COMPASS Therapeutic Notes on Management of Parkinson's Disease

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Glossary of terms	
Dementia	Progressive decline in cognitive function due to damage or disease in the brain beyond what might be expected from normal ageing
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
Athetosis	Slow, writhing motions of fingers and hands
Dystonia	Involuntary spasms of muscle contractions that cause abnormal movements and postures
Bradykinesia	Slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions
Specificity	The ability of the test to identify correctly those who do not have the disease. It is the number of subjects who have a negative test and do not have the disease divided by the number of subjects who do not have the disease. A test with high specificity has few false positive results
MRI	Magnetic Resonance Imaging
CT	Computed Tomography
PET	Positron Emission Tomography
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
RCT	Randomised Control Trial
SC	Subcutaneous
UPDRS	Unified Parkinson's Disease Rating Scale
CSCI	Continuous Subcutaneous infusion

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Introduction, Symptoms & Diagnosis

A brief history of Parkinson's Disease (PD)

PD was first described in 1817 by James Parkinson (an apothecary living in London) when he wrote "An Essay on the Shaking Palsy"[96]. 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)[96].

Initially, anticholinergics 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[100]. 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[100].

What is PD?

PD is a chronic progressive neuro-degenerative condition[2]. 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[1].

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[2]. Motor symptoms occur only after the majority of nigrostriatal dopaminergic terminals have been lost and compensatory processes overwhelmed[121]. Thus, by the time PD becomes clinically overt, neurodegeneration will have been ongoing for some time[121]. During this time, non-motor manifestations may offer key markers of the disease process, e.g. cognitive dysfunction, loss of sense of smell, dream enactment behaviour, and a variety of autonomic abnormalities[121].

PD affects many areas of a patient's health and life. On-going rehabilitation though a multidisciplinary healthcare team is required.

What is "Parkinsonism"?

Parkinsonism is a generic term for the main symptoms of PD (hypokinesia, bradykinesia, rigidity, and 4–6 Hz tremor when at rest). PD is the most common form of parkinsonism[1]. See later 'What are the symptoms of PD?' for detailed range of PD symptoms.

It is important to distinguish PD from the other forms of Parkinsonism as the other forms will respond less well or not at all to treatment used for PD, and prognosis will also be different[2]. See **TABLE ONE**.

TABLE ONE: COMMON MIMICS OF PD[2]

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

How common is PD?

A general practice, with 6000 people registered, could expect to have 6–12 people with PD. This equates to 100 to180 people per 100,000 of the population[3].

Is PD gender-related?

PD is thought to be 1.5 times more common in men than in women[3].

Is PD age-related?

Age is perhaps one of the main risk factors for PD[96]; both prevalence and incidence increase with age[1].

The mean age at onset of PD is 57 years[86].

4 to 8% of people with PD are younger than 50 years of age[6].

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 just 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[63].

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[63].

Does lifestyle play a role in the development of PD?

People who exercise regularly may be less likely to develop PD or have slower disease progression[131].

What are PD stages?

PD may be classified as:

- Diagnosis stage
- Maintenance stage
- Complex stage

What is the prognosis with PD?

PD is a chronic disease. It is usually slowly progressive, but progression is variable[8]. With the drug treatments now available, life expectancy is slightly reduced compared to the general population for the same age[173].

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 a lugubrious stiff face, a hangdog appearance, a flexion of one arm with lack of swing, a monotonous quality to the speech, and an extreme slowing down[96]. These changes are rarely noticed by the patient. The early physical signs are often erroneously ascribed to old age, introspection, or rheumatism[96]. A delay of 2 to 3 years from the first symptoms to diagnosis is not unusual[96].

What are the symptoms of PD?

Symptoms of PD are usually **unilateral** in the early stages, but become **bilateral** as the disease progresses[1]. Symptoms can be classified as motor or non-motor.

PD is suspected if the patient presents with any of the following motor symptoms[1,3]:

- 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
- 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)
- 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

The following non-motor symptoms may also be present **early** in the disease (and *may precede* motor symptoms):

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

Other non-motor symptoms may occur in later stages of PD.

How is PD diagnosed?

The diagnosis of PD is largely clinical, depending on:

- Presence of characteristic signs and symptoms (see earlier)
- Absence of atypical features
- A slowly progressive course
- A response to drug therapy*
- Ultimately, neuropathological confirmation at post mortem[2].

(* Not in acute diagnosis. Patients initially considered to have a possible diagnosis of PD may benefit from a trial of dopamine replacement therapy[2])

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[2].

What about non-motor features of PD?

PD progression is currently defined by degree of motor disability, which is not necessarily associated with progression of non-motor features that may begin prior to or after the onset of motor features. Non-motor features are indeed an integral part of the syndrome[170]. Often it is the non-motor features of the disorder which can present with the greatest management challenge[107]

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.

Common non-motor features of PD[107,121]:
See **TABLE TWO** .

Unreported and unrecognised
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[99]. Even when identified, there is a common perception that many of these features are untreatable[99]. This can impact negatively on a patient's quality of life and can lead to hospitalisation or institutionalism[99]. 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[128].

TABLE TWO: Common non-motor symptoms of PD

Non-motor problems

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[170]
- Aspiration pneumonia
- Pressure sores

Drug therapy for non-motor features of PD?
Effective drug therapy for motor features of PD has been successful in managing these symptoms[83]. However, the development of treatment strategies that encompass non-motor features would greatly reduce the burden of PD[121].

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[99].

Management of depression, dementia and psychosis in PD are discussed in detail later. Many other 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[128]. See later 'Drugs that can induce Parkinsonism'.

Do non-motor symptoms only occur in advanced PD?
Non-motor symptoms of PD occur not only in advanced disease but also in early stages, and some symptoms such as olfactory deficit, constipation, rapid-eye movement (REM), sleep behaviour disorder, and depression might precede the expression of motor symptoms by more than a decade[99]. A 'premorbid personality' has been described in several studies. The typical personality of patients with PD is mainly characterised by emotional and attitudinal inflexibility, introversion, and a depressive tendency, which can precede the development of motor abnormalities by many years[94].

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. In the later stages of PD, non-motor symptoms can start to dominate quality of life. These may be associated with complications derived from chronic dopaminergic treatments[94] and therefore the withdrawal of some drugs may be considered.

Drug Treatment for Parkinson's Disease – Early

Should treatment be initiated in Primary Care?
No, patients with suspected PD should be referred, **quickly and untreated**, to a specialist with expertise in movement disorders[2,3]. NICE recommends that patients with suspected mild PD should be seen within 6 weeks, and those patients with later disease (presenting for the first time) or with more complex problems should be seen within 2 weeks[3]. Diagnosis of PD should be reviewed regularly (every 6–12 months) by the specialist, and reconsidered if any atypical clinical features develop[3].
Tremor, often combined with slowness and stiffness in an arm, presents frequently in general practice. It may be caused by essential tremor, which affects 2-3% of the population. PD is less common. Differentiating essential tremor from PD can be difficult, even for experienced physicians[107].

