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REVIEW

Review: management of Parkinson's disease

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Abstract: Parkinson's disease (PD) is one of the most frequent neurological diseases. Despite the modern imaging and nuclear techniques which help to diagnose it in a very early stage and lead to a better discrimination of similar diseases, PD has remained a clinical diagnosis. The increasing number of available treatment options makes the disease management often complicated even when the presence of PD seems undoubted. In addition, nonmotor symptoms and side effects of some therapies constitute some pitfalls already in the preclinical state or at the beginnings of the disease, especially with the progressive effect on patients. Therefore, this review aimed to summarize study results and depict recommended medical treatments for the most common motor and nonmotor symptoms in PD. Additionally, emerging new therapeutic options such as continuous pump therapies, eg, with apomorphine or parenteral levodopa, or the implantation of electrodes for deep brain stimulation were also considered.

Keywords: Parkinson's disease, disease management, side effects, nonmotor symptoms, DBS, pump therapies

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder, initially characterized by a loss of dopaminergic neurons in the substantia nigra that spreads over the course of the disease to almost the whole central nervous system. But although the first description of the "shaking palsy" by James Parkinson was published almost 200 years ago, there is still a lack of understanding of the causes of PD. However, great insight into the pathomechanisms was gained during the last decades, identifying in microscopic postmortem studies ubiquitous Lewy bodies as histological correlates of cell death.[1]

Nevertheless, PD remains a clinical diagnosis with cardinal motor symptoms such as akinesia, rigidity, and tremor. Yet, advances in different imaging techniques, such as functional magnetic resonance imaging or nuclear imaging techniques, provide supplementary information allowing a precise distinction from differential diagnosis, such as essential tremor or other parkinsonian syndromes.[2,3] Additionally, they allow a classification of subtypes, allowing a more accurate and even earlier diagnosis.[4,5] This is crucial for avoiding a delayed therapy for evolving symptoms and therefore improving quality of life (QOL). Also, it could offer in the near future the possibility of designing and studying disease modifying drugs able to slow neurodegeneration, and tailoring patient-specific therapy strategies. One possible way might be the development of alternative and more invasive options that have emerged recently, such as pump therapies or deep brain stimulation (DBS). All these treatments have shown promising results in terms of reducing motor symptoms (tremor, akinesia, and/or rigidity).

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Nonmotor symptoms have also gained importance, as patients report them impairing their daily life. For physicians, however, they appear at times difficult to treat and even to identify, as they often intermingle with comorbidities. In this respect, many results have been published lately concerning different medical agents and their efficacy and possibilities, but also their restrictions in PD management. Therefore, this review aims to summarize current recommendations and therapeutic strategies for PD patients.

Nonpharmacologic therapies

From clinical experience and by what patients report, exercise, physical therapy, and speech and/or occupational therapy have a sustainable effect for PD patients in terms of maintaining the status quo and improving QOL. For this purpose, there are numerous offered approaches; yet, listing all of them would certainly go beyond the scope of this work. Still, only a few methods have been tested in high-standard studies and constitute effective therapies.

Methods considered helpful include multiple forms of physical exercise such as tai chi or LSVT BIG™ (LVST Global, Inc, Tucson, AZ, USA) but also speech therapy with the Lee Silverman Voice Treatment.[6–11] Nevertheless, they can hardly be considered a replacement of pharmaceuticals, but rather a basis which has to be extended by medical treatment. Particularly, patients suffering from axial signs such as freezing of gait, camptocormia, or severe gait and speech problems do benefit from regular physical and/or speech therapy, and attention can be drawn to movement strategy training or cueing. All other PD patients should also receive regular physical and/or speech therapy and should be motivated to regular exercise. In agreement with other authors, well-designed trials are needed to demonstrate efficient but also cost-effective approaches for nonpharmacological therapies in PD.[12]

Medical treatment of PD

Therapy should be started as soon as the diagnosis of PD is made. A delayed start of the treatment cannot be justified with the risk of motor fluctuations and one has to keep in mind that patients show the best results when treated early. In addition, the authors believe that the mere attendance of a professional is a consequence of a decreased QOL and therefore an indication for therapy. However, the numerous available possibilities make the best choice difficult for the different indications.

Disease modification

One of the foci in recent PD research has addressed pathomechanisms in an early state for hampering disease progression. This deceleration of the progress in PD has been demonstrated in animal models with selegiline,[13] rasagiline,[14] pramipexole,[15] and coenzyme Q10.[16] To date, however, few results were reproducible in humans. Thus, 1 mg rasagiline daily over 18 months possibly delays clinical progression in early stages of PD.[17] This is why it is still considered – despite being inconclusive with prior studies[18] – a good choice for younger patients with only mild symptoms. These patients not only benefit from the possible disease modification but also from the improvement in motor symptoms. When rasagiline is not sufficient, it can also be safely combined with other agents, eg, dopamine agonists (DA). In contrast, studies investigating the latter ones alone (eg, pramipexole)[19] did not show conclusive neuroprotective properties and can therefore not be recommended for this purpose.

Further insight into disease modification and current investigation can be found in the review by Hart et al.[20] The properties of rasagiline as a possibly disease modifying drug can be found in Table 1.

Management of motor symptoms (eg, akinesia, rigidity, and tremor)

Dopaminergic medication

Levodopa

Levodopa in combination with a peripheral decarboxylase inhibitor is still the most effective medication available.[18,21] Oral application of levodopa is available in different galenic formulations. The wide range of possibilities allows a selective choice if either fast delivery is needed (eg, in the morning) or long-lasting effects are desired (eg, during the night). Alternatively, "on" phases might be prolonged when using combinations such as catechol-O-methyltransferase (COMT) inhibitors with levodopa.[22–24] However, patients treated with levodopa tend to develop motor complications after 4–6 years.[25]

Complications after long-term levodopa treatment involve medically refractory fluctuations and/or dyskinesias. Therefore, the primary use of levodopa should only be considered when there is a lack of efficiency with DAs or side effects impede sufficient symptom control in younger patients with agents other than levodopa. In contrast, levodopa is recommended in older patients as monotherapy or in combination with other drugs even as the first-line option, as it shows high efficacy and good safety.[26]

DAs

This group of pharmaceuticals comprises medications that activate the dopaminergic receptor with an individual affinity

Table 1 Possible disease modifying agents in the treatment of Parkinson's disease

Substance	Mechanism	Dosage	Adverse events	Special monitoring	Evidence
MAO_B inhibitors					
Rasagiline	Selective inhibition of $MAO_B \rightarrow$ less metabolization of monoamines including dopamine	1 mg/day	Nausea, dizziness, abdominal pain, dry mouth, vivid dreams, and/or hallucinations, dyskinesias, might improve tremor at the beginning	None required but possibility of inducing serotonin syndrome effect together with SSRI, for example, is feasible (although improbable)	Possibly delays progression in early stages of the disease,[17] but at present insufficient evidence for a role in prevention/delay of PD[28]

Abbreviations: MAO_B, monoamine oxidase B; PD, Parkinson's disease; SSRI, selective serotonin reuptake inhibitor.

to the distinct subtypes of it (pharmacokinetic properties and details can be found in Kvernmo et al).[27] In general, there are two different groups: (1) ergoline and (2) nonergoline derivates. The former are not recommended as first-line medications anymore since they can produce several severe side effects which may cause a considerable risk if they are not specially monitored.[28] The nonergoline DA, in contrast, are considered efficacious and safe and are therefore especially recommended for treatment in younger patients in combination with levodopa or as a monotherapy.[28] Therefore, a wide range of agents and galenic formulations allows individual therapy, providing constant levels of medication and, eventually, good motor control. In addition, motor complications due to long-term treatment are not as likely as with levodopa therapy and can even be reduced by treatment with DA.[29–31] Nevertheless, it should be noted that DAs have a worse short-term risk profile compared to levodopa, causing more psychiatric and nonmotor side effects and making regular follow-up necessary.

