Parkinson's disease

1. Parkinson's disease

The prevalence of Parkinson's disease is rising as the world population ages. However, diagnostic processes and management have not changed greatly in recent years. In primary care, our most valuable role may be in recognising the early symptoms, prompt referral for specialist diagnosis, and the management of non-motor symptoms. This article looks at some of the epidemiology and pathogenesis of Parkinson's disease, and summarises the older, but still relevant, NICE guidance. We also look at some of the developing areas in the management of motor and non-motor symptoms of Parkinson's disease (NICE 2017 NG71 Lancet 2015;386:896, Lancet 2024; 403:293, Lancet 2024;403:305, Lancet 2024;403:283, Lancet 2024;403:219).

This article was updated in December 2024.

1.1. Background

Parkinson’s disease (Parkinson's) is a neurodegenerative condition characterised by loss of dopaminergic neurones in the brain. This lack of dopamine results in the poor quality of movement that we classically see in Parkinson's (Lancet 2015;386:896).

Epidemiology

- Parkinson’s is the most common neurodegenerative disorder after Alzheimer’s disease (Lancet 2024;403:219).
- Prevalence is expected to rise to 12-17 million worldwide by 2040, due to ageing populations;; an increase of around 21% from 1990 (Lancet 2024;403:219).
- Parkinson’s is more common in males than in females (4:1 ratio) (Lancet 2024;403:283).
- Parkinson’s is only one possible cause of parkinsonism, which is the umbrella term for the constellation of tremor, rigidity and bradykinesia. Other causes of parkinsonism are listed within our summary of the NICE guidance.

Aetiology and pathogenesis

- The key feature is loss of dopaminergic neurones within an area of the midbrain called the substantia nigra.
- The hallmark of Parkinson’s is Lewy body pathology: abnormally-folded alpha synuclein protein forms inclusions within cell bodies (Lewy

bodies) or processes (Lewy neurites) of neurones.

- Typically, this occurs in the substantia nigra in the midbrain, but Lewy body pathology can be found elsewhere in the body which may explain some of the non-motor features of Parkinson's (spinal cord, peripheral nervous system, sympathetic ganglia, cardiac plexus, enteric nervous system and salivary glands).
- Neurodegeneration in Parkinson's is not just due to Lewy pathology. Other proteins and neuroinflammation are also thought to be involved.
- The cause is still unknown. A complex interplay of genetic and environmental factors are thought to be involved. Possible contributory factors are wide ranging and include pesticide exposure, rural living, prior head injury and beta-blocker usage (Lancet 2024;403:293).
- Pathognomonic features such as Lewy bodies are only found at post-mortem, which is not particularly helpful for our patients (Lancet 2024;403:283)! Imaging such as radionuclide positron emission tomography (PET) or single photon emission computed tomography (SPECT) have been proposed as ways to identify loss of dopaminergic neurones and diagnose Parkinson's. Unfortunately, these changes are also seen in other conditions such as supranuclear palsy and multiple system atrophy so are not specific to Parkinson's alone (Lancet 2015;386:896). **For now, the diagnosis of Parkinson's remains a clinical one.**

1.2. Anxiety and Parkinson's disease

Anxiety is known to be one of the possible prodromal symptoms of Parkinson's disease. A retrospective UK-based cohort study looked at adults aged ≥50y presenting with new-onset anxiety, and found a strong

association with later diagnosis with Parkinson's disease (BJGP 2024;74:e482).

The group with new anxiety had double the risk of Parkinson's disease diagnosis when compared with the non-anxious group, even after adjustment for lifestyle, age, sex, social deprivation, history of head injury, severe mental illness or dementia.

The study also identified other symptoms in the group with anxiety that were associated with increased risk of later Parkinson's disease: depression, fatigue, sleep disturbance, cognitive impairment, hypotension, tremor, rigidity, balance problems and constipation.

1.3. NICE guidance: Parkinson's disease diagnosis

The NICE guidance on Parkinson's was updated in 2017. It covers primary and secondary care management, but focuses on drug treatments and secondary care (NICE 2017, NG71). The headlines for us in primary care are:

- If we think someone has Parkinson's, refer them promptly to secondary care where a definitive diagnosis can be made.
- Management of motor symptoms will be a secondary care decision, but we should ensure these drugs are not stopped abruptly.
- Identify **non-motor symptoms** of Parkinson's and treat these or refer to neurology.
- Be aware of **impulse control disorders** (a side-effect of dopaminergic treatment), and refer promptly to neurology if these occur.

