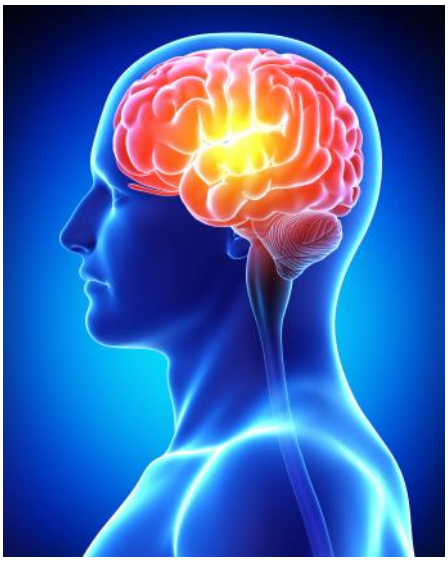
Therapeutic Notes on the Management of Parkinson's disease



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Glossary	
Athetosis	Slow, writhing motions of fingers and hands.
Bradykinesia	Slowness of voluntary movement with progressive reduction in speed and amplitude of repetitive actions.
Dyskinesia	Involuntary movement, typically 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.
Hypokinesia	Decreased bodily movement.
Dystonia	Involuntary spasms of muscle contractions that cause abnormal movements and postures.
Livedo reticularis	A mottled brown rash on the legs.
Neuroleptic malignant syndrome	A serious and unpredictable idiosyncratic drug reaction, characterised by four groups of symptoms: altered mental state, fever, extrapyramidal symptoms and autonomic instability.
SPECT scan	A single-photon emission computerized tomography investigation.
Tachyphylaxis	rapidly diminishing response to successive doses of a drug, rendering it less effective.

Introduction and background

Parkinson's Disease (PD) was first described in 1817 by James Parkinson (an apothecary living in London) when he wrote "An Essay on the Shaking Palsy"[1]. In acknowledgment of this work, the French neurologist/pathologist Jean Martin Charcot (known as the founder of Neurology) proposed that the syndrome should be called Maladie de Parkinson (Parkinson's disease).[1] Initially, anticholinergic drugs (developed in the 19th century) were the only treatment option for PD before the introduction of levodopa. Anticholinergics reduced tremor associated with PD, but they did not affect the slowness of movement which is the other trademark symptom of PD.[2]
When levodopa was first introduced, it often produced dramatic results in patients who had been suffering from movement disorders for years. However, such results were not seen in all patients, and unacceptable side effects were associated with its use.
In the 1970s the dopa-decarboxylase inhibitors were introduced which greatly improved the side effect profile of levodopa, leading to the more widespread use of levodopa.[2]

PD is a chronic progressive neuro-degenerative condition.[3] It is caused by loss of dopamine-containing cells in the substantia nigra. PD is not clinically apparent until 60–80% of dopaminergic cells have been lost.[4]

What do we mean by the term "Parkinsonism"?

Parkinsonism is an umbrella term for the main symptoms of PD: hypokinesia, bradykinesia, rigidity, tremor (4–6 Hz tremor when at rest), and a range of non-motor symptoms. PD is the most common form of parkinsonism.[4] It is important to distinguish PD from common mimics of PD as these will respond less well or not at all to treatment used for PD, and prognosis will also be different.[3] See **TABLE ONE**.

TABLE ONE: Common mimics of PD [3]

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

Drugs that can induce Parkinsonism [4]

Most commonly:

- Antipsychotics – typical antipsychotics (e.g. fluphenazine, haloperidol, chlorpromazine) are more likely than atypical antipsychotics (e.g. olanzapine, quetiapine, risperidone) to cause Parkinsonism
- Anti-emetics – prochlorperazine, metoclopramide, cyclizine

More rarely:

- Antidepressants, e.g. SSRIs
- Cinnarizine
- Amiodarone
- Lithium
- Cholinesterase inhibitors, e.g. donepezil
- Methyldopa
- Sodium valproate
- Calcium-channel blockers
- Pethidine
- Ranitidine

How common is PD?

It's thought around 1 in 500 people are affected by PD, which means there are an estimated 127,000 people in the UK with the condition.

Is PD age-related?

Age is one of the main risk factors for PD [1]; both prevalence and incidence increase with age.[4] The mean age at onset of PD is 57 years.[5] 4 to 8% of people with PD are younger than 50 years of age.[6]

Is PD gender-related?

PD is thought to be 1.5 times more common in men than in women.[4]

Does lifestyle play a role in the development of PD?

The cause of PD remains unknown. It seems to result from a complex interplay of genetic and environmental factors.[4] Most data regarding environmental risk factors are conflicting: although coffee consumption and smoking may be protective; rural living or pesticide exposure possibly increase risk.[7,8]

What is the prognosis with PD?

PD is a chronic disease. It is usually slowly progressive, but progression is variable.[9] With the drug treatments now available, life expectancy is only slightly reduced compared to the general population for the same age.[10]

What about Early-onset PD?

Early-onset forms of PD are often inherited (although not always); some have been linked to specific gene mutations. People with one or more close relatives with PD have an increased risk of developing the disease, but the total risk is still only 2 – 5%, unless the family has a known gene mutation for the disease. An estimated 15 – 25% of people with PD have a known relative with the disease.[11] In very rare cases, Parkinsonian symptoms may appear in people before the age of 20 ('Juvenile Parkinsonism'). It is most commonly seen in Japan, but has been found in other countries. Juvenile Parkinsonism often runs in families and is sometimes linked to a mutated parkin gene.[11]

Diagnosis

How does PD first present?

The onset of PD is gradual – the earliest symptoms might go unnoticed or misinterpreted for a long time. Fatigue and stiffness are common but non-specific complaints. Work colleagues or family members might notice an expressionless face, a stooped appearance, a flexion of one arm with lack of swing, a monotonous quality to the speech, and an extreme slowing down.[1] These changes are rarely noticed by the patient. The early physical signs are often erroneously ascribed to old age, introspection, or rheumatism.[1] A delay of 2 to 3 years from the first symptoms to diagnosis is not unusual.[1]

When to refer to secondary care?

PD should be suspected in people presenting with tremor, stiffness, slowness, balance problems and/or gait disorders. They should be **referred quickly to a specialist with expertise in the differential diagnosis of this condition prior to treatment**.[12]

If PD is suspected in a patient currently taking a drug known to induce Parkinsonism, the drug should be stopped or dose reduced as appropriate. **Referral should not be delayed to assess the response.**

How is PD diagnosed?

The diagnosis of PD is largely clinical, depending on:

- The presence of characteristic signs and symptoms
- Absence of atypical features such as early and severe autonomic failure
- A slowly progressive course
- A response to drug therapy*
- Ultimately, neuropathological confirmation at post mortem.[3]

*Not in acute diagnosis. Patients initially considered to have a possible diagnosis of PD may benefit from a trial of dopamine replacement therapy by a specialist with a retrospective review of response by the specialist.[3]

There is, however, poor specificity of a clinical diagnosis of PD in the early stages. This uncertainty should be taken into account when providing information to patients and planning management.[3]

What is the role of a DaTSCAN?

While the diagnosis of PD is predominately clinical, imaging with a form of SPECT imaging known as a DaTSCAN can be useful in some situations when there is uncertainty. A DaTSCAN can distinguish between PD (reduced tracer uptake) and the following:

- Other tremor disorders (e.g. severe essential tremor or dystonic tremor)
- Drug induced Parkinsonism
- Vascular Parkinsonism.

However, a DaTSCAN cannot at present distinguish between PD and other degenerative causes of clinical Parkinsonism such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA) or corticobasal degeneration (CBD) (as a DaTSCAN will be abnormal in all of these conditions).[13] Delineating the differential diagnosis may also require CT or MRI studies.

