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REVIEW ARTICLE

Therapeutic Strategies to Treat or Prevent Off Episodes in Adults with Parkinson's Disease

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Abstract

Parkinson's disease is a chronic, neurodegenerative disease, which manifests with a mixture of motor, cognitive and behavioural symptoms. Levodopa is the most effective antiparkinsonian treatment to date, although chronic use engenders a mixture of complications in a substantial proportion of patients. Amongst these is the occurrence of episodes of worsening symptoms—'off' phenomena. These episodes can manifest with either motor or non-motor symptoms or a combination of these features and have been found to have profound impacts on patients' quality of life. Although preventative measures are poorly evidenced, avoiding excessive total daily levodopa intake in selected populations that are deemed to be of a higher risk for developing these episodes warrants further exploration. Methods to improve levodopa bioavailability and delivery to the brain are currently available and are of value in addressing these episodes once they have become established. These include modifications to levodopa formulations as well as the use of complimentary agents that improve levodopa bioavailability. The deployment of device-assisted approaches is a further dimension that can be considered in addressing these debilitating episodes. This review summarises the clinical manifestations of 'off' phenomena and the current approaches to treat them. Although we briefly discuss clinical advances on the horizon, the predominant focus is on existing, established treatments.

Key Points

'Off' phenomena in Parkinson's disease commonly occur as a result of long-term levodopa use and can have a profound impact on patients' quality of life.

Avoiding inappropriately high total levodopa daily dosage in high-risk cohorts could potentially mitigate their risk of occurrence.

In patients suffering from 'off' phenomena, fractionating levodopa dosages, the addition of adjunctive agents (e.g. dopamine agonists, monoamine oxidase-B inhibitors, Catechol-*O*-methyltransferase inhibitors) or the introduction of device-assisted therapies (apomorphine infusion, deep brain stimulation, levodopa-carbidopa intestinal gel) can significantly improve symptom burden.

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1 Introduction

Parkinson's disease (PD) is the second most highly prevalent neurodegenerative condition and results in substantial patient morbidity and care-giver burden [1]. Although motor features such as bradykinesia, rigidity, postural instability and rest tremor have become synonymous with the disease, patients with PD also experience a range of non-motor symptoms (NMS), which also impose negatively on quality of life (QOL) [2, 3].

Dopaminergic deficiency remains a key aspect of the pathogenesis and clinical manifestations of the disease [4], therefore treatment approaches targeting replacement of dopamine remain paramount. L-dopa (3, 4-dihydroxy-L-phenylalanine), was engineered to achieve this outcome over 50 years ago and still remains the gold standard for symptomatic management of PD today [5, 6]. This molecule is converted to dopamine by the enzyme aromatic amino acid-decarboxylase (AADC) largely upon crossing the blood–brain barrier. This increases presynaptic dopamine concentrations, synaptic release of dopamine and therefore post-synaptic dopamine receptor stimulation in the basal ganglia with resultant improvements to symptoms [7–9].

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The beneficial effects of L-dopa replacement, although substantial, tend to wane as the disease progresses. The numerous explanations for this will be discussed in detail later. The net result is of an increasing frequency of rapid and, at times, unpredictable cycles between good therapeutic motor responses ('on' states), poorly controlled symptoms ('off' states)- known as motor fluctuations (MF) and involuntary movements (dyskinesia), collectively considered as motor complications. There is an increasing awareness that non-motor fluctuations (NMF) can also occur and mirror levels of dopamine release, which can be harder to detect because they are less obviously manifest to carers or clinicians [10, 11].

Fluctuations are a major source of disability and result in a substantial reduction to QoL. Modifying treatment approaches to prevent or improve fluctuations have therefore become a major focus of therapeutics in PD. Here, we aim to provide an overarching view of these occurrences and the principles and specific therapies currently utilised in their management. This review will focus on the 'off' state and does not encompass specific techniques employed for the management of dyskinesia although the majority of treatments described, potentially provide overlapping benefits for both 'off' periods and dyskinesia.

1.1 Clinical Characteristics

While subtle variations in PD motor severity are not uncommon, abrupt "On–Off" phases in the setting of chronic levodopa therapy are unique to patients with PD and were observed soon after the first introduction of L-dopa therapy into clinical practice [12]. A variety of terms have subsequently been coined to describe variations in their nature. These differences are depicted in Fig. 1 and predominant underlying mechanisms in Fig. 2.

First, the more gradual transitions in clinical symptom control noted towards the end of doses are described as 'wearing off' phenomenon or end-of-dose deterioration [13].

The occurrence of slowness or immobility in a patient's waking hours prior to the first medication dose is considered an early morning 'off' state (EMO). This is related to low plasma levodopa levels from a lack of overnight medication.

The term delayed 'on' is a further term often used to describe the lengthy latency for a levodopa dose to start working and can commonly occur with the first morning dose or after a meal [14].

In contrast, a dose failure or no 'on' refers to times when the medication fails to work.

When the symptoms experienced during 'off' states are of a non-motor nature, these can be referred to as a non-motor 'off' state, or non-motor fluctuation (NMF) [15].

The constellation of motor symptoms experienced by patients in the 'off' state is broad and variable. Although some report a mixture of slowness, stiffness, incoordination or reduced dexterity and muscle cramping, others experience difficulties in their ability to stand up, balance, or even swallow. Patients can also suffer changes in their voice and breathing while experiencing posturing (dystonia) in their hands, feet or legs. On occasion, a profound worsening of tremor and the emergence of gait freezing can be seen [16]. The non-motor symptoms commonly reported can be divided into neuropsychiatric, autonomic and sensory domains. Neuropsychiatric symptoms can manifest with fluctuations in cognition, attention, and mood (anxiety, depression, apathy). Autonomic symptoms on the other hand comprise altered sweating, light headedness, abdominal pain or bloating, and urinary urgency. Patients experiencing sensory symptoms report a mixture of visual disturbances, pain, dysaesthesia, akathisia and restless legs. A number of non-motor endo-phenotypes have also been described and comprise subtypes of either a depressed, anxious, or anxious-depressed variety. Though neurobehavioural syndromes [impulse control disorders (ICDs), punding and dopamine dysregulation syndrome] are not strictly considered NMFs, they can masquerade as such considering their varying occurrences with L-dopa intake. The phenomenon of anticipation of an impending 'off' period-metacognition is a

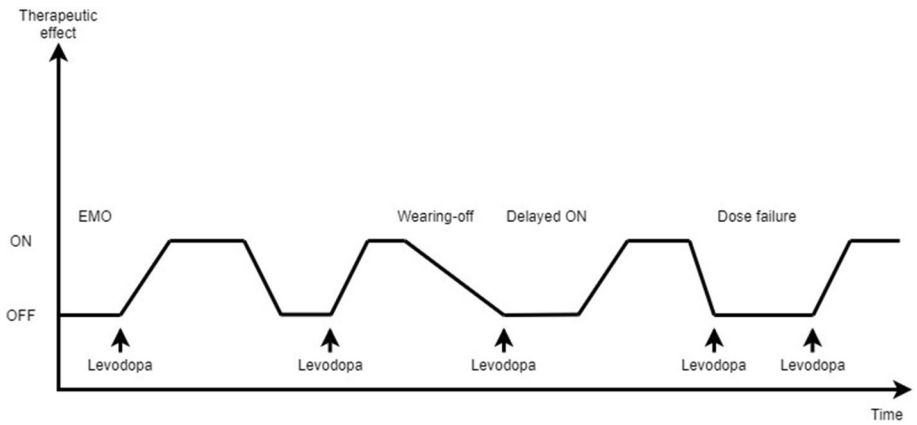

Fig. 1 Schematic depiction of different motor fluctuations and their relation to levodopa intake. *EMO* early morning 'off'

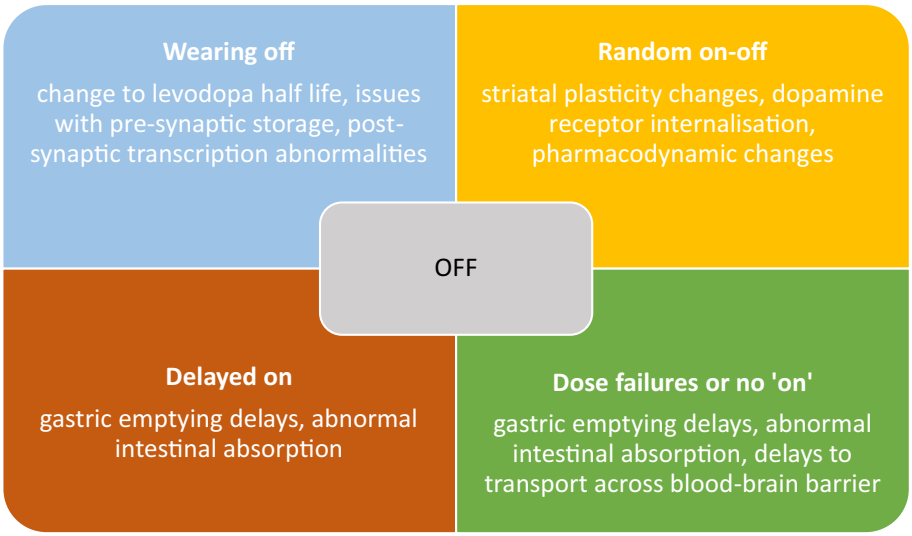

Fig. 2 Different 'off' phenomena and varying mechanisms resulting in their development. EMO = Early morning OFF

further non-motor manifestation and can worsen the distress and severity of the fluctuation [17, 18].

