Parkinson's Disease- Treatment: medical, surgical and physical – the state of the art.

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Summary

While dopamine replacement therapy remains a core component of Parkinson's disease (PD) treatment, the onset of motor fluctuations and dyskinetic movements may require a range of medical and surgical approaches from a multi-disciplinary team, and important new approaches in the delivery of dopamine replacement are becoming available. The more challenging wide range of non-motor symptoms can also have a major impact on the

quality of life of a patient with PD, and requires careful multi-disciplinary management using evidence-based knowledge as well as appropriately tailored strategies according to an individual patient's needs. Disease modifying therapies are urgently needed to prevent the development of the most disabling refractory symptoms including gait and balance difficulties, cognitive impairment and dementia, and speech and swallowing impairments. In this review, we present the latest evidence supporting the optimal treatment of PD, while also describing an expert approach to those many aspects of treatment choice where an evidence base is lacking.

Introduction

This is the third article in a series of masterclass reviews on Parkinson's disease (PD) aiming to provide cutting edge information for the specialist, while remaining useful and accessible to the generalist. The first article describes the epidemiology and diagnosis, the second article covers the pathophysiology, and in this third article we describe the latest medical and surgical approaches for the treatment of PD. The Movement Disorder Society commissioned evidenced based reviews on the treatments for Motor[1] and Non-Motor symptoms (NMS)[2] for PD, published in 2018. Our purpose here is to provide a narrative of the recent developments in the treatment of PD since 2018, referencing the published evidence, while also providing expert opinion on PD treatment, particularly where the evidence base remains incomplete.

While all of the authors have considerable experience in the treatment of patients with PD, and supportive evidence has been sought where possible, any consensus opinion held by a small group of experts is to some extent subjective. Moreover, the availability and acceptability of some of the therapeutic approaches listed differs from country to country. It also cannot be assumed that these treatments will have equivalent benefits and side effect profiles in ethnically diverse populations.

Search strategy

We did our primary search of the PubMed database in April 2023 searching from 1st Jan 2017 up to January 2023. Searches were done for clinical trials published in English of medical or surgical or physical/non-pharmacological treatments for PD using the phrases "Parkinson's disease" and "Randomised trial". Abstracts were scrutinised and relevant articles were selected based on the expertise and the experience of the authors. Additional studies considered to be of major importance outside this time window, were also included, and expert opinion provided in instances where robust trial data were sparse or lacking.

Initial treatment of motor PD

The initial treatment of PD should follow an in-depth discussion about the diagnosis, as well as its variable natural history and the range of treatment options available. The patient should be aware that the role of treatment should be to maintain functional independence and preserve quality of life, that different treatment regimens exist and that choice and the timing of treatment introduction should take into consideration the type of presenting symptom and the patient's lifestyle and personal situation. Advice on diet and exercise, wellbeing and stress management[3] and signposting to reliable sources of information and

support are part of best management. From the outset, patients should be advised to keep well hydrated and to have a high fibre diet to reduce the risk of constipation. While large randomised trial data are lacking, cross sectional data would support the recommendation of a Mediterranean type diet[4], which in a small trial also improved cognition.[5] Where appropriate, aerobic exercise should be encouraged[6], while also taking into account of an individual's baseline fitness and frailty, to minimise the risk of injury.

The optimal pharmacological treatment of PD relies on knowledge and understanding of the published trial evidence alongside personal clinical experience. Clinical trial data can reveal that a treatment choice is more effective than placebo, but they are of little help in deciding the best medication regime for an individual patient.

Between the late 1980s and the first years of the new millennium, there was an erroneous concern related to the use of L-dopa early in the disease[7] with a recommendation by many but not all experts, that a long acting orally active dopamine agonist, or a monoamine oxidase B inhibitor (MAO-Bi) should be the initial drug treatment of choice. However, randomised trial data have confirmed that L-dopa is most likely to relieve motor symptoms of PD with the fewest side effects [8,9], although nausea, daytime sleepiness or postural hypotension may need to be addressed in a minority of patients. Initiating therapy with low doses of L-dopa (<400mg/day) is unlikely to accelerate the emergence of long-term complications such as dyskinesia and patients should be reassured about this.[8] Indeed, a delayed start study has shown no evidence of benefit nor harm from the earlier introduction of L-dopa indicating no evidence for earlier dyskinesia nor for disease modifying effects.[10] The American Academy of Neurology (AAN) recently published an evidence-based guideline for the treatment of early PD[11], aligned with NICE guidelines[12], both highlighting the greater symptomatic efficacy of L-dopa compared with dopamine agonists and recommending that L-dopa should be the initial treatment of PD, with the caveat that dopamine agonists might be preferable first-line treatment in patients with additional risk factors for dyskinesia.

Long term L-dopa use can lead to elevated plasma homocysteine which is a risk factor for stroke, heart disease and dementia and this can be prevented by routine supplementation with oral vitamin B12 and folic acid.[13] Patients unwilling to start L-dopa as monotherapy may prefer once daily (non-ergot) dopamine agonist or MAO-Bi preparations but should be counselled (as well as their partners) that impulsive behaviours may be seen in association with dopamine agonist use, possibly related to specific genetic polymorphisms[14], and if unrecognised can lead to major financial or marital strain. See Table 1 for an update of the treatment options for the motor symptoms of PD.

Adjunctive treatment of motor PD.

Inadequate symptom relief despite initial treatment may occur particularly among patients with tremor dominant disease, and escalating doses of L-dopa may sometimes be required, although if rigidity or bradykinesia are refractory to L-dopa despite good compliance, then it may be important to revisit the possibility of atypical parkinsonism. Among patients experiencing a good initial response to L-dopa, disease progression can lead to the re-emergence of troublesome motor symptoms. The decision in this circumstance is whether

to continue monotherapy at an increased dose, or to introduce adjunctive medication. Figure 1 shows an algorithm that can help guide the decision process. Frequently patients will experience optimal symptom control with fewest side effects by using low or moderate doses of multiple agents rather than using the higher doses of any single class of dopaminergic replacement.

Further progression of PD leads to the onset of the complex phase of PD which is characterised by a variety of motor fluctuations including; early morning OFF symptoms, end of dose wearing OFF, dose failures, and delayed ON time. Trial data supports the use of dopamine agonists[15], catechol-O-methyl-transferase (COMT) inhibitors, (including entacapone or more recently, the once daily opicapone[16 17]) or any of the MAO-Bi [18] in reducing OFF time in PD patients with motor fluctuations. As well as considering tools to ensure good compliance with prescribed treatment, it is important to make patients aware that L-dopa absorption can be delayed by slow stomach emptying and blocked by concurrent protein intake, and they should adjust the timings of their doses or meals to separate them by at least 1 hour. An extended release oral formulation of L-dopa, IPX066, can reduce OFF time by ~1 hour per day when compared with immediate release L-dopa[19] but requires a careful dose conversion strategy.[20]

The limitations of increasing dopaminergic replacement include the onset of L-dopa induced dyskinesia, symptomatic orthostatic hypotension, impulsive behaviours and the onset of distressing visual hallucinations. While there is a paucity of modern trial data regarding the efficacy of amantadine for initial symptoms of PD, it has dopaminergic effects as well as anti-glutamatergic effects which may be of use in the early treatment of PD as well as its more established role as an anti-dyskinetic therapy.[21] Indeed, amantadine is the only proven medical treatment to reduce dyskinesia although may worsen visual hallucinations. [22,23] Clozapine can have beneficial effects on dyskinesia and hallucinations but requires close monitoring given the risks of agranulocytosis [24], and patients should have a baseline ECG given risks of clozapine induced tachycardia.[25]

Non-oral therapies for the complex phase of Parkinson's disease

The strategy of providing continuous dopaminergic or electrical stimulation aims to address the narrow therapeutic window between patients' OFF symptoms and peak dose dyskinesia that emerges as part of the complex phase of PD.