Driving Advice 

On diagnosis of PD, patients should inform the Driver and Vehicle Licensing Agency (DVLA) and their car insurance company of their condition.
Advise people with PD who have daytime sleepiness and/or sudden onset of sleep not to drive (and to inform the DVLA of their symptoms) and to think about any occupation hazards.[12]

TABLE TWO: DVLA guidelines for people with PD	
Group 1 drivers (car or motorcycle)	Person may drive as long as safe vehicle control is maintained at all times. If the individual's condition is disabling and/or there is clinically significant variability in motor function, the licence will be refused or revoked. If driving is not impaired, licensing will be considered subject to satisfactory medical reports. A licence may be issued subject to regular review.
Group 2 drivers (lorry, bus or taxi)	Person may drive as long as safe vehicle control is maintained at all times. If the individual's condition is disabling and/or there is clinically significant variability in motor function, the licence will be refused or revoked. If driving is not impaired, licensing will be considered subject to satisfactory medical reports and assessment. A licence may be issued subject to annual review.
The latest information from the DVLA regarding medical fitness to drive can be obtained at: www.gov.uk/dvla/fitnesstodrive.	

Symptoms

PD is principally a movement disorder. However, the neurological involvement causes symptoms across many different functional areas, including mental health, bowel, bladder and blood pressure.[3] As such, symptoms are classified as **motor** or **non-motor**.

Motor symptoms

Motor symptoms of PD are usually **unilateral** in the early stages, but become **bilateral** as the disease progresses.[4] Motor symptoms occur only after the majority of nigrostriatal dopaminergic terminals have been lost and compensatory processes overwhelmed.[14] Thus, by the time PD becomes clinically overt, neurodegeneration will have been ongoing for some time.[14] See **Box 1** below for summary of motor symptoms.

Box 1: Motor symptoms

1. **Bradykinesia** (slowness of movement) or **hypokinesia** (poverty of movement), for example:
   - Reduced facial expression, arm swing, or blinking
   - Difficulty with fine movements such as buttoning clothes and opening jars, or small and cramped handwriting
   - Slow, shuffling gait, or difficulty turning in bed
2. **Stiffness or rigidity**, which may be:
   - Lead-pipe rigidity (the constant resistance felt when a limb is passively flexed in the presence of increased tone without tremor) or
   - Cogwheel rigidity (the regular intermittent relaxation of tension felt when a limb is passively flexed in the presence of tremor and increased tone)
3. **Rest tremor**, which:
   - Usually improves on moving
   - May appear at the thumb and index finger ('pill-rolling'), the wrist, or the leg
   - Is absent in up to 30% of people at disease onset.

Non motor symptoms

The following non-motor symptoms may be present early in the disease (and may precede motor symptoms by more than a decade):

- Depression, anxiety and fatigue
- Reduced smell
- Cognitive impairment
- Sleep disturbance
- Constipation

Often it is the non-motor features of the disorder which can present with the greatest management challenge. [15] Non-motor features, particularly psychiatric and cognitive problems, often limit therapeutic options for management of motor features: optimising treatment to control motor features can negatively impact on non-motor features and vice versa. Patients are often susceptible to deterioration following even minor changes in medication.

Research suggests that the non-motor features of PD are frequently unrecognised by clinicians and remain untreated. Patients often do not present to healthcare professionals with these symptoms – some through embarrassment, some because they are not aware that they are linked to PD.[16] Even when identified, there is a common perception that many of these features are untreatable.[16] This can impact negatively on a patient's quality of life and can lead to hospitalisation or institutionalism.[16]
Such features often present in primary care so it is important that they are recognised and managed promptly. Increased and early identification of these symptoms can result in a significant improvement in the quality of life of patients with PD.[17] See **Box 2** on page 4 for summary of non-motor symptoms.

Box 2: Non-motor symptoms

Mental health problems:

- Depression, anxiety, and apathy
- Psychosis
- Impulse control and related disorders
- Dementia and cognitive decline
- Insomnia

Autonomic disturbances:

- Dysphagia and weight loss
- Orthostatic hypotension
- Constipation
- Urinary incontinence
- Sexual dysfunction
- Hyperhidrosis and sialorrhoea (excessive sweating and saliva)

Other complications:

- Nausea and vomiting
- Falls
- Pain
- Fatigue
- REM sleep behaviour disorder
- Daytime hypersomnolence
- Periodic limb movements of sleep [18]
- Aspiration pneumonia
- Pressure sores.

Early stage treatment of motor symptoms

All people with confirmed PD should be under the care of a specialist in movement disorders and a multidisciplinary team including a PD nurse specialist, who can advise on management issues and provide ongoing support.[4,12]

In the 2017 update to the NICE guidance on Parkinson's disease in adults (NG71), NICE place an emphasis on an individualised approach to management. Current symptoms should be considered in the context of comorbidities, polypharmacy, individual preferences, needs and goals.[12] The potential benefits and harms of the different drug classes (listed in **TABLE THREE**) should be discussed with the person before starting treatment.[12]

What does the term dopaminergic drug mean?

Dopaminergics are drugs that influence the function of dopamine. They work by different mechanisms:
1) Release dopamine (e.g. levodopa) OR
2) Mimic dopamine (e.g. dopamine agonists) OR
3) Prevent the degradation of dopamine (monoamine oxidase inhibitors (MAOBIs))
NB – Antimuscarinics are not dopaminergics.

Drug therapy for non-motor features of PD?

Many non-motor features will respond to similar treatment measures as those used in the general population – note, however, that drugs with a potential to increase Parkinsonian symptoms should be avoided.[17] See earlier 'Drugs that can induce Parkinsonism'.
Non-motor features are typically regarded as being non-responsive to dopaminergic therapy. However, studies have shown that some non-motor features of PD may have a dopaminergic contribution. It has therefore been suggested that, some of these features might respond to targeted dopaminergic therapy. This would however need to be balanced against the fact that some non-motor features might be exacerbated by dopaminergic drugs.[16] Non-motor symptoms are discussed later in this COMPASS Therapeutic Note.

TABLE THREE: Early stage treatment of motor symptoms — Potential benefits and harms of dopamine agonists, levodopa and MAOB inhibitors[12]

	Levodopa (e.g. co-beneldopa, co-careldopa)	**Dopamine agonists** (e.g. pramipexole, ropinirole)	**MAOB inhibitors** (e.g. rasagiline, selegiline)
Motor symptoms	More improvement in motor symptoms	Less improvement in motor symptoms	Less improvement in motor symptoms
Activities of daily living	More improvement in activities of daily living	Less improvement in activities of daily living	Less improvement in activities of daily living
Motor complications	More motor complications	Fewer motor complications	Fewer motor complications
Adverse events	Fewer specified adverse events*	More specified adverse events*	Fewer specified adverse events*

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

As PD advances, management of patients becomes increasingly complex; many different healthcare professionals will be involved. Regular assessment will therefore be required by PD specialists.

The person (and their family/carers) should be given written information and additional sources of information and support, such as the charity Parkinson's UK.

Patient resources

Parkinson's UK produce many information resources for people with PD, including

- An introductory booklet Parkinson's and you. A guide for people new to the condition.
- A leaflet Parkinson's information and support outlining sources of patient information and advice.
- A leaflet Drug treatments for Parkinson's.

See website: https://www.parkinsons.org.uk/

What is the recommended first line treatment for PD?

