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Modern treatment in Parkinson's disease, a personal approach

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Abstract There are many guidelines available concerning the treatment of Parkinson's disease. Most of these advocate treating young-onset patients with a dopamine agonist and older patients with levodopa. The rationale behind this recommendation has its origins in the side effects associated with each of these drug classes: whilst levodopa leads to dyskinesia, which may not be relevant for patients with a limited life-expectancy, dopamine agonists have a much longer plasma half life which probably leads to more continuous dopamine receptor stimulation and thus decreases the occurrence and severity of dyskinesia. However, the side effects associated with the use of dopamine agonists, such as sleepiness, orthostatic problems, hallucinations and impulse control disorders are a drawback. In this overview, the hypothesis will be put forward that perhaps such a strict distinction is no longer needed. A new idea may be the early combination of levodopa with a dopamine agonist which would provide good clinical efficacy and, because of the relatively low doses involved, would reduce the side effects associated with both substances. MAO-B inhibitors may be a good option for early treatment and especially for patients who experience first motor fluctuations. Similarly, and particularly if a wearing-off symptom is present, COMT inhibitors smoothen and prolong the action of levodopa. More invasive escalation therapy comes into play when patients reach the advanced stages with problems of insufficient motor control, such as bradykinesia, rigidity and resting tremor, combined with on-time dyskinesia. The use of all oral and invasive treatment has to be individualized to gain a good motor and non-motor control and especially a good quality of life.

Keywords Parkinson disease · Treatment · Dopamine agonists · Levodopa · Monoamine oxidase inhibitors · Safinamide · Deep brain stimulation · Continuous levodopa intestinal gel therapy

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder which seems to follow certain rules or pathways. Braak et al. (2002) have established a staging system for PD which is based on the distribution of Lewy bodies and alpha-synuclein staining in the brain and the enteric nervous system. They claim that PD starts in the olfactory bulb and the dorsal vagal nerve (Braak et al. 2002). The observations of Braak fit well with the clinical progression of the disease, as was described by Wolters and Braak (2006). Clinicians subdivide PD into the premotor phase which consists of the possible occurrence of hyposmia, REM-sleep behavior disorder, constipation and depression. This is followed by the first subtle motor signs such as a reduced arm swing, impairment of dexterity, frozen shoulder or the occurrence of a slight tremor when patients are under pressure. Thereafter, typical motor signs such as bradykinesia, rigidity, resting tremor and later postural instability occur (Hoehn and Yahr 1967). In the advanced phase patients present with motor complications, disturbances of the autonomic nervous system and neuropsychiatric problems such as depression, anhedonia, apathy, fatigue or dementia. In addition, many patients suffer from pain and sleep problems. This underlines that PD treatment

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needs to be individualized and needs to address both motor and non-motor symptoms.

Which patients should be treated?

In previous years the guidelines of the German Neurological Society emphasized that only patients who presented with impairment of their quality of life should be treated. Thus, a watchmaker with a slight resting tremor would get treatment and a brick-layer with the same symptomatology would not get treatment if he did not feel impaired in his personal or work life. In my view, we should reconsider this suggestion and maybe take time to convince each patient—even those with only mild symptoms—to agree to early treatment. The reasons behind this viewpoint are manifold. First of all, various double-blind, randomized controlled-studies showed that even within a year the patients in the placebo group deteriorated by 8–14 points on the Unified Parkinson's Disease Rating Scale (UPDRS) (Parkinson Study Group 1993; Parkinson Study Group 2002; Shoulson et al. 2002; Fahn et al. 2004). This illustrates that without treatment, the vast majority of our patients may deteriorate to such a degree that they will shortly require treatment anyway. Many patients are afraid of treatment since they fear side effects. In this context, a study by Grosset et al. (2007) nicely demonstrates that early treatment improves quality of life whereas a delay in treatment leads to a deterioration of the patients' quality of life. Finally, we demonstrated that the addition of dopaminergic treatment to the endogenous production of dopamine decreases the overproduction of dopamine in the remaining neurons in the substantia nigra, which may reduce the danger of oxidative stress and further cell death (Storch et al. 2013a).

How to start treatment in PD

Up to now, most authors advocated that early treatment in PD should be directed by the biological age of the patient. Schapira (2007) and the German guidelines (Eggert et al. 2012) advocate that young patients should be treated with a dopamine agonist and the elderly with levodopa. The reason for this difference lies in the risk of side effects. Due to the good tolerability of levodopa and the shorter life-expectancy of older patients, the threat of levodopa induced motor complications is not as high as in young patients (Kostic et al.1991). The young patients are supposed to get treatment with a long-acting dopamine agonist such as rotigotine, ropinirole, pramipexole or piribedil to prohibit or delay the occurrence of motor complications.