NICE on Parkinson's disease: DIAGNOSIS (NICE 2017 NG71)

Diagnosis in primary care

Parkinson's is a CLINICAL diagnosis.
Suspect Parkinson's in people presenting with:

- Tremor.
- Stiffness.
- Balance problems/gait disorders (not related to visual, cerebellar, vestibular or proprioceptive dysfunction).

Initially, the symptoms of Parkinson's are usually unilateral; however, they can become bilateral as the disease progresses.
In primary care, if Parkinson's is suspected, refer promptly to secondary care. Do not commence treatment in primary care.

Differential diagnosis of tremor

- **Rest tremor:**
  - Parkinson's disease.
- **Postural and action tremor:**
  - Essential tremor.
  - Exaggerated physiological tremor.
  - Hyperthyroidism.
  - Drug-induced, e.g. salbutamol.
  - Dystonic tremor.
- **Inattention tremor:**
  - Cerebellar disorders.

Differentiating Parkinson's disease from other forms of parkinsonism

Not all parkinsonian syndromes are Parkinson's.
Other causes of parkinsonism that are not Parkinson's:

- Alzheimer's disease.
- Multiple cerebral infarction.
- Drug-induced parkinsonism, e.g. phenothiazines.
- Progressive supranuclear palsy.
- Multiple system atrophy.

Diagnosis in secondary care

- Clinical diagnosis should be based on the UK Parkinson's Disease Society Brain

Bank Criteria (see below).

- SPECT imaging may be used in a specialist setting to differentiate essential tremor from parkinsonism if required. No other imaging modalities are recommended in the differential diagnosis of parkinsonian syndromes.
- Acute levodopa/apomorphine challenge tests and objective smell testing are not recommended.

UK Parkinson's Disease Society Brain Bank Criteria used in secondary care:
Step 1 is recognition of suspected parkinsonism in primary care; see 'Diagnosis in primary care' box above.
Step 2 and 3 are further inclusion and exclusion criteria and are used in secondary care.

Step 2: exclusion criteria for Parkinson's (secondary care)	**Step 3: supportive criteria for Parkinson's (secondary care)** (≥3 required for diagnosis of Parkinson's)

• Repeated strokes with stepwise progression.
• Repeated head injury.
• Antipsychotics or dopamine-depleting drugs.
• Definite encephalitis and/or oculogyric crisis on no drug treatment.
• More than one affected relative.
• Sustained remission.
• Negative response to large doses of levodopa.
• Strictly unilateral features after 3y.
• Other neurological features:
  • Supranuclear gaze palsy.
  • Cerebellar signs.
	• Unilateral onset.
	• Rest tremor present.
	• Progressive disorder.
	• Persistent asymmetry affecting the side of onset most.
	• Excellent response to levodopa.
	• Severe levodopa-induced chorea.
	• Levodopa response for >5y.
	• Clinical course >10y.

• Early severe autonomic involvement. • Babinski sign. • Early severe dementia with disturbance of language, memory or praxis. • Exposure to known neurotoxin. • Cerebral tumour or communicating hydrocephalus on neuroimaging.	

A Lancet series looking at developing areas of Parkinson's disease care highlighted that biomarker-based criteria for diagnosis in preclinical disease are becoming a possibility, with research showing that α-synuclein seed amplification assays can accurately distinguish Parkinson's disease (Lancet 2024;403:219, Lancet 2024;403:283). Genetic testing for the eight most common genes associated with increased risk of Parkinson's is also now possible, with around 15% of cases linked to genetic inheritance (Lancet 2024;403:283).

1.4. NICE guidance Parkinson's disease: management

The aim of management in Parkinson's disease is to maintain functional independence and quality of life (Lancet 2024;403:305).

NICE on Parkinson's disease: MANAGEMENT (NICE 2017 NG71)

- **Advise people with Parkinson's who drive that they should inform the DVLA and their car insurer at the time of diagnosis.**
- Patients with Parkinson's should see a neurologist/specialist nurse every 6–12m. Secondary care should advise regarding:
    - Pharmacological management of motor symptoms.
    - Pharmacological management of non-motor symptoms (more about these later).
    - An MDT approach, including physiotherapy, occupation therapy, speech and language therapy and dietitian input.
    - Diagnosis should be reconsidered if atypical features develop.
- NICE suggests discussing with patients the possibility of brain tissue donation after death to aid diagnostic confirmation and research.