- **Levodopa** (given with a dopa decarboxylase inhibitor, e.g. co-beneldopa or co-careldopa) should be offered to people in the early stages of PD whose **motor symptoms impact on their quality of life**.[12]
- For those in the early stages of PD whose motor symptoms do **not** impact on their quality of life, a choice of **dopamine agonist** (e.g. pramipexole, ropinirole)**, levodopa or MAOB inhibitor** (e.g. selegiline, rasagiline, safinamide) should be offered.[12]
- Do **not offer ergot-derived dopamine agonists** (e.g. cabergoline, pergolide) as first line treatment for PD.[12]

Levodopa

Levodopa is the precursor of dopamine. It is metabolised centrally and peripherally by dopa decarboxylase, catechol-O-methyltransferase (COMT), and monoamine oxidase to dopamine.[4] Levodopa can cross the blood brain barrier but dopamine cannot. Levodopa is given with a dopa decarboxylase inhibitor (DDI) to reduce the metabolism of levodopa to dopamine peripherally, allowing a greater proportion of levodopa to reach the brain. This both increases concentration of dopamine in the brain (increased therapeutic effect) and decreases peripheral availability of dopamine (reduced side effects). The combination of levodopa plus DDI is often still described as "levodopa monotherapy".

What are the common side effects of levodopa?

Long term treatment with levodopa is associated with motor complications, including response fluctuations and peak-dose dyskinesias. After around 3-8 years' use of levodopa, patients, particularly those under 40 years, commonly develop motor fluctuations and dyskinesias.[20]

Response fluctuations are characterised by large variations in motor performance, with normal function during the 'on' period, and weakness and restricted mobility during the 'off' period. 'End-of-dose' deterioration with progressively shorter duration of benefit can also occur. Modified-release preparations may help with 'end-of-dose' deterioration or nocturnal immobility.[21] In order to postpone these side effects, it is common practice to delay starting levodopa until motor symptoms are impacting on the person's quality of life.[22]

Choice of levodopa: co-beneldopa or co-careldopa?

Two levodopa / DDI combinations are commonly used:

- **Co-beneldopa** (levodopa plus benserazide)
- **Co-careldopa** (levodopa plus carbidopa).[3]

Co-beneldopa and co-careldopa are used equally and there is no evidence of benefit of one over the other.[23]

NI Formulary choices

Levodopa first choice:

Co-beneldopa

Or

Co-careldopa

http://niformulary.hscni.net

What dose and frequency should be used?

Levodopa therapy should be initiated at a low dose and increased in small steps.[21] The dose should then be adjusted according to response.[21] Intervals between doses should be chosen to suit the needs of the individual patient. The lowest effective dose should be used to minimise the incidence of adverse effects.[3]
A usual maximum daily dose of levodopa is 800mg daily in 3 to 4 divided doses. Higher doses may be necessary under specialist advice.[23]
For co-careldopa preparations, the total daily dose of carbidopa should be at least 70mg, as a lower dose may not achieve full inhibition of extracerebral dopa-decarboxylase, with a resultant increase in side-effects.[21]

Get it on time

- Patients with PD should be encouraged to take their medication as regularly as possible, and this is particularly relevant in situations where they are not self-medicating (e.g. hospital admission or care homes). Medication regimens should only be adjusted after discussion with a specialist.[23]
- Antiparkinsonian drug therapy should never be stopped abruptly as this carries the risk of developing acute akinesia or neuroleptic malignant syndrome*.[12,21]
- These medications are not optional and are essential for the patients' wellbeing.[23]
- **The practice of withdrawing patients from their antiparkinsonian drugs (so called 'drug holidays') to reduce motor complications should not be undertaken because of the risk of neuroleptic malignant syndrome**.[12]
- Situations such as gastroenteritis or severe constipation can alter drug pharmacodynamics and lead to treatment failure.

*Neuroleptic malignant syndrome is a rare, life-threatening idiosyncratic reaction which may occur if dopaminergic drugs are stopped abruptly in a person with PD. Symptoms include fever, altered mental state, muscle rigidity, and autonomic dysfunction.[4]

What influences the choice of formulation?

Formulation options include:

Immediate release preparations

- Often used for initiation of therapy.
- Co-careldopa 10mg/100mg is not recommended for initiation of therapy as the dose of carbidopa may be inadequate for full inhibition of dopa-decarboxylase. Co-careldopa 10mg/100mg may have a use in patients on more than 700mg levodopa.[23]

Modified-release formulations

- Not recommended for initiation of therapy.
- May be useful for end-of-dose deterioration or nocturnal immobility and rigidity.[23]

Dispersible

- Useful in patients with swallowing difficulties.
- Useful where rapid absorption is desired, e.g. first thing in the morning.
- Often an inactive sediment remains in the glass.[23]
- Only available as co-beneldopa. However may be used in patients receiving co-careldopa at equivalent levodopa doses if considering a switch.

How should nausea and vomiting associated with levodopa therapy be managed?

- To reduce the risk of nausea, levodopa should be taken initially with food and the dose increased slowly.
- If nausea or vomiting are mild, reassure the person that this often settles over time as tolerance occurs. It may help to take their medication with food.[4]
- If nausea or vomiting are persistent or severe, consider prescribing low dose domperidone (a peripheral D2 antagonist), reducing or stopping it when the nausea or vomiting settles. **There is a risk of ventricular arrhythmia or sudden cardiac death with domperidone, particularly at doses greater than 30mg daily and in patients over the age of 60.[24] Advise the person to seek urgent medical attention if symptoms such as syncope or palpitations occur during treatment.[4]**
- If domperidone is ineffective or not tolerated, seek specialist advice.[4]
- Do NOT use metoclopramide or prochlorperazine as they can exacerbate parkinsonism.

Prescribing Points – Levodopa

► Nausea and vomiting are common side effects of levodopa therapy.

► Levodopa should be taken initially with food and the dose increased slowly.

► Protein may interfere with levodopa absorption.[23] However, the individual effect can be variable. The PD specialist can offer individualised advice, e.g. some people can benefit from a protein redistribution diet — where most of the protein is taken in the evening time allowing the treatment to be more effective during the day.[10]

► May colour the urine red — patients should be counselled about this.[23]

► If transferring patients from another levodopa / DDI preparation, the previous preparation should be discontinued at least 12 hours before.[21]

► If switching from MR levodopa to dispersible co-beneldopa, reduce dose by approximately 30%.[21]

► Regular measurement of intraocular pressure is advisable in patients with open-angle glaucoma, as levodopa theoretically has the potential to raise intraocular pressure (levodopa is contraindicated in close-angle glaucoma).[25,26]

Dopamine agonists

Dopamine agonists induce an antiparkinsonian effect through actions on either D(1)-like or D(2)-like dopamine receptors, and the multiple receptor subtypes present in the brain may provide further opportunities to improve the treatment of PD [27]. Dopamine agonists do not need to be converted in the brain to active compounds [4].

There are two types of dopamine agonists: ergot derived and non-ergot derived. **Non-ergot agonists** are considered one of three possible first choice options for early PD.[3,12]

Non-ergot derived	Ergot derived
Apomorphine (SC) Pramipexole (oral) Ropinirole (oral) Rotigotine (transdermal)	Bromocriptine (oral) Pergolide (oral) Cabergoline (oral)

Who are dopamine agonists suitable for?

Dopamine agonists are an option as monotherapy in early stages of PD for people whose motor symptoms do not impact on their quality of life.[12] Specialists commonly begin treatment with a dopamine agonist in early PD to postpone the start of levodopa therapy (and associated response fluctuations and drug-induced dyskinesias).[22] However, other factors will need to be considered, e.g. many young patients may require fine motor skills at work and so levodopa may be a more suitable option (as levodopa treats motor symptoms better than dopamine agonists).

Due to their side effect profile (increased risk of neuropsychiatric complications — see below) they are generally avoided in those with increased risk of dementia / psychosis.

Dopamine agonists may also be used as adjuvant treatment — see later 'Adjuvant treatment of motor symptoms.'