What if drug-induced Parkinsonism is suspected?
If PD is suspected in a patient currently taking a drug known to induce Parkinsonism (see 'Drugs that can induce Parkinsonism'[1]), the drug should be stopped or dose reduced as appropriate. **Referral should not be delayed to assess the response**.

Drugs that can induce Parkinsonism[1]

Most commonly:
- Antipsychotics – typical antipsychotics (such as fluphenazine, haloperidol, chlorpromazine, flupentixol, and zuclopenthixol) are more likely than atypical antipsychotics (such as amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, and zotepine) to cause parkinsonism
- Anti-emetics – prochlorperazine, metoclopramide, cyclizine

More rarely:
- Antidepressants: SSRIs and tranylcypromine
- Cinnarizine
- Amiodarone
- Lithium
- Cholinesterase inhibitors
- Methyldopa
- Sodium valproate
- Calcium-channel blockers
- Pethidine

What other specialist support is available?
NICE recommend that people with PD should be offered an accessible point of contact with specialist services. This could be provided by a Parkinson's disease nurse specialist[3].
Both oral and written communication should be provided throughout the course of the disease, which should be individually tailored and reinforced as necessary[3].

Is drug therapy a cure?
No, current treatment options are aimed at control of symptoms only[2,140]. Much research has been (and still is being) carried out to develop neuroprotective interventions that prevent or halt the development of PD[107,140]. However, there is currently no evidence to support neuroprotective treatments[2,107].

How significant is a DAT scan?
The diagnosis of PD is still predominantly a clinical diagnosis. The Queen Square Brain Bank diagnostic criteria serves as a useful template to base clinical assessment.
A DAT scan can however be useful in certain situations when there is clinical uncertainty such as distinguishing other tremor disorders (such as severe essential tremor or dystonic tremor) from PD, distinguishing drug induced parkinsonism from PD and it can sometimes be useful in distinguishing vascular parkinsonism from PD. At present, it is not useful in distinguishing PD from the other degenerative causes of clinical parkinsonism such as PSP, MSA or CBD as a DAT scan will be abnormal in all of these conditions[172].

When is treatment started?
It is thought that early treatment may improve outcomes and delay disability[47,161]. There are no well-established biomarkers to determine if the disease is present[137]. Therefore, early treatment relies on early diagnosis, which can be difficult to achieve because the diagnosis of PD is based on motor symptoms, is clinical in nature, and is complicated by potential presentation of non-motor symptoms prior to motor symptoms[137].

Monotherapy or combination therapy?
Monotherapy is used initially, in early stages of PD. Combination therapy with two or more antiparkinsonian drugs may be necessary as the disease progresses [5]. See later 'Drug Treatment for Parkinson's Disease – Motor Complications' for discussion of adjuvant treatments.

What are the drug treatment choices in early disease[2,3]
There is no universal first choice drug therapy for early PD. NICE recommend that patients with early PD and motor symptoms may be considered for treatment with one of the following three options[3]:
1) Levodopa (in combination with a dopa decarboxylase inhibitor) OR
2) Oral/transdermal NON ERGOT dopamine agonists OR
3) Monoamine Oxidase B Inhibitors

Evidence from randomised controlled trials and systematic reviews supports the efficacy of each of these drug classes. It is not always clear which class to choose in any given clinical situation[107].
Anticholinergic drugs and ERGOT-derived dopamine agonists should not be used as first line treatment[2].

Choice of agent depends on a combination of factors:
- Relative effectiveness
- Nature and stage of the disease
- Side effect profile of the drug
- Patient co-morbidities
- Patient's age
- Patient's cognitive state
- Patient's employment status
- Clinician experience
- Patient preference

NB – Both choice of drug and timing of when to start treatment are made on an individual patient basis[2].
These factors will be discussed later under individual drug treatments.

Patients with swallowing difficulties
Seek specialist advice if patient is unable to swallow or unable to take PD meds enterally.

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) Preventing the degradation of dopamine (MAOBIs)
NB – Antimuscarinics are not dopaminergics.

Prescribing Points – Compliance
► 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). Medication regimens should only be adjusted after discussion with a specialist[47].
► Antiparkinsonian drug therapy should never be stopped abruptly as this carries the risk of developing acute akinesia or neuroleptic malignant syndrome[3,5].
► These medications are not optional and are essential for the patients' wellbeing[47].
► 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[3].

Impulse Control Disorders
- Treatment with levodopa and dopamine agonists is associated with Impulse Control Disorders (ICDs).
- Pathological gambling, binge eating, hypersexuality, excessive shopping/consumerism.
- Patients and their carers should be informed about this risk.

How to manage a patient with ICDs?
If patient experiences an ICD, withdrawal or dose reduction of the drug should be *considered*[5]. However, the risk of withdrawal syndrome (especially with dopamine agonists) should also be considered. Severity of the ICD (and associated problems) should be evaluated and weighed up against positive clinical benefits of dopaminergic medications and risks associated with dopaminergic medication withdrawal. Sometimes vigilance from doctor/patient/spouse/family in mild cases of ICD will be all that is required.

1) LEVODOPA

What is it?
Levodopa has been used since the early 1970s as the mainstay treatment for PD. Levodopa is the precursor of dopamine. It is metabolised centrally and peripherally by dopa-decarboxylase, catechol-O-methyltransferase (COMT), and monoamine oxidase[1] to dopamine. Levodopa can cross the blood brain barrier but dopamine cannot. Levodopa is given with a dopa decarboxylase inhibitor (DDI). DDI is also not able to cross the blood brain barrier. DDI reduces 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".

Who is levodopa suitable for?

Levodopa is effective and well tolerated in the majority of patients[5].
Levodopa is a useful first line drug for older/frailer patients to optimise control faster[47].
Alternative drug choices e.g. dopamine agonists, may be considered in some patients to delay motor complications associated with levodopa therapy[5].
Levodopa remains the gold standard for symptomatic efficacy and should not be withheld from patients in whom sufficient symptomatic control cannot be otherwise obtained[95].
The dose of levodopa generally does not need be adjusted in patients with renal failure or hepatic disease[103].

What are the common side effects?

Levodopa is associated with disabling dyskinesias following long term treatment: patients treated with levodopa for four to six years have a 40% likelihood of developing motor fluctuations and a 40% risk of dyskinesias[2].
Motor complications are particularly problematic in young patients treated with levodopa[5].

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)[2].

Co-beneldopa and co-careldopa are used equally and there is no evidence of benefit of one over the other[47].

Prescribing Point
► When transferring patients from another levodopa/DDI preparation, the previous preparation should be discontinued at least 12 hours before[5].

What dose and frequency should be used?

The dose of levodopa should be kept as low as possible to maintain good function in order to reduce the development of motor complications [2,3].
Levodopa therapy should be initiated at a low dose and increased in small steps[5].
Intervals between doses should be chosen to suit the needs of the individual patient[5].