Although fluctuations become more prevalent as the disease progresses, the frequency noted seems to vary between cohorts, presumably in view of discrepancies in ascertainment approaches. Broadly speaking however, 10% of patients will develop MF annually from the onset of initiation of levodopa [19]. Over time, this results in a compounded average of approximately 40% of patients reporting MF after 4–6 years [19] and an almost universal occurrence after 10 years [20, 21]. 'Wearing off' in isolation tends to predate dyskinesia and has been reported in up to 50% of patients within 2 years of starting levodopa, although it can be observed within months of initiation [22], indicating that the disease duration likely has the greater influence on MF development rather than the duration of L-dopa exposure. EMOs are the most common initial manifestation reported with a recent survey of 320 patients suggesting over 40% of early disease patients and 60% of patients overall suffer from it [23], although paradoxical transient improvement in symptom control following sleep is also well recognised. However, 'end of dose wearing off' is the most common L-dopa-related phenomenon overall with delays to 'switching on' from the following dose being strongly associated [24, 25].

Despite best current medical management, a large observational study suggested 'off' episodes continue to trouble patients on average 2–3 h per day stressing the need for more ambitious treatment approaches [26]. The prevalence of NMFs in conjunction with MF varies (17–100%) depending on evaluation tools utilised and populations tested [27]. While EMO was noted in approximately 60% of a cohort, almost 90% of patients reported severe NMS (such as urinary frequency, anxiety, depression, pain, dribbling of saliva) on awakening. Despite their commonly noted co-occurrence with MF, NMF can also occur in an isolated and heterogeneous manner and predate their motor counterpart. While anxiety, fatigue, pain, and paraesthesia commonly complicate motor fluctuations, their co-occurrence is also common with dyskinesia [28]. Psychiatric symptoms and pain appear to frequently fluctuate according to L-dopa replacement, while concentration difficulties, fatigue, depression and anxiety can persist in the on state while being worsened during 'off' states [29]. Apathy and panic attacks tend to characterise more severe NMFs and are amongst the most disabling presentations [27]. Although there is some suggestion of specific NMF endophenotypes occurring alongside MF, this finding is inconsistent [30].

Factors contributing to the development of fluctuations have been extensively studied and found to be similar for both MF and NMFs [31, 32]. These include a younger onset age, female gender, more severe disease, and higher levodopa dosages [33–36]. The practical implications of these identified factors are elaborated on in the discussion of preventative approaches. Although a number of genetic factors have been implicated in the development of dyskinesia [37–40], their role in the development of 'off' phenomena specifically is less clear.

Taken together, fluctuations of all types are undoubtedly highly disabling, although patients seem to be particularly troubled by 'off' phenomena in view of the functional disability, pain and distress associated with these periods [41, 42]. This assertion is further validated by consequent reductions in QoL scores and patients reporting a preference for the ON state with dyskinesia over the OFF condition [43]. Despite a traditional clinical bias for addressing MF, more recent demonstrations of relatively greater NMS and NMF impact on QoL (mood symptoms and pain in particular) have propelled these aspects into a more central consideration

of patient care [27, 44]. Nevertheless, much more clinical education and better detection tools addressing these phenomena are still needed moving forward.

1.2 Pathogenic Mechanisms

'Off' phenomena need to be contextually understood in conjunction with how MFs develop as a whole. However, it is crucial to first understand that the development of fluctuations relies on the presence of dopaminergic therapy, in particular levodopa [45, 46]. Levodopa therapeutics consist of a short duration response (SDR) and long-duration response (LDR) [45]. The SDR impacts on symptoms over minutes to hours after an individual drug dose in accordance with the drug's pharmacokinetic profile. In contrast, the LDR is a sustained antiparkinsonian effect resulting from prolonged levodopa treatment. Both these entities occur from initiation of levodopa therapy [47]. The predominant manifestation of the LDR at the beginning can mask the true clinical nature of SDRs despite fluctuations in plasma levodopa levels. A subsequent progressive decay of the LDR makes the magnitude of the SDR effect more apparent with the resultant clinical observation of fluctuations [48]. Change to the balance between LDR and SDR over time is a result of peripheral factors related to L-dopa pharmacokinetics, absorption, and transport, as well as central pharmacodynamic alterations [49] (Fig. 2).

Peripheral factors can make levodopa delivery to the brain less reliable because of their impact on the consistency of levodopa plasma levels. Clinically, they tend to be more responsible for the development of the delayed 'on' phenomena or dose failures, although they may also have some bearing on other MF [50]. Distinct abnormalities that contribute to PD include delayed gastric emptying and therefore delayed or absent proximal small intestine levodopa absorption as well as swallowing impairment. Oral cavity abnormalities (epiglottic valleculae, pyriform sinus) and oesophageal alterations (non-peristaltic swallows, belching, segmental spasms, dilatation, and gastro-oesophageal reflux) can also further compound the situation by impairing the physical transit of the drug or delaying its absorption [51–54].

A common issue relates to ingestion of high protein meals, which reduce the absorption of levodopa by virtue of competition for transfer across the intestinal mucosa and the blood–brain barrier [55]. The presence of *Helicobacter pylori* colonisation has been further demonstrated to partly contribute to the occurrence of 'on–off' phenomena by virtue of reducing levodopa absorption [56], although there is not yet unequivocal evidence that eradication of *H. pylori* can reliably improve MF. The impact of an individual's unique gut microbiome architecture on PD therapeutics is also currently a topic of active exploration although evidence for specific causation of MF is far from conclusive [57].

Centrally, changes in the duration of the effects of levodopa occur partly as a result of the loss of presynaptic dopaminergic terminals due to the ongoing neurodegenerative processes of PD. This reduces the capacity of the striatum to store dopamine and buffer against the consequences of oscillations of plasma levodopa levels [58, 59]. Furthermore, postsynaptic changes occur as a result of chronic non-physiological dopaminergic stimulation via alterations in striatal genes and proteins mediating receptor expression and intracellular activity, as well as functional abnormalities in basal ganglia output pathways [60–62].

The normal functioning of the nigrostriatal dopaminergic system depends on tonic dopaminergic activity and phasic bursts of dopamine release during times of activity. Initially, dopaminergic terminal loss can be 'passively stabilised' by the endogenous tonic input [63]. Over time however, exogenous levodopa becomes necessary to improve symptoms of PD and during the first years can effectively reduce the severity of the symptoms of most patients with PD. However, exogenous levodopa replacement does not restore normal dopaminergic physiology [64]. The administration of repeated doses of short-acting levodopa results in alternating high and low concentrations and therefore "pulsatile" receptor stimulation [49, 65, 66]. This pulsatile pattern of dopaminergic release is thought, at least in part, to be responsible for MF and wearing 'off' [67].