NI Formulary choices

First choice:

Ropinirole

Or

Pramipexole

http://niformulary.hscni.net

What are the main side effects of dopamine agonists?

Acute adverse effects of dopamine agonists are similar to levodopa and include nausea, vomiting and postural hypotension.[28] These acute effects tend to diminish over time, as tolerance develops.[28]

Dopaminergic adverse effects such as excessive sleepiness, hallucinations and impulse control disorders occur more frequently with dopamine agonists compared to levodopa or MAOB inhibitors.[12] People are more likely to discontinue dopamine agonists than levodopa for this reason.[3]

Ergot-derived agonists are associated with a risk of cardiac valvulopathy and serosal fibrosis (pleural, pericardial and retroperitoneal) and as such are **not** considered as a first line option.[12]

Impulse control disorders

Managing and monitoring impulse control disorders as an adverse effect of dopaminergic therapy.

Impulse control disorders (ICDs) can develop in a person with PD who is on any dopaminergic therapy at any stage in the disease course.[12]

ICDs can include: compulsive gambling, hypersexuality, binge eating and obsessive shopping. These disorders can occur with all of the dopaminergic drugs, but especially dopamine agonists.

The following are associated with an increased risk of developing ICDs:

- Dopamine agonist therapy.
- A history of previous impulsive behaviours.
- A history of alcohol consumption and/or smoking.[12]

It is important that people with PD and their family / carers are given information at the start of diagnosis on the possibility of ICDs developing as an adverse effect of treatment, and monitored throughout. ICDs may be concealed by the person affected.[12]

Ergot-derived dopamine agonists: risk of fibrotic reactions

There is a risk of fibrosis, particularly cardiac fibrosis associated with chronic use of ergot-derived dopamine agonists.[29] The risk of cardiac fibrosis is higher with cabergoline and pergolide than with the other ergot-derived dopamine agonists.[29] For further information see MHRA Drug Safety Update, 2008.

TABLE FOUR: Pramipexole Base and Salt Dose Equivalents

Doses and strengths should be stated in terms of pramipexole (base).

Pramipexole base	Pramipexole dihydro-chloride monohydrate (salt)
Immediate-release preparations	
88 micrograms base	125 micrograms salt
180 micrograms base	250 micrograms salt
350 micrograms base	500 micrograms salt
700 micrograms base	1 mg salt
Modified-release preparations	
260 micrograms base	375 micrograms salt
520 micrograms base	750 micrograms salt
1.05 mg base	1.5 mg salt
1.57 mg base	2.25 mg salt
2.1 mg base	3 mg salt
2.62 mg base	3.75 mg salt
3.15 mg base	4.5 mg salt

Caution is needed to ensure the correct strength is prescribed and dispensed.

Prescribing Points – Dopamine agonists

► Nausea and vomiting are common side effects of all dopamine agonists.[21] For apomorphine, the person must be established on domperidone (ensure MHRA safety advice regarding domperidone is followed), usually 10mg three times daily for at least two days prior to initiation of therapy.[30]

► Hypotensive reactions can occur in some patients taking dopamine-receptor agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.[21]

► Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine-receptor agonists. Patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery.[21]

► Note that for pramipexole, doses are expressed as pramipexole base. A number of prescribing and dispensing errors have occurred over confusion between strengths of the salt and the base.[21]

► If treatment is to be stopped, do not stop abruptly as this carries a small risk of neuroleptic malignant syndrome — instead taper dose gradually. Remain vigilant for the development of depression after discontinuing dopamine agonist.[21]

Monoamine oxidase B (MAOB) inhibitors

MAOB inhibitors inhibit the breakdown of dopamine in the brain, thereby increasing synaptic dopamine.[31,32]

Who are MAOB inhibitors suitable for?

MAOB inhibitors are an option as monotherapy in early stages of PD for people whose motor symptoms do not impact on their quality of life.[12] As monotherapy, MAOB inhibitors may be used to delay the need for levodopa therapy.[22]

They are an option for patients with less severe, newly diagnosed PD.[31] MAOB inhibitors have a lesser effect on the main motor features and are therefore an option for patients with mild disability. Dopamine agonists and levodopa are needed for patients with greater impairment or whose professional work and performance on activities of daily living will be affected.[28]

They tend to cause fewer adverse effects such as excessive sleepiness, hallucinations, and impulse control disorders compared with other drug classes.[4]

MAOB inhibitors may also be used as adjuvant treatment for "end of dose fluctuations"— see later.

Are MAOB inhibitors neuroprotective?

Some initial laboratory studies suggested that MAOB inhibitors might be neuroprotective. However, these models had significant limitations and there is not good evidence that MAO-B inhibitor drugs are neuroprotective.[12,32] Indeed, NICE stipulate 'do not use MAOB inhibitors as neuroprotective therapies for people with PD, except in the context of clinical trials'.[12]

How does safinamide▼ compare to rasagiline and selegiline?

There is no evidence comparing the efficacy or safety of the more established MAOB inhibitors, rasagiline and selegiline.

Safinamide▼ is a relatively new MAOB inhibitor, launched in the UK in May 2016.[33] It is licensed only as adjuvant therapy (see later) with levodopa (alone or in combination with other PD medicinal products) in mid-to late-stage fluctuating patients.[34] Safinamide▼ appears to produce a similar reduction in off-time to other MAO-B inhibitors.[35] However, there are no head-to-head studies comparing the efficacy and safety of safinamide▼ with other MAOB inhibitors.[33] It is more expensive than other MAOB inhibitors: 30 day treatment costs are £3.34, £9.67 and £69.00 for rasagiline, selegiline and safinamide▼ respectively.[33,36]

NI Formulary choices

First choice:

Rasagiline

Or

Selegiline

http://niformulary.hscni.net

What are the main drug interactions with MAOB inhibitors?

MAOB inhibitors have the potential to interact with many medicines due to their inhibition of monoamine oxidase, which may not be fully selective for MAOB.[37] See **TABLE FIVE** on the next page.

TABLE FIVE: Examples of drug interactions with MAOB inhibitors	
Interacting drug	**Consequences / action to be taken**
Pethidine	MAOB inhibitors are predicted to increase the risk of side-effects when given with pethidine. Manufacturer advises avoid and for 14 days after stopping MAOB inhibitor.
Other MAO inhibitors, e.g. moclobemide	Risk of serotonin syndrome. Moclobemide is predicted to increase the effects of MAOB inhibitors. Manufacturer advises avoid.
SSRIs, e.g. fluoxetine	Risk of serotonin syndrome.
Adrenaline	Risk of a hypertensive crisis. Manufacturer advises avoid.
Bronchodilators, e.g. salbutamol, salmeterol	Risk of a hypertensive crisis. Manufacturer advises avoid.
Midodrine	Risk of a hypertensive crisis. Manufacturer advises avoid.
Pseudoephedrine	Risk of a hypertensive crisis. Manufacturer advises avoid.
Refer to BNF or product literature for full list of drug interactions.	

Do MAOB inhibitors interact with tyramine-containing foods?

At their licensed doses, selegiline (10mg daily), rasagiline (1mg daily) and safinamide (100mg daily) are selective MAOB inhibitors. As such, no dietary restrictions are required (patients on non-selective MAO inhibitors should be warned to avoid tyramine-containing foods). However, the precise dose at which these selective MAOB inhibitors become non-selective has not been determined. Therefore with doses greater than those licensed, there is a theoretical risk of hypertension after ingestion of tyramine-rich food.[38,39] Such foods include: mature cheese, pickled herring, broad bean pods, Bovril®, Oxo® and Marmite®.[21]

What are the main side effects of MAOB inhibitors?