Communication challenges in Parkinson's disease

- Loss of facial expression in Parkinson's can mask emotions and a possible need for emotional support.
- Parkinson's can impair communication and cognitive ability, or co-exist with depression. Oral and written information about the condition and its treatment should be provided routinely.
- A care plan should be agreed between the patient, family/carers (as appropriate) and secondary care.
- An accessible point of contact with secondary care should always be available, often a Parkinson's nurse specialist.

Pharmacological management of motor symptoms

Initiation/titration will be secondary care decisions. I have summarised NICE's suggestions later in this article for reference.
For us in primary care, the salient points from NICE are:

- Anti-parkinsonian medicines **should not** be withdrawn abruptly because this runs the risk of acute akinesia or neuroleptic malignant syndrome.
    - Risks are increased further if doses are missed or there is poor absorption,

e.g. gastroenteritis, abdominal surgery.

- Drug holidays are not recommended because of the risks of acute akinesia or neuroleptic malignant syndrome.
- The timing of doses is paramount; patients living in care homes may need to self-medicate to ensure medication times are adhered to.

- Deep brain stimulation may be offered if there is advanced Parkinson's and symptoms are not controlled by best medical therapy.

Pharmacological management of non-motor symptoms

People with Parkinson's often have non-motor symptoms associated with their disease. These can be more distressing than the motor symptoms, and include:

- Mood disturbance.
- Behavioural changes.
- Altered cognition.
- Sleep disorders and daytime hypersomnolence (excessive sleepiness).
- Altered sensation of smell.
- Bladder or bowel disturbance.
- Parkinson's dementia.
- Hypersalivation (drooling).
- Orthostatic hypotension.
- Unexplained pain.

In primary care, we are well-placed to identify and manage these symptoms/refer back to neurology.
Detailed management of these conditions is outlined later in this article.

Non-pharmacological management of motor and non-motor symptoms

Secondary care support, usually in the form of a Parkinson's specialist nurse, is key to facilitating:

- Regular access to clinical monitoring and medicines adjustment.
- A continuing point of contact for support, including home visits if required.

- Access to information about clinical and social matters.

For all patients with Parkinson's, refer to:

- Physiotherapy if balance/motor function difficulties (consider the Alexander technique).
- Occupational therapy if difficulties with activities of daily living.
- Speech and language therapy if difficulties with communication, swallowing or saliva. Expiratory muscle strength training may help with swallowing and minimise risk of aspiration. Attention-to-effort therapies may aid speech and communication (encouraging patients to listen carefully to their voice and ensuring speech is distinct, comprehensible and with even tone). Alternative and augmentative communication equipment may be required (such as sign language, touch technology or written information).
- If early in the disease, patients may benefit from referral to these services for assessment, education and advice.

Nutrition:

- Consider referral to a dietitian for all patients with Parkinson's.
- If on levodopa, recommend eating most of their daily protein in final meal of the day. This can help alleviate motor fluctuations for those on levodopa (but, in doing so, make sure their total protein intake does not fall).
- Advise over-the-counter vitamin D supplementation because of the risk of falls.
- Do not offer creatinine supplements to people with Parkinson's.

Impulse control disorders

- Impulse control disorders are a group of psychiatric conditions characterised by repetitive reward-based behaviours. There is a lack of ability to resist a certain urge to harm oneself or another. They are related to dopaminergic drug administration, and affect 14–24% of patients on medication for Parkinson's so are not uncommon. Examples are:
    - Compulsive shopping.
    - Binge eating.
    - Hypersexuality.

- Pathological gambling.

- Impulse control disorders can affect anyone on dopaminergic treatment but are more likely if:
  - On a dopamine agonist.
  - Premorbid history of impulsive behaviour.
  - History of alcohol consumption or smoking.
- Impulse control disorders can happen at any age, and men and women are thought to be equally affected (although men are more likely to experience hypersexuality).
- Impulse control disorder can be very distressing for patients and carers, and can even result in financial difficulties and criminal convictions.
- People affected will often cover up the symptoms, so carers and medical professionals should be aware of this association and ask about it.
- When carrying out a medication review, we should ask about symptoms if on dopaminergic treatment, especially a dopamine agonist.
- Liaise with neurology if you think a patient has developed an impulse control disorder:
  - Medication may be changed, e.g. reduction in the dose/stopping of dopamine agonists.
  - CBT may also be offered.
- **Do not stop dopaminergic treatment in primary care; stopping treatment suddenly runs the risk of neuroleptic malignant syndrome.**
- A useful information leaflet for patients is available on the Parkinson's Disease UK website (see useful resources, below).