Apomorphine

Clinical pharmacological studies carried out in the 1980s showed that 'OFF periods' occurring during long-term L-dopa therapy could be reversed by intravenous L-dopa or subcutaneous apomorphine.[26] These findings led to the use of apomorphine injections as a rapidly acting and reliable 'rescue' treatment for nocturnal immobility, delayed start up time, and individual oral dose failures. At the same time, patients with a more brittle and unpredictable response to oral medication were treated with waking day infusions of apomorphine.[27] A double-blind controlled trial with an open label extension period has endorsed the impression from 30 years clinical experience that apomorphine is an effective treatment for ON-OFF effects[28,29]. High quality evidence is also now available to support the use of nocturnal infusions to improve sleep maintenance and morning immobility in

patients unable to sleep at night.[30] The commonest reasons for discontinuation of apomorphine treatment are sedation, dizziness related to orthostatic hypotension and neuropsychiatric disturbances linked to incipient dementia. Autoimmune haemolytic anaemia is a very rare complication but it is recommended that an ECG, full blood count, reticulocyte count and Coombs test is done at 6 monthly follow up visits. Neria ^{TM} guard infusion sets have significantly reduced the incidence of abdominal wall panniculitis and it is now very unusual for skin irritation to be a cause for discontinuation of apomorphine. Dedicated PD specialist nurses experienced in dealing with device assisted therapies can greatly improve the long term success of this therapy. Guidelines for the use of invasive therapies in PD have recently been published.[31]

A sublingual formulation of apomorphine has been developed which can also allow rapid improvement of OFF periods although one third of trial participants had to stop the sublingual preparation due to oropharyngeal side effects.[32] An inhaled formulation of apomorphine has trial data demonstrating rapid beneficial effects although can cause transient throat irritation.[33]

L-dopa/Carbidopa Intestinal Gel

L-dopa/carbidopa intestinal gel (LCIG) administered through an intrajejunal percutaneous tube is another equally effective treatment of severe fluctuations that was introduced in Europe in 2004.[34] A systematic review confirms its long term efficacy. [35] Complications related to the gastro-jejunostomy are common and include tube kinking and dislocation, 'buried bumper syndrome' (retrograde migration of the internal bumper into the percutaneous gastrostomy tract) and infection. Peripheral neuropathy is uncommon but is a serious complication, the cause of which remains poorly understood, but prophylactic vitamin B1, B6, B12 and folate supplementation is recommended to try to reduce the risk of its occurrence. Diphasic dyskinesias are another serious unwanted effect in some patients most commonly occurring after the pump is stopped at night.[36] Recently a combined intestinal formulation of L-dopa, a peripheral dopa decarboxylase inhibitor and the COMT inhibitor entacapone has been introduced which has the advantage of a lighter, smaller and less noisy pump device.[37] A responsive multi-disciplinary team including the PD Neurologist, PD specialist nurse and Gastroenterologist is essential for the success of this approach.

Novel formulations of L-dopa

By bypassing the enteral administration route, the issues of delayed gastric emptying and interaction between dietary protein and L-dopa absorption can be avoided. An L-dopa inhaler can allow rapid symptoms relief [38] with randomised data demonstrating clinical efficacy and safety up to 12 months.[39] Subcutaneous preparations have been developed to enable continuous infusions of levodopa/carbidopa or foslevodopa/foscarbidopa and thus avoid the need for jejunal tube placement. Trial data from these approaches confirms improvement in OFF time accompanied by reduction in troublesome dyskinesia.[40] [41] Infusion site reactions are however not uncommon and advice on how best to deal with these to optimise long term tolerability will be important. The use of these therapies can be tailored according to an individual's requirements i.e. whether used for daytime only or for 24 hours, and whether used as monotherapy or as an accompaniment to oral medication.

Deep brain stimulation (DBS)

Following the first clinical description in 1995, [42] deep brain stimulation of the subthalamic nucleus (STN-DBS) has proven an effective therapy in several randomized controlled trials for PD patients with motor fluctuations by improving severe 'OFF-period' akinesia and 'ON-period' troublesome dyskinesia.[43] Randomized controlled trial data using quality of life (QoL) as the primary outcome parameter have confirmed benefits from neurostimulation compared with a medically treated, non-stimulated control group.[44] The focus has thus shifted from physicians' judgement of motor benefits to a more patient-centered evaluation of NMS, perceived stigma and psychosocial functioning after DBS. Given the positive effects on QoL of STN-DBS, it has been proposed for earlier stages of PD with motor complications and younger patient populations to reduce not only motor but also neuropsychiatric complications.[45]

A recent meta-analysis of five randomized controlled trials of STN-DBS against best medical treatment confirmed neurostimulation as superior to best medical treatment. Mean motor improvement of 35.4% was reported in motor symptoms as measured with UPDRS III off-medication, alongside 50.8% OFF-time reduction and 49.1% reduction of L-dopa induced dyskinesias.[46] Two trials have evaluated the globus pallidus pars interna (GPi) as a target for DBS [47,48] and both STN and GPi targets are accepted for DBS in PD with comparable improvement of motor symptoms, however, STN-DBS leads to a higher medication dosage reduction and is used more widely, while GPI-DBS has greater anti-dyskinetic effects. [49] Patients with tremor as the major disabling symptom may benefit from DBS of the ventro-intermediate thalamic nucleus (VIM-DBS).[50]

Careful patient selection is essential for DBS, and the preoperative L-dopa response is considered an important predictor of the motor improvement with STN-DBS.[51] An exception is drug-refractory parkinsonian tremor, which can be well treated by DBS. Cognitive impairment or acute psychiatric disorders are exclusion criteria since executive functions can worsen under DBS and surgery and STN-DBS may induce (transient) affective adverse effects. Importantly, postoperative reduction of dopaminergic medication after STN-DBS can improve neuropsychiatric fluctuations and hyperdopaminergic behavior such as dopamine agonist-induced impulse control disorder, so the presence of these symptoms are more recently considered additional arguments for DBS.[52] The latter is important when advocating STN-DBS in younger PD patients who have a higher risk to develop hyperdopaminergic syndrome leading to psychosocial dysfunctioning, loss of employment and reduced social participation early in the course of the disease. Importantly, improvement in QoL in the EARLY Stim cohort was correlated with improved NMS such as pain or depressive symptoms and associated with increased psychosocial functioning.[53] However, postoperative apathy and anxiety disorders may also occur if dopaminergic therapy is reduced rapidly, although this may not be the only contributing factor.[54] There are data to suggest that cognitive decline can be faster among patients with mutations in the GBA1 undergoing STN DBS[55], and careful discussions about the risks and benefits are needed in such individuals.

In the long term, STN-DBS has constant effects on tremor and rigidity but its impact may be limited by emergence of L-dopa refractory axial motor symptoms with increased falls, gait

disturbance, hallucinations and cognitive decline[56] related to progressive neurodegeneration and older age. Multidisciplinary management at experienced centers and comprehensive counselling of patients is needed to balance the individual benefits and risks that patients can expect from DBS. While risks of bleeding or infection are low among well-selected patients, chronic stimulation can be associated with the development of dysarthria or DBS induced gait and balance difficulties that may require stimulation adjustment. Technical advances to improve targeting using innovative imaging approaches or postoperative parameter setting selection (including directional current steering, shorter pulse width or computational and neurophysiological approaches for contact selection) may increase the effectiveness of DBS and help to reduce side effects of the treatment. [31,57]

Both apomorphine and LCIG are alternatives to DBS for the treatment of severe fluctuations and dyskinesias but only indirect comparisons can be made. In our opinion, the apomorphine pump is the least invasive of the three procedures and can be easily started and discontinued. It is also much cheaper than LCIG [58]and may even be useful in patients with visual hallucinations[59], severe OFF period anxiety and nocturnal difficulties.[30] LCIG offers a potential treatment for fluctuating patients with mild cognitive impairment, day-time somnolence and autonomic disturbance, and both provide an option for patients unsuitable for DBS. In common with STN-DBS, both allow the possibility for a marked reduction in oral anti- PD medication.