Side effects include abnormal dreams, headache, aching joints, indigestion, stomatitis, conjunctivitis, constipation, urinary frequency, rhinitis, vertigo, flu-like symptoms, increased sweating, angina pectoris and depression.[21,10]

Prescribing Points – MAOB inhibitors

► MAOB inhibitors interact with a number of drug classes — see **TABLE FIVE**.
► Unlike other drug treatments for PD, MAOB inhibitors do not have to be started gradually.[10]
► Avoid abrupt withdrawal of MAOB inhibitor.[21]
► Caution when initiating rasagiline in patients with mild hepatic impairment (monitor liver function). Avoid use of rasagiline in patients with moderate or severe hepatic impairment.[39]
► Safinamide▼ is contraindicated in people with retinal disease.

Adjuvant treatment of motor symptoms

When patients start levodopa, they experience rapid improvement in their symptoms and quality of life. However this period is followed by decreased efficacy and levodopa-related motor complications.[37]
If a person with PD has developed dyskinesia and/or motor fluctuations, including medicines 'wearing off', seek advice from a healthcare professional with specialist expertise in PD before modifying therapy.[12]

What do we mean by motor complications?

One of the complications of long-term treatment of PD with levodopa is the development of motor complications. Most patients who are treated with levodopa in the early stages of PD (particularly at higher doses) will develop motor complications.[40]
Levodopa has a short half-life, which leads to fluctuations in plasma levodopa levels. This may, *in part*, explain the wearing-off that occurs with long-term levodopa therapy.[41] However other processes account for these motor complications: as PD progresses, dopamine-producing cells are gradually lost and those remaining work over-time to compensate for this dopamine loss.[10]
Box 3 summarises the motor complications that are seen.

Box 3: Motor complications

1) End of dose wearing off
With the loss of dopamine-producing cells, the capacity to produce dopamine, even when levodopa is administered, is exhausted more quickly. The effect of the usual dose does not seem to last until the next dose is due.[10]

2) Dyskinesias (involuntary movements)
The brain attempts to compensate for the lack of dopamine and therefore becomes more sensitive to smaller amounts of dopamine. When levodopa is taken, this leads to temporarily increased levels of dopamine and over-stimulation of the part of the brain responsible for motor control and involuntary movements.[10]

3) Fluctuations between 'on' and 'off' state
Fluctuating responses to levodopa are described as 'on and off' motor states:

The 'On' state: patient is responding well to their medications (primarily a response to levodopa). During such 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'. These may not need treated if mild or well tolerated by the patient.

The 'Off' state: 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 'off' periods and there may be non-motor manifestations such as low mood or fatigue. In the early stages, 'off' episodes usually occur prior to the time the next dose is due, i.e. 'wearing off.' effect [3] However as PD progresses, the 'on/off' fluctuations become less closely related to timing of levodopa dose, and more unpredictable.[10]

4) Freezing of gait
Freezing of gait is characterised by difficulty in stepping forward (at initiation or during walking), inability to lift the foot from the floor, and trembling of the legs.[4] It occurs during the 'off' phase, although it can sometimes occur during the 'on' phase. Freezing of gait is a common cause of falls in patients with PD.[4] People with PD are therefore advised to take a vitamin D supplement.[4,12]

How are motor complications managed?

When motor fluctuations are starting to become problematic, modification of levodopa therapy may be an option:

- Modified-release preparations: may help with 'end-of-dose wearing off' or nocturnal immobility and rigidity.
- Dispersible preparations: may be useful for patients who require a more rapid onset of action, e.g. from early morning or afternoon akinesia, or who exhibit 'delayed on' or 'wearing off' phenomena.
- Changing the frequency of immediate release preparations: an increase from three to five or six smaller daily doses, while maintaining the total daily dosage, ('fractionating') can be used.[1] By overlapping doses of immediate-release levodopa at intervals as close as 2 to 3 hours, this can be effective in achieving more continuous anti-parkinsonian effects.[42]

However, if modification of the dosing regimen does not correct motor complications, then combination therapy, via the addition of adjuvant medications, will be required.

What is the recommended first line adjuvant treatment for PD?

NICE recommend a choice of a dopamine agonist, MAOB inhibitor or catechol-O-methyl transferase (COMT) inhibitor as an adjunct to levodopa for people with PD who have developed dyskinesia or motor fluctuations despite optimal levodopa therapy.[12] As with monotherapy, the choice of adjuvant therapy should be based on the individual's clinical and lifestyle circumstances.[12] **TABLE SIX** shows the potential benefits and harms of dopamine agonists, MAO-B inhibitors, COMT inhibitors and amantadine.[12]

Does the dose of levodopa need to be reduced when given with adjuvant therapy?

Some adjuvant treatment are predicted to increase the effects of levodopa. Therefore the dose of levodopa should be reduced when used in combination with a MAO -B inhibitor or a COMT inhibitor.[21] The concurrent levodopa dose may need to be reduced by about 10–30%.[21]

Dopamine agonists

Dopamine agonists may significantly reduce "off" time when combined with levodopa, thereby improving motor impairment and disability and reducing the need for levodopa.[43-46] They are however associated with a greater risk of side effects compared to MAOB inhibitors and COMT inhibitors, including hallucinations.[12]

As with monotherapy, a non-ergot dopamine agonist should be chosen in most cases, because of the monitoring required with ergot-derived dopamine agonists.[12] Only consider an ergot-derived dopamine agonist as an adjunct to levodopa for people with PD who have developed dyskinesia or motor fluctuations despite optimal levodopa therapy and whose symptoms are not adequately controlled with a non-ergot-derived dopamine agonist.[12]

What is place in therapy for apomorphine?

Apomorphine is a potent non-ERGOT dopamine agonist.[4] It is used as an adjunct to levodopa and is indicated for treatment of motor fluctuations ("on-off" phenomena) in patients with PD who are not sufficiently controlled by oral anti-Parkinson medication.[30]
Due to extensive first pass metabolism, the oral route is unsuitable for apomorphine administration and so it is given as intermittent subcutaneous bolus injections and / or continuous subcutaneous infusion.[4]

Prescribing Points – Apomorphine

- Apomorphine should be initiated in a specialist clinic.
- A shared care guideline is available on the Interface Pharmacy website http://www.ipnsm.hscni.net/shared-care-guidelines/.[30]

TABLE SIX: Potential benefits and harms of adjuvant therapies (dopamine agonists, MAOB inhibitors, COMT inhibitors and amantadine)

	Dopamine agonists (e.g. apomorphine, pramipexole, ropinirole)	**MAOB Inhibitors** (e.g. rasagiline, selegiline)	**COMT inhibitors** (e.g. entacapone, tolcapone)	**Amantadine**
Motor symptoms	Improvement in motor symptoms	Improvement in motor symptoms	Improvement in motor symptoms	No evidence of improvement in motor symptoms
Activities of daily living	Improvement in activities of daily living	Improvement in activities of daily living	Improvement in activities of daily living	No evidence of improvement in activities of daily living
Off time	More off-time reduction	Off-time reduction	Off-time reduction	No studies reporting this outcome
Adverse events	Intermediate risk of adverse events	Fewer adverse events	Fewer adverse events	No studies reporting this outcome
Hallucinations	More risk of hallucinations	Lower risk of hallucinations	Lower risk of hallucinations	No studies reporting this outcome

MAOB inhibitors

All three MAOB inhibitors (rasagiline, safinamide▼ and selegiline) may be used as adjuvant therapy. As such, they are used for their levodopa-sparing effect.

MAOB inhibitors have been shown to:

- Reduce off-time by 1 to 2 hours a day [47]
- Reduce levodopa dose [21]
- Modestly improve motor impairment and disability.[12]

COMT inhibitors

Catechol-o-methyl transferase (COMT) inhibitors inhibit the peripheral breakdown of levodopa, thereby prolonging the half-life of levodopa, resulting in higher plasma levodopa levels and avoiding trough levels (and hence motor complications) of levodopa.[41,38] They are therefore used only as adjunctive therapy to levodopa.

