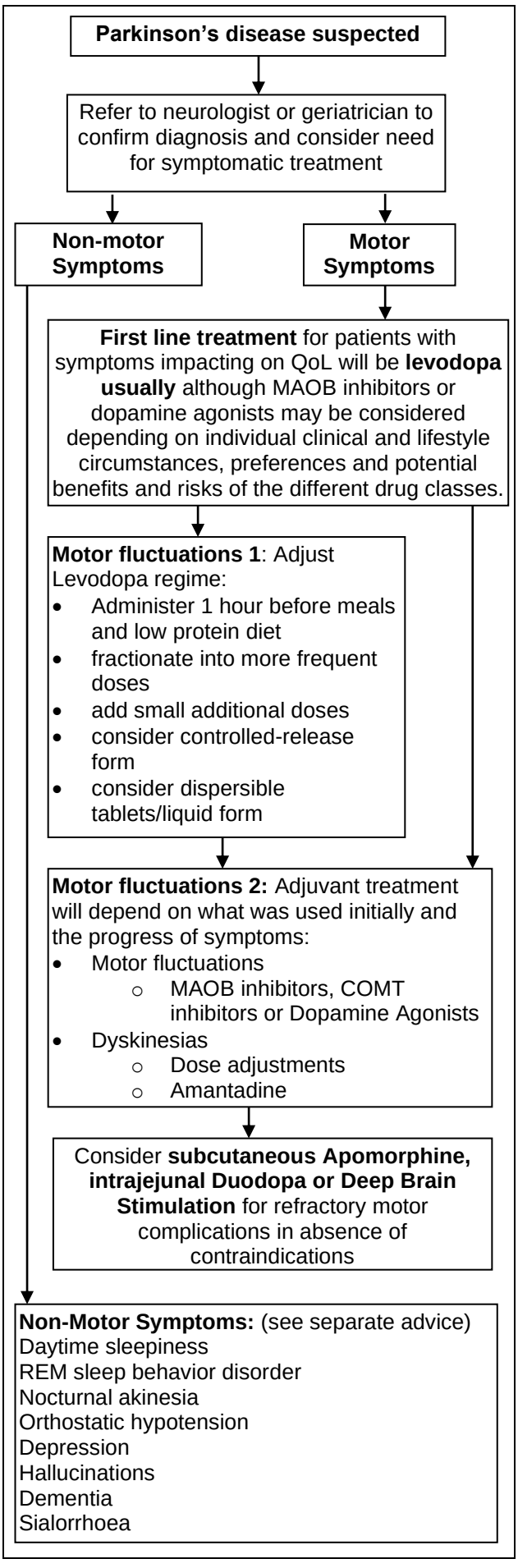
PHARMACOLOGICAL MANAGEMENT OF PARKINSON'S DISEASE



Principles of prescribing

- Referral to a specialist is advised to ensure accurate diagnosis and for treatment advice. **Younger** patients should be referred to a Neurologist and **Older** patients should be managed by Geriatrician with a special interest in Parkinson's disease. There is no absolute age cut off and the decision should be based on biological age, co-morbidities, and patient wishes

- Pharmacological measures should **not** be initiated prior to specialist referral. Drugs that have been categorised as green or amber may be initiated by or on the recommendation of the consultant. Any necessary monitoring and titration of doses will be undertaken by the consultants or specialist nurses.

- Non-pharmacological measures are extremely important and must be considered before initiating or increasing drug treatment. Parkinson's disease nurses are particularly qualified to give this support.

- The most recent NICE guidance advises that levodopa should be first line in patients in whom symptoms impact on their quality of life. However, individual clinical and lifestyle circumstances, patient preferences and the potential benefits and harms of the different drug classes will need to be taken into account [1]

- The use of Dopamine agonists should be tempered by common and/or serious side-effects: Impulse control disorders are a common problem (hypersexuality, gambling, compulsive spending etc.). Sleep attacks and sedation, visual hallucinations, psychosis and ankles oedema can also occur.

- Entacapone (or an alternative COMT inhibitor such as opicapone) may be used as an alternative to a dopamine agonist, in conjunction with levodopa, in late disease to reduce end-of-dose fluctuations.

- As the disease progresses most patients, will be on a cocktail of antiparkinsonian drugs that commonly include all three classes of drug [2]. See diagram at end of document.

- There is no evidence in favour of neuroprotection using MAO-B inhibitors, dopamine agonists, coenzyme Q10 or vitamin E which should **not** be offered in routine clinical practice.