Ablative neurosurgery

Despite the mounting use of DBS surgery, there remain several good reasons why the creation of a precise lesion may sometimes be more desirable than the implantation of hardware. PD tremor can be very effectively treated by a precisely placed lesion in the VIM nucleus of the thalamus and this has the advantage of avoiding the potential risk of infection in higher risk patients, has no implications on future need for MRI scans, and is not associated with the emergence of tolerance that is sometimes seen following chronic VIM-DBS. [60] While the risks of thalamic DBS and thalamotomy are similar, patient interest in thalamotomy has grown exponentially since the availability of high-intensity focused ultrasound that allows lesion creation without the need for scalp incision or burr hole placement.[61] Among patients in whom DBS is not desirable or available, pallidotomy [62] (or pallidothalamic tractotomy[63]) or subthalamotomy [64] can provide good control of dyskinesia or OFF symptoms respectively. Generally, lesions are performed unilaterally given the frequent adverse effects associated with bilateral procedures although bilateral subthalamotomy is being further explored. For further details, a detailed guideline for the use of invasive therapies in PD has recently been published by a joint task force of the MDS and European Academy of Neurology.[31]

Treatment of Non-Motor symptoms (NMS)

NMS in PD are the result of pathological involvement in a range of systems; including neuropsychiatric; autonomic; sleep and pain. Such symptoms may be more disabling than motor symptoms, with a significant impact on QoL. [65] The key to managing any NMS is a good history to determine timing of the symptoms in relation to dosing of L-dopa medication.[66] Thus, in many instances NMS may reflect a low level of dopamine in an OFF

state (especially anxiety, apathy, pain, some dysautonomia, sensory issues).[67] Equally, some symptoms may occur at the peak of L-dopa benefit and include psychosis, agitation, and euphoria. In such instances, treating the fluctuations with adjusting L-dopa dose, timing and adjunctive therapies may reduce the NMS.[68] However, a significant number of PD patients have NMS that do not fluctuate.[69] A review of the literature from 2018 – present has revealed some new treatment options but still many NMS remain challenging to treat (Table 2).

Depression & Anxiety

Neuropsychiatric issues experienced in PD include anxiety and depression. These symptoms may predate the onset of motor symptoms by several years. In such individuals, commencing dopaminergic therapy with the onset of motor symptoms may also alleviate depression and anxiety. Thus, MAO-Bi may alleviate depression in early PD but appear to have less benefit in advanced disease.[70] Use of dopamine agonists as antidepressants *per se,* benefits depression above their motor effects. [71,72] However, the concern of side effects with dopamine agonists, including impulse control disorders and sleep dysfunction, may limit their clinical usefulness. Tricyclic, serotonin selective reuptake inhibitors (SSRI), and serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants have all been evaluated for PD depression in small numbers of trials to date, with variable but generally positive outcomes.[2] Tolerability of SSRIs and SNRIs appears to favour this class of antidepressant above tricyclics but with no large comparative trials in PD patients to date, the choice of antidepressant remains pragmatic and relies on clinical judgment. Additional concerns about the rare risk of serotonin syndrome may lead to under prescribing of such antidepressants if subjects are on a MAOBi.[73] An RCT in 408 PD subjects is underway to compare escitalopram, nortriptyline or placebo for 8 weeks with 12 months follow up which may provide evidence to assist in treatment choices for depressive symptoms in PD.[74] Likewise, a lack of evidence based medicine (EBM) recommendations for therapies for anxiety in PD, means that pharmacological therapies, have to date, relied on widely available anxiolytics, including benzodiazepines and antidepressants. The common clinical scenario of anxiety occurring as an OFF-period symptom, should always remind clinicians to review the timing for this symptom in relation to L-dopa doses.

Non-pharmacological strategies for mood have seen an increase in recent years. For depression, these include repetitive transcranial magnetic stimulation (rTMS) that is effective in elderly non-PD depression [75] but has had limited adoption for PD-related depression.[76] Cognitive behavioural therapy, including use of virtual-options, has shown benefit in depression and anxiety.[77,78] Bright light therapy may have benefit with possible additive effects on sleep.[79] Acupuncture was also recently reported to improve anxiety after 8 weeks.[80] The exacerbation of anxiety with external stressors, such as leaving familiar surroundings, needs to also be managed and the importance of 'social prescribing' due to isolation has also been highlighted as a major benefit for PD patients with anxiety.[81] Apathy is a unique PD symptom that is extremely challenging to treat and can be pervasive. Non-pharmacological options for mood disorders using exercise and occupational therapy are discussed below.

Psychosis

PD-related psychosis consists of a range of symptoms, including illusions, well-formed visual hallucinations, less common other sensory–modality hallucinations and paranoid delusions. There is often co-existent cognitive impairment, and the pathophysiology involves cholinergic, serotonergic (especially 5HT2A) and dopaminergic dysfunction.[82] Management includes the exclusion of non-PD related medical triggers such as inter-current infection, constipation or metabolic upset, that are still the most frequent cause of acute or worsening of psychosis symptoms. Persistent and troublesome psychosis requires treatment with atypical antipsychotics, quetiapine, pimavanserin or clozapine. Quetiapine is often first line due to ease of use. To date, there are no comparator RCTs between these antipsychotics but a recent meta-analysis[83] reports clozapine remains the most effective for significant paranoid delusions, but lacks widespread use due to logistical challenges with prescribing due to required safety monitoring of white blood cell counts. For visual hallucinations, even in the absence of dementia, the cholinesterase inhibitors (ChEI), rivastigmine and donepezil can be very effective although RCT evidence is sparse.

Cognitive impairment

Cognitive decline from mild cognitive impairment (MCI) to dementia is a common NMS in PD. Pharmacological strategies using ChEI are thought to enhance cholinergic transmission in basal forebrain and cortical cholinergic areas. Donepezil and rivastigmine are both used clinically in PD dementia, although only rivastigmine has consistent positive outcomes in RCTs. [2] For more advanced cognitive impairment with DLB, a novel dopamine D1 agonist, mevidalen was assessed as a cognitive enhancer but was ineffective on cognitive measures.[84]

Preventing the development of dementia in PD MCI is a large area of research. Early use of ChEI has been evaluated but with no consistent benefits.[85] Other techniques including cognitive training[86]; dDCS [87] and rTMS combined with virtual reality [88] are other possibilities that need further investigation.

It is increasingly recognised that dementia in PD subjects can be due to mixed pathologies.[89] Thus, in addition to Lewy body pathology, vascular disease and co-existent Alzheimer's pathology may be contributing to cognitive issues, therefore needing better diagnostic tools to differentiate causes of dementia, manage treatable risk factors (such as BP) and develop future therapeutic targets.

Autonomic symptoms

Optimization of dopaminergic therapy may have limited effects on the autonomic aspects of the disease. Delayed gastric motility is a primary feature of PD, and adverse effects of medications may lead to nausea and vomiting. [90] Where clinically available, the peripherally acting dopamine antagonist, domperidone in a typical dose of 10 mg up to 30 mg/d, may reduce nausea, but requires ensuring a non-prolonged QTc interval on ECG prior to use. Dopamine D2 antagonists with central effect such as metoclopramide should be avoided due to the inevitability of them worsening PD motor symptoms.