COMT inhibitors have been shown to:

- Reduce off time by 1 to 1.5 hours per day [4]
- Reduce levodopa dose [21]
- Modestly improve motor impairment and disability.[3,48]

Choice of COMT inhibitor?

There are three COMT inhibitors on the market. Entacapone is the preferred COMT inhibitor (tolcapone requires extra monitoring and opicapone was not accepted through the NI Managed Entry process).[3,23] A triple combination preparation of levodopa, caridopa and entacapone (Stalevo® or Sastravi®) may be suitable for patients requiring entacapone who are having problems with concordance).[12,23]

What are the common adverse effects with COMT inhibitors?

The most common adverse effect with COMT inhibitors is dyskinesia which is usually managed by decreasing levodopa dose.[49] Other dopaminergic adverse effects such as nausea and vomiting can occur.

Tolcapone and hepatotoxicity

Due to the risk of hepatotoxicity, tolcapone should be prescribed under specialist supervision only, when other COMT inhibitors combined with co-beneldopa or co-careldopa are ineffective or not tolerated. LFT monitoring is required (see shared care guideline).

Is there a cardiovascular risk with entacapone products?

A small increase in the risk of heart attack, stroke or cardiovascular death was reported in clinical trials for Stalevo® (levodopa, carbidopa and entacapone). Subsequently, the FDA in the USA conducted a review into the cardiovascular safety of entacapone in people with PD (carbidopa and levodopa have been used extensively and have not been shown to have an increased cardiovascular risk). The FDA review found no increased cardiovascular risks with entacapone. Therefore, the prescribing materials remain unchanged.[50]

Prescribing Points – COMT inhibitors

► Entacapone may colour the urine reddish brown.[21]
► Tolcapone and its metabolites are yellow and may cause a harmless intensification in the colour of the patient's urine.[51]
► Abdominal discomfort is a common side effect.
► Reduce dose of levodopa by 10-30% in combination with a COMT inhibitor to avoid worsening dyskinesia.[37]

Amantadine

Amantadine was originally used as an antiviral drug for the treatment of influenza. However it has since been shown to improve the symptoms of PD.[52] Amantadine prevents the uptake of dopamine at the synapses and as such is a weak dopamine agonist with modest anti-parkinsonian effects.[21,37]

What is the place in therapy for amantadine?

Amantadine is relatively inexpensive and widely available but as **TABLE SIX** on page 9 shows, there are no large studies that demonstrate the value of amantadine in producing significant improvements in managing motor complications.[52-54] Clinical experience with amantadine is however extensive.
It is an option for the management of problematic dyskinesias not adequately managed by modifying existing therapy, but in specialist settings only.[12]

What are the common adverse effects with amantadine?

Problems associated with amantadine have led to decreasing use of the drug in recent years.[52]
Firstly, not all patients respond to amantadine. For those that continue with treatment, there is an unfavourable side effect profile including nausea, palpitations, livedo reticularis, hallucinations and confusion.[52]
Tolerance to its effects can develop (although it has been suggested that such tolerance is less pronounced when it is combined with levodopa).

Prescribing Points – Amantadine

► Increase dose slowly according to response.[21]
► Increasing doses are often required to overcome tachyphylaxis.[37]
► Counsel patients on the possibility of livedo reticularis and hallucinations.

Levodopa-carbidopa intestinal gel

When disease progresses to a point where dyskinesias become unmanageable and conventional treatments are ineffective, other therapies such as levodopa intestinal gel (or apomorphine or non-pharmacological therapies) may be possible options.[12,37]

Medicines Management in primary care

While much of the care of people with PD is co-ordinated by secondary care, medicines management is crucial at every stage of care — see Box 4.

Box 4: Medicines management of patients admitted to hospital or in care homes

Medicines management is crucial when patients with PD are admitted to hospital or placed in care homes. An abrupt withdrawal of long term levodopa may induce distress via pain and rigidity. These patients are often unable to express how they feel. Changes to the route of administration, e.g. a rotigotine patch, may be an option to ameliorate symptoms.

The OPTIMAL calculator is aimed at non-specialist healthcare professionals to help manage medicines in patients with PD when they are admitted to hospital or care homes. The calculator can be viewed at this link: http://www.parkinsonscalculator.com/.

Non-motor symptoms

People with PD should be under the care of a specialist multidisciplinary team. As well as advising on motor symptoms of PD, the specialist team can advise on the management of non-motor symptoms and complications.[4]

Non-motor symptoms may include:

- Constipation, nausea and vomiting
- Pain
- Sleep disturbance and daytime sleepiness
- Depression and anxiety
- Dementia and cognitive impairment
- Impulse control disorders and psychotic symptoms
- Orthostatic hypotension
- Dysphagia and weight loss
- Excessive salivation and sweating
- Bladder and sexual problems.[4]

This COMPASS Therapeutic Note will focus on depression, dementia and psychotic symptoms.

Management of depression in Parkinson's disease

How common is depression in PD?

Depression is very common in people with PD, affecting up to 50% of patients.[3] Of those who experience depression in PD, half will suffer from major depression. Many also develop anxiety spectrum disorders.[56] Some patients develop depression decades before motor symptoms of PD appear.[57] However, depression and anxiety can occur at any time during the course of the illness and do not parallel the course of the motor disturbance.[56,58]

Depression in PD predicts greater cognitive decline, deterioration in functioning, and progression of motor symptoms. This may reflect more advanced and widespread neurodegeneration involving multiple neurotransmitter pathways.[56]

What complicates diagnosis of depression in PD?

Diagnosis and management of depression in people with PD can be challenging.[57] It may be difficult to diagnose depression in PD because many clinical features overlap with those of the disease itself, such as:

- Social withdrawal
- Flattened affect (reduced facial expression)
- Psychomotor slowing
- Lack of motivation.[3,12,56,57,59]

What causes depression in PD?

Depression is more common in people with a long term condition than those who have good physical health.[60] However, rates of depression are higher again in people with PD compared with other chronic disabling conditions matched for disability.[58] This suggests that factors associated with the underlining disease process and/or its treatment(s) are involved.[58] Indeed, similar changes in serotonergic, adrenergic and dopaminergic pathways occur in depression in PD as found in major depression.[61]

Hypothyroidism is common in patients with PD and this can cause depression. This should be excluded in patients with PD.[56]

Fluctuation in motor symptoms can contribute to mood variability. Therefore manipulation of drug therapy for motor symptoms can play a role in managing depression.[58]
Depression may also occur after the withdrawal of dopamine agonists.[56]

What are the symptoms of depression in PD?

Similarly to depression in people without PD, core features of major depression are:

- A persistent and pervasive low mood
- Diminished ability to enjoy otherwise enjoyable undertakings (anhedonia) or decline in the interest level from the usual baseline.[58]

In addition, nonsomatic depressive features help to distinguish depressed from non-depressed PD patients:

- Excessive pessimism
- Negative ruminations
- Tearfulness
- Hopelessness
- Guilt.[58]

How should depression in people with PD be managed?

First of all, investigation into any potential underlying causes of depression should be carried out.
The anti-parkinsonian medication regimen should be optimal, as recommended by secondary specialist care.

Owing to a lack of guidance on management of depression in people with PD, management of depression is managed in generally the same way as for people without PD.[4] Choice of treatment will therefore depend on individual patient preference, the likely impact of potential adverse effects, the likely impact on motor symptoms of PD, the person's current medication and presence of co-morbidities.[3,62,63] Oral antidepressants, electroconvulsive therapy or cognitive behavioural therapy are currently used in the treatment of depression in PD.[62] **TABLE SEVEN** on page 12 provides a summary of antidepressants and points to consider in patients with PD.