Although specific underlying mechanisms contributing to NMFs are far more varied and often less clear, the higher incidence of non-motor symptoms in the motor 'off' state and their partial responsiveness to dopaminergic therapy point to some partial role for dopaminergic denervation [68] at least to some of the non-motor symptoms. Furthermore, evidence from electrophysiological studies suggest links between MFs and NMFs have a physiological basis. In particular, while abnormal synchronisation of neuronal activity in the primary motor cortex is implicated in akinesia, a similar mechanism in the prefrontal areas potentially results in some non-motor symptoms [69]. Further parallels related to excessive synchronisation in motor areas as a result of chronic non-physiological stimulation may underpin the onset of dyskinesia, while excessive gamma synchronisation in the cognitive and limbic basal ganglia loops can conceivably lead to psychosis as well as cognitive and affective abnormalities [18, 70, 71]. However, these concepts are not an all-encompassing explanation for NMF and co-occurring mechanisms are likely to be involved. These include further involvement of serotonergic, noradrenergic and cholinergic pathways and aberrant release of dopamine as a false transmitter from these neuronal populations. Dysfunction in these systems potentially explains some of the diversity

in the presentation and treatment responses noted between MF and NMF. Also, the variable degree of degeneration of these neurotransmitter systems between different people with PD results in interactions between both the dopaminergic and non-dopaminergic factors that ultimately underlie NMF [70–72].

2 Prevention Strategies

Community-based studies performed over several decades have suggested that younger age, greater disease severity, and higher levodopa doses are consistent risk factors for developing motor complications [36]. The ELLDOPA study compared the effect of initiating treatment with different L-dopa doses. Although higher doses provided increased clinical benefits at 9 months, patients were at an increased risk of developing both 'off' periods and dyskinesia [33]. The longer (approximately 4 years) STRIDE-PD study specifically compared the risk of developing dyskinesia and wearing 'off' in patients randomised to L-dopa/carbidopa or L-dopa/carbidopa plus the Catechol-*O*-methyltransferase (COMT) inhibitor, entacapone [34]. Although the addition of entacapone did not modify the risk of developing 'off' time, a subsequent multivariate analysis suggested that younger age and higher L-dopa doses (> 600 mg per day) were critical risk factors for the development of dyskinesia. A further crucial observation was that this risk also applied to patients developing 'off' phenomena, which to some would seem counterintuitive given the presumption that higher L-dopa doses would reduce 'off' time.

These observations implicate levodopa pharmacodynamic and pharmacokinetic factors in the development of not only dyskinesia but also wearing 'off'. The possibility of these findings reflecting that these patients might simply have had worse disease and by virtue of this, higher dose requirements, was not supported by close scrutiny of the ELLDOPA study. In this study, patients were not only randomised to fixed levodopa doses, but there were also statistical subanalyses suggesting that higher levodopa doses increased the risk of developing wearing 'off' independently of the UPDRS motor score and disease severity [35].

This study of risk factors for MF is useful in potentially tailoring preventative management of MF in early PD patients. Considering that strategies utilising higher levodopa doses are associated with an increased risk of developing 'off' time, it may be that in higher-risk people, e.g. younger women with relatively low weight, prescribing L-dopa on a mg/kg basis may be a worthwhile tactic. Based on this premise, we might also suggest that levodopa be used in the lowest dose that provides a satisfactory clinical response, and that using low doses of multiple drugs in combination may minimise the need of raising levodopa doses to higher doses until clinically necessary. Anecdotally, this potentially delays the onset of MF although specific studies examining this are lacking. Arguments for this approach are that first, crossing a certain dopaminergic threshold (and by extrapolation dosage) seems to be necessary for fluctuations to develop. Also, levodopa-sparing agents (e.g. dopamine agonists, monoamine oxidase inhibitors) tend not to lead to the pulsatile dopamine receptor stimulation like levodopa, and therefore are less likely to evoke fluctuations. Dopamine receptors can be divided into D1 (D1 and D5) and D2 (D2–D4) families. The D1 receptor family is more involved in the nigro-striatal pathway and agents acting on them such as levodopa tend to be more efficacious in managing motor symptoms in contrast to agents predominantly acting on D2 receptors (e.g. ropinirole, pramipexole). This lack of D1 'efficacy' could partly explain the lower tendency for fluctuations to develop with these agents. However, these potential merits, have to be weighed against the substantial down sides of these agents compared to levodopa, e.g. impulsive compulsive behaviours and lower efficacy in motor symptom relief. Although previously argued, the approach of delaying levodopa in favour of levodopa sparing agents initially to delay the onset of fluctuations has now been fairly conclusively dispelled. The recent LEAP trial was conducted in early PD patients (up to 2 years since diagnosis, treatment-naïve) with the aim of distinguishing between disease-modifying and symptomatic effects of levodopa [73]. The lack of difference in motor progression as well as rates of motor fluctuations between immediately treated and delayed start patients in the study provided clear evidence that delaying levodopa does not prevent MF. Therefore, L-dopa should be initiated when the clinician deems it to be clinically appropriate with subsequent consideration to a balanced multi-agent approach (bearing in mind the potential risks and benefits of each medication type) in order to achieve the minimum necessary dosages of medication to ameliorate symptoms while avoid accelerating the onset of fluctuations.

3 Treatment Strategies

Treatment approaches to deal with fluctuations have evolved over several decades, although the targets for intervention have broadly speaking remained unchanged. The main approaches capitalise first on strategies to bypass some of the peripheral impediments to levodopa absorption described. This has resulted in an expansion in the number of levodopa formulations being developed with the goal of extending the duration of action of each dose. Also, a number of alternative therapeutic targets have been formulated to complement levodopa while potentially minimising the dosage required for optimal treatment. The modes of action

of these agents are summarised in Fig. 3. Therapies that achieve improvements with greater consistency often require the assistance of devices for administration and the use of these has revolutionised the effectiveness of levodopa treatment for a sub-group of PD patients. Figure 4 presents a recommended approach towards addressing 'off' symptoms in a stepwise manner.

3.1 L-Dopa Preparations

Immediate-release (IR) L-dopa is a short acting agent with pharmacokinetics resulting in unstable plasma L-dopa concentrations. Peak plasma levels occur within an hour of oral administration dropping to less than 10% within 5 h in healthy adults [74]. This is further compounded by potential variability in bioavailability that is influenced by gastrointestinal hypo-motility [75]. Strategies to improve oral levodopa pharmacokinetics (adjusting timing/interval and/or improving absorption) are the mainstay of initial management of fluctuations. Dividing the levodopa dosage into smaller but more frequent doses (levodopa dose fractionation) is a practical first step in attempting to address fluctuations. This approach has been demonstrated in an open-label trial to be as effective at reducing 'off' time as adding an adjunctive agent to achieve this outcome [76]. Dose reduction with fractionation may not result in the full 'on' response patients tend to be accustomed to. Shortening of inter-dose intervals while maintaining an individually optimal and often increased dose may therefore be required. Clinical experience suggests that these benefits tend to be short lived with eventual alternative approaches becoming necessary.

Meals have been established to affect levodopa absorption with consequent fluctuations in plasma peak concentrations [77]. This is particularly the case with high-protein meals or large oral intake of neutral amino acids [50]. A competition between levodopa and other amino acids seems to occur at the absorption stage as well as at the blood-brain barrier although the composition and chemical properties of a protein meal could also have an impact on gastric emptying. A useful strategy to alleviate this is to advise patients to take their levodopa medication on an empty stomach, ideally at least 30–60 min before meals. Although protein restriction has also been proposed, this approach carries substantial potential side effects (dyskinesia, weight loss, malnutrition) and should therefore not be encouraged [78]. The use of gastro-prokinetic agents such as domperidone or camicinal may be worth exploring in patients with repeated delayed 'On' symptoms. These agents can enhance gastric emptying, encourage more rapid absorption of L-dopa in the small bowel and therefore result in reductions in 'off' time [79].

Levodopa is routinely combined with a dopa-decarboxylase inhibitor (carbidopa or benserazide), which improves its absorption and reduces levodopa peripheral metabolism [80]. Controlled-release formulations of levodopa–carbidopa have been manufactured with the aim to produce more consistent plasma levels than the IR formulations; however, these agents also seem to be marred by erratic gut absorption and therefore variable plasma concentrations [81–83]. A recent formulation of extended-release (ER) levodopa–carbidopa (IPX066/Rytary®/Numient®) is a capsule formulation in a 1:4 ratio of carbidopa:levodopa in four distinct dosages [84]. Levodopa in this agent is rapidly absorbed with a resultant concentration peak (C_{max}) within 1 h [85]. A sustained-release of levodopa subsequently follows with stable concentrations for approximately 4–5 h; thus, theoretically reducing the pulsatile stimulation of dopamine receptors and this mechanism of contribution to motor complications [86]. IPX066 has been shown to reduce 'off' time as a percentage of waking hours in comparison to standard IR formulations as well as levodopa–carbidopa–entacapone preparations in patients with motor complications that were not improved by previously available prolonged-release levodopa–carbidopa formulations [87, 88]. Common adverse effects of IPX066 are similar to other levodopa formulations, as is their incidence. An similar agent IPX203 has also shown similar promise and is currently being evaluated in a Phase 3 study (NCT03670953).