Palliative care

People with Parkinson's should be offered oral and written information regarding:

- Progression of Parkinson's.
- Advance care planning, including DNACPR decisions, Advanced Decisions to Refuse Treatment (ADRT) and Lasting Power of Attorney.

- An opportunity to discuss end-of-life care, care needs and referral to the palliative care team as appropriate.

1.5. Drugs for motor symptoms

NICE on drugs for MOTOR symptoms

Initiation and drug titration takes place in secondary care. The information provided l wanting greater detail.

- All drugs used for motor symptoms provide *symptomatic relief only*; none affect the the disease.
- Initial levodopa treatment has better control of motor symptoms and improvemen dopamine agonists. However, levodopa also runs a higher risk of long-term motor complications/dyskinesia.
- Levodopa can be used in combination with another dopaminergic drug (an adjunct) have developed dyskinesia or motor fluctuations.
- There is not currently a good evidence base for adding an adjunct *at the beginning* o treatment. The theory is that doing this would mean lower doses of levodopa could b hopefully decrease the risk of motor complications down the line; this is an area NICE more research.
- **N.B. NICE does not mention decarboxylase inhibitors (carbidopa, benserazide, et but remember that levodopa is always co-prescribed with one.**

First-line treatments

- For early Parkinson's:
  - *Offer* levodopa if motor symptoms impact quality of life.
  - *Consider* levodopa, a non-ergot-derived dopamine agonist or MAO-B inhibitor do not impact quality of life.
- Ergot-derived dopamine agonists should not be offered as first-line treatment (see

Adjuvant treatment of motor symptoms

- Patients may be offered levodopa plus adjuvant treatment in the form of a non-erg dopamine agonist, MAO-B inhibitors or COMT inhibitor if they have developed dyski fluctuations.
- If symptoms continue despite levodopa plus an adjunct, amantadine may be consid consensus rather than evidence).
- Anticholinergics should not be used as adjuncts in Parkinson's:
  - No evidence of benefit.
  - Significant risk of adverse effects, including effects on cognition, hallucination retention.
- When patients start any dopaminergic treatment for Parkinson's, they should rece written counselling regarding the risks of:
  - Impulsive control disorders.
  - Excessive sleepiness and the risk of sudden onset of sleep.
  - Hallucinations and delusions.

The risk of developing any of these is increased by all dopaminergic treatment, but the risk i dopamine agonists.

Why not ergot-derived dopamine agonists first line?

- Ergot-derived dopamine agonists, e.g. bromocriptine, cabergoline and pergolide, ar recommended first line because of a risk of cardiac valvulopathy and serosal fibrosis.
- If an ergot-derived drug is used, patients should undergo baseline echocardiogram ESR/creatinine, and have regular follow-up (within 3–6m of initiation of treatment an 12m) (BNF, accessed July 2023).

Summary of drugs for motor symptoms

-	**First line for most**	**Adjuvant treatments for mos**		
	Levodopa	**Dopamine agonists**	**MAO-B inhibitors**	**COMT inhibitors (given with levodopa)**
How it works	Converted	Stimulate	Blocks	Block the

	into dopamine	nerve cells in the brain like dopamine would	breakdown of dopamine in the brain	breakdown of levodopa
Effect on motor symptoms	Most improvement	Some improvement	Some improvement	Some improvemer
Effect on ADL	Most improvement	Some improvement	Some improvement	Some improvemer
Improvement in off time	N/A	Most improvement	Some improvement	Some improvemer
Motor complications	**Highest risk**	Less risk	Less risk	Less risk
Adverse events	Less likely	**Highest risk**	Less likely	**High risk**
Adverse events defined as: excessive sleeping, hallucinations and impulse control disc				

As well as the well-known MAO-B inhibitors selegiline and rasagiline, a newer MAO-B inhibitor, safinamide, has come to market. It has only been compared with placebo. The DTB reviewed the evidence surrounding safinamide and concluded that, in view of the absence of data comparing it with selegiline or rasagiline and its significantly higher cost, it could not recommend its use over existing MAO-B inhibitors (DTB 2018;56(5):54).