- Excessive daytime sleepiness and sudden onset of sleep can occur with dopamine agonists (and more rarely with madopar/co-beneldopa and sinemnet/co-careldopa). Patients should be advised accordingly.

Formulary

4.9.1 Dopaminergic drugs used in parkinsonism

Levodopa

Co-beneldopa
Co-careldopa

Most effective treatment for motor disability and side effects are milder compared with some other treatments. May be considered as a **first-line** choice. Drug doses should not be escalated too rapidly. A clinical response would usually be expected at 300mg per day and it is unusual for patients to require more than 400-600mg per day.

A modified-release form may be useful for motor fluctuations and nocturnal akinesia. Due to decreased bioavailability, it is necessary to increase the dose by 30-50%. Absorption can be unpredictable and it may also be necessary to supplement the regimen with conventional tablets, particularly in the morning, to offset their slower onset of action. As a general rule, patients find the standard formulation preferable during the day.

Modified release levodopa should not be used to delay motor complications.

Nausea and vomiting are rarely dose-limiting but domperidone may be useful in controlling these effects. An ECG is needed pre and 2 weeks after starting domperidone to screen for prolonged QTc. Taking levodopa with food can limit nausea, but later in the disease, mealtimes are best avoided to aid absorption.

N.B. Duodopa® is an intestinal gel licensed for administration via an enteral tube. It is available in accordance with NHS England commissioning policy through specialist centres only.

Dopamine agonists

Pramipexole
Ropinirole
Rotigotine

The dopamine agonists are used either first line or as adjunctive treatment
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Choice:

- first-line choices are the non-ergoline agonists ropinirole or pramipexole.
- Rotigotine is a more expensive option available in a patch formulation which may be used for those patients who cannot tolerate the first-line oral agents.
- Pramipexole and ropinirole are available in once daily oral formulation which provide improved night time cover. Initial choice of agent should include consideration of the cost-effectiveness.

- If an agonist is tolerated in full dosage but without sufficient efficacy it is unlikely that an alternative agonist will be of more benefit.

- Excessive daytime sleepiness and sudden onset of sleep (sleep attacks) can occur with **all** dopamine agonists;

- Patients and their partners should be carefully counseled regarding the risk of impulse control disorders (ICDs) and hallucinations, and this conversation **formally documented**. Other risk factors for ICD aside from **dopamine agonist use** itself are a **history of previous impulsive behaviours** and a **history of alcohol consumption and/or smoking** [1]. There is a Parkinson's UK consent form to document this discussion which we would recommend is used (attached).

N.B. The ergot-derived dopamine agonists, bromocriptine, cabergoline, and pergolide are associated with pulmonary, retroperitoneal and pericardial fibrotic reactions. As a

consequence, these are no longer recommended routinely.

COMT inhibitors

By inhibiting metabolism of levodopa, entacapone allows a reduction in dose of levodopa and reduces end-of-dose deterioration.

COMT inhibitors can be used as an adjunct to levodopa therapy in patients who cannot be stabilised, particularly those with "end-of-dose" fluctuations.

Entacapone

This is available both as a preparation to be taken with each dose of levodopa and in a combined preparation containing levodopa, carbidopa and entacapone. The combination product reduces the number of tablets that patients need to take and ensures levodopa and entacapone are taken together. May be considered for patients:

- receiving levodopa and entacapone for whom compliance is a problem;
- receiving treatment with levodopa at the point at which entacapone would have been introduced;
- who have difficulty swallowing larger tablets.

Opicapone

This is a new once-daily COMT inhibitor which may be used in cases where entacapone has not been effective or tolerated.

Tolcapone

Use of tolcapone is not routinely recommended (red) due to the risk of adverse effects and requirement for rigorous liver function tests on a continual basis. It is however more effective than entacapone and opicapone.

Monoamine Oxidase Inhibitors (MAOI)

Rasagiline
Selegiline

Rasagiline or selegiline can be useful at the onset of motor fluctuations as an alternative to dopamine agonists or COMT inhibition. Consideration of the adverse effect profiles, contraindications and cautions may be used to determine the most appropriate first-line option.

The evidence for any neuroprotective effect in early disease is **not** established.[2]

There is a risk of **potentially hazardous** interactions with antidepressants and rasagiline or selegiline taken concomitantly although this is very rare. Specialist advice should be sought.

Safinamide is a new MAOI which is thought to have some additional anti-dyskinetic properties, although this has not yet been borne out by the clinical trials. It is currently non-formulary in Dorset.