DM-1992 is another novel long-acting Levodopa formulation that is under clinical investigation. This agent consists of an IR levodopa layer and a novel expanding core of ER Levodopa with stomach retention of up to 9 h, and therefore a more stable pharmacokinetic profile [89]. The crossing over of patients from IR Levodopa to DM-1992 in a small cohort seemed to yield a reduction of an hour in 'off' time although worsening of gait and the occurrence of dizziness was more common with DM-1992 [89, 90] and this has deterred further progress to Phase 3 efficacy trials.

The Accordion Pill is another slow-release agent currently being investigated [91]. This medication comprises multiple layers of carbidopa combined with both IR and controlled release (CR) levodopa with a stomach retention of up to 14 h [92]. Plasma levodopa levels were found to fluctuate less in healthy controls when compared to IR levodopa while expected benefits to 'on' time and reductions in total daily L-dopa dosages have been noted [93]. The ACCORDANCE Phase 3 trial [94] compared IR levodopa with the Accordion Pill. Despite known improvements in the variability of plasma levodopa levels with the pill, no superiority in daily 'off' time or 'on' time without troublesome dyskinesia was noted (ClinicalTrials.gov ID: NCT02605434). The role of this agent in future practice is currently uncertain considering this outcome.

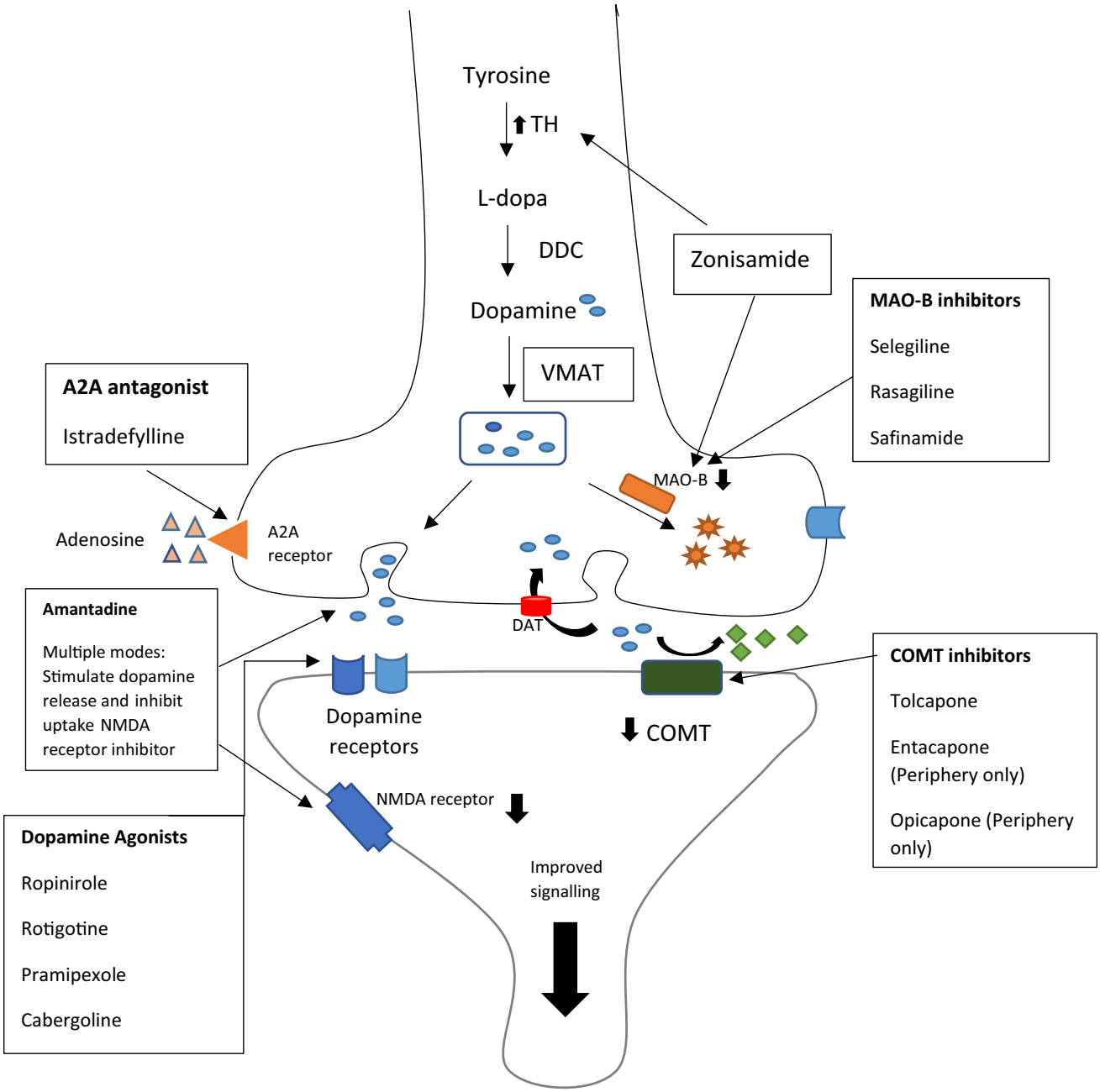

Fig. 3 Summary of modes of action of different medication groups at the synaptic level in improving dopaminergic signalling. *A2A* adenosine 2A, *COMT* catechol-*O*-methyltransferase, *DAT* dopamine transporter, *DDC* dopa decarboxylase, *MAO-B* monoamine oxidase type B, *NMDA* *N*-methyl-D-aspartate, *TH* tyrosine hydroxylase, *VMAT* vesicular monoamine transporter

3.2 Adjunctive Therapies

3.2.1 Catechol-*O*-Methyltransferase Inhibitors

A further strategy to reduce MF is to increase levodopa peak plasma concentrations and action duration. Adjunctive medications are a means to achieving this by interfering with dopamine and levodopa metabolism without needing to increase the total levodopa daily dose. Levodopa is metabolised peripherally by catechol-*O*-methyl transferase (COMT). Drugs inhibiting COMT increase the elimination half-life of levodopa thus increasing its bioavailability and stabilising plasma levels [95]. This provides more sustained brain dopaminergic stimulation thus decreasing 'off' time, and in some instances decreasing the required daily levodopa dose.

Entacapone is a selective, reversible inhibitor of COMT and primarily acts to block levodopa metabolism in the