Other drugs

Besides levodopa and DAs, there are other medications which have proven efficacious for treatment of motor symptoms in PD.[28] These drugs improve the plasmatic levels of levodopa and/or dopamine (monoamine oxidase B [MAO_B] inhibitors or COMT inhibitors). Due to their distinct mechanisms, however, each of these substances has advantages and properties that need to be considered. COMT inhibitors, for instance, have no intrinsic effect but increase plasmatic levels of levodopa. It has been proven efficacious for adjunct therapy with levodopa and for the treatment of motor fluctuations.[28] Still, there are side effects to be considered, especially tolcapone leading to hepatotoxicity.[32] Therefore, entacapone – particularly combined with levodopa – is widely applied in clinical practice, improving activities of daily living and reducing the "off" time[23] in fluctuating patients.[33] Similar characteristics can be found for MAO_B inhibitors as they also provide higher levels of dopamine, decelerating its metabolization. Hence, it is effective as monotherapy for motor symptoms and also as an adjunct to levodopa.[28] Additionally, both available medications (selegiline and rasagiline) are recommended due to their good safety. Taken together, the symptoms of PD might also be positively influenced, targeting the metabolization of dopamine.

On the other hand, neurotransmitters other than dopamine have also shown efficacy for the treatment of PD. Amantadine, for instance, possibly works by antagonizing N-methyl-D-aspartic acid receptors. However, the role is not clear and interference with other neurotransmitters is also feasible. Despite its unclear mechanism of action, it is recommended for therapy of motor symptoms in young patients[28] and appears to be useful in decreasing levodopa-induced dyskinesias.[34,35] Other target structures, eg, the adenosine receptor, are currently under investigation and show promising results.[36–38] This should motivate the expansion of ongoing basic research in order to discover further ways for symptomatic treatments for PD.

A summary of the recommended treatment of motor symptoms in PD with the distinct pharmaceuticals can be found in Table 2.

Management of special motor symptoms

Dyskinesias and fluctuations

The underlying pathogenesis of dyskinesias and fluctuations is probably the iatrogenic discontinuous administration of dopamine, which is in contrast to the physiologic steady concentrations.[39] As a consequence, dyskinesias and fluctuations often emerge due to early and longstanding levodopa therapy. Thus, the best treatment is the delay of levodopa in favor of DA or drugs with other target structures.

If, however, fluctuations occur, a practical approach is to reduce levodopa intervals and keep the dosage constant or to increase it only slightly, being aware that

Table 2 Management of motor impairments in Parkinson's disease

Substance	Mechanism	Dosage	Adverse events	Special monitoring	Evidence
Dopaminergic medication					
Levodopa together with peripheral aromatic acid decarboxylase inhibitor in a standard formulation	Precursor to dopamine	Depending on patient and the therapeutic effect, up to 1000–1500 mg/day	Hypotension, nausea, disorientation and confusion, insomnia and/or vivid dreams, hallucinations, somnolence	None required	Efficacious for symptomatic monotherapy and for the treatment of motor complications[18,28]
levodopa together with peripheral aromatic acid decarboxylase inhibitor in a controlled release formulation	Precursor to dopamine	Depending on patient and the therapeutic effect, up to 1000–1500 mg/day	Hypotension, nausea, disorientation and confusion, insomnia and/or vivid dreams, hallucinations, somnolence	None required	Efficacious for symptomatic monotherapy but insufficient evidence for treatment of motor complications[18,28]
Pramipexole	Partial or full dopamine receptor agonist with different affinity to the distinct dopamine receptor subtypes[27]	3 × 0.35–0.7 mg/day	Leg swelling, somnolence, fatigue, nausea, constipation and edema, impulsive or compulsive behavior	Psychiatric side effects should be taken into consideration and monitored cautiously	Efficacious for symptomatic monotherapy, symptomatic therapy adjunct to levodopa, the prevention/delay and the treatment of motor complications[28]
Ropinirole	Partial or full dopamine receptor agonist with different affinity to the distinct dopamine receptor subtypes[27]	6–24 mg/day	Leg swelling, somnolence, fatigue, nausea, constipation and edema, impulsive or compulsive behavior	Psychiatric side effects should be taken into consideration and monitored cautiously	Efficacious for symptomatic monotherapy, symptomatic therapy adjunct to levodopa, the prevention/delay and the treatment of motor complications[28]
Rotigotine	Partial or full dopamine receptor agonist with different affinity to the distinct dopamine receptor subtypes[27]	Once-daily transdermal patch 4–16 mg/day	Local skin reactions. leg swelling, somnolence, fatigue, nausea, constipation and edema, impulsive or compulsive behavior	Skin reactions at the application site have to be considered. Psychiatric side effects should be taken into consideration and monitored cautiously	Efficacious for symptomatic monotherapy, symptomatic therapy adjunct to levodopa, the prevention/delay and the treatment of motor complications[28]
Piribedil	Partial or full dopamine receptor agonist with different affinity to the distinct dopamine receptor subtypes[27]	150–250 mg/day	Leg swelling, somnolence, fatigue, nausea, constipation and edema, impulsive or compulsive behavior	Psychiatric side effects should be taken into consideration and monitored cautiously	Efficacious for symptomatic monotherapy, symptomatic therapy adjunct to levodopa[139,28]
COMT inhibitors					
Entacapone	Reversible inhibition of COMT → less inactivation of levodopa/dopamine	Together with levodopa 300–1200 mg/day	Digestive symptoms such as diarrhea and/or nausea, orthostatic hypotension, urine discoloration	None required	Efficacious as symptomatic adjunct to levodopa in PD patients with motor fluctuations (but not in patients without motor fluctuations) as first-line option[28]
Tolcapone	Reversible inhibition of COMT → less inactivation of levodopa/dopamine	Together with levodopa 300–600 mg/day	Hepatotoxicity, digestive symptoms such as diarrhea and/or nausea, orthostatic hypotension, urine discoloration	Regular follow-up and control of liver transaminases required	Efficacious as symptomatic adjunct to levodopa in PD patients with motor fluctuations as second-line option (after entacapone)[28]

Selegiline	Selective inhibition of MAO_B → less metabolization of monoamines including dopamine	1–2 × 5 mg/day	Nausea, dizziness, abdominal pain, dry mouth, vivid dreams and/or hallucinations, dyskinesias, might improve tremor at the beginning	None required but possibility of inducing serotonin syndrome effect together with SSRI, for example, is feasible (although improbable)	Efficacious for symptomatic monotherapy, symptomatic adjunct to levodopa, treatment of motor complications[28]
Rasagiline	Selective inhibition of MAO_B → less metabolization of monoamines including dopamine	1 mg/day	Nausea, dizziness, abdominal pain, dry mouth, vivid dreams and/or hallucinations, dyskinesias, might improve tremor at the beginning	None required but possibility of inducing serotonin syndrome effect together with SSRI, for example, is feasible (although improbable)	Efficacious for symptomatic monotherapy, symptomatic adjunct to levodopa, treatment of motor complications[28]
Other drugs					
Amantadine	Unclear, possibly the interaction of several pharmacological mechanisms	2–3 × 100–200 mg/day	Reversible corneal edema, nervousness, anxiety, agitation, insomnia, exacerbations of preexisting seizure disorders and psychiatric symptoms	None required	Likely efficacious for symptomatic monotherapy, symptomatic adjunct to levodopa, treatment of motor complications[28]