Other medicines used for motor symptoms:

Amantadine

May be used for suppression of dyskinesias in advanced disease. Tolerance to its effects may develop and ankle oedema, livedo reticularis, confusion and hallucinations may occasionally occur.

Anticholinergic drugs used in parkinsonism

Trihexyphenidyl hydrochloride

Anticholinergics may be used` as a symptomatic treatment typically in young people with early PD and severe tremor, but should not be a drug of first choice due to limited efficacy and the propensity to cause neuropsychiatric side effects, which are common in elderly patients and should therefore be **avoided**. They are **contra-indicated** in cognitive decline, prostatism and glaucoma.

Advanced treatment in PD:

These are used for patients with medically-refractory motor complications of PD in whom there are no other contraindications.

Apomorphine

Subcutaneous Apomorphine may be considered for refractory motor fluctuations **not** controlled by levodopa or other dopaminergic drugs.

Treatment is managed by the Parkinson's disease specialist nurses. Given sub-cutaneously either by injection (in young patients with short off-periods) or by infusion in more disabled patients.

Other advanced treatment options include **intrajejunal duodopa** and **Deep brain stimulation, which are commissioned by NHS England.**

Non-motor symptoms in PD

Non-motor symptoms are increasingly recognized as a common cause of reduced quality of life in Parkinson's disease. Please see diagram at end of document for important considerations in approach to management. Non-pharmacological measures are often very important, as are drug side effects. Potential drug treatment options are listed:

Daytime sleepiness:
This is common and often a side effect particularly of dopamine agonists. Sometimes **modafinil** is used for secondary narcolepsy in PD where a detailed sleep history has excluded reversible pharmacological and physical causes. The NICE guideline states: "At least every 12 months, a healthcare professional with specialist expertise in Parkinson's disease should review people with Parkinson's disease who are taking modafinil. Patients will require regular blood pressure monitoring."

REM sleep behavior disorder:
This is common and often precedes the motor symptoms of PD, sometimes by many years. If troublesome small doses of **clonazepam**, or alternatively **melatonin PR** (within license for short term use in over 55's) can help.

Orthostatic hypotension:
This is rarely problematic but if so can be marked. Other medication (particularly treatment for hypertension etc.) and non-pharmacological measures are very important. NICE (2017) recommend **midodrine** (shared care guideline available) first line, and fludrocortisone if this is not tolerated or contraindicated.

Depression:
No specific advice but caution with SSRIs and MAOB inhibitors (small risk of serotonin syndrome)

Hallucinations:
These are also common but should only be treated if there is a clinical need to. Adjusting medication and intercurrent medical illnesses may be relevant. Options otherwise include low dose **quetiapine**.

Parkinson's disease dementia:
This may be managed via the Memory Services but more likely by the Parkinson's Disease specialists. The options include **Cholinesterase inhibitors** (**rivastigmine**, **donepezil**) or **memantine**.

Sialorrhoea:
There are various pharmacological options if non-pharmacological management is ineffective, including **glycopyrronium bromide, topical 1% atropine**, and hyoscine **patch** (all off-label). Where these options are ineffective, not tolerate or contra-indicated **botulinum toxin (Xeomin®)** in accordance with NICE TA605 may be considered.

Urinary urgency and urge incontinence:
This can be complicated by constipation and other medicines. Sometimes anticholinergics including **trospium** or **solifenacin** can be helpful. Alternatively, **mirabegron** may be preferred.

Constipation:
Education for lifestyle changes such as increasing fluid intake to at least 8 glasses of water per day and increasing fibre in the diet and getting regular exercise should be given. Consider use of laxative drug treatments particularly macrogol, titrated according to response. Suppositories (e.g. glycerin) and enemas may be required in resistant cases.

Contact names and numbers for Parkinson's Disease specialist nurses:

Name	Trust	Phone number
Sharon Atkins	Dorset Healthcare University NHS Foundation Trust (covering Christchurch/Ferndown /St Leonards/West Moors)	01202 979401
Anne Martin Angela Fong	Poole Hospital NHS FT	01202 448012
Cindy Cox	Royal Bournemouth & Christchurch Hospitals NHS FT	01202 705320
Hazel Greenman	Dorset County Hospital NHS FT	01305 254789
Carole Walker	Dorset Healthcare University NHS Foundation Trust (covering North and West Dorset, Bridport)	01258 394127

References

1. NICE Clinical Guideline no. 71, Parkinson's Disease, July 2017.
2. Management of Parkinson's Disease in 2017. Personalized Approaches for Patient-Specific Needs JAMA 2017 318(9): 791-2