Dose (expressed as levodopa): initially 50mg levodopa up to three times daily. Increase at weekly intervals if necessary according to response. Max 800mg levodopa daily in 3-4 divided doses. Higher doses may be necessary under specialist advice[47].

Choice of formulation?

TABLE THREE summarises the levodopa preparations available currently. Formulation options include:

Immediate release preparations
- For initiation of therapy.
- Sinemet 110® (co-careldopa) is not recommended for initiation of therapy as the dose of carbidopa may be inadequate for full inhibition of dopa-decarboxylase. Sinemet 110® may have a use in patients on more than 700mg levodopa[47].

Modified-release formulations
- Not recommended for initiation of therapy.
- May be useful for end-of-dose deterioration or nocturnal immobility and rigidity[47].
- According to NICE, modified-release levodopa preparations should not be used to delay the onset of motor complications in people with early PD[3].

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[47].
- Only available as co-beneldopa. However may be used in patients receiving co-careldopa at equivalent levodopa doses if considering a switch.

Prescribing Point
► When switching from modified-release levodopa to dispersible co-beneldopa, reduce dose by approximately 30%[5].

Caution
Please note the pharmaceutical formulation and strength when prescribing or dispensing levodopa preparations as errors have occurred[60].

TABLE THREE: Available Preparations

Generic Name	Brand Name	Drug Components			
		Levodopa	Benserazide	Carbidopa	Entacapone
Co-beneldopa	Madopar 62.5 caps	50mg	12.5mg	-	-
	Madopar 125 caps	100mg	25mg	-	-
	Madopar 250 caps	200mg	50mg	-	-
	Madopar dispersible tabs	50mg	12.5mg	-	-
		100mg	25mg	-	-
	Madopar CR	100mg	25mg	-	-
Co-careldopa	Co-careldopa 10/100 tabs	100mg	-	10mg	-
	Co-careldopa 25/100 tabs	100mg	-	25mg	-
	Co-careldopa 25/250 tabs	250mg	-	25mg	-
	Sinemet 62.5 tabs	50mg	-	12.5mg	-
	Sinemet 110 tabs	100mg	-	10mg	-
	Sinemet Plus tabs	100mg	-	25mg	-
	Sinemet 275 tabs	250mg	-	25mg	-
	Half Sinemet CR tabs	100mg	-	25mg	-
	Sinemet CR tabs	200mg	-	50mg	-
	Stalevo 50/12.5/200	50mg	-	12.5mg	200mg
	Stalevo 75/18.75/200	75mg	-	18.75mg	200mg
	Stalevo 100/25/200	100mg	-	25mg	200mg
	Stalevo 150/37.5/200	150mg	-	37.5mg	200mg
	Stalevo 200/50/200	200mg	-	50mg	200mg

Prescribing Points – Levodopa

► Nausea and vomiting is a common side effect of levodopa therapy. This can be treated with domperidone (a *peripheral* D2 antagonist) at a dose of 10-20mg three times a day[14]. NB – the lowest effective dose of domperidone should be used: 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[174].

► Prochlorperazine, metoclopramide and cyclizine should be avoided since they may exacerbate or induce parkinsonism[47].

► To reduce the risk of nausea, levodopa should be taken initially with food and the dose increased slowly. Protein may interfere with levodopa absorption[47].

► May colour the urine red[47].

► Dopamine dysregulation syndrome (DDS) occurs when patients self-escalate doses of levodopa (and/or apomorphine) to levels above those required to manage motor symptoms. Consequently patients often experience severe dyskinesia and 'off' period dysphoria[14]. A key associated feature is the development of Impulse Control Disorders (ICDs), however ICDs can also occur independently (see warning box for ICDs).

Driving Advice

On diagnosis, patients should inform the Driver and Vehicle Licensing Agency (DVLA) and their car insurance company. Sudden onset of sleep without awareness or warning signs has been reported rarely during treatment with levodopa or dopamine agonists (including apomorphine).
Patients should be informed of this and advised not to drive (and also to consider any other occupational hazards) if sudden onset of sleep occurs.

DVLA Guidance
Group 1 entitlement (cars and motorcycles): "Providing medical assessment confirms that driving performance is not impaired, can be licensed. A 1-, 2-, or 3-year licence may be required. Should the driver require a restriction to certain controls, the law requires this to be specified on the licence".
Group 2 entitlement (large lorries and buses): "Licence refused or revoked if condition is progressive or disabling. If driving would not be impaired and condition stable, can be considered for licensing subject to satisfactory reports and annual review (individual basis)".
The latest information from the DVLA regarding medical fitness to drive can be obtained at www.dvla.gov.uk/medical/ataglance

Any significant drug Interactions with levodopa?
See **TABLE FOUR**

2) DOPAMINE AGONISTS

What are they?

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[106].
Dopamine agonists do not need to be converted in the brain to active compounds[1].

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[2,3]. ERGOT-derived agonists are **not** considered as a first line option[2,3].

NON-ERGOT derived:	ERGOT derived
Apomorphine (SC)	Bromocriptine (oral)
Pramipexole (oral)	Pergolide (oral)
Ropinirole (oral)	Cabergoline (oral)
Rotigotine (transdermal)	

Who are dopamine agonists suitable for?

Dopamine agonists are often used as initial therapy, before starting levodopa[5].
Dopamine agonists cause fewer motor complications in long term treatment compared with levodopa, but the overall motor performance improves slightly less[5]. It is thought that, as dopamine agonists have a longer half-life than levodopa, they produce a more continuous stimulation of brain dopaminergic receptors. Continuous stimulation is thought to be relevant to the reduced risk of motor complications[95].

Many specialists use dopamine agonists for younger patients, to delay the onset of motor complications. 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).

Which dopamine agonist to choose?

The Northern Ireland Primary Care Formulary recommends either ropinirole or pramipexole as first choice of dopamine agonist for monotherapy or adjunctive therapy[47].
Pramipexole has the same clinical profile when administered as a once daily extended release preparation, as an immediate release preparation administered three times daily[152].

Prolonged release ropinirole tablets are only licensed for patients with established adequate symptomatic control on immediate release ropinirole. Substitution should be supervised by an appropriate specialist in PD[47].

Other Formulations
Rotigotine is available as a patch which can be useful in patients who are unable to take oral medication[2].
Adverse effects reported with rotigotine patches include nausea, application site reactions, somnolence and fatigue[16].
The patch formulation may also improve night-time (and therefore reduced sleep disturbances) and morning motor functioning in patients[141,154].
Apomorphine is given SC – see later.

Dosages?

A dopamine agonist should be titrated to a clinically efficacious dose. If side effects prevent this, another agonist or a drug from another class should be used in its place[3]. Therefore start at a low dose and titrate slowly and carefully[1].

Common adverse effects with dopamine agonists?