1.6. Drugs for non-motor symptoms

NICE on drugs for NON-MOTOR symptoms

- Non-motor symptoms can be more debilitating than motor symptoms of Parkinson's.
- **Some non-motor symptoms are managed in secondary care, but there are many that we can manage in primary care, including depression, constipation, genitourinary and sexual symptoms, and pain.**
- Non-motor symptoms can often precede the presentation of motor symptoms – by up to 10y in the case of sleep disturbance and change in smell!
- Postural instability, cognitive impairment and orthostatic hypotension are more likely to be seen later in the course of the illness.
- There is a lack of evidence-based treatment for many of these symptoms. Some symptoms, such as olfactory disturbance, have no treatment options, and many of the other symptoms are treated off-licence.

This table is based on the 2017 NICE guidance on Parkinson's disease, with additions from a more recent Lancet review where relevant (NICE 2107 NG71, Lancet 2024;403:305).

Symptom	Treatment options
Daytime hypersomnolence	Advise patients if they have daytime sleepiness or sudden onset of sleep: • Not to drive, and to inform the DVLA of this change in their condition. • To consider occupational hazards. • To liaise with their Parkinson's specialist who may alter their Parkinson's drugs. Think about causes: • Side-effects of dopamine agonists or other sedative drugs. • Altered sleep pattern due to nocturnal urination. • Depression or anxiety.

	• Impulse control disorder. • REM sleep disorder. A stimulating daytime environment with bright light and regular exercise should be recommended (Lancet 2024;204:305). NICE recommends modafinil be considered in the treatment of excessive daytime sleepiness. • This use is off licence but is recommended by NICE. • Some patients respond well to this treatment; others have minimal response. • There is an MHRA warning about the risk of Stevens–Johnson syndrome with modafinil. • This is a secondary care decision! • All patients on modafinil should have a review with a Parkinson's specialist once a year, and need their blood pressure and heart rate monitored annually due to cardiovascular risks.

Nocturnal akinesia	• This is waking at night and being unable to move. It happens when levels of dopaminergic stimulation fall overnight.
	• It is not practical to wake in the middle of the night to take levodopa, and even if patients did this, there is a time delay of approximately 40min before the drug becomes active.
	• In the presence of nocturnal akinesia, a Parkinson's specialist may either:
	  • Introduce a modified-release preparation of levodopa at bedtime, or
	  • Use an oral dopamine agonist to treat the symptoms.
	  • Transdermal dopamine agonists can be used if oral treatments are not effective.

Orthostatic hypotension	NICE acknowledged the difficulty of treating co-existing supine hypertension and orthostatic hypotension.
	When assessing orthostatic hypotension, systolic BP is more important than diastolic BP.
	• Review regular medications. Common causes are:
	  • Antihypertensives (including diuretics), dopaminergics, anticholinergics and antidepressants.
	• Pharmacological treatment of orthostatic hypertension:
	  • NICE suggests midodrine first line as it is the only licensed treatment (see below).
	  • If midodrine is contraindicated/not tolerated/ineffective, consider fludrocortisone.
	  • Fludrocortisone is second line as its use is off licence. Before fludrocortisone is started, cardiac risks should be assessed (SPC advises can cause hypertension, fluid retention and oedema).
	• Domperidone has been used historically but is NOT recommended by NICE due to MHRA concerns regarding prolongation of the QT interval.
	Using midodrine
	• Midodrine is contraindicated in certain cardiac conditions, severe prostate disease, narrow-angle glaucoma, phaeochromocytoma and proliferative diabetic retinopathy.
	• Liver and renal function should be checked before starting and at regular intervals while on treatment.
	• Lying and standing BP should also be checked regularly because use is associated with the risk of supine hypertension.
	• There have been no head-to-head trials between midodrine and medications such as fludrocortisone. NICE outlined its reservations in making midodrine the first-line choice treatment; however, if felt it should be first line in view of good prescribing practice requirements imposed by

	regulatory and professional bodies. The Lancet suggests that if midodrine or fludrocortisone are used, they should be given earlier in the day to avoid night-time hypertension (Lancet 2024;204:503).

