Q10 and dopamine agonists, have not been proven to be effective. Early studies of co-enzyme Q10 and dopamine agonists have indicated some slowing of disease progression.<sup>4</sup> NICE generally advises against the use of neuroprotective agents except when part of a clinical trial.<sup>5</sup>

**Levodopa** is the precursor of dopamine and is used because dopamine does not cross the blood brain barrier. It is given with a dopa-decarboxylase inhibitor (usually 4:1 ratio) to minimize peripheral conversion to dopamine and reduce nausea and hypotension. Sinemet and Madopar are levodopa preparations combined with a dopa-decarboxylase inhibitor. Doses are started low and titrated upwards in response to the therapeutic effect. Particular care needs to be taken with older patients and those with other co-morbidities.

**Dopamine agonists** include bromocriptine, ropinirole, lisuride and apomorphine. Bromocriptine and lisuride are ergot derivatives, while ropinirole is a non-ergot derivative. These drugs directly stimulate dopamine receptors and are effective alone or combined with levodopa for symptoms of early Parkinson's disease and to help manage motor fluctuations. Bromocriptine and lisuride require regular monitoring (renal function, ESR and chest X-ray) but ropinirole has the advantage of requiring less monitoring and is generally the first choice dopamine agonists.<sup>5</sup>

Response and side effect profiles are the other determinants of drug choice. Apomorphine is only available as subcutaneous injection and is reserved for severe "off" periods and motor fluctuations which are not responding to other treatments.

**Selegiline (a MAO-B inhibitor)** gives mild symptomatic improvements in patients with early Parkinson's disease.<sup>2</sup> It is also used as adjuvant therapy for patients with Parkinson's disease and motor fluctuations.

**Anticholinergic agents** (benztropine, procyclidine and orphenadrine) are useful to treat disabling tremors, particularly in younger people with preserved cognitive function. In older people (> 70 years) their use is limited by their side effect profile including a high incidence of postural hypotension, urinary retention, constipation and neuropsychiatric adverse effects.<sup>4</sup>

**Amantadine** (originally marketed as an antiviral agent) has been shown to reduce tremor, rigidity and akinesia, in people with Parkinson's disease.<sup>4</sup> It may be useful in some patients but supporting evidence is relatively weak.

**Table 4: Medication for Parkinson's disease**

<b>Medication</b>	<b>Indications and comments</b>	<b>Adverse effects</b>
<b>Anticholinergics:</b> <i>Benzotropine (Cogentin),                      Procyclidine (Kemadrin)                      Orphenadrine (Disipal)</i>	Useful for symptomatic control of Parkinson's disease (benefits are mild to moderate); associated with more adverse effects than other drugs	Dry mouth, dry eyes, constipation, hypotension, cognitive impairment, urinary retention
<i>Carbidopa/levodopa Immediate and carbidopa/levodopa SR (Sinemet).                       Benserazide/levodopa (Madopar – similar to Sinemet – dispersible tablet may be useful for people with swallowing difficulties)</i>	Levodopa is the most effective medication and remains the primary treatment for symptomatic Parkinson's disease; no added benefit for motor complications with sustained-release versus immediate-release preparations	Nausea, somnolence, dyskinesia, hypotension, hallucinations. Long term use is limited by motor complications and drug-induced dyskinesias.
<b>COMT inhibitors:</b> <i>Entacapone (Comtan)</i>	Useful for managing motor fluctuations ('wearing-off' effect) in patients taking levodopa; levodopa dose may need to be reduced if dyskinesia appears.	Diarrhoea; exacerbates levodopa adverse effects; bright red-brown urine
<i>Tolcapone (Tasmar)</i>	Not generally recommended due to hepatotoxicity. Entacapone is preferred.	Diarrhoea, exacerbates levodopa adverse effects; rare liver failure (liver function monitoring needed)
<b>*Dopamine agonists:</b> <i>Bromocriptine (Parlodel)</i>	Useful for early disease and in patients with Parkinson's disease and motor fluctuations	Nausea, headache, dizziness. Pleuropulmonary changes, CNS effects, retroperitoneal fibrosis (long term use). Regular monitoring required.
<i>Lisuride (Dopergin)</i>	Useful for early disease and in patients with Parkinson's disease and motor fluctuations	Similar to bromocriptine and other ergot derivatives.
<i>Ropinirole (Requip)</i>	Useful for early disease and in patients with Parkinson's disease and motor fluctuations	Nausea, sleep attacks, edema, hallucinations, hypotension
<b>MAO-B inhibitors:</b> <i>Selegiline (Eldepryl)</i>	Useful for symptomatic control of Parkinson's disease (benefits are mild to moderate) and as adjuvant therapy for patients with Parkinson's disease and motor fluctuations	Nausea, insomnia, drug interactions with other MAO inhibitors/tyramine
<b>NMDA receptor inhibitor:</b> <i>Amantadine (Symmeterel)</i>	Useful for treating akinesia, rigidity, tremor, dyskinesia	Nausea, hypotension, hallucinations, confusion, edema

\*Pergolide is another dopamine agonist available in New Zealand but has been associated with significant cardiac and pulmonary fibrosis. Other agents are preferred.