Abbreviations: COMT, catechol-O-methyltransferase; MAO_B, monoamine oxidase B; PD, Parkinson's disease; SSRI, selective serotonin reuptake inhibitor.

additional medications often lead to compliance problems. Furthermore, expansion of medical treatment can also be recommended. In particular, DA, MAO_B inhibitors,[40] and amantadine[41] demonstrated good efficacy and COMT inhibitors (eg, combined with levodopa) provide more stable plasmatic levels and are therefore a good option. On the contrary, side effects such as the worsening of nonmotor symptoms or the emergence of hallucinations in generally older patients have to be kept in mind. Eventually, therapy options such as pump therapies or the implantation of electrodes for DBS should be contemplated as they are often very efficacious (see below), providing regular and therefore more physiologic dopaminergic stimulation.

Tremor

Tremor as a cardinal symptom in PD mainly manifests as resting or reemerging tremor during holding tasks and might be effectively addressed by classic antiparkinsonian agents in many cases. First-line medications include levodopa or DAs, which show good efficacy. A subgroup of PD patients, on the other hand, is only affected to a lesser extent by akinesia and rigidity and often presents with a slower progression of the disease.[42,43] Thus, classic antiparkinsonian medication might be ineffective. Additionally, there are patients having contraindications due to, for example, an uncommon manifestation like a postural tremor because of medication intolerance or as a result of psychiatric comorbidities. Therefore, at times alternative medication is required for the treatment of tremor.

Depending on the tremor manifestation and the individual patient profile, other medications can be considered for treating tremor-dominant PD patients. Propranolol, for instance, might be beneficial when there is a significant postural tremor and no concomitant cardiac problems. Also, anticholinergics are suitable when akinesia and rigidity are mild, and use is not restricted by bladder dysfunction or neuropsychiatric symptoms such as cognitive impairments. In the latter case, another possible medication is clozapine, which appears to be effective in many cases for treating tremor.[44] Clozapine is particularly beneficial when patients manifest tremor and psychosis and when possibly life-threatening side effects are monitored cautiously. However, the high demand for family physicians constitutes a significant problem in practice, making the treatment of tremor with medical options challenging.

Finally, DBS as a surgical procedure also represents a feasible therapy for tremor. Classic target points such as thalamic DBS have been abandoned lately in favor of DBS of the subthalamic nucleus (STN-DBS), as the latter addresses tremor as well as akinesia and rigidity, while the former target

lacks efficiency for therapy of these symptoms.[45] However, when tremor is the dominant source of disability, thalamic DBS still constitutes a feasible and very efficacious therapy option in refractory tremor or when contraindications against medical treatment are present.

Axial motor signs

Axial motor signs entail symptoms which affect the patient's axis and therefore have no lateral preference (eg, akinesia, tremor). Treatment of axial motor signs is particularly challenging since there is often no good response on classical parkinsonian medication or STN-DBS.[1,46,47] This disparity might be attributable to different pathomechanisms, as nondopaminergic neurotransmitters have been postulated to play a crucial role in the emergence of freezing of gait (FoG) or camptocormia – two of the most frequent axial motor signs.

FoG

FoG is a paroxysmal phenomenon, most commonly found in patients with advanced PD; however, freezing behavior can also affect speech and the upper limbs. The underlying pathophysiology remains uncertain, causing difficulties for identifying a concrete medical or surgical target. Physical therapy and speech therapy and rehabilitation approaches for FoG are highly effective and should therefore be recommended. Several studies have been published recently which show attentional strategies and cueing being useful[48–50] and highly effective to overcome FoG.[51,52] Other rehabilitative strategies address exercise in groups[53] and treadmill training, and can also be recommended to patients suffering from FoG. This can be regarded independently from possible surgical or medical treatments.

The medical therapy of FoG requires a differentiation between freezing during "on" or "off" periods in the first instance. The "on" freezing can be treated by reducing medication. The "off" freezing, on the other hand, is more common and typically responds to treatments aimed at improving "on" time. Occasionally, however, levodopa deteriorates FoG and consequently it may be necessary to reduce dopaminergic medication. Furthermore, MAO_B inhibitors have been associated with a decreased likelihood of developing FoG. However, these agents rarely reduce freezing behavior once it has developed.[54] The contradictory role of dopamine in FoG is clarified by studies that have shown that patients suffer more often from FoG when receiving DA than those treated with placebo,[55] yet withdrawing DA rarely improves FoG. Hence, nondopaminergic targets and drugs have been investigated including amantadine, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, methylphenidate, and botulinum toxin injections in leg muscles. Although these studies have shown promising results, a solid recommendation is still impossible as the studies were small and uncontrolled (for further review see Giladi).[56] The difficulty in finding effective relief for freezing behavior has also led to the investigation of therapies besides medical treatment.

The surgical therapy options for FoG such as DBS might be beneficial, although results are highly controversial. Particularly forms appearing in the "off" time might be treated with STN-DBS.[57,58] At the same time, it has been reported that FoG is induced by STN-DBS.[57] This situation becomes even more complicated as reducing the frequency of STN-DBS has also been reported to ameliorate FoG,[59] and new target points such as the pedunculopontine nucleus are under investigation, with conflicting results.[60] In summary, the efficacy of DBS for FoG requires further investigation. Currently, in the authors' opinion, DBS should be considered for individual therapeutic attempts and when regular follow-up is possible for frequent changes in stimulation parameters. As previously mentioned, all surgical or medical therapy attempts should be supported by intensive physical and/or speech therapy.

Camptocormia

Camptocormia describes a severe flexion of the trunk, presenting in a sitting position but classically worsening when standing or walking. There are several possible theories explaining camptocormia, such as paraspinal myopathy, axial dystonia, or drug-induced forms. To date, however, there is no consistent pathophysiological concept available. This lack of understanding and few high-standard studies make all recommendations rely on empirical knowledge. The adjustment of dopaminergic therapy (controlled release levodopa therapy or levodopa with entacapone) has been reported to not only improve lateral symptoms but also camptocormia;[61] other patients profit from the injection of botulinum toxin into rectal abdominal muscles, emphasizing a dystonic component in its genesis.[62] In the authors' own experience, however, patients describe physical exercise and the use of equipment such as walkers or rollators as helpful, especially when the handle bars are adjusted to a high position.

All presented results of the treatment of special motor restraints such as dyskinesias, tremor, or axial motor signs can be found in Table 3.