Acute adverse effects of dopamine agonists are similar to levodopa and include nausea, vomiting and postural hypotension[95]. These acute effects tend to diminish over time, as tolerance develops[95]. However, dopaminergic adverse effects are more common with dopamine agonists, and patients are more likely to discontinue dopamine agonists than levodopa for this reason[2].
Dopamine agonists are associated with more psychiatric adverse effects compared with levodopa[5].

Adverse effects with *all* dopamine agonists:
- Drowsiness[1]
- Impulse control disorders (see earlier)[14,15,95].
- Daytime somnolence
- Peripheral oedema
- Postural hypotension[1,47]
- Nausea
- Dizziness
- Hallucinations
- Constipation[17]

Fibrotic reactions
Adverse effects with ERGOT derived dopamine agonists:
- Cardiac valvulopathy (moderate to severe)[18-20*]
- Serosal fibrosis (pleural, pericardial and retroperitoneal)[21,22]
- Reddening of the legs[1]

ERGOT derived dopamine agonists should not be used as first line treatment for PD[2].
- Regular monitoring required if prescribed[5].

Prescribing Point – Dopamine agonists
► Dopamine agonists are emetogenic; patients prescribed apomorphine must be pre-treated with domperidone 10–20mg three times daily for 48 hours, continued for at least 4 weeks after which it may usually be safely withdrawn[47].
► Pramipexole – reduce dose in renal impairment[5].
► Pramipexole – a number of dispensing and prescribing errors have occurred due to mix-ups between strengths of salt and base. Refer to BNF.
► Dopamine Agonist Withdrawal Syndrome – taper dose of dopamine agonist gradually if it is to be discontinued – vigilance for development of depression required.

Any significant interactions with Dopamine Agonists?
See TABLE FOUR

3) MONOAMINE OXIDASE B INHIBITORS (MAOBIS)

What are they?
MAOBIs inhibit the breakdown of dopamine in the brain, thereby increasing synaptic dopamine[66,139].
MAO-B inhibitors have also been studied for possible neuroprotective or disease-modifying actions. There is laboratory evidence that MAOBIs exert some neuroprotective properties, at least in the PD models currently available. However, these models have significant limitations and so caution is required in extrapolating these results to clinical trials[139]. Furthermore, it is not known what concentrations are needed to exert a protective effect in vivo, and whether such concentrations are actually achieved in the human brain[139].

Who are MAOBIs suitable for?
Rasagiline and selegiline may be used as monotherapy in patients with early PD with motor symptoms[2]. They are an option for patients with less severe, newly diagnosed PD[66].
MAOBIs 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[95].
MAOBIs may delay the need for levodopa[2,5].
MAOBIs are also used as adjuvant therapy in advanced PD – see later.

Prescribing Point – Rasagiline
Rasagiline should not be used in patients with liver impairment[66].

Choice of MAOBI?
There is no evidence to suggest any preference between rasagiline and selegiline. The Northern Ireland Primary Care formulary recommends either rasagiline or seligiline as first choice MAOBI[47].

What dosage is used?
Rasagiline – 1mg per day (may be taken at any time during the day). Increasing the dose will not increase therapeutic effect, but may increase the risk of adverse effects. This is likely due to reduced selectivity for MAO-B inhibition at higher doses[66].
Selegiline – 5mg in the morning, increasing to 10mg after 2 to 4 weeks if tolerated[5].

Common adverse effects with MAOBIs?
Withdrawal due to adverse effects is common with MAOBIs[2].
Adverse effects include:
- Nausea
- Dyskinesia
- Dizziness
- Hallucinations
- Orthostatic hypotension
- Dry mouth, mouth ulcers
- Urinary disorders
- Sleep disorders/vivid dreams
- Myalgia [1,5,66].

Significant drug interactions with MAOBIs
See TABLE FOUR

OTHER TREATMENT OPTIONS FOR EARLY PD

Tyramine-containing foods and MAOBIs
At their licensed doses, selegiline (10mg daily) and rasagiline (1mg daily) are selective MAOB inhibitors. As such, no dietary restrictions are required (patients on non-selective MAOIs should be warned to avoid tyramine-containing foods). However, the precise dose at which these selective MAOBIs 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[157,58]. Such foods include: mature cheese, pickled herring, broad bean pods, Bovril®, Oxo® and Marmite®[5].

ANTICHOLINERGICS (ANTIMUSCARINICS)
These include orphenadrine, procyclidine and trihexyphenidyl[5]. They may be used as monotherapy or as an adjunct to other antiparkinsonian drugs. However they are not recommended as first line treatment option[2].

BETA BLOCKERS
According to NICE, beta blockers may be used in the symptomatic treatment of selected people with postural tremor in PD, but should not be drugs of first choice[3].

AMANTADINE
According to NICE, amantadine may be used as a treatment for people with early PD although should not be a drug of first choice.

TABLE FOUR: Drug Interactions with drugs used in Parkinson's Disease

Drug used in Parkinson's Disease	Interacting drug	Nature of the interaction
Levodopa e.g. co-beneldopa or co-careldopa	COMT inhibitors (e.g. entacapone)	A reduction of the dosage of levodopa may be necessary[48]
	Ferrous sulphate	Decreases the maximum plasma concentration and the AUC of levodopa by 30 to 50%. This may not be clinically significant in all patients[48]
	Antihypertensives	Enhanced hypotensive effect[5]
	MAOI Antidepressants (e.g. phenelzine)	Risk of hypertensive crisis when levodopa given with non-selective MAOIs, avoid levodopa for two weeks after stopping non-selective MAOI[5]
	Antimuscarinics	Absorption of levodopa possibly reduced
	General anaesthetics (volatile liquid)	Increased risk of arrhythmias[5]
Dopamine agonists e.g. pramipexole, ropinirole	Antipsychotics	Manufacturer of pramipexole advises avoid concomitant use of antipsychotics (antagonism of effect)[5]
	Cimetidine	Excretion of pramipexole reduced by cimetidine (increased plasma concentration)[5]
	Memantine	Effects of dopaminergics possibly enhanced by memantine[5]
	Methyldopa	Antiparkinsonian effect of dopaminergics antagonised by methyldopa[5]
	Ciprofloxacin	Metabolism of ropinirole inhibited by ciprofloxacin (increased plasma concentration)[5]
	Oestrogens	Plasma concentration of ropinirole increased by oestrogens[5]
	Metoclopramide, cyclizine	Antagonism of effect[5]
MAOBIs e.g. rasagiline, seligiline	Pethidine/opioid analgesics	Serious adverse reactions (CNS toxicity) have been reported with the concomitant use of pethidine and MAOBIs. The concomitant administration of pethidine and MAOBIs is contraindicated. Pethidine should be avoided for two weeks after stopping a MAOBI[5]. Other opioids should be used with caution.
	CYP1A2 Inhibitors E.g. ciprofloxacin, cimetidine, fluvoxamine.	Plasma concentration of rasagaline increased[66].
	Antidepressants	Interactions with antidepressants have also been reported – see later – Management of Depression in PD 'Drug interactions with antidepressants'
Entacapone (COMT inhibitor)	Selegiline	The daily dose of selegiline should not exceed 10 mg[62]
	Rasagiline	Entacapone possibly reduces plasma concentration of rasagiline[5]
	Non-selective MAOIs	Avoid concomitant use[5]
	Warfarin	Entacapone enhances anticoagulant effect of warfarin[5]
	Apomorphine	Entacapone possibly enhances effects of apomorphine[5]
	Antidepressants – TCAs and venlafaxine	Caution advised by manufacturers[5]