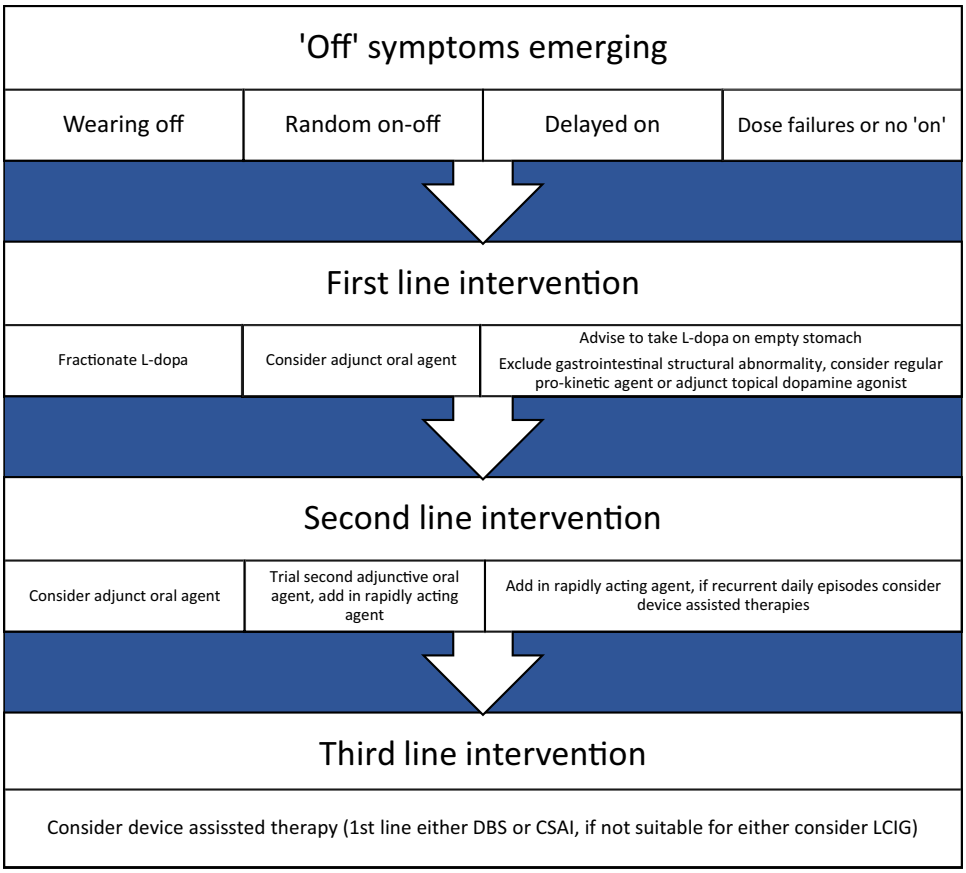

Fig. 4 Summary of proposed step-wise approach towards managing 'off' symptoms. Each column addresses individual 'off' symptoms and specific intervention steps to improve them

periphery and improve levodopa absorption [95]. Repeated administration of 200 mg taken at the same time as each dose of levodopa/carbidopa increases plasma levodopa concentration by approximately 30% [94]. Three randomised trials evaluating entacapone as an adjunctive treatment to levodopa in patients with wearing-'off' motor fluctuations, demonstrated superiority in 'off' times (on average an increase in daily 'ON' time by 0.8 h) and UPDRS motor scores [96–98]. However, this approach can result in a higher rate of dyskinesia (STRIDE-PD study), which may necessitate adjustment to individual patient levodopa doses [34, 95]. Formulations of L-dopa combined with entacapone (Stalevo®, Stanek®, Sastravi®) are also available and reduce the pill burden for patients and thus may ease administration, although their clinical outcomes are thought to be largely similar to levodopa/entacapone taken separately.

Tolcapone is an alternative COMT inhibitor with greater potency by virtue of its combined central and peripheral action on COMT [99] that improves 'on' time by approximately 1.8 h over a 24-h period [100]. This agent was however linked to three cases of hepatotoxicity [101, 102] and therefore requires regular monitoring of liver function tests to allow its safe use. This need for regular blood tests has greatly reduced its usage in clinical practice. Another recently available alternative is opicapone [103] which is a selective, peripherally acting, once-daily COMT inhibitor. At a dose of 50 mg daily, levodopa bioavailability is significantly higher than that achieved by entacapone[[104]. Phase III studies demonstrated superiority over placebo and non-inferiority when compared to entacapone [105, 106]. Scrutiny of 'off' time reductions however suggests a modest benefit in favour of opicapone over entacapone (116.8 min vs 96.3 min) [106]. The medication is generally well tolerated though dyskinesias, orthostatic hypotension and hallucinations can occur though some of this can potentially be overcome by concurrent lowering of levodopa doses [105, 106].

3.2.2 Monoamine Oxidase-B Inhibitors

Monoamine oxidase-B inhibitors (MAO-Bi) selectively and irreversibly block MAO-B, the main enzyme responsible for degrading dopamine in the synaptic cleft, and therefore increase dopamine concentrations in the brain. Their effects on dopaminergic stimulation is relatively modest which is largely explicable by the additional presence of presynaptic dopamine transporters which rapidly remove dopamine from the synaptic cleft. Selegiline (Deprenyl®) was the first available MAO-Bi, followed by rasagiline (Azilect®) and

these remain the most commonly prescribed options. The PRESTO trial randomised 472 patients experiencing motor fluctuations to receive either rasagiline 0.5 mg or 1 mg/day with a reduction in the mean total daily 'off' or an approximate gain of 0.85 h/day in 'on' time without troublesome dyskinesias when added to L-dopa [107, 108]. The safety and efficacy of rasagiline was further explored in the LARGO trial and found to be comparable with entacapone [107, 109]. Evidence for the use of selegiline relies on lower quality studies demonstrating a modest reduction in daily 'off' time [110]. The drug is extensively metabolised in the liver with a resultant 10% bioavailability, variable pharmacokinetics and high metabolite concentrations. Selegiline orally disintegrating tablets aim to mitigate this by allowing direct absorption into the systemic circulation via the oral mucosa and therefore bypassing the gastrointestinal system and the first-pass metabolism. Selegiline metabolism can produce amphetamine like compounds which has led to concerns in patients with pre-existing cardiac conditions [111].

MAO-Bi can rarely induce hallucinations, confusion, and hypertensive crises. Furthermore, simultaneous administration with tricyclic antidepressants, selective serotonin and serotonin–norepinephrine reuptake inhibitors potentially increases the risk of serotonin syndrome although this does not tend to occur at the low therapeutic doses used (higher doses result in loss of selectivity and resultant inhibition of MAO-B and MAO-A, with a resultant increased risk of serotonin syndrome) [112]. The concomitant use of rasagiline/selegiline and selective serotonin reuptake inhibitors (SSRIs) is not recommended/contraindicated according to product monographs/labels. Nonetheless, to date, the only report of serotonin syndrome in this context is from the Parkinson Study Group survey suggesting an incidence of 0.24%, which is consistent with the authors own experience of safely using these drugs in combination [113].

Safinamide is a recently available highly selective, reversible MAO-B inhibitor with additional effects of blocking voltage-dependent sodium and calcium channels as well as reducing glutamate release and transmission [114]. This agent is given orally (50–100 mg/day) and provides increases in daily on time without troublesome dyskinesias to a magnitude similar to rasagiline [115–117]. A recent meta-analysis suggested that safinamide may be less effective than both rasagiline and selegiline though had comparable efficacy to entacapone [118]. Available follow-up studies suggest however sustained responses and tolerability to Safinamide over 2 years and the possibility of lower occurrence of dyskinesia, while headache and hypertension can feature in a small proportion of cases albeit less frequently with the 50 mg dose [115, 116].

3.2.3 Dopamine Agonists

Dopamine agonists (DA) mimic the action of dopamine by stimulating striatal post-synaptic receptors [119]. Dopamine receptors are widely distributed in the central nervous system and periphery. These receptors can be divided into the D1 (D1 and D5 receptors) and D2 (D2–D4) families. The nigro-striatal pathway is largely mediated by D1–D3 receptors [119]. Agonists are classified as either ergot derived (e.g. bromocriptine, pergolide, cabergoline, lisuride) or non-ergot derived (e.g. apomorphine, ropinirole, pramipexole, and rotigotine) and each agent has a slightly variable affinity for different receptors [120, 121]. DAs can be valuable as adjunctive therapy to levodopa for patients with motor complications by offering a further avenue to improve 'off' times without increasing levodopa [122]. Pramipexole and ropinirole are examples of this class of medication that have been demonstrated to significantly reduce 'off' time when compared with placebo. While initial interest revolved around IR formulations of these agents, the more novel extended-release (ER) formulations offer the benefit of reductions in 'off' time by promoting more stable plasma levels while reducing the number of medication intakes. Ropinirole ER is one such example and has been demonstrated to be more efficacious in maintaining a reduction in 'off' time of up to 20 % when compared with ropinirole IR formulations [123, 124]. Pramipexole ER has also been demonstrated to deliver up to an additional hour of 'on' time per day when compared with placebo though appears to be approximately equivalent to the IR formulation while tolerability of these agents are largely similar [125, 126]. The choice may therefore depend on individual tolerability and preference. Rotigotine, is a topical, non-ergot dopamine agonist with broad affinity for dopamine (D1–D5) receptors [127]. Rotigotine is non-inferior to the other agonist options though use of this agent is limited in some individuals by the potential to develop application-site reactions. Rotigotine also offers a 24-h transdermal delivery (2–16 mg/24 h) which results in the additional value of improving early-morning motor dysfunction and nocturnal sleep disturbances [128, 129]. Rotigotine may also be effective in addressing swallowing dysfunction and improving gastric emptying potentially via a reduced inhibition of the myenteric plexus and central dopaminergic augmentation of D1 receptors on gastro-intestinal motility though further studies are necessary before this medication can be recommended for this indication [130, 131].