When to seek specialist advice?

- If there is doubt about whether an antidepressant can be safely prescribed.
- If there is suspicion that the antidepressant prescribed may be affecting motor control or causing adverse effects.

Is there a role for dopamine agonists in managing depression in PD?

Dopamine agonists such as pramipexole are sometimes used to manage depression in PD. Studies are needed to determine whether dopamine agonists are as efficacious as other therapies for depression in patients with PD.[57,80] However pramipexole might represent an alternative to antidepressant drugs to treat depressive symptoms in PD without adding the risk of antidepressant adverse events, and avoid polypharmacy.[64]
Pramipexole itself is however not without risk, e.g. increased risk of impulse control disorders and development of psychosis.[56]

TABLE SEVEN: Summary of antidepressants and points to consider in patients with PD	
Selective serotonin reuptake inhibitors (SSRIs)	• Most commonly used in PD.[4] • Considered to be first line pharmacological treatment.[56] • Can worsen motor symptoms such as restless legs, periodic limb movements, and rapid eye movement (REM) sleep behaviour disorder (although rare).[4,56,62] • Less anticholinergic effects compared with TCAs. • Interactions with MAOB inhibitors – see 'Drug Interactions: MAOBIs and Antidepressants'. • Should be used with caution in people taking COMT inhibitors. • Apomorphine, citalopram, escitalopram and venlafaxine prolong the QT interval. Most manufacturers advise avoiding the use of two or more drugs that are associated with QT prolongation.
Tricyclic antidepressants (TCAs)	• May be more effective than SSRIs but their use is limited by the risk of adverse effects. • Anticholinergic effects can worsen cognitive symptoms and cause constipation. • Alpha-blocking effects can worsen symptoms of autonomic dysfunction. • Avoid in patients with postural hypotension, falls, or dementia. • Caution in patients with cardiovascular disorders. • Should not be used without specialist advice by people taking MAOB inhibitors. • Use with caution in people taking entacapone or tolcapone.
Irreversible monamine oxidase-A inhibitors (MAOIs)	• Should not be used with levodopa, MAOB inhibitors or COMT inhibitors.
Moclobemide	• Should not be used with MAOB inhibitors, and should be used with caution in people taking COMT inhibitors and levodopa.
Venlafaxine and duloxetine	• Interactions with selegiline and rasagiline – see 'Drug Interactions: MAOBIs and Antidepressants'. • Should be used with caution in people taking entacapone or tolcapone (risk of serotonin syndrome).
Always refer to the most up-to-date product literature before prescribing or dispensing any new medicine.	

Drug interactions: MAOB inhibitors and antidepressants — Risk of serotonin syndrome

Selegiline

- Selegiline should not be used in patients who are being treated with antidepressant drugs, including MAO inhibitors (e.g. phenelzine, isocarboxazid, tranylcypromine), tricyclic antidepressants, serotonin noradrenaline reuptake inhibitors (SNRI) (e.g. venlafaxine) and selective serotonin reuptake inhibitors (e.g. citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline).[65]
- Selegiline should not be started for 5 weeks after stopping fluoxetine, 2 weeks after stopping sertraline, and one week after stopping other SSRIs [and SNRIs].
- SSRIs [and SNRIs] should not be started for 2 weeks after stopping selegiline.[66]

Rasagiline

- Rasagiline should not be used with other MAO inhibitors, fluoxetine or fluvoxamine. Other antidepressants should be used with caution.[39]
- Rasagiline should not be started for 5 weeks after stopping fluoxetine.
- Fluoxetine or fluvoxamine should not be started for 2 weeks after stopping rasagiline.[66]

Safinamide

- Safinamide is predicted to interact with SSRIs [and SNRIs] similarly to other MAO-B inhibitors.[66]

Management of dementia in Parkinson's disease

How common is dementia in PD?

While depression and anxiety can occur at any time in people with PD, dementia and psychosis are more prevalent in the later stages.[56]

The risk of dementia is two to six times higher in people with PD than in the general population. Around a third of people with PD have some cognitive decline at diagnosis[67,68], and up to 80% will develop dementia.[69-71] Two main types of dementia affect people with PD: Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB).[10]

What are Lewy bodies?

Lewy bodies are found in several neurological conditions including dementia and PD.[72] Lewy bodies are protein deposits that develop inside some nerve cells in the brain, causing cell death. It's not yet understood why Lewy bodies occur in the brain and how they cause this damage.[73]

What is the difference between Parkinson's dementia and dementia with Lewy bodies?

PDD and DLB are distinguished somewhat arbitrarily on the basis of whether or not parkinsonism precedes dementia by more than a year:

Parkinson's dementia: motor symptoms present for at least a year before experiencing dementia. Some people develop dementia after living with PD for some time.

Dementia with Lewy bodies: symptoms of dementia present either before, or at the same time, as developing Parkinson's-like problems.[72]

How do PDD and DLB present?

Similarly to other forms of dementia such as Alzheimer's disease, PDD and DLB can cause cognitive difficulties leading to problems with memory and reasoning. However, the following symptoms are more common and pronounced in people with PDD or DLB compared to other forms of dementia:

- Visual hallucinations
- REM sleep behaviour disorder
- Fluctuations in cognition
- Mood changes
- Autonomic dysfunction (e.g. changes in blood pressure, temperature regulation, bladder and bowel disorders)
- Problems with balance (e.g. fainting and falling)
- Sensitivity to antipsychotics.

How is dementia in PD managed?

Firstly, other possible causes of cognitive impairment should be ruled out, e.g. infection, dehydration, constipation, electrolyte imbalance, or subdural haemorrhage.[3,4]

Review medication with a view to maximising motor control but minimising impact on cognition.[3] Stop, reduce or seek an alternative to any medication that is likely to be contributing towards cognitive impairment, such as:

- Antimuscarinic drugs, e.g. tricyclic antidepressants, tolterodine, and oxybutynin.
- Benzodiazepines.

Specialist review of the person's anti-parkinsonian medication should be carried out: all forms of dopaminergic treatment can contribute to cognitive and neuropsychiatric difficulties; levodopa therapy should be optimised (without causing psychosis).[3]

Referral should be made to a specialist memory service if dementia is suspected.[4]

Anticholinergic burden in PD patients

- Some commonly prescribed medicines are associated with increased anticholinergic burden.[81]
- An anticholinergic burden can contribute to or aggravate non-motor symptoms of PD such as cognitive impairment, urinary retention, falls and constipation.[82]
- Anticholinergic burden in PD patients is most commonly caused by medicines that are not used for motor symptoms.[82]
- There are validated tools for assessing anticholinergic burden, e.g. the Anticholinergic Cognitive Burden Scale[81] and ACB calculator.
- Consider minimising the use of medicines associated with increased anticholinergic burden, and if possible look for alternatives. [81]
- The theoretical advantage in managing tremor or salivary drooling in younger patients via systemic anticholinergics is often outweighed by the disadvantages listed in older people with PD.

What is the drug treatment of choice for dementia in people with PD?

NICE advise that a cholinesterase inhibitor (donepezil, rivastigmine or galantamine) may be offered for people with PD and dementia [off-label].[12]
Memantine may be considered if cholinesterase inhibitors are not tolerated or are contraindicated [off-label].[12]
NB — ensure patient is not receiving a cholinesterase inhibitor and anticholinergic medication.

Management of psychosis in Parkinson's disease

How common is psychosis in PD?