TABLE FIVE: Summary of options for initial pharmacotherapy in early PD (taken from NICE CG35)

Initial therapy for early PD	First choice option	Symptom control	Risk of side effects	
Levodopa	✓	+++	↑	↑
Dopamine agonists	✓	++	↓	↑
MAO-B inhibitors	✓	+	↓	↑
Anticholinergics	×	Lack of evidence	Lack of evidence	Lack of evidence
Beta-blockers	×	Lack of evidence	Lack of evidence	Lack of evidence
Amantadine	×	Lack of evidence	Lack of evidence	Lack of evidence

Key

+++ Good degree of symptom control

++ Moderate degree of symptom control

+ Limited degree of symptom control

↑ Evidence of increased motor complications/other adverse events

↓ Evidence of reduced motor complications/other adverse events

Drug Treatment for Parkinson's Disease – Motor Complications

What are motor complications?

Loss of smooth motor control happens in almost all patients treated with levodopa. Such symptoms range from mild and non-disabling to severely incapacitating.
Signs of loss of smooth motor control:
1) End of dose wearing off
2) Dyskinesias such as athetosis and dystonia
3) Random fluctuations between the 'Off' state to the 'On' state
4) Freezing of gait – inability to start or continue walking[1].

Why do motor fluctuations occur?

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[87].
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[127]. 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[173].

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[173].

2) Dyskinesias

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[173].

3) Fluctuations between the 'On' and 'Off' state

Fluctuating responses to levodopa are described as 'on and off' motor states.

The 'On' state is when a 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 refers to 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. the effect of the medication is 'wearing off'[2]. However as PD progresses, the 'on/off' fluctuations become less closely related to timing of levodopa dose, and more unpredictable[173].

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[1]. It occurs during the 'off' phase, although it can sometimes occur during the 'on' phase.
There is a disturbance of balance associated with freezing of gait, which is a common cause of falls in patients with PD[1].

How are these motor complications managed?

Options include:
- Manipulation of drug therapy (oral/topical)
- Invasive drug treatments, e.g. apomorphine infusion or intraduodenal levodopa
- Neurosurgery[2]

Can levodopa therapy be modified?

This approach may be useful when motor fluctuations are just becoming apparent[1]. The precise approach depends on the extent of on/off phenomena and dyskinesia which need to be considered separately.
- **Modified-release** levodopa preparations may be used to reduce motor complications in people with later PD, but should not be a first choice option[3] as they can increase 'off' time[1].
- Oral **dispersible** levodopa may also be used to manage motor complications[1].
- Change **frequency** of immediate-release preparations – an increase from three to 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[105].
- Levodopa **gel into the duodenum** can also be used – see later.

ADJUVANT THERAPY

Adjuvant drugs to take alongside levodopa have been developed with the aim of reducing these motor complications and improving quality of life[3].

When to start adjuvant treatment?

There are no robust clinical indicators as to when to start adjunctive therapy; clinical experience is used to determine when to start. Adjunctive treatment may be warranted when either a patient's symptoms have worsened OR the effect of treatment has decreased[2].

Risks and benefits of adjuvant therapy:

Risks
- Increased dyskinesia
- Numerous other side-effects

Benefits
- Reduces off-time,
- Reduces levodopa dose
- Improves UPDRS scores in PD patients who develop motor complications on levodopa therapy[87].

Which adjuvant therapy if recommended?

On a background of levodopa, any one of the following may be used [2,87]:
1) Dopamine agonist OR
2) COMT inhibitor OR
3) MAOBI

Despite trials having shown that these drugs are beneficial compared to placebo, it remains unclear as to the best way to treat patients experiencing motor complications and whether one class of drug is more effective than another[87].

Dopamine agonists may be more effective, but may also have a greater risk of side-effects, particularly in elderly patients. The choice of a less effective drug class, such as a COMT inhibitor or MAOBI, may be considered more appropriate in view of the lower risk of side-effects (at least with MAOBIs)[87].

What about patients commenced on non-levodopa monotherapy?

The decision to *add* levodopa should be taken on an individual patient basis[2]. The patient's symptoms (motor and non-motor) and risk of adverse effects should be taken into account[2].

See 'Drug Treatment for Parkinson's Disease – Early' for more prescribing information on dopamine agonists and MAOBIs.

Prescribing Point – Selegiline (as adjuvant)
► Avoid or use with caution in postural hypotension when used in combination with levodopa[5].
► Reduce dose of levodopa when used in combination: by 10-30% in steps of 10% every 3 to 4 days[5].

3) CATECHOL-O-METHYL TRANSFERASE (COMT) INHIBITORS

Place in therapy?

Entacapone and tolcapone are used only as an adjunct to levodopa.

Choice of COMT inhibitor?

Entacapone is the preferred COMT inhibitor due to the side effect profile of tolcapone.[2,47]
For patients stabilised on co-careldopa and entacapone, Stalevo® may be a more suitable option (patient compliance is an important consideration in PD)[3,47].

How do they work?

Entacapone inhibits the peripheral breakdown of levodopa, prolonging the half-life of levodopa, resulting in higher plasma levodopa levels and avoiding trough levels (and hence motor complications) of levodopa[127,157].

COMT inhibitors have been shown to:
- Reduce off time by 1 to 1.5 hours per day[1]
- Reduce levodopa dose
- Modestly improve motor impairment and disability[2,32]

Methods of administration

Entacapone and tolcapone have different methods of administration:
Entacapone – must be given with each dose of levodopa (up to ten times a day).
Tolcapone – given three times a day; does not need to be taken at same time as levodopa[1].

Prescribing Point
► Concurrent levodopa dose may need to be reduced by approx. 10 to 30% when used in combination with entacapone[5].

Any significant interactions with entacapone?

See **TABLE FOUR**

Common adverse effects?

The most common adverse effect with COMT inhibitors is dyskinesia which is usually managed by decreasing levodopa dose[150]. Other dopaminergic adverse effects such as nausea and vomiting can occur. Tolcapone causes severe diarrhoea more often than entacapone[150].

Caution with tolcapone – Hepatic toxicity
Tolcapone has been associated with fatal hepatic toxicity. As such it has strict licensing criteria including frequent blood monitoring[32]. SIGN recommend that entacapone should be used in preference to tolcapone[2]. Tolcapone should only be continued beyond three weeks if there is substantial improvement in symptom control[47]. 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[47].