Constipation is a prevalent symptom observed in all stages of PD, including the prodromal phase, and may manifest several years before the appearance of motor symptoms.[91] Constipation increases the risk of complications such as pseudo-obstruction, volvulus, and bowel perforation and also interferes with L-dopa absorption.[90] Initial management is usually non-pharmacological, including increasing exercise, diet changes (fibre and probiotics), adequate hydration and avoiding medication that can worsen this symptom, such as anticholinergics and opioids. [92] If these measures are insufficient, osmotic agents, bulking agents, suppositories and motility stimulants can also be added if tolerated. Involving a gastroenterologist may be appropriate if constipation is refractory to such measures.

Bladder dysfunction represents a significant burden on patients' QoL, including nocturia, urinary urgency, urinary frequency, and incontinence.[93] Non-pharmacological measures to reduce urgency and incontinence include limiting fluid consumption before bedtime and reducing caffeine. Pharmacological management includes optimizing dopaminergic therapy, anticholinergics such as solifenacin or fesoterodine (caution as they can worsen constipation, cognition and psychosis) and mirabegron, a β3-adrenoceptor agonist.[94] Botulinum toxin type A injections into the detrusor muscle may become an option in refractory cases and must be performed by trained urologists.[95] Sexual dysfunction in PD includes erectile dysfunction in men, difficulty reaching orgasm, decreased libido, and decreased genital sensitivity in both sexes. Men with erectile dysfunction can use phosphodiesterase inhibitors like sildenafil, tadalafil and vardenafil if there are no contraindications.[96] However, women's sexual dysfunction remains an area to be further explored.

Sialorrhea is a frequent problem for patients with PD. When mild, it mainly occurs at night, but as PD progresses, it can occur any time during the day, causing embarrassment, stigma and severe aspiration risks. Non-pharmacological strategies to reduce sialorrhea include recommending chewing sugar-free gum to trigger spontaneous swallowing. [97] Pharmacological strategies include use of sublingual atropine drops or glycopyrrolate. [98] However, side effects are similar to any anticholinergic drug, including mouth dryness, blurry vision, constipation, urinary retention, and worsening hallucinations and memory problems. Botulinum Toxin injections targeting the parotids and submandibular glands reduce saliva production with an appropriate safety profile if performed by trained physicians. [99]

Orthostatic hypotension (OH) in PD is common, particularly as the disease progresses. OH, is defined as an orthostatic fall of at least 20 mmHg in systolic or 10 mmHg in diastolic BP within 3 minutes of standing. Importantly, patients with PD may also experience delayed OH, with drops after 3 minutes of standing or extended periods. Other OH symptoms include light-headedness, headache, shoulder pain and cognitive slowing with postural changes or postprandially.[100] An initial management strategy still relies on reducing blood pressure lowering drugs if possible, although this can be challenging when using specific drugs for treating overactive bladder symptoms, or clozapine that also results in lowered BP. Non-pharmacological approaches can be effective including increasing salt and water intake, avoiding large meals, and elevating the head of the bed. Compressive stockings or abdominal binders have been suggested but in clinical practice, these measures can be

problematic and have suboptimal effects.[101] If symptoms persist, domperidone about an hour prior to L-dopa; early day dosing of midodrine and fludrocortisone[102] (to avoid nocturnal high BP) and droxidopa, can be added to the treatment according to local availability and monitoring specific side effects, including nocturnal supine hypertension. [101]

Disorders of sleep & wakefulness

Sleep can be widely disturbed in PD. Insomnia is multifactorial due to motor symptoms during the night, effects of some antiparkinsonian medications, neuropsychiatric symptoms and nocturia. Sleep hygiene and assessing concomitant medications that could be causing insomnia are the first step in management. Sedative drugs that cause drowsiness during the day should be avoided. [103] Nonbenzodiazepine cyclopyrrolones, doxepin, melatonin, trazodone and mirtazapine can be helpful for insomnia in selected cases.[104] If excessive daytime sleepiness is present, a stimulating daytime environment, exposure to intense light during the day, and regular exercise should be recommended. [105] Decreasing dopamine agonists, anticholinergics, and amantadine may help reduce these symptoms. In addition, caffeine may be helpful in selected cases but results in randomized trials have only shown marginal benefits on somnolence which attenuated over time. [106]

Frequent bouts of REM behaviour disorder (RBD) can lead to complications, including sleep disruption and injuries to the patients or their bed partners. This can occur even in the pre-motor stages of PD. Patients need to be educated about potential injuries and assess bed-safety measures. SSRIs and tricyclic antidepressants can trigger or worsen RBD, and their use may have to be reconsidered. Clonazepam and melatonin at low doses before bedtime had been broadly recommended with a limited level of evidence based on clinical experience.[107]

Finally, restless leg syndrome (RLS), is a common condition among individuals with PD. It is characterized by an uncomfortable sensation in the legs, which causes an irresistible urge to move them. [108] RLS can cause significant sleep disturbances, which can worsen other symptoms of PD. The management of RLS in PD involves several approaches. Lifestyle modifications such as regular exercise, avoiding caffeine and alcohol, and practicing good sleep hygiene can be helpful. In some cases, addressing underlying conditions such as iron deficiency can improve RLS symptoms. Dopamine agonists, alpha-2-delta ligands, and opioids can be also effective but these treatments for RLS in PD have not been evaluated in controlled trials.[109]

Pain

Pain can severely affect patients' QoL. Pain in PD is usually considered PD related when temporally related to the disease onset, symptoms or treatment. [110] Patients with PD also experience PD-unrelated pain or aggravations of previous chronic pains due to indirect effects of the disease. PD-related pain often occurs during OFF periods but can also be associated with dyskinesias and early morning dystonia. Possible non-pharmacological interventions include stretching, exercise and massage.[111] Over-the-counter pain medication may help but should be recommended cautiously and under physician supervision. Dystonic pain mostly responds to PD drugs or botulinum toxin injections in the affected muscles.[112]

The role of Allied Health professionals

In the past there was a paucity of evidence for the effectiveness of intervention from allied health professionals (AHPs), but recent studies, particularly physiotherapy studies [113] [114] [115] have demonstrated that AHP intervention can help mitigate NMS and motor symptoms, addressing issues that medication alone cannot resolve.[116] [117] A multidisciplinary team (MDT) or integrated approach is recommended [118] [119] [120] to enable symptoms to be addressed holistically by the appropriate disciplines and to ensure best outcomes for individuals. Physiotherapy, Occupational Therapy (OT) and Speech & Language Therapy (SLT) have increasing evidence for efficacy in the management of PD.,[116,121,122] [123]

Early referral to physiotherapy for assessment, advice and intervention, including encouraging engagement in physical activity and exercise is recommended [12] [113] , although beneficial effects may depend on the precision of the intervention. [124] Randomised trial evidence suggests that exercise, especially aerobic, can reduce motor severity, increase functional outcomes, and improve NMS including cognition and mood. [125] [126] [127] Intensity and duration are important elements to be included in exercise advice and there is evidence this can reduce risk of hospital admissions.[128] However, many patients with PD, especially older adults, struggle to achieve recommended levels of activity and are largely sedentary, spending only 6% of the day in moderate to vigorous activity.[129] Clinicians can encourage conversations around activity from diagnosis, and the Moving Medicine website [130] offers practical suggestions for introducing the topic even when consultation time is short. However, this should be followed by referral to physiotherapy for an individualised and tailored programme to be recommended and to identify and address any barriers.