Major concerns with DAs relate to their adverse effects. These typically include mild peripheral oedema, excessive daytime sleepiness, constipation, hallucinations, nausea, and postural hypotension. Neuropsychiatric issues, are of particular concern and include Impulse Control Disorders (e.g. hypersexuality, pathological gambling, and compulsive shopping), punding, and dopamine dysregulation syndrome

[132]. Patients should be routinely warned about the possibility of ICD prior to prescription of all DAs and their presence should be enquired about from patient/carer at all subsequent follow up appointments. Although these concerns can effectively be managed with a reduction and subsequent withdrawal of the agent, the concern of a dopamine agonist withdrawal syndrome (DAWS) can emerge if doses are reduced or withdrawn too precipitously. This condition includes withdrawal symptoms such as anxiety, panic, agoraphobia, fatigue, dysphoria, nausea, vomiting, diaphoresis, as well as suicidal ideation [133]. These symptoms do not seem to be ameliorated by replacement with levodopa and the re-introduction of the agonist may sometimes be in the only solution [134]. A further serious adverse event is of fibrotic reactions (heart valves, pleuropulmonary, retroperitoneal) which seem to relate to ergot DA agents specifically [135]. This has led to the discontinuation of these agents in many countries. In general, DAs are best avoided in the most elderly patients as they tend to be more prone to these adverse effects. Specifically, there is some suggestion that the rotigotine patch and ropinirole ER may result in lower rates of ICDs when compared to patients taking levodopa together with other agonists [136, 137] regardless of patients' ages [138] though this isolated report is unlikely to change overall clinician aversion towards the use of these agents in elderly patients.

3.2.4 Other Agents

Amantadine is a non-competitive NMDA receptor inhibitor which selectively blocks activated open receptor channels with both direct and indirect downstream effects on glutamatergic and dopaminergic signalling [139]. Although primarily used to treat dyskinesia, Amantadine also has the potential to reduce 'off' time [140], and gait freezing [141]. A daily dose up to 200–400 mg is typically used. Higher doses are more likely to induce side effects such as hallucinations, dry eye, dry mouth, constipation, and cognitive dysfunction. Much of the data currently available are from open label studies and well-designed randomized long-term trials addressing the efficacy and safety of this drug are still needed [142, 143].

Amantadine ER is a novel extended-release once-daily formulation that is currently available in selected countries. At the recommended dosage, plasma amantadine concentrations are 1.4- to 2.0-fold higher than IR formulations while peak plasma concentrations are reached more gradually while remaining sustained throughout the day (prolonged T_{max}) [144]. This agent has a once-daily bed-time dosing scheme while the switch from IR to ER consists of administering 137 mg for 1 week and increasing to the target dose of 274 mg thereafter. This has been shown to induce a significant primary reduction in the Unified Dyskinesia Rating Scale score, and a secondary increase in 'on' time without troublesome dyskinesias when compared to placebo [145, 146]. Amantadine ER can achieve an 18% reduction in dyskinesias with a resultant 2.8 h of increase in 'on' time without troublesome dyskinesia though the side effect profile seems to be similar to the IR formulation [147].

Istradefylline is a selective adenosine A2A receptor antagonist utilised for adjunctive treatment of motor fluctuations [148]. It was developed in Japan and the majority of the experience with this drug is in Japanese patients. This agent modulates striatopallidal GABAergic output neurons and reduces daily 'off' time by approximately 0.7 h though trial data of its benefits have been inconsistent [149, 150]. Post marketing surveillance however suggests improvements in 'off' time in approximately 40% of people [151]. Commonly reported adverse effects include dyskinesia and hallucinations [151, 152]. Currently this agent is not widely available although there are plans to launch it in Europe and the USA.

Zonisamide (25–50 mg/day) increases dopamine levels by activation of tyrosine hydroxylase in the striatum as well as via some moderate inhibition of MAO-B. The further inhibition of T-type calcium channels and glutamate release potentially also exerts inhibition on the indirect pathway in the basal ganglia. A placebo-controlled randomised trial over 1 year in patients with wearing-off symptoms suggested a modest benefit in reducing 'off' time, without increasing dyskinesia [153]. Zonisamide is now approved for the treatment of PD in Japan.

3.2.5 Rapid-Acting Agents

Despite best efforts to optimize oral dopaminergic therapy, chronic PD patients can suffer up to 2–3 h of 'off' time per day on average [26]. Rapid-acting medications can potentially bridge symptom control by addressing unpredictable 'off' periods, and dose failures, while prolonging the latency of L-dopa effectiveness. It should be stressed however, that while options currently available are efficacious, their reliability can be variable (oral preparations) or limiting from a logistical perspective (sub-cutaneous apomorphine). Also, clinicians should be cautious regarding the use of these options on a regular basis considering the theoretical concerns of potent pulsatile dopaminergic stimulation. Patients using these agents on a regular basis should therefore be considered for the more reliable and continuous device assisted treatments available.

Dispersible benserazide-L-Dopa, (Madopar®) was developed to enable PD patients with difficulties swallowing pills to receive medication in a liquid form. The drug has similar efficacy, and dosage equivalence to conventional levodopa formulations without side effect differences. The agent has a significantly shorter T_{max}, arguably owing to its accelerated absorption from a lack of disintegration by gastric fluid

[154]. This rapid acting agent has a much faster and more constant onset of action than the standard preparation (25 vs 46 min) [155] and can therefore be considered as first line for the treatment of EMO and unpredictable 'off' symptoms. This proven efficacy is often less reliable in clinical practice because of its shorter duration of action, necessitating the development of other potent, rapidly acting agents.

Apomorphine, an aporphine alkaloid derived from acidification of morphine, is a potent DA with a broad spectrum of effects on both D1- and D2-like receptors [156]. This is in contrast to the oral DAs that mainly bind to D2 and D3 receptors. In addition, apomorphine also has antagonistic properties towards serotonergic and adrenergic receptors [157]. It has limited oral bioavailability therefore parenteral administration has been favoured. Apomorphine has a similar volume of distribution, plasma clearance and half-life following subcutaneous infusion therefore intravenous infusion can be avoided [158–160]. A number of factors influence its subcutaneous absorption. These include the injection site (abdominal injections have better results), volume and depth of injection (greater volume reduces the T_{max}), skin state (temperature, vascularization, body fat) and the presence of nodules (a common feature following chronic apomorphine use) which hinder absorption [161]. After a subcutaneous injection, peak blood concentration is typically reached within 10 min, with a maximum cerebrospinal fluid concentration achieved after 30 min [160] with a brain-to-blood concentration ratio of approximately 8:1 [162]. Also, the rapid metabolism and clearance of the drug results in a $T_{½}$ of around 33 min [160]. Although intra-individual variability in its pharmacodynamic effect is low, inter-individual variability is high resulting in a need for individual titration to identify the optimal dose during the initiation process. On balance, a clinical response tends to be appreciated within 10 mins of an injection and can last for close to 1 h [163].

Currently available formulations are a subcutaneous multi-dose pen or a subcutaneous pump (continuous subcutaneous apomorphine infusion-CSAI-discussed in the section on device assisted therapies). The subcutaneous apomorphine pen is arguably the most potent rapid treatment approach for 'off' symptoms. Injections can be administered following either an inpatient dose titration process or an outpatient approach. Efficacy of the apomorphine pen has been demonstrated in several randomised evaluations [164–166]. The injections have been demonstrated to be more reliable than dispersible L-dopa in reducing time to 'on' [167]. Improvements have been noted in the treatment of early-morning akinesia [168] as well as daytime 'off' periods. Furthermore, observational and randomised controlled studies seem to suggest consequent gains in 'on' time of up to 2 h per day [164–166, 169–173]. While improvements in urinary dysfunction and pain [174] have been noted, convincing evidence for improvements in NMF are lacking. The apomorphine pen is not infrequently accompanied by side effects such as nausea, yawning, somnolence, dizziness, orthostatic hypotension and dyskinesia. While this can be an effective long term therapy in some people, up to one-third of patients discontinue apomorphine within a year of initiation [164–166, 172].