Cardiovascular caution with Stalevo®
Healthcare professionals should regularly evaluate the cardiovascular status of patients who are taking Stalevo®, especially if they have a history of cardiovascular disease. In a meta-analysis that included 15 clinical trials comparing entacapone/carbidopa/levodopa to carbidopa/levodopa alone, a small increase in the risk of heart attack, stroke, or cardiovascular death was found in the group treated with entacapone/carbidopa/ levodopa[47].

OTHER TREATMENT OPTIONS

Treatment of levodopa-induced dyskinesia can be difficult, particularly in patients with severe "on-off " fluctuations as any minor reduction in levodopa or dopamine agonist dose to reduce dyskinesia may lead to "off " episodes. Oral delivery of amantadine is one pharmacological option for managing severe levodopa-induced dyskinesias[111]. Infusions of apomorphine, intraduodenal levodopa and modified release levodopa may also be used[1]. Deep brain stimulation is also an option for later PD (this is however beyond the remit of this publication)[1].

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[33]. Amantadine is a weak dopamine agonist with modest anti-parkinsonian effects[5].

Place in therapy?

Amantadine improves mild bradykinetic disabilities, tremor and rigidity. It may be useful in dyskinesias in more advanced disease[3,47,139].
Problems associated with amantadine have led to decreasing use of the drug in recent years[33]. Amantadine may be considered if other strategies fail[1].

Problems with amantadine?

- Not all patients respond to amantadine.
- Current evidence does not support the value of amantadine in producing significant improvements in managing motor complications[33-35].
- Unfavourable side effect profile (including nausea, palpitations, hallucinations and confusion)[33].
- Tolerance to its effects can develop (although it has been suggested that such tolerance is less pronounced when it is combined with levodopa).

APOMORPHINE

What is it?

Apomorphine is a potent NON-ERGOT dopamine agonist[1].

Place in therapy?

Apomorphine is used as an adjuvant to levodopa[1]. It is sometimes helpful in advanced disease for patients experiencing unpredictable 'off' periods with levodopa treatment[5]. It can also be useful in patients experiencing peak-dose dyskinesia (as it allows for a reduction in levodopa dosage[1]).

Apomorphine should be initiated in a specialist clinic and is approved for use under a Shared Care protocol – for details see: http://www.ipnsm.n-i.nhs.uk[47]

Methods of administration

Apomorphine may be administered as either:
- Intermittent SC bolus doses OR
- Continuous SC infusion[1].

Prescribing Points – Apomorphine
► A minimum two day pre-treatment with domperidone for nausea and vomiting is required[5]. Once treatment has been established it may be possible to gradually reduce or withdraw domperidone[5].
► The patient's treatment with levodopa, with or without dopamine agonists, should be optimised before starting apomorphine[171].
► Some protocols use an overnight withdrawal of oral antiparkinsonian medication to induce an 'off' episode and determine the threshold dose of apomorphine. Oral antiparkinsonian medication is then restarted[5].
► For intermittent bolus use, the patient is taught how to self-administer by SC injection into the lower abdomen or outer thigh at the first sign of an 'off' episode[5].

intermittent
- Dose range: 3 to 30mg daily by SC injection in divided doses. The maximum single dose is10mg, the maximum daily dose is 100mg[171].
- Used as a rescue agent in advanced disease to treat severe 'off' episodes[1].
- Provides rapid and consistent rescue from 'off' periods (within a few minutes)[1]
- Short duration of effect (up to 100 minutes).

Continuous infusion
- Used in patients who respond well to intermittent injections, but whose control remains poor and they require frequent injections[1].
- Provides a constant therapeutic effect[1].
- For patients requiring division of dose into more than about 6 to10 SC injections daily, continuous SC infusions are used (during waking hours only) at a usual rate of 1 to 4mg/hour, with the site being changed daily[171].
- Long term continuous apomorphine infusions can significantly reduce both 'off' periods and dyskinesia, as well as allowing withdrawal of oral medication[1].

Common adverse effects?

Dopaminergic adverse effects such as confusion and hallucinations have been reported with apomorphine. Injection-site reactions are also a possibility[1].

Monitoring
Patients using apomorphine AND levodopa should have regular haematological monitoring (e.g. every 6 months)[1] for haemolytic anaemia and thrombocytopenia[5].

INTRADUODENAL GEL LEVODOPA (Duopoda®)

What is it?

Duodopa® gel contains co-careldopa 5/20 (carbidopa 5 mg as monohydrate, levodopa 20 mg)/mL[5] via jejunostomy. The gel is delivered via infusion directly into the duodenum[2]. This delivery mechanism has been shown to be safe and tolerable in most patients[2].

Place in therapy?

Duodopa® is indicated for treatment of advanced levodopa-responsive PD with severe motor fluctuations and/or severe dyskinesia, when available combinations of Parkinson medicinal products have not given satisfactory results[61].
The manufacturers recommend a positive test for the clinical response to Duodopa® (administered via a temporary nasoduodenal tube) before a permanent tube is inserted[61].
It may reduce off-periods and improve motor function[1].
There is insufficient evidence to support routine use[2]. Use is limited by cost and need for a jejunostomy[1]. However it may be an alternative to deep brain stimulation for some patients[146].

Table SIX: Summary of options for adjuvant pharmacotherapy in later PD (taken from NICE CG 35)

Adjuvant therapy for later PD	Risk of side effects	First choice option	Symptom control	Risk of side effects	
				Motor complications	Other adverse events
Dopamine agonists		✓	++	↓	↑
COMT inhibitors		✓	++	↓	↑
MAO-B inhibitors		✓	++	↓	↑
Amantadine		×	NS	↓	↑
Apomorphine		×	+	↓	↑

Key
+++ Good degree of symptom control
++ Moderate degree of symptom control
+ Limited degree of symptom control
↑ Evidence of increased motor complications/other adverse events
↓ Evidence of reduced motor complications/other adverse events
NS Non-significant result

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[2]. Half of these will suffer from major depression, with the other half experiencing milder forms of depression. Many also develop anxiety spectrum disorders[4].
Depression and anxiety can occur at any time during the course of the illness[4].
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[4].
Patients may develop depression decades before motor symptoms of PD appear[110].

What complicates diagnosis of depression in PD?

Diagnosis and management of depression in patients with PD can be challenging[110]. It may be difficult to diagnose depression in PD because many clinical features overlap with those of the disease itself, such as: [2-4,10,110]
- Social withdrawal
- Apparent flattened affect due to reduced facial expression
- Psychomotor slowing
- Lack of motivation

Symptoms of depression in PD:

● Anhedonia (defined as low mood and an impaired interest or ability to experience pleasure[50,110]).
● Low mood[50]
● Pessimistic thoughts[50]
● Lethargy and fatigue[50]
● Restlessness and irritability[50]
● Sleep disturbance*
* Either excessive sleeping periods OR waking many times during the night – in either case the patient does not feel refreshed when they do get up[50].