Depression	Remember to think of it! It can be difficult to diagnose because of overlap of symptoms, e.g. flat affect, sleep disturbance, motor retardation. It is common in Parkinson's patients.
	• Depression is commoner in people with chronic diseases in general.
	• Neurotransmitters such as serotonin can also decrease in Parkinson's and make depression more likely.
	• Depression can predate motor symptoms in Parkinson's by several years (Lancet 2024;403:305).
	• There is no specific guidance regarding depression in Parkinson's. NICE advises following its guidance on Depression in adults with a chronic physical health problem: recognition and management (NICE 2022, NG222).
	  • For people on MAOIs, SSRIs are contraindicated due to the risk of serotonin syndrome.
	  • The NICE guidelines on depression recommend that if taking MAOIs and co-existing depression, consider mirtazapine, trazodone, reboxetine or mianserin.
	  • There is evidence for the effectiveness of the tricyclic antidepressant desipramine and nortriptyline. Slow-release venlafaxine and dopamine agonist pramipexole can also be tried (Lancet 2024;403:305).
	• Non-drug strategies for mood disorder in Parkinson's include CBT, bright light therapy, transcranial magnetic stimulation, acupuncture and social prescribing (Lancet 2024;403:305).

Psychotic symptoms	Remember to ask about auditory or visual hallucinations and delusions. These can occur with dopaminergic drugs, but especially dopamine agonists. A collateral history from a carer may be useful. If psychotic symptoms are present, review for any underlying organic cause and treat appropriately. If no underlying cause is found, refer back to neurology: • If hallucinations/delusions are well tolerated and dopaminergic treatment is providing good disease control, treatment is not always warranted. • If treatment is recommended, quetiapine (first line) or clozapine (second line) may be used for psychotic symptoms. • Clozapine is licensed for this indication but quetiapine is not. • If a patient is commenced on clozapine, weekly blood monitoring is required for the first 18w, then fortnightly for 1y and monthly thereafter. This is because of the risk of agranulocytosis. Clozapine use has also been associated with intestinal obstruction, cardiomyopathy and fatal myocarditis (BNF, accessed June 2024). • Olanzapine is not recommended. • Other antipsychotic medications such as phenothiazones and butyrophenones can worsen motor symptoms of Parkinson's.
REM sleep behaviour disorder	This can be dangerous to the patient and whoever they share a bed with as there is a risk of injury! For this reason, treatment is often recommended. • There are no licensed treatments for REM sleep disorder. • Clonazepam or melatonin can be considered off licence by secondary care. • Rivastigmine is not recommended. Before we refer, we should carry out a medication review

	to assess for any causative agents. Also, don't miss the differential of restless legs in these patients! This can present in a similar way, and may benefit from management with exercise, avoidance of caffeine and alcohol, or oral iron (Lancet 2024;204:305). For more detail on the management of restless legs, you may find our article on that topic helpful.

Parkinson's disease dementia	Dementia affects 48–80% of people with Parkinson's. There are two types of dementia associated with Parkinson's:
	• Dementia with Parkinson's disease:
	  • Develops more than 1y after the onset of motor symptoms.
	  • Occurs as other neurotransmitters also decline in Parkinson's – loss of cholinergic stimulation can cause cognitive impairment, resulting in dementia.
	• Dementia with Lewy bodies:
	  • Dementia symptoms develop within 1y of the onset of motor symptoms.
	Both subtypes are managed in the same way; these will be secondary care decisions:
	• A cholinesterase inhibitor should be *offered* for people with mild or moderate Parkinson's dementia.
	• A cholinesterase inhibitor should be *considered* for people with severe Parkinson's dementia.
	• Memantine can be considered if cholinesterase inhibitors are not tolerated or contraindicated.
	Refer to the dementia NICE guidance (NICE 2018, NG97) for information on supporting people with dementia and their carers.

Saliva management	There is no specific evidence-based treatment for saliva management in Parkinson's. The treatment options

(drooling)	outlined here are from a body of evidence for patients with different neuromuscular conditions, *including* Parkinson's. • First-line treatment is non-pharmacological, e.g. speech and language therapy. • If speech and language therapy has not been effective, consider glycopyrronium bromide to manage drooling of saliva in people with Parkinson's: • Glycopyrronium bromide is contraindicated in people with cognitive impairment, hallucinations or delusions, or a history of adverse reactions to anticholinergic treatment. • If glycopyrronium is ineffective or contraindicated, consider botulinum toxin A. • Only consider other anticholinergic agents if benefits of use are thought to outweigh risks of cognitive adverse effects. Use topically if possible to reduce the risk of adverse events (e.g. patches or sublingual preparations). • The Lancet review suggests chewing sugar-free gum to prompt swallowing and reduce pooling of saliva, and also ipratropium bromide spray or sublingual atropine drops (!) (Lancet 2024;403:305).
Gastrointestinal symptoms	Parkinson's disease can trigger autonomic GI tract problems, including (Lancet 2024;204:305): • Delayed gastric motility, leading to nausea and vomiting: may benefit from domperidone. • Constipation: this is a common prodromal symptom and can predate clinical Parkinson's disease by several years. Constipation can also interfere with levodopa absorption if significant. Manage with exercise, high-fibre diet, increased hydration and laxatives where needed. Avoid triggering medications such as anticholinergics and opioids.
Genitourinary	• Bladder dysfunction symptoms of Parkinson's can