In addition to drug induced side effects, some patients struggle with apomorphine due to needle phobia, or difficulty administering a pen injection during an acute 'off' phase. Alternative less invasive delivery systems are in active development. An apomorphine powder formulation via an inhaler device (VR040) has been subjected to randomised trials. This device is well-tolerated, with reasonable efficacy in the management of MF [175]. Further studies have suggested rapid absorption (2–7 min) and reversal of the 'off' state (10 min) without significant pulmonary safety concerns [176, 177]. Sublingual apomorphine is a further option with comparable symptomatic effects to its subcutaneous counterpart. A novel bilayer film of sublingual apomorphine (APL-130277) helps reduce the time taken for its sublingual dissolution and absorption and it has been demonstrated in Phase 3 studies to allow full achievement of on states within 15–30 min of administration [25, 178]. Side effects noted are broadly similar to subcutaneous apomorphine although up to a third of patients may develop a combination of lip or oropharyngeal swelling and erythema. A Phase 3 crossover trial evaluating APL-130277 against subcutaneous apomorphine in patients with MF is currently underway (Clinical-Trials.gov identifier: NCT03391882) and will be crucial in informing its use in clinical practice.

A levodopa inhaled powder known as CVT-301 is a novel dry powder formulation in capsules which are inserted into and administered via a breath-actuated device [179]. This agent is rapidly absorbed through the pulmonary epithelium, avoiding first-pass metabolism and therefore achieving peak plasma concentrations within 15 min of inhalation [180]. Clinical effects are noted within 5–15 min with benefits lasting up to the fixed 90 min evaluation mark of the study [181]. This agent has been further demonstrated to achieve plasma levodopa concentrations more rapidly than oral levodopa while maintaining more stable concentrations over 60 min. On average, patients using two inhalations per day appeared to gain about 0.8 h/day in 'ON' time when compared to placebo [179–181]. The most common side effect is the predictable occurrence of a cough which does not seem to abate on lower doses while other respiratory side effects (upper respiratory tract infections, discoloured sputum, and throat irritation) occur less frequently and without any detrimental impact on lung function [182]. Hypotension and atrial fibrillation are potentially serious adverse events that have been less frequently described. Moving forwards, head-to-head comparisons between subcutaneous apomorphine, sublingual and inhaled formulations of apomorphine and

L-dopa would be of value prior to determining the relative usefulness of these agents in the hierarchy of managing 'off' episodes, however it is unlikely that the commercial manufacturers would risk supporting randomised comparisons of any of these agents other than against placebo.

4 Device-Assisted Therapies

Despite best efforts with a mixture of approaches described thus far, a proportion of patients will continue to experience debilitating 'off' phenomena for significant proportions of their day. Device-assisted treatments (often termed advanced therapies) are crucial in managing these cases considering the potency of their effects, albeit with their greater invasive nature. While their modes of action vary, these treatments collectively capitalise on their superiority in delivering continuous dopaminergic (or electrical) stimulation. The exact timing for introducing these treatments into care remains controversial though expert consensus can be useful in this regard. In a Delphi-panel consensus [183], recommendations for device assisted therapies included for; patients with troublesome motor fluctuations (≥ 1 h of troublesome dyskinesia/day, ≥ 2 h "off" symptoms/day) on ≥ 5 oral levodopa doses/day with functional impairment and difficulty with activities of daily living [183]. Patients with good levodopa response, good cognition, and age < 70 years were deemed good candidates for the three main device-assisted therapies though other specific patient related considerations should also be factored into decision making processes when considering the most appropriate individualised option [183].

4.1 Infusions

Infusion therapies inevitably achieve more stable plasma drug concentrations in comparison to their more traditional oral counterparts. The Levodopa–carbidopa intestinal gel (LCIG) infusion is one such approach that provides a continuous jejunal infusion of levodopa/carbidopa [184]. LCIG is delivered by an external pump which administers small doses of levodopa/carbidopa approximately once every minute to the small intestine [185]. This bypasses the unpredictable nature of gastric emptying and therefore overcomes irregular absorption [186]. LCIG provides stable plasma concentrations throughout the day which is likely to be the explanation for its superiority to orally administered levodopa [185, 186]. For the majority of patients, the external pump is used to deliver the agent continuously over 16 h during the waking day via a percutaneous gastrojejunostomy tube (PEG-J). In a small proportion of cases where uncertainty of the degree of L-dopa responsiveness exists, a prior trial of the agent with a naso-jejunal phase may be necessary [187]. Some patients may benefit from 24 h administration of the infusion to improve nocturnal symptoms [188] and it has even been proposed to improve freezing of gait [189] although this phenomenon often eventually becomes refractory to L-dopa therapy of any form. While a small proportion continue on oral agents, monotherapy is achievable in the vast majority, perhaps supplemented by CR oral L-dopa to cover the night-time period.

In a randomised, double blind trial, LCIG was found to increase 'on' time without troublesome dyskinesia by approximately 2 h per day with significant quality of life gains [190]. Although some non-motor symptom improvements have been demonstrated [191], the response of non-motor symptoms to LCIG are less predictable and specific studies demonstrating efficacy for NMF are lacking, therefore this treatment should only be routinely used in patients with significant MF. Despite the substantial advantages in MF seen with this treatment, the use of LCIG may be limited by device- and procedure-related complications such as blocked tubes, tube dislocations, stoma complications, superficial infections, peritonitis, and pneumoperitoneum [190, 192]. These issues can result in a proportion of patients discontinuing treatment, though systemic and procedural modifications have been demonstrated to minimise these occurrences [193–195]. Polyneuropathy has been noted in a small proportion of patients using LCIG, therefore prior surveillance for vitamin B12 deficiency (including measurement of homocysteine and methyl malonic acid) and parenteral B12 replacement may be useful in this regard [196, 197]. In view of the substantial undertakings and costs involved, some current guidelines suggest that the LCIG should only be utilised in cases of advanced PD where patients have either failed or do not qualify for alternative device-assisted modalities [198].

Continuous subcutaneous apomorphine infusion (CSAI) is a proven alternative to LCIG that is less invasive and considerably less expensive and thus should be discussed as an alternative treatment option with all patients considering LCIG. This infusion is administered via a portable pump system delivering a continuous dose, with the possibility of intermittent rescue boluses as needed. Infusions typically last 12–16 h (waking time), but a 24-h regimen can also be programmed to treat nocturnal hypokinesia [199, 200].

Suitable patients include those who have 'off' periods no longer controlled with optimised oral therapy, those who need apomorphine pen rescue doses too frequently or those who require an alternative to surgical or enteral therapy [90]. Patients starting CSAI should be administered domperidone 10 mg (or trimethobenzamide in countries where domperidone is not available) three times daily from 1 day before initiation to 3–7 days in total to prevent nausea. Prior to initiation of domperidone, an electrocardiogram demonstrating a normal QT interval should be performed (in view of an increased risk of ventricular tachyarrhythmia

and sudden cardiac death with domperidone) particularly in patients with PD and pre-existing cardiac disease [201]. Apomorphine infusions are typically started at a dose of 0.5 or 1 mg/h while anecdotally slow up-titrations (0.5 or 1 mg/h daily increments) targeting an infusion rate ranging from 4 to 7 mg/h tend to achieve better outcomes. A concomitant reduction of oral antiparkinsonian drugs is usual. Titration can also be achieved in the outpatient setting (after the initial exclusion of potential adverse reactions) with an inpatient test dose, although a slower increase process tends to be more typical [200].

It is crucial to note that apomorphine is the only agent shown to have similar efficacy to levodopa when treating PD motor symptoms, although as would be expected, patients experience a shorter duration of effect [167, 202]. Multiple open-label series have confirmed the efficacy of CSAI in reversing severe, sudden 'off' states in advanced PD despite optimised oral therapy [169, 172, 203]. A recent randomised, double-blind trial of a 16-h daily CSAI infusion has further demonstrated similar improvements in 'on' time to LCIG (i.e. approximately 2-h reduction in 'off' time) while patients were also able to reduce their daily levodopa equivalent medication by more than 300 mg [204]. Some emerging evidence also suggests efficacy in the management of non-motor symptoms, in particular sleep, mood, gastrointestinal, perceptual problems and urinary domains [174, 205], although approaches using CSAI purely to treat NMF cannot be recommended currently without further conclusive evidence of benefit in this regard.