## LATE PARKINSON'S DISEASE

Late Parkinson's disease refers to people who are taking levodopa and have developed motor complications, typically with wearing off and on-off phenomena.

The approach to treating motor complications is varied. Adjustment of dosage, use of controlled release preparations and adjusting timing of medications may help.

Long acting levodopa preparations (Sinemet CR, Madopar HBS) can be useful in reducing the frequency of dosing for patients especially overnight, and for addressing wearing off phenomena. If doses need adjustment, this should generally be done one drug at a time to assess response.

The addition of a MAO-B inhibitor (Selegiline), a dopamine agonist or a COMT inhibitor may provide an improvement to motor complications.<sup>2,4</sup>

Dopamine agonists have been shown to significantly reduce off time, improve motor function and reduce the need for levodopa.<sup>4</sup> They are generally useful as adjunct therapy in people already taking levodopa.

COMT inhibitors (entacapone (Comtan) and tolcapone (Tasmar)) are used with levodopa to reduce its breakdown and increase its half-life. Consequently they can be effective in reducing the end of dose wearing-off effect and the duration of off time. Tolcapone should not generally be used due to the risk of hepatotoxicity. Monitoring of liver function tests is required for the first year of treatment.<sup>5</sup>

At some point there may be little benefit from ongoing adjustment of antiparkinsonian medication; doses may need to be reduced and treating associated problems may be more useful. This should be done in discussion with the patients. Some prefer being mobile and tolerating dyskinesia while others find dyskinesia intolerable and prefer to be more bradykinetic.

***“Initiation of drug treatment for early Parkinson's disease is usually delayed until functional problems develop”***

## NON-MOTOR FEATURES OF PARKINSON'S DISEASE

Non-motor symptoms such as depression, psychoses, sleep disturbance and hypotension are commonly associated with Parkinson's disease. These symptoms and their management are outlined in Table 5.

When managing non-motor symptoms or other concurrent conditions, care should be taken to check if drug therapy could aggravate symptoms of Parkinson's disease or interact with existing medication. For example for nausea, prochlorperazine and metoclopramide should be avoided whereas domperidone is very unlikely to cause extrapyramidal effects. An SSRI, selected to treat depression may interact with selegiline causing serotonin syndrome.

***“Late Parkinson's disease is associated with motor complications from the levodopa wearing off and on-off phenomena. Adjusting dose, timing and release of medications may help”***

**Table 5: Management of non-motor features of Parkinson's disease**

<b>Symptom</b>	<b>Management strategies</b>
<i>Cognitive impairment</i>	Evaluate for and treat medical problems (e.g. dehydration, metabolic disorders, infection); adjust antiparkinsonian medications; decrease or discontinue anticholinergics, dopamine agonists, amantadine (Symmetrel), and selegiline (Eldepryl).
<i>Constipation</i>	Patients should increase fluid and fibre intake; increase physical activity; discontinue anticholinergics; and use a stimulant laxative (e.g. Coloxyl with Senna), stool softeners, or enemas as needed.
<i>Depression</i>	Initiate counseling; consider drug therapy with selective serotonin reuptake inhibitors or tricyclic antidepressants (because of side effect profile, use tricyclic antidepressants with caution).
<i>Dysphagia</i>	Perform a swallowing evaluation and refer the patient to a speech language therapist specialist; increase "on" time (the period when symptoms are decreased), and encourage patients to eat during this time; patient should eat soft foods.
<i>Orthostatic Hypotension</i>	Discontinue antihypertensive medication; the head of the patient's bed should be elevated, and patient's should rise slowly from a prone position; consider support stockings and fludrocortisone (Florinef).
<i>Psychosis, hallucinations or delirium</i>	Decrease or discontinue anticholinergics, dopamine agonists, amantadine, and selegiline; decrease levodopa; consider low-dose quetiapine.
<i>Sleep disturbance</i>	Daytime somnolence and sleep attacks; discontinue dopamine agonists, general methods to improve sleep hygiene. Nighttime awakenings because of bradykinesia; consider a bedtime dose of long-acting Sinemet or Madopar, adjuvant entacapone (Comtan), or a dopamine agonist. Rapid eye movement sleep behaviour disorder; decrease or discontinue night time use of antiparkinsonian drugs, (consider ropinirole for restless leg syndrome).
<i>Urinary urgency</i>	Reduce evening fluid intake; Confirm aetiology of urgency before using an anticholinergic agent such as oxybutynin (Ditropan).