Characteristic physical features of depression in PD:

● Weight loss, loss of appetite
● Turning downwards of the corners of the mouth
● Vertical furrowing of the centre of the brow
● Bent shoulders and lowered head[50].

What causes depression in PD?

The cause of depression in patients with PD is not well understood. Possible causes include:
● The disease process itself – similar changes in serotonergic, adrenergic and dopaminergic pathways occur in depression in PD as found in major depression. Indeed, the underlying pathology of PD itself is thought to have more of a role in causing depression rather than a reactive response[37].
●Behavioural response to the psychosocial aspects of the illness[37,110].
● Pre-existing dementia is an established risk factor for the development of depression[4].
● Depression may also occur after the withdrawal of dopamine agonists[4].
● Hypothyroidism is common in patients with PD and this can cause depression. This should be excluded in patients with PD[4].

What treatment options are available for depression in PD?

First of all, investigation into any potential underlying causes of depression should be carried out.
Oral antidepressants, electroconvulsive therapy or behavioural therapy are currently used in the treatment of depression in PD[50]. There is a lack of evidence on suitable treatment options for depression in PD[129]. Some evidence exists for nortriptyline and desipramine[175]. However the importance of this is offset by significant adverse effects[2,110].

Individual patient preference, the likely impact of potential adverse effects, the likely impact on motor symptoms of PD, and the person's current medication will determine the choice of antidepressant medication[2,50,129].

Drug Interactions: MAOBIs and Antidepressants
► **Selegiline:** The possibility of serotonin syndrome occurring with selegiline and SSRIs or venlafaxine is established, although the incidence is very rare. This follows case reports of serotonin syndrome (and other serious CNS disturbances) when selegiline was given with fluoxetine or venlafaxine. Other SSRIs and SNRIs are expected to interact with selegiline similarly. Such an interaction is expected to be rare as, at therapeutic doses, selective MAO-B inhibitors produce no significant MAO-A inhibition[129]. However, following the case reports, the manufacturer of Eldepryl® (selegiline) contraindicates concurrent treatment with all antidepressants[57,59].
People taking selegiline may *cautiously* use trazodone or mirtazapine (off-label use for selegiline)[1].
► **Rasagiline:** Rasagiline is expected to interact in the same way as selegiline. The manufacturer of Azilect® (rasagiline) recommends that concurrent treatment with other MAOIs, fluoxetine or fluvoxamine should be avoided. Other antidepressants should be used with caution[58,59].

TABLE SEVEN: Summary of Antidepressants and Points to consider in patients with PD

Drug Class	Comments
Selective serotonin reuptake inhibitors (SSRIs)	● Most commonly used in PD. ● Considered to be first line treatment[4]. ● Can worsen motor symptoms, but this occurs rarely[4,50]. ● Less anticholinergic effects compared with TCAs. ● Interactions with selegiline and rasagiline – see 'Drug Interactions: MAOBIs and Antidepressants'. ● Should be used with caution in people taking entacapone or tolcapone.
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 selegiline or rasagiline. ● Use with caution in people taking entacapone or tolcapone.
Irreversible monamine oxidase-A inhibitors (MAOIs) (phenelzine, isocarboxazid, tranylcypromine)	● Should not be used with levodopa, selegiline, rasagiline, entacapone, or tolcapone.
Moclobemide	● Should not be used with selegiline or rasagiline, and should be used with caution in people taking entacapone, tolcapone, 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).

NB –There are no known contraindications to the use of any type of antidepressant in people taking amantadine, apomorphine, or oral dopamine agonists[2].

Cognitive behavioural therapy

Cognitive behavioural therapy may aid in conjunction with antidepressants or as sole therapy in mild depression to encourage patients back into a more normal daily routine by reducing anxiety and pessimistic symptoms[50].

Other options:
● Ensure anti-parkinsonian medication regimen is optimal.
● Augmentation with dopamine agonists/releasers such as pramipexole – may be considered to manage depression in PD. This strategy could offer a combined, yet independent, benefit on motor disability and depressive symptoms. Future studies are needed to determine whether dopamine agonists are as efficacious as other therapies for depression in patients with PD[110,133]. 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[148].
Pramipexole itself is however not without risk: development of impulse control disorders and psychosis[4].
● Atomoxetine – has not been shown to be effective[4].

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.

Management of Dementia in Parkinson's Disease

How common is dementia in PD?
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[12,13], and up to 80% will develop dementia[4].
Dementia is more prevalent in the later stages of the illness[4].
PD dementia is associated with increased mortality, care-giver stress and nursing home admission[3].

How does dementia present in PD?
PD dementia is progressive and characterized by impairment of visuo-spatial abilities, impaired concentration, daytime sleepiness, visual hallucinations and delusions[13].

What causes dementia in PD?
Dementia in PD may be due to the illness itself or drug-induced: some medicines used in the management of motor symptoms can have adverse effects on cognition due to their anticholinergic effects[2].

What are Lewy bodies?
Lewy bodies are protein deposits that develop inside some nerve cells in the brain, causing cell death. The loss of these cells causes dementia. It's not yet understood why Lewy bodies occur in the brain and how they cause this damage[54].
Lewy bodies are found in several neurological conditions including dementia and PD[53]. Indeed, Lewy bodies are the defining pathological feature of idiopathic PD[53].
In the general population, dementia with Lewy bodies (DLB) is perhaps the second most common cause of dementia (Alzheimer's being the most common cause)[53].

Dementia with Lewy Bodies or Parkinson's Dementia?
There are two types of dementia associated with PD: Dementia with Lewy Bodies (DLB) and Parkinson's Dementia (PDD). The clinical features of DLB and PDD have much in common and are distinguished primarily on the basis of whether or not parkinsonism precedes dementia by more than a year[53]:
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[53].

How is dementia in PD managed?
● Rule out other causes of cognitive impairment: infection, dehydration, electrolyte imbalance, or subdural haemorrhage[2].
● Review medication with a view to maximise motor control but minimise impact on cognition[2]. Options include:
  - Consider discontinuing CNS-acting non-Parkinsonian drugs such as antidepressants with antimuscarinic properties (e.g. tricyclic antidepressants) and benzodiazepines.
  - Consider withdrawing anticholinergic medication, amantadine, selegiline and dopamine agonists.
  - Optimising levodopa therapy (without causing psychosis)[2].
● Consider treatment with a cholinesterase inhibitor.

What drug therapy options are available?
There is evidence to suggest a correlation between pathological changes in the cholinergic neurotransmitter system in PD and the level of cognitive decline[38]. Both PDD and DLB are characterised by severe cholinergic deficits. Cholinergic enhancement treatments by use of cholinesterase inhibitors have been tried in both disorders[97]. Cholinesterase inhibitors such as rivastigmine or donepezil may be considered[2].

Role of rivastigmine and donepezil
Cholinesterase inhibitors have been shown to improve cognition, delusions and hallucinations in patients with DLB (which has similarities to PD). Motor function may deteriorate. Improvements in cognitive functioning are modest[4]. Further research is recommended to identify those patients who will benefit from this treatment[3].
Only rivastigmine is licensed for dementia in patients with idiopathic PD.