As PD progresses, access to physiotherapy is important to address emerging problems including gait, balance (including falls prevention), posture and transfers issues. Falls are common in PD. Physiotherapy intervention can reduce incidence of falls in those with lower severity PD, although not in those whose PD is more progressed.[131,132] Freezing of gait is a falls risk and can be impacted by NMS such as anxiety. An MDT approach, whereby anxiety management is offered by the OT, and gait rehabilitation including cueing techniques (e.g. laser pens, music & metronomes) by the physiotherapist, can be more effective in reducing FOG incidence.

Systematic reviews highlight the benefits of OT for individuals with physical activity, handwriting and activities of daily living (ADL)[133], as well as improving quality of life.[119] The OT role is also important in addressing NMS, including cognition, anxiety, fatigue, sleep and apathy. Cognitive strategies, and advice on anxiety or fatigue management as well as sleep hygiene advice can support patient self-management. For individuals of working age, addressing work-place issues is also an integral part of the role. Signposting to local agencies and carer support is important throughout all stages of the condition but particularly as it advances.

Changes in voice quality including reduced loudness, and a weak or breathy voice quality can occur early and contribute to communication issues. Early referral to SLT can enable the

individual to develop strategies and management techniques that may offset problems at a later stage. [134] As the condition progresses, problems with speech initiation, or fast speech can reduce intelligibility. SLT intervention can offer voice techniques (including the use of Lee Silverman Voice Therapy [117,135]) and advice on communication aids where appropriate. Advice can also be given for excessive drooling which can be a distressing and embarrassing problem. Dysphagia is more common in the later stages and assessment, education and advice on texture modification are an essential SLT role. Involvement of dieticians, social work teams, and other sources of carer support is of increasing priority with disease progression.

Future studies

The onset of dopa refractory gait and balance difficulties often coincides with worsening autonomic and cognitive function and the symptomatic therapies at this stage are woefully inadequate. Improvements in the routine integrated provision of palliative care for patients is a priority, as this has trial evidence of its impact on quality of life[136], as and more studies are needed examining individualised approaches to management with respect to gender e.g. hormone replacement therapy[137], or within other subphenotypes of PD.

What is most needed is an intervention that can prevent progression to the more complex phases of the disease. This far, there have been no agents that have been conclusively proven to modify the progression of the disease, and while there have been recent disappointments in phase 3 trials of repurposed agents [138-140], there remain hopes that a number of other repurposed agents including e.g. GLP1 receptor agonists may offer benefit by reducing neuroinflammation in a broad population of patients [141], while agents targeted to specific subgroups such as a LRRK2 inhibitor for LRRK2 patients [142], or a GCase chaperone for GBA1 patients may yet also be proven to be effective. [143] Immunotherapy using antibodies against alpha synuclein epitopes has shown mixed results[144,145], but at least 1 antibody approach is still undergoing further trial evaluation. Gene therapy approaches using antisense oligonucleotides (ASOs) or viral vectors may also be best directed to subgroups of patients according to specific genotypes, while potentially still having potential relevance even for gene negative PD patients[146]. Alongside targeting specific therapies to specific patient subgroups, efforts to increase the number of interventions being tested, improved measures of target engagement and outcome measurement should also improve the likelihood of identifying agents that usefully slow down disease progression[147,148]. Multi-arm, multi stage platform trials should address some of these issues.[149]

Conclusions

Despite the breadth of successful medical and surgical treatment options for motor symptoms of PD, there is a large unmet clinical need for targeted and specific treatments for NMS in PD. For many PD subjects, NMS are not able to be treated in isolation, as many have ‘clusters’ of symptoms such as anxiety, cognitive impairment and low BP occurring together. Thus, a clinical challenge is using pharmacological therapy for one issue without side effects. The clinical features and hence pathophysiology of many NMS in PD such as depression, orthostatic hypotension, sleep disorder, GI issues in PD are likely different from these symptoms in non-PD patients. There therefore remains a need for more preclinical

and clinical research to enable ‘PD-specific’ pharmacological therapies. For symptoms where multiple options exist, it remains unclear which option to choose due to lack of comparator RCTs for treating e.g. depression, sleep and pain. The increase in non-pharmacological approaches such as mindfulness, CBT and others has promise to help more NMS and in particular better individualise therapy[150].

While L-dopa remains of major importance in the treatment of patients with PD, there is increasing recognition of the L-dopa refractory elements of PD, and the role of different neurotransmitter systems in their origin. The holistic treatment of patients with PD requires enquiry of the broad range of motor and NMS and the involvement of the multi-disciplinary team in their effective long-term management. In the absence of primary preventative strategies, effective, safe and well tolerated agents that reliably slow down the progression of PD are urgently required.

Legend to Figure 1.
Algorithm for the approach to treating PD- authors’ personal recommendations.

Table 1. Non invasive treatments for the motor symptoms of Parkinson's disease

INTERVENTION	MDS EBM RECOMMENDATION (Fox et al 2018)	UPDATE 2018 - 2022	Expert comments
MAO-Bi	Rasagiline useful as monotherapy, adjunctive therapy or for motor fluctuations. Selegiline useful as monotherapy. Zonisamide and Safinamide useful treatments for motor fluctuations.	Selegiline [18] demonstrated to be clinically useful for motor fluctuations.	Inhibition of MAO-B has a modest but useful effect in enhancing dopamine levels. They are generally well tolerated, so can have a potential role as monotherapy in those people with minor disability. There is a theoretical risk of serotonin syndrome when co-administered with serotonin selective reuptake inhibitors, but this is very rarely seen in clinical practice despite the frequent co-administration of these agents.[73]
Non-Ergot Dopamine Agonists*	Each of the non-ergot dopamine agonists (Pramipexole, Ropinirole, Rotigotine) has evidence to support their use as monotherapy, adjunctive therapy or as treatment for motor fluctuations.	Sublingual apomorphine is an effective on-demand treatment for OFF episodes in PD, although oropharyngeal side effects can limit its tolerability.[32] Ropinirole patch preparation has been shown to be non-inferior to Ropinirole tablets.[151]	Pramipexole, Ropinirole and Rotigotine all have acceptable efficacy and safety profiles in PD. All patients should have counselling regarding the risk of impulsive compulsive behaviours and these agents are best avoided in patients with a history of impulsive compulsive behaviours. It is important however that clinicians do not develop a phobia of using these agents, as they have an important role particularly as adjunctive agents to allow for lower doses of L-dopa to be used, thus avoiding accelerating the appearance of L-dopa induced dyskinesia.
L-dopa/ DDI	Standard, controlled release and extended release formulations of L-dopa are all effective as monotherapy, while extended release L-dopa and intestinal L-dopa can all improve motor fluctuations.	Inhaled L-dopa has been shown to be effective for Off episodes in PD.[38,152] Transcutaneous infusions of L-dopa have encouraging efficacy data but with concerns regarding long term tolerability.[40,41] Routine supplementation of Vitamin B12 and folic acid may prevent elevations in Homocysteine levels associated with chronic L-dopa use.[13]	The AAN guidelines recommend that the initial treatment choice for PD should be L-dopa unless there are additional concerns regarding the risk or the impact of the development of dyskinesia- a view we completely endorse. Novel formulations of L-dopa that are not limited by enteral absorption issues are appealing but long term tolerability data are required. Similar to other device assisted therapies, patients may require additional support for any device or skin related complications.
COMT inhibitors	COMT inhibitors are not useful as monotherapy but are useful as a treatment for motor fluctuations. %	Additional trial data have demonstrated the usefulness of opicapone in the treatment of motor fluctuations.[16,17]	Tolcapone is infrequently used because of the recommendation for frequent blood tests to check for rare liver toxicity. Opicapone has the advantage of fewer side effects compared to entacapone (orange discolouration of bodily secretions), and also has the advantage of once daily administration. Hyperdopaminergic side effects may necessitate lowering of L-dopa doses.
Adenosine A2A antagonist	Istradefylline not useful as monotherapy but likely useful for motor fluctuations.	A further trial has concluded that Preladenant is not useful as monotherapy.[153]	It is unclear whether istradefylline can lead to an improvement in OFF time in comparison to adjunctive treatment with dopamine agonists, COMT inhibitors and/or MAO-B inhibitors. The mechanism of action and safety profile of istradefylline may however allow improvement of OFF time while reducing overall dopaminergic dosage thus potentially reducing hyperdopaminergic side effects. Weight loss and constipation can complicate istradefylline use.
Anticholinergics	Useful as monotherapy or adjunctive therapy.	No new data.	Major role is for patients with tremor, particularly if unresponsive to L-dopa replacement. Cognitive side effects as well as peripheral anticholinergic side effects often limit their usefulness.
Amantadine	Useful treatment for dyskinesia	Trial data supportive on the efficacy of Amantadine extended release to reduce dyskinesia and improve OFF time.[22]	Amantadine can be highly effective at reducing dyskinesia, with additional anecdotal support for improvements in fatigue or gait freezing. Tolerability is limited with disease