## **OTHER MANAGEMENT**

### **Education**

Patients and their families may be alarmed by the diagnosis of Parkinson's disease. Many have known people who have had disabling symptoms. Care should be taken not to over expose newly diagnosed patients to information regarding all the potential end stage features. Many patients never progress to this stage.

Education should under pin all management decisions. Many patients will be making a series of lifestyle changes to attempt to slow the effects of the disease. Early contact with the Parkinson's society either via the local field officer or through the national office ([www.parkinsons.org.nz](http://www.parkinsons.org.nz)) may be helpful and provides ongoing information and support.

## **Exercise and physiotherapy**

Regular exercise may encourage a healthy life style in people with Parkinson's disease. Specific help may be obtained from physiotherapists who can develop an individualised exercise programme. This can help to promote flexibility, prevent rigidity and flexed posture and maintain balance and strength to help prevent falls.

Fractures often have devastating consequences for people with Parkinson's disease. Consideration should be given to management of any co-existent osteoporosis. Mobility aids and falls prevention programmes may be needed.

## **Occupational Therapist**

An occupational therapist can assist with promoting leisure, work and home activities. They also can perform cognitive assessments if cognitive loss is becoming apparent. Home based assessments are often helpful and aids, equipment and household modifications facilitated. Silky sheets and night wear and an Adams pole insert on the bed side may help bed mobility.

## **Social Worker and Needs Assessor**

Younger patients should be encouraged to remain actively involved in the work force. A social worker may be able to assist if difficulties arise. With time, many people may struggle to maintain their activities of daily living and a Needs Assessor can help with determining needs and liaising with service providers to co-ordinate support. General practitioners can allocate carer support and a disability allowance.

## **Speech language therapist**

Communication and swallowing problems may occur in time and early referral to a speech-language therapist can provide assessment and exercise programme for patients.

## **Nutrition**

For most people early in the disease course, a normal, healthy diet is appropriate. For patients who begin to develop motor fluctuations, dietary modification to improve drug absorption may be helpful. Theoretically, certain proteins compete with dopamine absorption and hence advice is to take medications on an empty stomach. However some patients may experience nausea and taking medications with food helps. Compliance may be improved by taking medications at meals times. Large meals high in fats may slow gastric emptying and impede medication absorption.

Many patients lose weight as the disease progresses and any dietary restrictions may lead to inadequate caloric intake. Attempts should be made to avoid weight loss and weight should be routinely monitored.

If swallowing is impaired, foods may need to be pureed.

## **Driving**

Care should be taken in monitoring the patient's safety to drive. It is advisable to check with family members if there have been any concerns and to ask about any accidents. Some of the medications used can cause daytime drowsiness or abrupt onset of sleep..

## **Enduring Power of Attorney (EPOA)**

All patients should be encouraged to contact their lawyer to have a welfare guardian and a property manager designated through the EPOA process.

## **References**

1. Clarke CE. Medical Management of Parkinson's disease. J Neurol Neurosurg Psychiatry 2002; 72 (suppl 1): 22-27.
2. Miyasaki JM, Martin W, Suchowersky O, et al. Practice parameter: initiation of treatment for Parkinson's Disease: an evidence-based review: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology, 2002; 58(1):11-17.
3. Goetz CG, Poewe W, Rascol O, Sampaio C. Evidence based medical review update: pharmacological and surgical treatments of Parkinson's disease: 2001 to 2004. Mov Disord 2007; 22(1):41-47.
4. Rao SS, Hofmann LA, Shakil A. Parkinson's Disease; Diagnosis and Treatment. Am Fam Physician 2006;74:2046-54.
5. NICE, 2006. Parkinson's disease. Diagnosis and management in primary and secondary care. National Institute for Health and Clinical Excellence. NICE clinical guideline 35, June 2006. Available from [www.nice.org.uk/CG035](http://www.nice.org.uk/CG035). Accessed July 2007.