Psychosis and dementia frequently co-exist and therefore, similar to dementia, psychosis is more prevalent in the later stages of the illness.[4,56,74]
Psychosis has been reported to occur in up to 40% of people with PD who are taking dopaminergic drugs. Psychosis deeply affects patients' quality of life which can eventually bring them to permanent placement in nursing homes.[75]

What causes psychosis in PD?

The exact cause of psychosis in PD is unknown but abnormalities in dopamine, serotonin and acetylcholine neurotransmission have been suggested.[56] Drugs used to treat PD are thought to be the main precipitant of psychosis in patients with PD, rather than the disease itself (i.e. chronic exposure to dopaminergic medication).[56,75]

How does psychosis present in PD?

Psychosis in PD can present from mild symptoms such as mild illusions or vivid dreams to more severe,[76]

symptoms such as disturbing visual hallucinations and paranoid delusions.[76] Hallucinations are mostly visual; olfactory hallucinations may also occur; auditory and tactile hallucinations are less common in PD.[3,56]
Initially patients usually have insight, so that the hallucinations are benign in terms of their immediate impact. However as hallucinations become more vivid, insight may be lost and the patient may start acting upon hallucinations.[12,76,77,78]
Psychosis in PD has poor prognostic implications: increased risk of dementia, worsening functional performance and mortality. Delusions occur in about 5-10% of drug treated patients and are considerably more disruptive, being paranoid in nature, e.g. spousal infidelity or abandonment by family.[12,77,78]

What are the risk factors for psychosis in PD?

- Increased age
- Cognitive impairment
- History of depression
- Sleep disorders (abnormal REM sleep regulation)
- Anticholinergics
- Medication used in treating PD, e.g. selegiline, amantidine, dopamine agonists, COMT inhibitors, and levodopa (dopamine agonists appear to be associated with a higher risk than levodopa or COMT inhibitors)
- Genetic susceptibility.[56,76,79]

How should psychosis in people with PD be managed?

Psychosis is a major cause of patient and carer distress and requires appropriate management.[56]
As many drugs for PD can exacerbate psychosis, and drugs for psychosis might worsen motor symptoms, clinical management is difficult.[3]

At review appointments and following medicines changes, people with PD and their family members and carers (as appropriate) should be asked if the person is experiencing hallucinations (particularly visual) or delusions.[12]

Firstly, possible underlining causes should be addressed, such as:

- PD itself and anti-parkinsonian medication (particularly dopamine agonists).
- Delirium caused by infection, constipation, pain, dehydration, electrolyte disturbance, or medication.
- Dementia
- Depression.[4]

Mild psychotic symptoms in people with PD may not need to be actively treated if they are well tolerated by the person and their family members / carer.[12]

The dosage of any anti-parkinsonian medication that might have triggered hallucinations or delusions should be reduced, taking into account the severity of symptoms and possible withdrawal effects. Seek advice from a healthcare professional with specialist expertise in PD before modifying therapy.[12]

When the above measures fail, drug treatment with an antipsychotic may become necessary.[76]

Points to consider:
Antipsychotics for psychosis in PD

- Lower doses of quetiapine and clozapine are needed for people with PD than in other indications.[12]
- Clozapine is a Red list drug and therefore should NOT be prescribed or dispensed in primary care. Patient, prescriber and supplying pharmacist must be registered with the relevant clozapine patient monitoring service through secondary care.[21]
- Antipsychotics have been associated with an increased risk of vascular events and mortality in the elderly.[56]
- Any potential improvement with antipsychotics must also be balanced against potential side effects, including sedation, motor deterioration, QT-prolongation, deterioration in cognition in patients with dementia, and severe neuroleptic sensitivity in certain Lewy body disorders.[63]
- Antipsychotics may be less effective in patients with co-existing dementia. Such patients may be more prone to developing motor and cognitive adverse effects.[56]
- Severe rebound psychosis has been reported when antipsychotics have been discontinued.[56]

What is the antipsychotic of choice for psychosis in PD?

Quetiapine may be considered to treat hallucinations and delusions in people with PD who have no cognitive impairment [off-label].[12]
If quetiapine is not effective, clozapine may be offered.[12]
Note: clozapine is a red list drug and registration with a patient monitoring service is needed.

Are there antipsychotics to be avoided in PD?

Olanzapine should NOT be offered to treat hallucinations and delusions in people with PD as it has not been shown to be helpful in controlling symptoms of psychosis.[12]
Other antipsychotic medicines such as phenothiazines (e.g. chlorpromazine) and butyrophenones (e.g. haloperidol) can worsen the motor features of PD and should therefore be avoided.[12]

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COMPASS THERAPEUTIC NOTES ASSESSMENT

Therapeutic Notes on the Management of Parkinson's Disease

COMPASS Therapeutic Notes are circulated to GPs, nurses, pharmacists and others in Northern Ireland. Each issue is compiled following the review of approximately 200 papers, journal articles, guidelines and standards documents. They are written in question and answer format, with summary points and recommendations on each topic. They reflect local, national and international guidelines and standards on current best clinical practice. Each issue is reviewed and updated every three years.

Each issue of the Therapeutic Notes is accompanied by a set of assessment questions. This edition can contribute 3 hours towards your CPD/CME requirements. Submit your MCQs online (see below). Assessment forms for each topic can be submitted in **any order** and at **any time**.

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Successful completion of these assessment questions equates with **3** hours Continuing Professional Development time. Circle your answer TRUE (T) or FALSE (F) for each question. When completed please submit your answers online:

- **Doctors and nurses** should submit their answers at: **www.medicinesni.com**
- **Pharmacists** should submit their answers at: **www.nicpld.org**

1	**In the General Management of Parkinson's Disease**			
	a	Patients should be referred quickly and untreated to a specialist with expertise in movement disorders.	T	F
	b	If drug-induced Parkinsonism is suspected, referral should be delayed to assess the response.	T	F
	c	Levodopa or a non-ergot dopamine agonist or a MAOB inhibitor may be chosen as first line monotherapy.	T	F
	d	People taking levodopa should be considered for drug holidays.	T	F
2	**In the Adjuvant Management of Motor Complications of Parkinson's Disease:**			
	a	There is a greater risk of hallucinations with MAOB inhibitors compared to dopamine agonists.	T	F
	b	The dose of levodopa should be increased if a MAOB inhibitor is added.	T	F
	c	Entacapone is a suitable choice for combination therapy.	T	F
	d	There is extensive research on the benefits of amantadine as adjuvant therapy.	T	F
3	**In the Management of Depression in Parkinson's Disease:**			
	a	Depression in Parkinson's disease occurs only in the later stages.	T	F
	b	Diagnosis of depression in Parkinson's disease is usually straightforward.	T	F
	c	Pramipexole is the first line drug of choice.	T	F
	d	Venlafaxine is a good choice of antidepressant for patients also taking selegiline.	T	F
4	**In the Management of Dementia in Parkinson's Disease:**			
	a	Dementia usually presents in the later stages of Parkinson's disease.	T	F
	b	Dementia with Lewy Bodies usually presents either before, or at the same time, as the development of motor symptoms.	T	F
	c	Visual hallucinations, REM sleep behaviour disorder, fluctuations in cognition and autonomic dysfunction are more common in people with Parkinson's disease with dementia than on other forms of dementia.	T	F
	d	Donepezil, or rivastigmine, or galantamine may be offered to people with Parkinson's disease and dementia.	T	F
5	**In the Management of Psychosis in Parkinson's Disease:**			
	a	Drugs used to treat Parkinson's disease are thought to be the main cause of psychosis in patients with Parkinson's disease, rather than the disease itself.	T	F
	b	Hallucinations are usually visual.	T	F
	c	Typical antipsychotics (e.g. phenothiazines) are preferred in the management of Parkinson's disease.	T	F
	d	Olanzapine may be helpful in improving psychosis in Parkinson's disease.	T	F