			progression and hallucinations are orthostatic hypotension are common side effects.
Clozapine	Useful as a treatment for dyskinesia.	No new data.	Clozapine prescription requires specialist blood count monitoring in view of the risk of agranulocytosis. It can also cause symptomatic hypotension, tachycardia and myocarditis.

*Ergot dopamine agonists are known to increase the risk of cardiac fibrosis, and are less frequently used in PD as a result.

% While Tolcapone can enter the CNS and slow metabolism of endogenous dopamine, given the known risks of hepatotoxicity with Tolcapone, it is not appropriate for symptomatic monotherapy.

$While Clozapine can reduce tremor associated with PD, the need for close monitoring of patient's blood tests restricts its widespread use.

Table 2; Treatment of non-motor symptoms of Parkinson Disease

DEPRESSION			
INTERVENTION	**MDS EBM RECOMMENDATION (Seppi et al 2018)**	**UPDATE 2018 - 2022**	**Expert comments**
Drug class			
Dopamine Agonists	Pramipexole, Clinically Useful; Rotigotine; investigational	Meta-analysis of depression scores as secondary outcomes in RCTs of pramipexole[71] and Rotigotine[72] both reported significant benefit on depression.	Class effect of dopamine agonists report positive outcome on depression that maybe separate from motor benefit. Side effect profile of DA remains concern.
MAO-B inhibitors	All investigational	Metanalysis of 6 trials using Selegiline, rasagiline and safinamide (4 in early PD) reported overall benefit.[70]	Effects on depression in early PD are likely related to enhanced dopamine with secondary motor benefit. There seems less benefit in advancing disease. Additive effects of MAO-Bi and other anti-depressants are not seen in clinical practice but have not been formally evaluated.
Serotonin-Norepinephrine Reuptake Inhibitors SNRI Serotonin-Selective Reuptake Inhibitors SSRI	Venlafaxine Clinically useful; Atomoxetine possibly useful All possibly useful	Duloxetine v Paroxetine/Escitalopram (open label) both effective on depression.[154]	SSRI and SNRI remain widely used despite lack of RCTs. Theoretical concerns of Serotonin syndrome with concomitant use of MAO-Bi and antidepressants can limit prescribing effectively, although clinically significant symptoms rarely seen.
Tricyclics	Possibly useful	No new trials.	Ongoing RCT comparing nortriptiine (TCA) and escitalopram (SSRI).[74]
Selective norepinephrine reuptake inhibitor		No new trials.	
rTMS	Possibly useful	No new trials.	rTMS is approved in many regions for treatment of non-PD depression and can improve depression as effectively as antidepressants.[76] Long term efficacy data in PD is lacking; as is duration and site of stimulation to determine best site to target rTMS.
Cognitive Behavioural Therapy (CBT)	Possibly useful	Multiple new studies report benefit. [77,155-157]	Benefits of CBT have also been shown when delivered via virtual methods[158]– increasing accessibility.
'Mindfulness'	n/a	Yoga as beneficial as resistance stretching.[159]	Benefit of mindfulness exercises on many PD symptoms.
Bright-light therapy	n/a	Variable results; metanalysis of 5 RCTs shows overall benefit[79] Negative trial [160]	Benefit on sleep as well as depression; thus likely multiple mechanisms of action. However low cost, non-expensive therapy that can be widely used.
Chinese Herbal therapy		Pingchan benefit[161]	Pharmacology of herbal supplements variable – mechanism of action thus unclear
5-hydroxy-tryptophan	n/a	Positive effect after 4 weeks[162]	
ANXIETY			
Pharmacological	None specifically fulfilled EBM criteria	No new trials.	Clinical use of anxiolytics and anti-depressant continues off label with variable results. Increased use of non-pharmacological techniques mindfulness strategies are also being employed, Remote use of these strategies was increased during the pandemic. The added burden of social isolation increased anxiety in the PD population. The importance of 'social prescribing' has been highlighted as a major benefit for PD patients with anxiety[81].
Non-pharmacological	n/a	CBT Positive effects. [77 163] Sensory Focused Exercise Positive effects[164] Acupuncture positive effects[80] Yoga positive benefit on mood (as well as other motor aspects of PD) [165 166]	
APATHY			

Antidepressants	n/a	No effect using SNRI (duloxetine) with SSRIs (paroxetine, escitalopram)[154]	Very little research focussed on apathy. Difficulties with measuring and differentiating from other PD symptoms.
Dopamine agonists	Piribidil – possibly useful Rotigotine Investigational	No new trials.	
Cholinesterase Inhibitors	Rivastigmine – clinically useful	No new trials.	
5-HTP		No effect on apathy [162]	No side effects were reported.[162]
MAOB-I	Safinamide	No effect on apathy[167]	
IMPULSE CONTROL DISORDERS			
Discontinue Dopamine agonist and Switching to levodopa CR	n/a	Open label study (n =50) reported reduced ICD in LDCR group [168]	Recent years have seen a reduction in use of dopamine agonists due to concerns raised with ICDs. If present, slowly reduce (slow to prevent Dopamine agonist withdrawal syndrome) and eventually discontinue the DA. Adjustment of levodopa dosing according to symptoms (both motor and non-motor) are then required. Rarely ICDs can occur with L-dopa alone.
NMDA	Amantadine Investigational	No new trials	A few individuals will continue with ICD despite discontinuing Dopamine agonists. Limiting dose of dopaminergic therapy may be necessary.
OPIOID Antagonism	Naltrexone – investigational	No new trials	
CBT	Possibly useful	No new trials	
PSYCHOSIS			
Atypical antipsychotics	Clozapine; Pimavanserin efficacious Quetiapine Insufficient evidence Olanzapine – Non efficacious	Meta-analysis of 17 trials using clozapine had largest efficacy without worsening motor symptoms but high drop out.[83] Open label extension of prior RCT pimavanserin for 4 weeks showed benefit in PD psychosis without dementia although not significant vs placebo.[169] Pimavanserin reduces psychosis in PD subjects with dementia.[170]	Clozapine remains most efficacious for PD psychosis. Logistical challenges related to monitoring while blood cell count limit wider use. Side-effects can include sedation and hypotension.[171] Quetiapine remains first line for clinical ease despite lack of EBM recommendations. Pimavanserin has mild efficacy in treating PD psychosis. Safety and tolerability are similar to quetiapine with no worsening of PD motor symptoms reported. Prolongation of QTc interval occurs with any atypical antipsychotic thus ECG is required prior to prescribing clozapine, quetiapine or pimavanserin.[172] All other atypical antipsychotics can worsen PD motor symptoms and are discouraged from use.
Cholinesterase inhibitors (ChEI)	Anecdotal evidence for reduction in visual hallucinations.	Rivastigmine (3-6mg) was not effective in reducing 'minor' Visual Hallucinations in PD.[173] Use of donepezil as early treatment for PD did not prevent development of psychosis. [85]	Evidence for cholinergic dysfunction underlying visual hallucinations in PD, without dementia is clear rationale for use of ChEI. However, evidence from RCTs has been variable and partly relates to challenges in conducting RCTS in psychosis with PD due to fluctuating nature of symptom. Also highlights that the clinical management of psychosis in PD needs to rule out non-PD causes. Unclear if ChEI long term can prevent development of worsening psychosis i.e. prevent minor visual hallucinations transitioning to paranoid delusions. ChEI may cause prolonged QTc interval, thus ECG is required prior to prescribing. Side effects include nausea, vomiting and worsening tremor [174].
DEMENTIA			
Cholinesterase inhibitors (ChEI)	Donepezil ; insufficient evidence due to conflicting results Rivastigmine; Efficacious Galantamine; insufficient evidence	Early use of donepezil in PD subjects without cognitive issues may slow cognitive decline in subject with Apo-epsilon4 carriers ; no effect in non-carriers[85] Post hoc of RCTs evaluating rivastigmine in PD reported that efficacy on cognition maybe enhanced in subjects who also had a low BP[174] No new studies	Slowing or preventing cognitive decline remains an important clinical need. However, ChEI do not have benefit. Cognitive decline in PD is also due to low BP, thus a remediable risk factor.