What about memantine and galantamine?
Emerging evidence suggests that memantine might also be useful[67]. Further studies are however required.
There is insufficient evidence that galantamine is effective in patients with PD and dementia[2].

Management of Psychosis in Parkinson's Disease

How common is psychosis in PD?
Psychosis occurs in 40% of people with Parkinson's disease who are taking dopaminergic drugs.
Psychosis and dementia frequently co-exist[1,4,68].
Psychosis is more prevalent in the later stages of the illness[4].
Psychosis deeply affects patients' quality of life and eventually brings them to permanent placement in nursing homes[169].

How does psychosis present in PD?
Visual hallucinations is the most frequent psychotic symptom in patients with psychosis in PD. Auditory hallucinations and delusions are less common (usually occurring in younger patients)[4]. Olfactory hallucinations may also occur[1,2].
Initially patients usually have insight so that the hallucinations are benign in terms of their immediate impact. However psychosis in PD has poor prognostic implications: increased

risk of dementia, worsening psychotic symptoms 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 [3,11,158].

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[4]. Drugs used to treat PD are thought to be the main cause of psychosis in patients with PD, rather than the disease itself (i.e. chronic exposure to dopaminergic medication)[4,169]. On rare occasions they occur in patients not taking medication for PD[158].

What are the risk factors for psychosis in PD?

- Increased age
- Cerebral atrophy
- Presence and severity of depression
- Abnormal REM sleep regulation[4,52]
- Dose of dopaminergic drugs in early stages*
- Combination therapy
- High doses of anticholinergics[52]

* Anticholinergics and dopamine agonists appear to be associated with a higher risk than levodopa or COMT inhibitors[4,52].

What management options are available?

Psychosis is a major cause of patient and carer distress and requires appropriate management[4].
As many drugs for PD can exacerbate psychosis, and drugs for psychosis might worsen motor symptoms, clinical management is difficult[2].

First of all, other treatable causes should be excluded before initiating antipsychotic medication[2,158]:

- Control medical conditions: other systemic illness or infections[52,158]
- Dehydration and electrolyte disturbances
- Reduce polypharmacy with antiparkinsonian medicines*
- Review other psychoactive medicines, e.g. anticholinergic antidepressants, anxiolytics, and sedatives[52,158]

* Consideration should be given to withdrawing gradually antiparkinsonian medication that might have triggered psychosis in people with PD, or reducing the dose to the lowest levels that allow tolerable motor function[158].

Treat in mild cases?

Mild psychotic symptoms in people with PD may not need to be actively treated if they are well tolerated by the patient and carer.

Drug treatment?

It is often difficult to reduce the dose of the antiparkinsonian drugs to a level that will lead to a resolution of drug-induced psychosis while maintaining sufficient symptomatic motor control. Therefore, drug therapy will become necessary[52].

ANTIPSYCHOTICS

Typical antipsychotic drugs (such as phenothiazines and butyrophenones) should not be used in people with PD because they exacerbate the motor features of the condition.

Atypical antipsychotics may be considered for treatment of psychotic symptoms in people with PD, although the evidence base for their efficacy and safety is limited[3]. Any potential improvement with atypical antipsychotic medication 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[129].

Prescribing Point with Antipsychotics[4]

► Severe rebound psychosis has been reported when antipsychotics have been discontinued.
► Antipsychotics have been associated with an increased risk of vascular events in the elderly.
► Antipsychotics may be less effective in patients with co-existing dementia. Such patients may be more prone to developing motor and cognitive adverse effects.
► Clozapine is a Red list drug and therefore should be prescribed and dispensed in secondary care. Patient, prescriber and supplying pharmacist must be registered with the relevant clozapine patient monitoring service[5].

Clozapine

- Low dose clozapine (start at 6.25mg – usual dose 25mg)[4] may be considered for patients with psychosis in PD[2].
- Clozapine has been shown to be effective and, in some cases, actually improves motor symptoms[2,129].
- Clozapine is licensed for psychosis in PD[2].
- Weekly blood monitoring is required for the first 18 weeks of treatment, followed by fortnightly monitoring for the first year, and monthly thereafter[2]. The elderly are more susceptible to developing serious blood dyscrasia[4].

Quetiapine

- Low dose quetiapine may be used for patients who are unable to comply with weekly blood monitoring for clozapine[2].
- Quetiapine is the only other anti-psychotic free of motor side effects[158].
- There is insufficient evidence to conclude on the efficacy of quetiapine for the treatment of psychosis in PD.
- The practice implications are that quetiapine is investigational for the treatment of psychosis in PD.
- Quetiapine is not licensed for psychosis in PD[2].

Olanzapine

- Olanzapine is not helpful in improving psychosis in PD and worsens motor symptoms[2,129].

Other measures?

- Acetylcholinesterase inhibitors have shown some benefit in trials. Cognitive impairment has been consistently shown to be a risk factor for psychosis in PD and drug treatment of cognitive features may ameliorate psychotic features in PD[129]. However, further controlled studies on the effect of cholinesterase inhibitors on psychosis in demented and non-demented patients with PD are required[129,158].

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COMPASS THERAPEUTIC NOTES ASSESSMENT
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 250 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.
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- **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 MAOBI may be chosen as first line monotherapy.	T	F
	d	'Drug holidays' for Parkinson's Disease medicines should be recommended.	T	F
2	**In the Management of Motor Complications of Parkinson's Disease:**			
	a	Most patients who are treated with levodopa in the early stages of Parkinson's Disease will develop motor complications.	T	F
	b	Freezing of gait is a common cause of falls in patients with Parkinson's Disease.	T	F
	c	Entacapone is a suitable choice for combination therapy.	T	F
	d	The dose of levodopa should be increased if a MAOBI is added.	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	Symptoms such as reduced facial expression can make it difficult to diagnose depression in patients with Parkinson's Disease.	T	F
	c	Dosulepin is considered first line treatment choice antidepressant for patients with Parkinson's Disease.	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	Anticholinergic drugs used in the management of Parkinson's Disease can cause symptoms of dementia.	T	F
	b	Dementia with Lewy Bodies is the most common cause of dementia in the general population.	T	F
	c	Galantamine has been shown to be effective for dementia in Parkinson's Disease.	T	F
	d	Rivastigmine is licensed for dementia in patients with Parkinson's Disease.	T	F
5	**In the Management of Psychosis in Parkinson's Disease:**			
	a	Mild symptoms may not need to be treated if they are tolerated by patient and carer.	T	F
	b	Antipsychotics have been associated with an increased risk of vascular events in the elderly.	T	F
	c	Typical antipsychotics (e.g. phenothiazines) should be used in the management of Parkinson's Disease.	T	F
	d	Olanzapine may be helpful in improving psychosis in Parkinson's Disease.	T	F