Medical treatment of nonmotor symptoms in PD

Sleep disorders

Different forms of sleep disorders can be detected among patients suffering PD and can also possibly indicate a

Table 3 Treatment of special motor restraints in Parkinson's disease patients

Symptom/ substance	Mechanism	Dosage	Adverse events	Special monitoring	Evidence
Dyskinesias					
Pramipexole	Partial or full dopamine receptor agonist with different affinity to the distinct dopamine receptor subtypes[27]	3 × 0.35–0.7 mg/day	Leg swelling, somnolence, fatigue, nausea, constipation and edema, impulsive or compulsive behavior	Psychiatric side effects should be taken into consideration and monitored cautiously	Patients treated with pramipexole showed a significantly lower risk of motor complications in dyskinesias especially and wearing off[30,40,140]
Ropinirole	Partial or full dopamine receptor agonist with different affinity to the distinct dopamine receptor subtypes[27]	6–24 mg/day	Leg swelling, somnolence, fatigue, nausea, constipation and edema, impulsive or compulsive behavior	Psychiatric side effects should be taken into consideration and monitored cautiously	Patients treated with ropinirole (also with prolonged release formulation) showed a significantly lower risk of motor complications in dyskinesias especially and wearing off[40,141,142]
Amantadine	Unclear, possibly the interaction of several pharmacological mechanisms	2–3 × 100–200 mg/day	Reversible corneal edema, nervousness, anxiety, agitation, insomnia, exacerbations of preexisting seizure disorders and psychiatric symptoms	None required	Clinically useful for treating levodopa-induced dyskinesias[34,35,41,143]
Clozapine	Antagonist at the 5-HT_{2A}, dopamine, and several other receptors	25–50 mg/day	Agranulocytosis, cardiac toxicity, hypersalivation, fatigue, weight gain	Regular blood testing is mandatory and regular echocardiograms can be performed	Possibly useful in the treatment of levodopa-induced dyskinesias[144]
Tremor[3]					
Propranolol	Antagonist at adrenoreceptors (sympatholytic)	3 × 80 mg/day	Nausea, diarrhea, bronchospasm, exacerbation of Raynaud's syndrome, bradycardia, hypotension, hallucinations, erectile dysfunction, sleep disturbances, alteration of glucose metabolism	None required	Possibly useful, particularly when there is postural tremor
Biperiden	Antagonist at muscarinic M_1 receptors	3–16 mg/day	Drowsiness, vertigo, agitation, anxiety, delirium, and confusion; additionally, peripheral side effects may be observed (eg, dry mouth, obstipation, and mydriasis)	None required	Efficacious for symptomatic monotherapy and symptomatic adjunct to levodopa for treating tremor[145]
Clozapine	Antagonist at the 5-HT_{2A}, dopamine, and several other receptors	12.5–50 mg/day	Agranulocytosis, cardiac toxicity, hypersalivation, fatigue, weight gain	Regular blood testing is mandatory and regular echocardiograms can be performed	Treatment of levodopa-resistant tremor[146]

Abbreviation: 5-HT_{2A}, 5-hydroxytryptamine receptor 2A.

clinical symptom. Rapid eye movement behavior disorder, for instance, shows a higher prevalence in PD and half of all rapid eye movement behavior disorder patients will develop PD, dementia with Lewy bodies, or multiple system atrophy within 10 years. Hence, α-synuclein pathology possibly starts decades before the first motor symptoms.[63] Possible therapy of rapid eye movement behavior disorder consists in adding clonazepam (0.5–2.0 mg at night), which might reduce the symptoms significantly.[64]

Nevertheless, insomnia in PD is the most common sleep disorder. It involves difficulty with initiation, duration, and/or maintenance of sleep, and consequent daytime somnolence. In PD, and due to dopaminergic deficiency, levodopa in a controlled release formulation at night is possibly efficacious,

although there are controversial results.[28] For DAs, there is a lack of controlled studies. Only pergolide should not be used; it improves sleep mildly but its use is accompanied by a considerable number of adverse events.[28] Additionally, side effects of DAs especially, but also levodopa (eg, excessive daytime sleepiness, sudden onset of sleep), have a severe repercussion on QOL. This should be kept in mind when prescribing medication at first instance. Other drugs tested during recent years without direct effect on dopamine, such as eszopiclone or melatonin, did not show any conclusive results in terms of efficacy for treating insomnia and cannot be recommended.[65]

Restless legs syndrome (RLS) can also be detected more frequently in PD patients. RLS leads to an irresistible urge to move the legs accompanied by uncomfortable sensations worsened at rest and exacerbated in the evening or at night. Therapy for RLS associated with PD is the same as in other forms and includes general measures such as maintaining a regular sleep pattern, moderate exercise, massaging the legs, and using heating pads or ice packs. Possible medications are levodopa, benzodiazepine, gabapentin, opioids, and pregabalin.[66] DAs or gabapentin enacarbil as a first-line medical option show very good results. The former are particularly useful as they treat motor symptoms and RLS at the same time. In addition, it has been shown that in long-term treatment, some DAs cause less augmentation compared to levodopa.[67] This phenomenon depicts worsening of RLS and the spread to previously unaffected parts of the body. DBS for treating RLS cannot be recommended as there are inconclusive results and some authors suspect manifestation after electrode implantation, possibly due to the reduction of dopaminergic therapy.[71] Hence, the role of DBS for treatment in RLS remains elusive.

However, as STN-DBS provides regular dopaminergic stimulation and therefore improves nocturnal mobility and/or dystonic symptoms, it might be helpful for reducing unease in PD patients.[68,69] Apart from subjective improvement, there are also objective measurements showing better sleep quality.[70] Therefore STN-DBS might be helpful, compared to thalamic high-frequency stimulation of the thalamus, which does not influence sleep.[72]

Lastly, advice about sleep hygiene, treatment of concomitant depression, and the reduction of hypnosedative agents are all considered common sense measures.[73] Medical interventions for improvement of sleep problems in PD are listed in Table 4.

Excessive daytime sleepiness

Patients treated with DA or levodopa often experience excessive daytime sleepiness and sudden onset of sleep as side effects. However, sleep disturbances and possible changes in daytime alertness were already described by James Parkinson and might therefore be a symptom of the disease itself. Medications aiming to reduce excessive daytime sleepiness are rare. Modafinil has been tested as a possible treatment, providing inconclusive results and therefore not recommended. It is important to keep in mind the rare dermal side effects (eg, Stevens–Johnson syndrome, drug rash with eosinophilia, systematic symptoms) and the risk of inducing mania, delusions, hallucinations, and/or aggression.[65] In the authors' opinion, the only possible advice so far is to reduce dopaminergic medication as far as needed and possibly switch to alternative medications as far as practicable.

Autonomic dysfunctions in PD

Autonomic dysfunction constitutes important constraints in the course of PD. The possible cause are Lewy bodies in brain areas involved in the control of vegetative functions, such as the hypothalamus or the dorsal vagus nucleus, but also in the spinal cord, sympathetic ganglia, and the plexus of the digestive tract.[74] The most common autonomic symptoms are orthostatic dizziness, gastrointestinal problems, and bladder and erectile dysfunction.

Concerning orthostatic hypotension and dizziness, nonpharmacological interventions should be attempted first, such as sleeping in a head-up position, fragmentation of meals, avoidance of low sodium and carbohydrate-rich meals, increased water (2–2.5 L/day) and salt intake (>8 g or 150 mmol/L), or wearing support stockings. For medication, fludrocortisone and domperidone might have beneficial effects.[75]

In contrast, urinary disturbances should be treated primarily with proper medications. These constraints are not only very frequent but also have a severe impact on QOL. Therapeutic options are an optimization of dopaminergic therapy, as this might improve storage properties in PD patients.[76,77] However, study results are contradictory. An alternative might be the prescription of peripherally acting anticholinergics such as trospium chloride (10–20 mg two to three times daily) or oxybutynin (2.5–5 mg twice daily). Nevertheless, there are not enough high-standard studies to assure efficacy.