NMDA Antagonist	Memantine; insufficient evidence	No effect in PD-MCI[175] [175]	Limited benefit in PD dementia.
Dopamine D1 agonists	Mevidalen	Not effective on cognition (Dementia with Lewy Body)[84]	Cardiovascular safety concerns with high dose may limit further development of this target.
Non-invasive transcranial stimulation	Insufficient evidence	T-DCS unclear. single session was ineffective on visual working memory[176] while repetitive sessions over 5 days improved delayed recall and executive functions for MCI.[87] TMS – repetitive stimulation for 3 days – positive benefit on visuospatial cognitive function. [177] Integrating rTMS with Virtual Reality may have added benefit for MCI. [88]	The interventions may have transient benefits; however variable techniques including site of stimulation, duration (single or multiple sessions) and frequency of stimulation make conclusions challenging. Long term benefit is also unclear. Logistical challenges with use as a treatment as need for repetitive application.
Cognitive training	Insufficient evidence	Overall most studies report no benefit in RCTs[178] [179] [180]	Variable interventions have been evaluated to date; predominantly computer based exercises with suggested benefit vs traditional pen-paper methods.[181] Use in cognitively normal PD subjects needs further evaluations.
AUTONOMIC DYSFUNCTION			
Drooling			
Ipratropium Bromide Spray	Insufficient evidence	No new studies.	Dry mouth and bad taste are the most common cause of discontinuation.
Glycopyrrolate	Efficacious	New RCT supports the efficacy of glycopyrrolate to treat sialorrhea related disability for up to 12 weeks. [98]	Dry mouth and bad taste are the most common cause of discontinuation.
Botulinum toxin B	Efficacious	New RCT showed that treatment with RimabotulinumtoxinB was well tolerated in adults (65.2% of the participants had PD) and reduced sialorrhea.[182]	The use of botulinum toxins A and B to manage sialorrhea in PD shows efficacy and a good safety profile when performed by a trained health provider with specialized monitoring to avoid the risk of complications. Repeated injections every 3-4 months may be a limitation for patients with PD with reduced mobility.
Botulinum toxin A	Efficacious	IncobotulinumtoxinA 100 U is an effective and well-tolerated treatment of chronic sialorrhea in adults, including over 64 weeks.[183]	
Dihydroergotoxine mesylate	n/a	An open-label study followed by crossover RCT showed improvement in the UPDRS sialorrhea subscore of the UPDRS and Sialorrhea Clinical Scale for PD.[184]	Potential treatment alternative if patients experience tolerance challenges with the previously described therapies. Mechanism of action includes α-adrenergic blocking agents and affinity to dopaminergic and serotonin receptors. This medication's toxicity in PD is not well known. Side effects may include nausea, vomiting, flushing, hypertension and hypotension.
Orthostatic hypotension			
Fludrocortisone	Insufficient evidence	A Cochrane systematic review confirmed that the evidence about the effects of fludrocortisone on OH in PD is very uncertain.[102]	Evidence continues to be scarce, but in clinical practice, fludrocortisone remains one of the leading choices for managing orthostatic hypotension in PD. Monitoring of salt and water retention symptoms and hypokalemia is needed.
Midodrine	Insufficient evidence	No new studies.	Midodrine continues to be used in clinical practice to manage neurogenic orthostatic hypotension. Supine hypertension is a risk and needs to be monitored.
Domperidone	Insufficient evidence	No new studies.	Similar to fludrocortisone and midodrine, domperidone is a potentially helpful strategy for managing orthostatic hypotension in PD. Specialized monitoring is required due to the potential risk of QT prolongation and sudden cardiac death in patients with a history of cardiac disease.
Yohimbine	No efficacious	No new studies.	
Droxidopa	Efficacious (short term)	Supporting efficacious evidence, a 12-week open-label study showed that droxidopa (100-600 mg, 3 times	Droxidopa is not globally available but seems to be a safe option for managing orthostatic hypotension in PD.

		daily) was associated with significant improvement from baseline in nOH symptoms and activities of daily living [185]	No clinically relevant changes in supine hypertension or adverse events were observed in the lengthier trial.
Urinary dysfunction (frequency, urgency and/or incontinence)			
Solifenacin	Insufficient evidence	No new studies.	Competitive muscarinic receptor antagonists remain a valuable alternative for managing overactive bladder symptoms in PD. However, anticholinergic central and peripheral effects need to be monitored, particularly in patients with PD dementia and MCI.
Fesoterodine fumarate	n/a	An RCT followed by an open-label phase showed improved overactive bladder symptoms in PD. [186]	
Mirabegron	n/a	Two new RCTs in patients with PD showed a significant improvement in overactive bladder symptoms and numbers, micturitions every 24 h and nocturia episodes per night over 12 weeks.[94,187]	Due to its mechanism of action (a selective agonist of beta-3 adrenergic receptors), mirabegron is a promising drug to control overactive bladder symptoms in patients with PD with an excellent safety profile. There is a potential risk of urinary retention in patients with other urological disorders, so interdisciplinary management with urology may be required.
Deep Brain Stimulation		RCTs post hoc analysis and prospective controlled studies showed a positive effect of STN and GPi DBS on overactive bladder symptoms in PD.[188,189]	Improvement in urinary symptoms after DBS may be linked to improvement in the overall motor function of PD patients and remains an interesting area of research.
Transcutaneous tibial nerve home stimulation		Two RCTs showed positive effects on overactive bladder symptoms in patients with PD in a six weeks trial [190] and women with PD in a 12 weeks trial.[191]	This technique has shown interesting results in non-PD patients with overactive bladder symptoms and two small RCTs in PD.
Behavioural therapy		An RCT of behavioural therapy compared to control conditions among adults with PD and incontinence showed that self-monitoring resulted in fewer urinary symptoms. [192]	Nonpharmacological therapies for overactive bladder symptoms in PD remain an interesting area to explore. Interdisciplinary approaches with the urology team are recommended for complex cases.
Erectile dysfunction			
Sildenafil	Efficacious	No new studies	Side effects may include headache, flushing, nasal congestion, impaired vision, muscle or back pain, nausea, dizziness, and in rare cases, serious side effects such as sudden loss of vision or hearing, chest pain, or prolonged erection.
Constipation			
Macrogol	Likely efficacious	No new studies	Polyethylene glycol is widely used to manage constipation in PD, usually daily. Side effects may include abdominal discomfort, nausea, bloating, diarrhea, and rarely, allergic reactions.
Lubiprostone	Likely efficacious	No new studies	Side effects may include nausea, diarrhea, abdominal pain, headache, and bloating.
Probiotics and prebiotic fibre	Efficacious	Multiple RCTs have confirmed the efficacy of multistrain probiotics formulations in improving constipation in PD. [193,194]	Multi-strain probiotics seem to be a successful strategy to improve constipation symptoms in PD. Ongoing research is focused on identifying specific strains that may target specific PD microbiome issues.
Abdominal massage	Insufficient evidence	No new studies	
Anorexia, nausea and vomiting associated with levodopa and/or dopamine agonist treatment			
Domperidone	Likely efficacious	No new studies	Domperidone is a possibly useful strategy for managing gastrointestinal symptoms in PD. Specialized monitoring is required due to the potential risk of QT prolongation and sudden cardiac death in patients with a history of cardiac disease.
DISORDERS OF SLEEP AND WAKEFULNESS			
Sleep fragmentation and insomnia			
Levodopa Controlled released formulation	Insufficient evidence	No new studies	
Dopamine agonist	Pergolide: insufficient evidence Piribedil: Insufficient evidence Rotigotine: Likely efficacious	A meta-analysis showed significant improvement in rotigotine-treated patients compared to control in terms of sleep quality outcomes.[195]	Optimizing dopaminergic therapy throughout sleep hours reduces night-time hypokinesia and usually improves the sleep quality of patients with PD. Managing overactive symptoms (nocturia) may also significantly benefit sleep quality.