and sexual dysfunction	include nocturia, urinary urgency and frequency, bladder irritability and incontinence (Lancet 2024;204:305). Management may include lifestyle measures to reduce caffeine and minimise fluids before bedtime, anticholinergic medications and botox. • Sexual dysfunction in Parkinson's has been widely reported in men, although there is limited research in women (Lancet 2024;204:305). Men may report erectile dysfunction, delayed or reduced orgasm, decreased libido and decreased genital sensitivity. Management of erectile dysfunction is covered in detail in our article on that topic.
Pain	• Around 40–80 % of patients with Parkinson's disease suffer with significant pain, and prevalence of pain in Parkinson's disease is greater than in other chronic conditions (BJGP 2024;384:e078078). • Pain can be one of the early prodromal features of preclinical Parkinson's disease. • Pain in Parkinson's disease may be secondary to other recognised causes such as osteoarthritis, or be directly disease related (defined as pain that starts after diagnosis, responds to treatment with Parkinson's disease medications, is worse on the more-severely Parkinson's affected side of the body and with no other identified cause). • There are no specific guidelines, and limited evidence, on the management of pain in Parkinson's disease. Management will mostly follow usual pain management guidelines. • Managing lifestyle, improving diet (to improve levodopa absorption and therefore stability of dopamine levels), exercise therapy and management of mood through the MDT is the recommendation of consensus expert guidance. Research into deep brain stimulation or NMDA is ongoing.

There are four main subtypes of pain in Parkinson's disease:

MSK pain

The most common type of pain in Parkinson's disease. Low back pain prevalence is 50% higher than in age-matched controls. Pain affecting the shoulder/arm can predate rigidity and bradykinesia, and can include aching, cramping, myalgia, arthralgia and joint tenderness.

Due to:

- Abnormal forward and/or lateral trunk flexion.
- Rigid muscles.
- Increased risk of osteoporosis.
- Abnormal pain modulation (due to dopamine changes in the brain).

Treatment choices include:

- NSAIDs.
- Physiotherapy.
- Occupational therapy.
- Robotics to help manage gait imbalance (Lancet 2024;403:219); this is an emerging area.

Central pain syndrome

Central neuropathic pain is thought to be due to dopamine depletion in the brain and defective pain processing.

Symptoms include:

- Bizarre visceral pain.
- Features of dysautonomia such as abdominal cramps and hot flushes.

Treatment includes:

- Rotigotine patches (may be more effective than dopamine for this group).
- Tricyclic antidepressants.
- Weak opioids.

- Neuropathic painkillers.

Peripheral neuropathic pain

- Peripheral neuropathic pain affects one-third to a half of patients with Parkinson's. Radiculopathy has a high incidence due to abnormal posture causing nerve impingement.
- Large fibre neuropathy occurs in around 16% of Parkinson's patients.

Symptoms include:

- Pins and needles.
- Burning sensations.
- Sharp pain.
- Pain in nerve root distribution.
- Oral or genital pain.

Treatment includes:

- Capsaicin.
- Tricyclic antidepressants.
- Gabapentin.

Pain due to akathisia or dystonia

- Seen as a presentation of the 'OFF' phenomenon, where Parkinson's disease symptoms re-emerge as plasma levodopa levels decrease.

Symptoms include:

- Restlessness.
- Urge to move.
- Sudden painful contractions of a muscle group.

Management is through optimisation of dopamine agonists.

1.7. Levodopa in early disease

When to start levodopa is often a difficult question (tasked to our secondary care colleagues!). Use of levodopa has historically been delayed or spared by using other drugs because of concerns around side-effects from levodopa treatment (involuntary movements/fluctuations of motor control). Previous studies looking at whether the timing of initiation of levodopa has any effect on disease progression have shown mixed results (NEJM 2019;380:389).

A randomised, double-blind, placebo-controlled study which ran over 18 months showed that initiation of levodopa at the outset of the trial (compared with initiation at 40w) did not have any disease-modifying effects (NEJM 2019;380:315). The rates of dyskinesia and levodopa-related fluctuations in motor symptoms did not differ significantly between the two groups.