Other frequent autonomic dysfunctions are gastrointestinal motility problems in PD. Therapy constitutes different approaches: constipation can be treated with macrogol effectively,[65] while nausea and/or vomiting in connection with the initial intake of levodopa can be antagonized by domperidone or ondasetron.[78] Dysphagia in late stages of PD is also a very disabling and potentially harmful symptom, as malnutrition, dehydration, aspiration, or even asphyxia may occur. Management includes a sufficient dopaminergic therapy, injection of botulinum toxin,[79] and different forms

Table 4 Treatment of sleep disorders in Parkinson's disease patients

Symptom/substance	Mechanism	Dosage	Adverse events	Special monitoring	Evidence
REM sleep behavior disorder					
Clonazepam	Benzodiazepine (allosteric modification of $GABA_A$ receptor)	0.5–2.0 mg at night	Drowsiness, confusion, irritability and aggression and/or psychomotor agitation, cognitive impairments, hallucinations	None required	Possibly effective, but only case reports and retrospective studies available[147,64]
Insomnia					
Levodopa together with peripheral aromatic acid decarboxylase inhibitor in a controlled release formulation	Precursor to dopamine	200 mg at night	Hypotension, nausea disorientation and confusion, insomnia and/or vivid dreams hallucinations, somnolence	None required	Possibly effective for increasing sleep time and nocturnal akinesia[148]
RLS					
Pramipexole	Partial or full dopamine receptor agonist with different affinity to the distinct dopamine receptor subtypes[27]	3×0.35–0.7 mg/day	Fatigue, nausea, constipation and edema, somnolence	Psychiatric side effects should be taken into consideration and monitored cautiously	Efficacious in the treatment of moderate-to-very severe RLS[149–151] and especially suited for PD
Ropinirole	Partial or full dopamine receptor agonist with different affinity to the distinct dopamine receptor subtypes[27]	6–24 mg/day		Psychiatric side effects should be taken into consideration and monitored cautiously	Efficacious in the treatment of moderate-to-very severe RLS[152,153] and especially suited for PD
Rotigotine	Partial or full dopamine receptor agonist with different affinity to the distinct dopamine receptor subtypes[27]	Once-daily transdermal patch 4–16 mg/day	Fatigue, nausea, constipation and edema, somnolence	Skin reactions at the application site have to be considered. Psychiatric side effects should be taken into consideration and monitored cautiously	Rotigotine as a transdermal patch is effective in the treatment of moderate-to-severe RLS[154,155] and especially suited for PD
Gabapentin enacarbil	Prodrug of gabapentin (see below)	600–1800 mg/day	Fatigue, dizziness, weight gain, edema, drowsiness	None required	Gabapentin enacarbil is effective in the treatment of moderate-to-severe RLS[156–160] but experience is lacking. Second-line option in PD
Levodopa together with peripheral aromatic acid decarboxylase inhibitor in a standard or controlled release formulation	Precursor to dopamine	200–400 mg at night	Hypotension, nausea, disorientation and confusion, insomnia and/or vivid dreams hallucinations somnolence	None required	Levodopa is effective in the treatment of RLS, but carries the risk of augmentation[161]
Gabapentin	Possibly inactivates the $\alpha_2\delta$-subunit of a voltage gated calcium-channel	600–1800 mg/day	Fatigue, dizziness, weight gain, edema, drowsiness	None required	Gabapentin may be used as it is effective in the treatment of mild-to-moderate RLS[162,163] but is considered second-line option due to possible side effects[66]
Opioids	Binding at different opioid receptors in the central and peripheral nervous system	Different agents available	Nausea and vomiting, drowsiness, dry mouth, myosis, constipation	Clinical monitoring of worsening of sleep apnea and potential of abuse	Opioids are effective in the treatment of RLS, especially for patients with RLS that is not relieved by other treatments[66]

(*Continued*)

Table 4 (*Continued*)

Symptom/substance	Mechanism	Dosage	Adverse events	Special monitoring	Evidence
Pregabalin	Possibly inactivates the $\alpha_2\delta$ subunit of a voltage-gated calcium channel	50–450 mg/day	Dizziness, drowsiness, increased appetite, euphoria, confusion, vivid dreams, attention changes, tremor, dysarthria, dry mouth, constipation	None required	Pregabalin is effective in the treatment of moderate-to-severe RLS[66]

Abbreviations: $GABA_A$, γ-aminobutyric acid type A; PD, Parkinson's disease; REM, rapid eye movement; RLS, restless legs syndrome.

of rehabilitative treatments.[80] Enteral feeding options such as a short-term nasogastric feeding tube or long-term feeding system (percutaneous endoscopic gastrostomy) can be considered as a final option.

For erectile dysfunction, sildenafil or other phosphodiesterase type 5 inhibitors might be efficacious when considering side effects/contraindications and interactions with other medications.[81]

The effects of STN-DBS on autonomic symptoms are currently being investigated and, to date, have been considered as investigational. A summary of medical options, their adverse effects, and the level of evidence can be found in Table 5.

Psychiatric comorbidity in PD patients and its treatment

Impulse control disorders, dopamine dysregulation syndrome, and punding

Possible long-term side-effects of dopaminergic treatment in PD are impulse control disorders, punding, or dopamine dysregulation syndrome. The latter describes craving for dopaminergic medication when medication effects are at its peak, but also other behavioral symptoms such as hypomania, hypersexuality and/or gambling, and dysphoria. In contrast, fatigue or apathy might occur towards the end of the dopaminergic effect.[82,83] Therefore, therapy recommendations include the reduction of dopaminergic therapy, in particular the switch from DA to levodopa. Amantadine as an add-on to dopaminergic treatment might also reduce impulsivity and compulsiveness, although this has only been proven so far in a small number of patients.[84] Lastly, in the authors' own experience, low dosage of an antipsychotic agent (eg, quetiapine 25–50 mg at night) also helps stabilizing such symptoms with only rare side effects, although no clinical trials are yet available in this context.[65]

Medication-induced psychosis

Psychotic disorders are rare in untreated PD patients[85] but more common after initiation of dopaminergic medication.[86] Besides treatment with levodopa and/or DAs, further predisposing risk factors for psychosis in PD are older age,[87–89] increasing severity of cognitive impairment or dementia,[88,90] disease severity,[88,89,91] and polypharmacy.[86]

Psychosis occurs in two different manifestations: (1) PD patients experiencing visual perceptual changes or visual hallucinations only (although other forms of hallucination can also occur);[90] and (2) patients classically presenting dementia and experiencing complex psychotic symptoms, including both hallucinations and systematized persecutory delusions in the context of dementia.[92] Dementia with Lewy bodies requires special mention as the cognitive decline progresses faster than in classical PD, and these patients tend to develop psychosis with delusions.[91] Compared to the first group, patients suffering from dementia with Lewy bodies and patients with complex psychotic symptoms typically do not have insight into their psychosis. However, once psychotic symptoms emerge, therapy for psychosis does not differ significantly between both groups.

General therapeutic recommendations include the switch to PD treatments with a smaller potential to enhance psychosis and the search for its underlying reasons. It is important to keep in mind that metabolic disorders or infection can be responsible – but also easily manageable – reasons for acute psychotic symptoms. Therefore, they should be ruled out before initiation of antipsychotic therapy. This is particularly important as classical neuroleptics have a substantial antidopaminergic effect, making their use in PD complicated.