Apomorphine	n/a	A RCT tested the subcutaneous nighttime only apomorphine infusion in patients with PD and insomnia showing improved sleep disturbances according to difference on PDSS score, with an overall safety profile consistent with previous studies in PD. [30]	Apomorphine infusion treatment might help manage sleep disturbances in patients with advanced PD and moderate to severe insomnia.
Rasagiline	n/a	New RCT suggests improvements in sleep quality as measured by polysomnography. [196]	Side effects may include headache, dry mouth, joint pain, depression, dizziness, and hallucinations, and the potential risk of serotonin syndrome when taken in conjunction with SSRIs or dual mechanism antidepressants.
Eszopiclone	Insufficient evidence	No new studies	Side effects may include drowsiness, headache, dizziness, dry mouth, bitter taste, nausea and allergic reactions.
Sodium oxybate		A small and short RCT showed improvement in nocturnal sleep quality in PD patients.[197]	Sodium oxybate, enhances gamma-aminobutyric acid (GABA) neurotransmission by binding to the GABA-B receptor and to a lesser extent, the GABA-A receptor. Side effects include nausea, dizziness, headache, somnolence, confusion, euphoria, depression, respiratory depression, and other serious central nervous system depressant effects.
Melatonin 3-5 mg	Insufficient evidence	New short RCT using prolonged-release melatonin suggests a beneficial effect on sleep quality.[104]	Evidence remains scarce. In clinical practice, melatonin is usually well-tolerated and might provide some improvement in the quality of sleep.
Trazodone	n/a	A randomized study comparing melatonin 3 mg/day, day, clonazepam 1 mg/day or trazodone 50 mg/day showed that overall all drugs were tolerable an effective in improving sleep quality in PD.[198]	Trazodone side effects may include dizziness, drowsiness, dry mouth, blurred vision, constipation, and priapism. Clonazepam side effects may include drowsiness, dizziness, coordination difficulties, memory problems, mood changes, and dependency or withdrawal symptoms with prolonged use.
Clonazepam	n/a		
Continuous positive airway pressure: Likely efficacious	Likely efficacious*	No new studies	This recommendation applies to PD patients with obstructive sleep apnea.
Exercise	n/a	New RCT showed that high-intensity exercise rehabilitation improves objective sleep outcomes in PD. [199] Similar results showed in an RCT testing the effects of resistance training. [200]	Evidence to support exercise recommendations for sleep improvement in PD continues to grow. Exercise plans should be adapted to the patient's mobility, interests, and local availability.
Bright light therapy	n/a	Meta-analysis suggest that bright light therapy improves overall sleep scores in PD.[79]	
Deep Brain Stimulation	n/a	A 36-month observational controlled study reports Class IIb evidence of beneficial effects of STN-DBS on quality of sleep associated with QoL improvement independent of depression and dopaminergic medication.[201]	
Rapid eye movement sleep behaviour disorder			
Cannabidiol	n/a	Negative results in a small RCT. [202]	
Safinamide	n/a	A pilot, randomized crossover study over three months, suggested some improvement in RBD symptoms using clinical and video polysomnographic changes.[203]	
Nelotanserin	n/a	Negative results in an RCT[204]	
Melatonin	n/a	Negative results in an RCT in which prolonged-release melatonin 4 mg did not reduce rapid eye movement sleep behaviour disorder in PD. No polysomnography measures.[205]	Melatonin and clonazepam are broadly used as the first line of treatment for RBD, with diverse degrees of success. Randomized trials with better assessment tools and polysomnography will help provide better evidence for the benefit of these drugs on RBD symptoms.
Clonazepam	n/a	Negative results in short RCT compared to placebo. No polysomnography measures.[206]	
Excessive daytime sleepiness			

Psychoactive drugs	Modafinil: Insufficient evidence Caffeine: Insufficient evidence	No new studies	
MAOB-I	n/a	An observational open-label study suggest the potential use of selegiline to reduce excessive daytime sleepiness.[207] A small pilot trial also shows an improvement in excessive daytime sleepiness in patients taking rasagiline when compared to controls[208]	
Pain			
Oxycodone-naloxone prolonged release	Insufficient evidence	No new studies	Close monitoring is needed in patients with PD using opioids, considering the risk of worsening other non-motor symptoms of the disease such as constipation, psychosis or cognitive impairment.
Rotigotine	Insufficient evidence	No new RCTs	Optimization of dopaminergic therapies minimizing OFF periods is an appropriate strategy to reduce OFF-related pain in many PD cases.
Safinamide	n/a	Post hoc analysis of RCTs suggests patients with PD and pain during OFF phases may benefit from the treatment with safinamide.[209,210]	
Botulinum Toxin	n/a	Two small pilot RCTs suggest a positive effect on dystonia related pain in PD. [211,212]	In clinical practice, botulinum toxin injections may help manage particular types of painful dystonia in PD. However, injections need to be performed by a trained physician and preferably using EMG or Ultrasound guidance.
Duloxetine	n/a	Negative results in a 10-week duration RCT. [213]	Side effects may include nausea, dry mouth, constipation, headache, dizziness, insomnia, and sexual dysfunction.
Fatigue			
Monoamine oxidase B inhibitors	Rasagiline: efficacious	No new studies	
Psychoactive drugs	Methylphenidate: Insufficient evidence Modafinil: Insufficient evidence	No new studies	
Nonpharmacological interventions	Acupuncture: Insufficient evidence	No new studies	

Declaration of Interests

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All authors contributed to writing and revising the manuscript. Specifically, TF wrote the section on the "Initial treatment and Adjunctive treatment of motor PD" and "Future Studies", AJL wrote the section on "Non oral therapies for the complex phase of PD", AK wrote the section on "Deep Brain Stimulation", VB and SF wrote the section on "The treatment of Non Motor symptoms", FL wrote the section on "The role of Allied Health Professionals". The same authors performed the literature searches for these respective sections, and read and approved the final combined version.

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