Following these studies, it is now understood that levodopa provides greater symptomatic relief than dopamine agonists, and should be the initial choice for treatment of almost all patients; this is with the exception of those with additional risk factors for dyskinesia, where dopamine agonists may be considered (Lancet 2024;043:305).

1.8. Management of late-stage disease

Management of patients with advanced Parkinson's disease can be difficult. It is crucial to remember that supporting people with increasing disability is about much more than the drug aspects of care. We also need to be thinking about advanced care planning and recognising when the end of life is

approaching.

In late-stage disease, abnormalities in other neurotransmitters contribute to symptoms. Motor and non-motor symptoms typically respond poorly to levodopa, leading to treatment-resistant symptoms (Lancet 2015;386:896):

- Freezing of gait and falls (up to 80% of those with disease for 17y).
- Dysphagia (up to 50% of patients with disease for 17y report choking).
- Dementia (83% of patients with disease for 20y).
- Autonomic symptoms: urinary incontinence, constipation with a need for daily laxatives, symptomatic postural hypotension.

There is a useful blog for carers and family members available on the Parkinson's Foundation website. It can provide a helpful starting point for discussions with carers about how we can help them to help their loved one Parkinson's Foundation - caregiving tips: helping a loved one in the later stages of Parkinson's. .

1.9. Neuroprotective agents

All medications for Parkinson's currently provide symptomatic relief ONLY. There is ongoing research into the **neuroprotective** effects of certain drugs to see if any drugs can slow the loss of dopaminergic neurones and therefore alter the underlying pathophysiology of Parkinson's.

NICE found there was no evidence for the use of vitamin E as a neuroprotective therapy (NICE 2017, NG71). Co-enzyme Q10, dopamine agonists and MAO-B inhibitors should not be used *as neuroprotective agents* in clinical practice, but are being used in the context of clinical trials (NICE 2017, NG71).

Parkinson's disease and urate levels:

- Some studies have suggested that hyperuricaemia may offer some protection against Parkinson's disease (BJGP 2017;67:284).
- This association was NOT demonstrated in a large BMJ umbrella review (BMJ 2017;357:j2376).
- A phase 3 trial of oral inosine (urate-elevating) treatment for people with early Parkinson's disease (not yet taking dopaminergic medication) was stopped early as interim analysis showed there was no difference in the rate of clinical disease progression compared with placebo (JAMA 2021;326:926).

GLP-1 mimetics

There is increasing interest in the prospect of GLP-1 mimetics to delay progression of Parkinson's disease. These drugs have been shown in animal studies to cross the blood–brain barrier and exert neuroprotective and neurorestorative effects. A UK-based longitudinal cohort study showed that, in people with type 2 diabetes, treatment with GLP-1 medications was associated with a reduction of more than 50% in the risk of Parkinson's disease compared with other diabetes treatments (Brain 2020;143(10):3067).

A very small (60 patients) double-blinded RCT assessed the use of exenatide in patients with Parkinson's (Lancet 2017;390:1664). Patients included were on dopaminergic treatment with wearing-off effects; they were randomised to weekly exenatide or placebo for 48w:

- There was an improvement of motor symptoms with exenatide compared with placebo.

A similar double-blind placebo-controlled trial (176 patients) into

lixisenatide looked at patients with early Parkinson's disease, diagnosed within the past 3 years (NEJM 2024;390:1176). Participants were randomised to either high-dose lixisenatide or placebo, and symptom scores were assessed at intervals up to 12 months using the Unified Parkinson's Disease Rating Scale. At 12 months, the treatment group had no change in their symptom scores, but the placebo group had worsened, showing greater motor disability. Adverse gastrointestinal effects (nausea and vomiting) were common, affecting 46% of those prescribed lixisenatide, and an associated editorial comments that further trials exploring the effectiveness of lower doses would be beneficial (NEJM 2024;390(13):1237.

	**Parkinson's disease** • If you suspect it, REFER. • Management of motor symptoms will be advised by secondary care. • Review for non-motor symptoms and treat/refer appropriately. • Assess for impulse control disorders and refer if they occur.
	Identify your practice population with Parkinson's disease: • Have they had an annual medication review? • Were non-motor symptoms or impulse control disorders discussed?
	**Useful resources:** *Websites (all resources are hyperlinked for ease of use in Red Whale Knowledge)* • Parkinson's UK – impulsive and compulsive behaviour in Parkinson's • Parkinson's UK – impulsive and compulsive behaviour checklist

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