Nevertheless, antipsychotics and especially atypical ones can and should be utilized. For example, clozapine has proven efficacious in several studies against psychotic symptoms.[21,93] Its risk of potential life-threatening agranulocytosis makes regular follow-up inevitable. Alternatives with a better risk profile are therefore highly desirable. As such, quetiapine has emerged during the last few decades, showing good effects in some small-sized and short-term studies;[65,94,95] in one study demonstrating similar benefits to those observed with clozapine.[96] However, there are also results showing

Table 5 Treatment of autonomic dysfunctions in Parkinson's disease patients

Symptom/ substance	Mechanism	Dosage	Adverse events	Special monitoring	Evidence
Orthostatic hypotension					
Fludrocortisone	Synthetic corticosteroid	0.05–0.3 mg/day	Edema, water and sodium retention, insomnia, fatigue	None required	Possibly effective,[164] but insufficient evidence for improvement due to methodological concerns[65]
Domperidone	Antagonist at dopamine receptors located outside the blood–brain barrier	3 × 10–20 mg/day	Extrapyramidal symptoms, increased levels of prolactin leading to gynecomastia or galactorrhea	None required	Possibly effective,[164] but insufficient evidence for improvement due to methodological concerns[65]
Urinary disturbance					
Trospium chloride	Muscarinic receptor antagonist	2–3 × 10–20 mg/day	Dry mouth, constipation, nausea, diarrhea, eye or eyesight problems, cognitive impairment	None required	Possibly useful for treatment of urge incontinence but insufficient evidence[65]
Oxybutynin	Muscarinic receptor antagonist	2 × 2.5–5 mg/day	Dry mouth, constipation, nausea, diarrhea, eye or eyesight problems, cognitive impairment	None required	Possibly useful for treatment of urge incontinence but insufficient evidence[65]
Gastrointestinal motility problems					
Macrogol	Polyethylene glycol which works as osmotic laxative	1–3 × 125 mL/day	Abdominal pain, diarrhea	None required	Likely efficacious for treatment of chronic constipation[165]
Domperidone	Antagonist at dopamine receptors located outside the blood–brain barrier	3 × 10–20 mg/day	Increased levels of prolactin leading to gynecomastia or galactorrhea, extrapyramidal symptoms	None required	Possibly useful for treatment of nausea/ vomiting due to medication[65]
Erectile dysfunction					
Sildenafil Tadalafil Vardenafil	Inhibition of cGMP-specific phosphodiesterase type 5	Sildenafil: 50 mg 1 hour before sexual activity. Tadalafil: 10 mg 0.5–12 hours before sexual activity. Vardenafil: 10 mg 0.5–1 hour before sexual activity	Headache, flushing, dyspepsia, nasal congestion, myocardial infarction	None required	Sildenafil is possibly useful for treatment of erectile dysfunction in PD[166]

Abbreviations: cGMP, cyclic guanosine monophosphate; PD, Parkinson's disease.

no superiority to placebo.[95] Hence, a recommendation is not possible currently and awaits further research. Finally, in special cases, possible agents are also cholinesterase inhibitors, which have demonstrated a decrease in hallucinations in patients suffering from dementia with Lewy bodies.[97]

Antidementive therapy in PD

Cognitive decline is one of the most disabling symptoms in PD during the later stages[98] and, as such, an important symptom to be treated. One of the underlying reasons might be the spread of neurodegeneration with cortical cholinergic deficiency.[99] Thus, anticholinergics and tricyclic antidepressants (TCAs) should be replaced where possible as they deteriorate cognitive performance. Available therapies for treating dementia are scarce and only two groups of medications are available. First, cholinesterase inhibitors – especially rivastigmine, which have demonstrated efficacy in the treatment of cognitive impairment in PD.[100] Other cholinesterase inhibitors were either not tested systematically (eg, galantamine) or showed conflicting results (eg, donepezil) and are therefore not recommended.[65] Also, it needs to be kept in mind that all cholinesterase inhibitors

should be monitored cautiously as a worsening of tremor, autonomic dysfunction, and the induction of psychosis are possible. The second structure to be targeted is N-methyl-D-aspartic acid receptor. Memantine as an N-methyl-D-aspartic acid antagonist appears to have a modest improvement in cognitive performance in PD patients[101,102] and might be considered for improving cognition and general clinical impression.

Antidepressive therapy in PD

Depression is a common manifestation either as preclinical symptom[103] or during the course of PD. Prevalence ranges between 2.7% and 90%, depending on diagnosis criteria and the types of depressive disorders included. In any case, many PD patients consider QOL most impaired by their decreased emotional state.[104] Yet, depression in PD is independent of motor symptoms[105,106] and should therefore be addressed separately; nevertheless, sufficient dopaminergic therapy needs to be ensured due to the importance of dopamine in the limbic system.[107] One possible way of addressing both problems might be pramipexole, as it helps with motor symptoms and has showed an antidepressant effect in experimental animal models[108,109] as well as in clinical routine.[110] For the clinical efficacy of actual antidepressants, there are only sparse high-standard studies. TCAs such as desipramine and nortriptyline have proven effective in improving depressive mood.[65] However, their use is restricted in many cases by side effects such as cognitive impairment, autonomic dysfunction, and orthostatic dysregulation. Therefore, TCAs should be used carefully, particularly in elderly PD patients. Alternatively, treatment with modern antidepressants has also provided good results in clinical routine. Again, systematic studies are lacking and side effects include a possible interaction with MAO_B inhibitors, leading to a serotonin syndrome. Nevertheless, these are very unlikely risks compared to those listed in older antidepressants (eg, TCA). Lastly, modern antidepressants such as atomoxetine could not show any beneficial effect on depression in PD patients and should therefore not be considered. Drugs such as omega-3 or interventions with transcranial magnetic stimulation have to be regarded, to date, experimental.[65] In summary, although high-standard studies are missing, the authors' would rather use modern antidepressants such as selective serotonin reuptake inhibitors to treat depression and/or, whenever possible, switch to pramipexole.

Finally, it should be emphasized that the basis of every antidepressant therapy should be an introduction to educational programs. These programs should be considered even in early stages of PD without heavy motor impairments and should, in particular, include the improvement of coping strategies regarding PD symptoms.

A summary of available pharmaceutical options against psychiatric comorbidities in PD can be found in Table 6.

Other therapeutic options in PD

Pump therapy in PD

Motor fluctuations and/or dyskinesias range among the major concerns in the management of advanced PD, as stated above. An underlying mechanism might be fluctuating plasmatic dopamine concentrations with oral intake; therefore, two different forms of continuous nonoral applications have been developed and tested recently: the apomorphine pump and the levodopa/carbidopa intestinal gel (LCIG) pump.

General indications for apomorphine infusion and LCIG (but also DBS) in PD are quite similar: patients with significant effect on dopaminergic medication and pronounced motor fluctuations not responding to classical pharmacological therapy. Contraindications differ significantly between DBS and pump therapies; older patients and significant psychiatric or cognitive problems are generally considered as contraindications for DBS but with regular follow-up and monitoring are not necessarily contraindications for infusional treatments and LCIG in particular.[111]

LCIG

Intestinal infusion of LCIG is an efficacious way of treating motor symptoms, as it has the same mechanisms of action as oral levodopa administration. Therefore, LCIG is infused into the proximal jejunum by means of a portable pump through a percutaneous endoscopic gastrostomy tube,[111,112] although temporary application via nasoduodenal for testing of clinical response is also possible. Besides the efficacy in motor symptoms, nonmotor symptoms as well as QOL seem to be ameliorated.[113] However, results have to be regarded carefully, since many of the available data originate from open-label and/or observational studies. In the authors' opinion, this method is especially suited for older patients with late sequelae of levodopa therapy such as motor complications and for patients with a high risk of hallucinations.