Skin nodules, nausea, and somnolence can commonly occur, although less common adverse effects such as severe hypotension, hallucinations, confusion, and infusion-site cellulitis can potentially be more concerning. Haemolytic anaemia and leucopenia have rarely been described [206–209]. The long-term tolerability of CSAI is variable with up to two-thirds of patients ceasing therapy after an average of 17.9 months due to complications such as hallucinations, and less common reports of impulse control disorder, and dopamine dysregulation [210–212]. An argument has been mounted by some suggesting an either neutral or remission effect of CSAI on psychotic symptoms and hallucinations due to the drugs shared piperidine moiety structure with antipsychotic agents, although this is not universally seen and the available evidence is insufficient to prompt clinicians to adopt this approach [210, 213, 214]. Although ICDs are a major concern with dopamine agonists, the lower D3:D2 ratio of apomorphine compared to oral agonists along with the lower incidence of ICDs noted in a number of studies suggests that patients should not be precluded from being considered for this treatment, even if they have experienced ICD symptoms previously [211, 215, 216], although more cautious titration approaches should be employed.

Difficulties related to the injection system (i.e. the technical aspects of the pump), the complexity of the initial titration schedule, the difficulty of tailing off levodopa and other oral dopamine agonists, the shorter duration of benefit in some people, and the risk of skin nodules and ulceration may account for its limited acceptance and explain why it is not used more widely. However, some of these cutaneous risks can be reduced through improved skin hygiene, changing the site of injection, using newer styles of needles, and using localised massage and ultrasound therapy [208].

A subcutaneous carbidopa-levodopa infusion (ND0612) through a small pump-patch is currently under investigation with preliminary pharmacokinetic studies suggesting stable plasma levodopa concentrations are achievable over 24 h. A number of Phase 2 studies have established that this agent provides more stable plasma levels of levodopa compared to oral medications, while one study suggests that ND0612 may result in higher total plasma levodopa, i.e. higher bioavailability [217, 218] and less inter- and intra-subject plasma level variability compared to LCIG [219–221]. Similar to LCIG and CSAI, these same studies also suggest that up to 2 h of reduction in 'off' time compared to optimal oral therapy is achievable with ND0612. A further finding showed an up to 80% reduction in oral L-dopa intake while only a small proportion of subjects were able to achieve monotherapy with the infusion. Significant improvements in sleep quality and early-morning motor symptoms in patients running infusions for 24 h is encouraging, although similar cutaneous concerns seem to occur in patients as with apomorphine [222]. A Phase 3 multicentre, randomised, double-blind placebo-controlled trial of ND0612 (INDIGO) is currently ongoing (ClinicalTrials.gov ID: NCT2726386) [223].

4.2 Neurosurgical Approaches

Deep brain stimulation (DBS) is a proven treatment for reduction in the severity and duration of MF in PD. It requires the surgical implantation of intracranial electrodes and a pacemaker device, which provides continuous stimulation to deep structures of the brain [224]. The exact mechanism of action in PD treatment is unclear, although modulation of pathological neuronal firing patterns within the cortico-basal ganglia networks is potentially implicated in the motor symptom improvements noted [225, 226]. The merits of this approach in addressing L-dopa-associated motor fluctuations is considerable. Compared to best medical therapy, DBS improves 'on' time without troublesome dyskinesia by approximately 4–5 h, with up to two-thirds of patients achieving meaningful improvements in motor fluctuations by 6 months [227, 228]. These positive effects appear to last longer than 10 years in several long-term

studies, although the net effects on quality of life in comparison to pre-operative status seem to wane after 5 years, presumably because of the inexorable progression of the disease [229, 230]. There has been recent interest in this treatment being considered earlier in the course of disease [231] and for DBS to be utilised as the first choice of device-assisted therapies when this is clinically appropriate. The optimal timing for DBS requires individual discussions with a considered balanced between the potential risks and benefits, as well as consideration of a patient's expectations and lifestyle.

The subthalamic nucleus (STN) and globus pallidus interna (GPi) are the most commonly targeted structures for DBS in PD patients, although the preferences are largely dependent on the clinical scenario being addressed [232, 233]. Although STN DBS improves the severity of the motor symptoms of PD and has the potential to reduce dopaminergic medication requirements, it is also associated with an increased risk of cognitive and psychiatric complications [234–236]. Conversely, GPi stimulation is less likely to negatively impact mood and cognitive processing while resulting in greater reductions in dyskinesia [227–229]. However, GPi DBS rarely allows for a major reduction in dopaminergic therapies [227–229]. Potential complications relate to the surgical procedure and hardware such as wound infections or erosions, lead migration/malposition, lead or extension fractures and component malfunctions [237, 238]. Other rare risks include the occurrence of post-implantation seizures, oedema and symptomatic intracerebral haemorrhage [239].

While reduction in medication requirement is usual after STN DBS, the majority of patients do not stop all their dopaminergic replacement and 'on' and 'off' motor states and decline in motor function can begin to recur with time, likely due to disease progression and development of stimulation and L-dopa-resistant symptoms [240]. The therapeutic effects noted can also be limited by inaccurate placement of electrodes as can side effects such as speech disturbance, gait impairment, paraesthesia, and diplopia [241]. While some of these aspects can be mitigated by adjustments to stimulation [242], the additional utilisation of longer-acting formulations or continuous infusions can at times be of value. An open-label study comparing DBS to LCIG and CSAI suggested superior control of dyskinesia and less procedure- or device-related complications [243] with DBS, although the lack of randomisation makes interpretation of this study less generalisable. Novel mechanisms to improve stimulation delivery are currently being developed and could potentially make the clinical benefits noted more durable into the future [244, 245].

5 Specific NMF Considerations

The management of non-motor symptoms is crucial in improving patients' quality of life. While each symptom provides unique management challenges, it is beyond the scope of this review to explore these finer aspects, although a recent Movement Disorder Society sanctioned evidence-based critique is a worthwhile source in this regard [246]. These guidelines do not address the treatment of NMF, which continues to lack a specific evidence base. Fluctuations in NMF severity in accordance with dopamine replacement therapy is highly suggestive that the NMF have a dopaminergic origin. Although current approaches towards NMF largely rely on principles established for motor fluctuations, specific pathophysiological considerations imply that some additional strategies are potentially warranted. Potential overarching principles could encompass targeting respective NMS with the combination of continuous dopaminergic stimulation and supplementary treatments targeting non-dopaminergic mechanisms when necessary [247, 248]. While non-dopaminergic symptom-oriented approaches should be trialled (e.g. antidepressant drugs for depressive mood fluctuations), many NMFs do not particularly respond to such treatment strategies. A secondary imperative is to establish if the different dopaminergic thresholds for improvement (i.e. the required level of medication adaptation) are similar for both MF and NMF [249]. This can be achieved by implementing the principles outlined thus far for management of MF but with clear attention to the fluctuation of NMS. Examples of this include medication reductions with the aim of improving neuropsychiatric symptoms and orthostatic hypotension or the utility of add-on therapy to improve sleep. Specific examples of useful add-on therapy include the potential benefit of safinamide [117] and tolcapone [250–252] in improving depression and sleep as well as dopamine agonists in addressing depression, sleep, apathy and pain [129, 166]. It is important to consider the potential risk of dopa dysregulation in patients with NMF, in whom escalating levels of dopaminergic medication can be seen despite little objective evidence of any motor disability.

Finally, although the evidence base for device-assisted therapies improving NMS is growing [205, 228, 253], specific improvements in NMF are largely limited to a small cohort study of STN-DBS suggesting a reduction in NMF of approximately 60% with greatest promise seen with pain fluctuations [254]. The dearth of specific evidence available for the management of NMF is a result of a poor understanding of pathophysiology, and a lack of quality detection tools [255]. Controlled trials targeting NMF as primary endpoints similar to those currently available motor fluctuations should be encouraged moving forward considering their known impact on patients' quality of life.

6 Conclusion

Motor fluctuations develop almost universally in PD patients with the progression of disease. While levodopa has not been conclusively determined to be causative of this phenomenon, patients generally only manifest with these episodes in its presence. Modifications of formulations and the mode of administration of this medication, in conjunction with adjunctive options, can initially be of value although many patients will ultimately require device-assisted therapies to manage these symptoms, provided they are otherwise fit enough to withstand their invasive nature/side effects. Future studies should focus on improving our understanding of the disease biology contributing to these occurrences as preventative approaches will be crucial moving forward.

Availability of data and material Not applicable.

Code availability Not applicable.

Compliance with ethical standards

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