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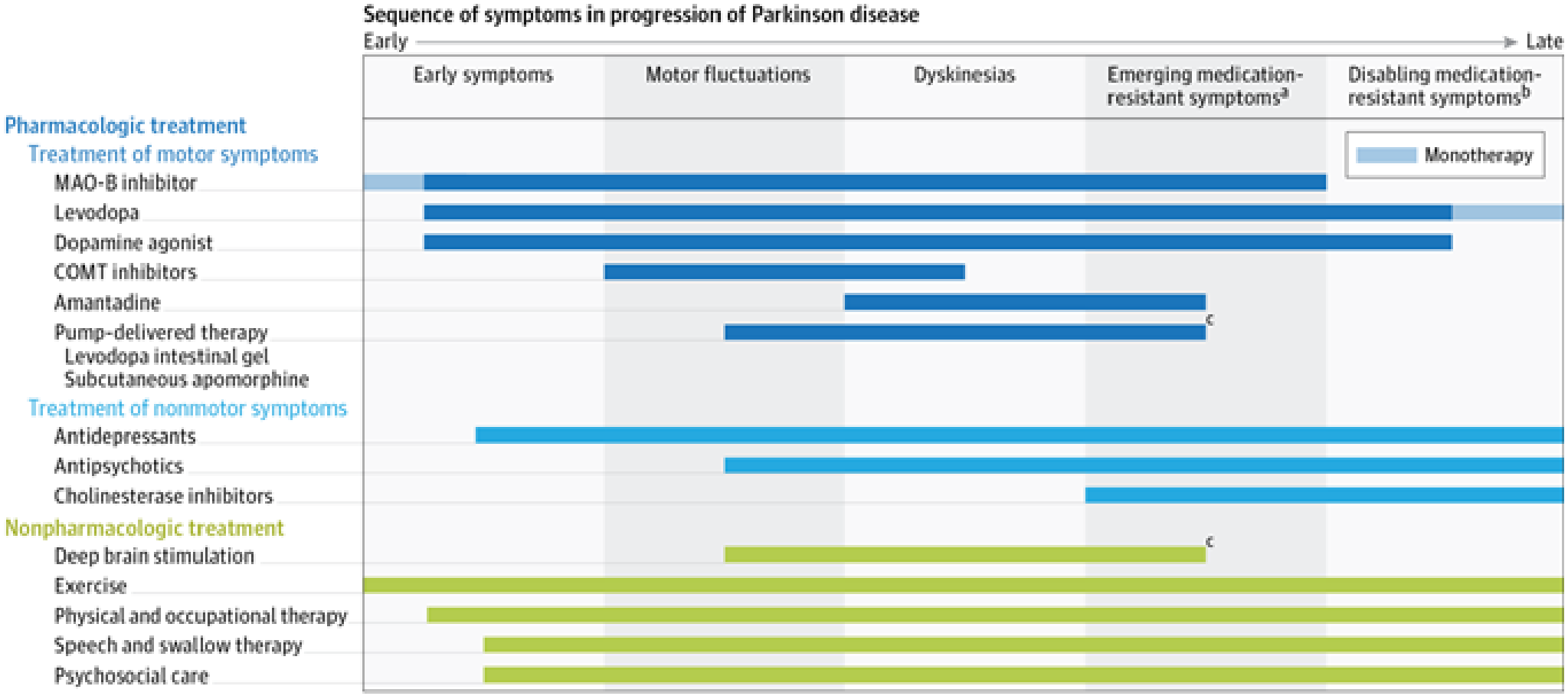

Bars indicate approximate periods of initiation and duration of each treatment except where noted. COMT indicates catechol-O-methyl transferase.

For the treatment of motor symptoms, drugs are usually added sequentially. Monoamine oxidase type B (MAO-B) inhibitor monotherapy may be started in the early symptom period followed by the addition of levodopa or a dopamine agonist. As symptoms progress, other drugs may be added and then discontinued as medication-resistant symptoms and adverse effects emerge. Levodopa may be continued through late stages of the disease as monotherapy.

Medication-resistant symptoms refer to symptoms resistant to medications for the treatment of motor symptoms.

[a] Gait dysfunction, soft speech (hypophonia), and memory and cognitive problems.

[b] Dysphagia, falls, and memory and cognitive problems.

[c] Beyond this point, pump-delivered therapy and deep brain stimulation should not be initiated but may be continued if already prescribed.