Apomorphine pump

Apomorphine is a potent DA showing good efficacy for treating motor symptoms in PD. It is characterized by reaching its plasmatic maximum in less than 10 minutes after subcutaneous application. Therefore, apomorphine rapidly

Table 6 Treatment of concomitant psychiatric symptoms in Parkinson's disease patients

Symptom/ substance	Mechanism	Dosage	Adverse events	Special monitoring	Evidence
Impulse control disorders, punding, dopamine dysregulation syndrome					
Amantadine	Unclear, possibly the interaction of several pharmacological mechanisms	2–3 × 100–200 mg/day	Reversible corneal edema, nervousness, anxiety, agitation, insomnia, exacerbations of preexisting seizure disorders and psychiatric symptoms	None required	Investigational as there is only a small study looking at medication-related impulse dyscontrol and pathologic gambling[84] and only for a few weeks
Quetiapine	Acts as antagonists for many neurotransmitters (at dopamine, serotonin, histamine, and adrenergic receptors)	25–75 mg at night	Somnolence, fatigue, dry mouth, dizziness, constipation, weight gain	None required	Personal experience without any studies available
Psychosis in PD					
Clozapine	Antagonist at the 5-HT_{2A}, dopamine, and several other receptors	12.5–50 mg/day	Agranulocytosis, cardiac toxicity, hypersalivation, fatigue, weight gain	Regular blood testing is mandatory and regular echocardiograms can be performed	Good evidence for efficacy in treatment of psychosis in PD[93,94,96]
Quetiapine	Acts as antagonists for many neurotransmitters (at dopamine, serotonin, histamine, and adrenergic receptors)	25–75 mg at night	Somnolence, fatigue, dry mouth, dizziness, constipation, weight gain	None required	Possibly useful for treatment of psychosis in PD,[94–96,167–169] but insufficient evidence due to methodological concerns
Donepezil	Acetylcholinesterase inhibitor	5–10 mg	Nausea, diarrhea, abdominal pain, transient increase of tremor severity	None required	Possibly useful for treatment of psychosis in patients suffering from Lewy body dementia[97]
Antidementive therapy in PD					
Rivastigmine	Acetylcholinesterase inhibitor	4.6–9.2 mg/day	Diarrhea, bradycardia, nausea, abdominal pain, transient increase of tremor severity	None required	Efficacious in the treatment of dementia in PD[65,100]
Memantine	NMDA receptor antagonist	20 mg/day	Confusion, drowsiness, headache, agitation and/or hallucinations	None required	Possibly useful but contradictory results in small studies[65,100–102,170]
Antidepressive therapy in PD					
Pramipexole	Partial or full dopamine receptor agonist with different affinity to the distinct dopamine receptor subtypes[27]	3 × 0.35–0.7 mg/day	Fatigue, nausea, constipation and edema, somnolence	Psychiatric side effects should be taken into consideration and monitored cautiously	Efficacious for the treatment of depressive symptoms in PD[141,171,172]
Desipramine	Norepinephrine and (to a lesser extent) serotonin reuptake inhibition		Cardiac arrhythmicity, dry mouth, constipation, orthostatic dysregulation, mild blurred vision	Cardiac monitoring	Likely efficacious for the treatment of depression in PD[173]
Nortriptyline	Norepinephrine and (to a lesser extent) serotonin reuptake inhibition	75–150 mg/day	Dry mouth, constipation, orthostatic dysregulation, mild blurred vision	None required	Nortriptyline possibly improves depression in PD patients,[174] but insufficient evidence up to now for the treatment of depression in PD[65]
SSRIs	Selectively inhibit the serotonin reuptake	Different agents available	Apathy, anhedonia, nausea/ vomiting, headache, diarrhea, weight gain, SSRI may induce tremor or worsen parkinsonian symptoms, especially at the beginning	Possibility of inducing serotonin syndrome effect together with MAO_B inhibitors, for example, is feasible (although improbable)	No clear evidence yet to be found,[65] but possibly clinically useful as SSRIs have a better safety profile compared to TCAs

Abbreviations: 5-HT_{2A}, 5-hydroxytryptamine receptor 2A; MAO_B, monoamine oxidase B; NMDA, N-Methyl-D-aspartic acid; PD, Parkinson's disease; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

increases the duration of "on" phases and is effectively applicable to patients with motor fluctuations.[114,115]

Two methods are available: (1) subcutaneous apomorphine injections "on demand;" or (2) continuous subcutaneous injection by means of a pump. Both forms might cause side effects, the most frequent being nausea and vomiting. This can be addressed effectively by administering domperidone several days before the first application. Another important problem to be considered is the emergence of cutaneous nodules in almost 100% of the cases, leading not only to a cosmetic problem but also to worse resorption. As a consequence, a regular change of the injection side is unavoidable. Eventually, psychiatric effects from hallucinations to acute psychotic syndrome may occur particularly in patients with preexisting psychiatric conditions. Taken together, and due to the common comorbidity of motor fluctuations and psychiatric symptoms in later stages of PD, the use of apomorphine is hence restricted. For patients suffering from motor complications, apomorphine is, nevertheless, a good choice providing satisfactory immediate and long-term results.[116]

Functional surgery in PD

In recent years, DBS has emerged as efficacious therapy for different medically refractory neurological symptoms using current pulses in different target areas. Origins of DBS go back to lesional/ablative approaches under which improvement of both tremor (eg, after thalamotomy) and akinesia/rigidity (eg, via pallidotomy) could be achieved. The mechanisms of action remain elusive but different approaches are discussed: (1) depolarizing blockade, (2) synaptic inhibition, (3) synaptic depression, and (4) simulation-induced disruption of pathological network activity.[117] From a clinician's point of view, in contrast, additional questions need to be answered, as there are different areas to be targeted and these involve distinct "pros" and "cons." Therefore, side effects or the best moment for surgery are nowadays subject of intensive investigation.

Target points and specific side effects

There are no guidelines for the target structure for DBS in PD. Different arguments can be used for an appropriate and individual clinical decision.

STN

Today, STN is considered the most effective for DBS in PD as it improves all cardinal symptoms. Also, it provides better long-term results in motor outcome compared to the classic target point – the internal globus pallidus (GPi). In addition, the STN shows less decay of motor efficacy in long-term studies.[118,119] From a short-term perspective, however, there are side effects due to the small size of the STN and the stimulation of adjacent structures as well as functional loops interconnected within the STN. Limbic and affective loops in particular seem to be afflicted by stimulation, leading to postoperative dysphoria and hypomania[120] and a higher risk of suicide.[121] In addition, cognitive decline has been attributed to STN-DBS, particularly in patients with advanced age, higher dopaminergic medications, and higher axial subscores of the Unified PD Rating Scale.[122] The reasons are unclear, although due to the heterogeneous results, electrode localization and/or the trajectory through the frontal lobe has been speculated playing a role in cognitive decline.[123] As a result, STN is indicated as an effective target when younger patients suffer from severe motor complications, such as dyskinesias or fluctuations.

GPi

The original operative PD treatment, the GPi has lost importance – compared to STN-DBS – due to its disadvantages. This was due to worse long-term results,[118,119] higher energy consumption, and the lack of possibility in reducing dopaminergic medications drastically with GPi-DBS. However, during the last few years, GPi-DBS is regaining importance for several reasons. First, GPi is easier to target, since it is a bigger structure than STN. Secondly, patients operated on in the GPi are less prone to develop psychiatric and cognitive implications. And finally, GPi-DBS appears to be more efficient in treating some of the nonmotor symptoms in PD. Also, worse long-term results could not be replicated in other studies.[124] Therefore, GPi will be possibly targeted in the future more frequently and should be taken into account in elderly patients who might develop psychiatric or cognitive impairments.

Ventral posterolateral nucleus of the thalamus (VLp)

The thalamus was the traditional target for stereotactic tremor surgery as ablative procedures in the VLp* showed good efficacy, and stimulation has also consistently shown long-lasting therapy of contralateral tremor. However, the structure has lost its importance in PD since other cardinal symptoms are not modified to the same extent. Therefore,

*The VLp partially corresponds to Hassler's ventral intermediate nucleus (Vim).[125] To maintain a uniform nomenclature, the Vim will be referred to as VLp.

VLp-DBS should only be considered in patients suffering from severe tremor and when other options appear less practicable. Advantages are mainly the fewer aforementioned side effects during VLp-DBS compared to equally effective target points such as STN or GPi.[45] Possible side effects of this target are on the one hand a stimulation of structures in the vicinity of the VLp with resulting dysarthria, paresthesias, or gait disturbances and on the other hand mild executive deficits (eg, in verbal fluency).[126] Therefore exact planning and meticulous intraoperative testing of tremor-dominant and elderly patients is required in order to stimulate segregated motor loops.[4,127]

Pedunculopontine nucleus

This brain area was introduced as an additional DBS target, with the purpose of ameliorating axial symptoms responding in an unsatisfactory way to DBS of other structures or medical treatment.[128,129] So far, it has been practiced as an add-on to STN-DBS, providing controversial results.[130,131] Therefore, no recommendation on DBS in the pedunculopontine nucleus can be made at this point.

General considerations

The safety and efficacy of DBS in PD has been proven not least because of the clinical experience with thousands of patients. However, there are several different open and general questions concerning DBS. For instance, there is still an open debate on how many targets should be operated on. As PD is a lateral disease, some centers conduct unilateral electrode implantation as studies have demonstrated unilateral DBS being associated with better QOL[132] and reduced surgery time. On the other hand, PD is a progressive disease which spreads to both sides, therefore making a second electrode in later stages necessary. This, however, leads to duplicated operation risks and therefore higher economic expenses for health care systems. Concerning medical issues, in contrast, there are no short-term differences for motor outcome between unilateral and bilateral implantation.[133,134] All in all, and subject to limited exceptions, the authors therefore plead in favor of a bilateral implantation.

However, having determined the amount of targets leads to the question as to when is the best moment for surgery. Nowadays, DBS is only practiced in patients suffering from medically refractory motor restraints. However, there is growing evidence that although not neuroprotective,[135] DBS leads to a better QOL.[136–138] Therefore, it is conceivable that early stimulation has great repercussions on QOL. Preliminary results of an international randomized and multicenter study (Controlled Trial of Deep Brain Stimulation in Early Patients With Parkinson's Disease; EARLYSTIM study) have been recently presented and the final results are expected in the near future.[176] Nevertheless, the risks of precipitated electrode implantation should be pointed out. First, there is a disproportional risk of confounding other or atypical parkinsonian syndromes in the first years of symptoms. And secondly, it should be kept in mind that patients can continue functioning well for years with only medical treatment without being exposed to the risks of surgery.

Regarding these open questions, the decision for surgery should be made by an interdisciplinary team. In the authors' center, neurologists, neurosurgeons, psychiatrists, and other specialists – depending on the underlying problems (eg, physical therapist, occupational therapist, speech therapist, social worker) – are involved in the decision. In addition, past medical history, current comorbidities, imaging studies, and the Unified PD Rating Scale in the "on" and "off" condition should be carefully considered when it comes to decide whether or not to operate, or which structure to target in PD patients. The authors believe that this increases the quality and the outcomes of this procedure, and therefore patients obtain satisfying results.

Summary

In summary, as the possibilities have increased dramatically in the last decades, first attempts to alleviate motor symptoms with just levodopa have been abandoned. Although still considered the most effective drug, the awareness of possible long-term risks has led to more sophisticated regimens with additional agents and additional therapeutic options such as infusional therapies or DBS. For a practical approach, the current German guidelines for PD therapy are referred to (Figure 1).

However, it needs to be remembered that such schemes are not suited for tailoring the best individual medication. The reason for this is that they focus on the treatment of the cardinal motor symptoms and do not include other therapeutic targets. Yet, the awareness of additional restraints and nonmotor symptoms is important, as they are often perceived as highly impairing. It therefore results in an even more complex situation for physicians, as every patient needs their risk profile and concomitant diseases considered.

Finally, as current therapies improve QOL and motor restraints in early stages of the disease, physicians face the problem of additional problems and long-term side effects in later stages. In many cases, these circumstances are especially

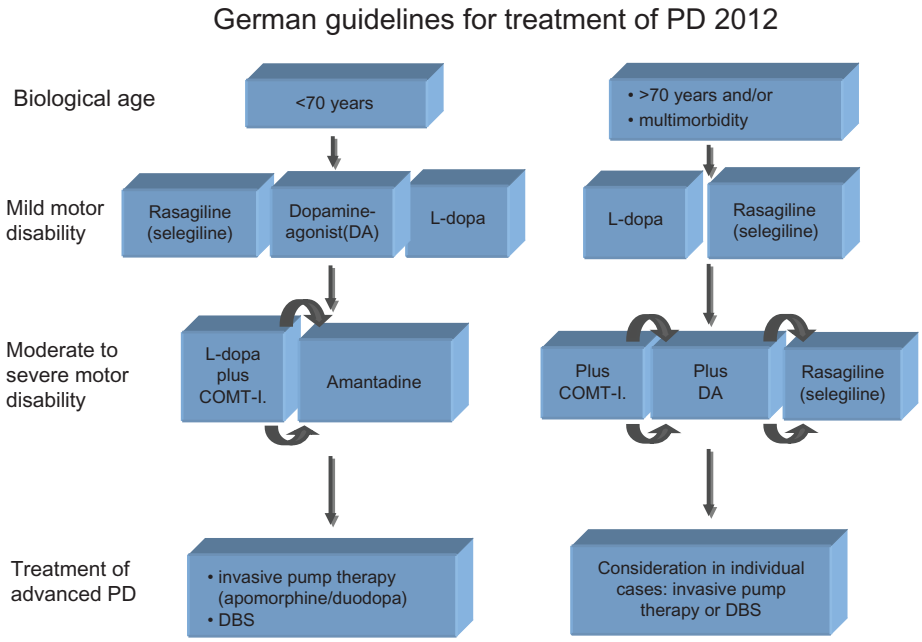

Figure 1 German guidelines for treatment of PD 2012.
Abbreviations: COMT-I, catechol-O-methyltransferase-linhibitor; DA, dopamine agonist; DBS, deep brain stimulation; PD, Parkinson's disease.

challenging as there is currently no effective response. Therefore, further investigation is highly desirable in order to develop even better therapies which allow the modification of the neurodegenerative processes and provide solutions for the existing additional motor and nonmotor symptoms in PD patients.

Disclosure

The authors report no conflicts of interest in this work.

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