Use of levodopa

This view may need modification. In some recent studies, i.e. PD MED (PD MED Collaborative Group 2014), ELLDOPA (Fahn et al. 2004) and STRIDE PD (Stocchi et al. 2010) it was shown that patients who receive less than 400–500 mg levodopa per day are less likely to develop dyskinesia than those with higher doses. In addition, it is becoming apparent that the dose given to females should be less than that recommended for more heavy men (Sharma et al. 2008, 2010; Olanow et al. 2013). Taking all of this into account, it may even be appropriate to start with levodopa in relatively young patients and increase the dose by 50 mg every 5 days and not go above 300 mg/d. If a higher dose is needed, the addition of a MAO-B inhibitor, a COMT-inhibitor or a dopamine agonist or amantadine may be a good strategy (compare with below). Examples for the early use of levodopa are patients who need immediate improvement and cannot tolerate major side effects due to their daily work load. Typical examples from my own practice include surgeons, politicians and musicians.

Use of dopamine agonists

In young-onset patients the use of dopamine agonists is still recommended and normally followed. Some years ago, dopamine agonists were associated with sudden sleep attacks (Frucht et al. 1999) and nowadays many physicians are concerned about impulse control disorders (ICD) (Voon et al. 2011; Weintraub et al. 2014). Binge eating, pathological gambling or shopping, hobbyism, and hypersexuality, are typical examples. Patients who were always novelty seekers or used drugs and have a family history of addiction are especially prone to develop such disorders. Anecdotal evidence indicates that long-acting dopamine agonists (24 h/day) which do not result in a rapid increase in plasma levels and dopamine receptor stimulation after intake seem to cause less impulse control disorders than dopamine agonists with a shorter plasma half life and a rapid increase in the plasma. In a poster presentation, Rizos (2013) claimed that the rotigotine patch may cause the lowest numbers of ICDs. Since it is really difficult to define when you should call behavior in PD an ICD, the figures of occurrence of ICDs vary between 5 and 20 %. In spite of these considerations it is still true and important to note that all pivotal studies with rotigotine (Parkinson Study Group 2003), ropinirole Rascol et al. 2000) and pramipexole (Parkinson Study Group 2000) resulted in lower dyskinesia rates than with levodopa, which is still the major argument for starting treatment in young patients with a long-acting dopamine agonist.

Initial use of other drugs

Another way to start treatment is the use of a MAO-B inhibitor such as rasagiline which showed excellent tolerability and good motor control in both the TEMPO (Parkinson Study Group 2002) and ADAGIO study (Olanow et al. 2009; Rascol et al. 2011). In at least some European countries, the use of amantadine is also an alternative due to its good efficacy and relatively good tolerability.

Tremor-dominant subtype

Patients with a tremor-dominant subtype of PD may benefit from anticholinergics (if they are young and not cognitively impaired), a dopamine agonist (e.g. pramipexole; Pogarell et al. 2002) or even clozapine (Bonuccelli et al. 1997) with all its limitations. In Germany, budipine is another option although some patients developed torsades de pointes when using budipine. My own experience is that patients with a normal ECG do well with this medication and there seems to be a low risk when close ECG monitoring is performed.

A recent study from the UK (PD MED collaborative Group 2014) investigated more than 1500 patients with PD to whom levodopa, monoamine oxidase B inhibitors or dopamine agonists were administered as the initial treatment. The follow-up of this observational naturalistic data collection based study was up to seven years and the authors reported a cessation of randomized trial medication in 72 % of participants for MAO-B inhibitors (probably due a loss of efficacy), in 50 % for dopamine agonists and in 7 % of participants for levodopa. Both levodopa and dopamine agonists resulted in the same percentage of dyskinesia after 7 years. This finding is in contrast to most other double-blind studies in which dopamine agonists were compared with levodopa (Chondrogiorgi et al. 2014). The reason for this discrepancy may stem from the low levodopa equivalent doses. Even after 3 years the patients did not use more than 300–400 mg levodopa or levodopa equivalent doses. Another important factor may be the UK healthcare system, which poses some restrictions on the use of PD medication. As stated above, due to this magic threshold of about 400 mg of levodopa, not much difference in regard to dyskinesia was seen between both treatment groups. A major point of criticism of this study is that the reported effects are based on questionnaires and not on personal examination by experienced neurologists or geriatricians.

The MAO-B-inhibitor, rasagiline, provided extremely good neuroprotection in cell culture and animal models (Weinreb et al. 2010). Thus, two studies were performed to detect disease- modification in patients with early PD. In the so-called TEMPO study, patients in whom initiation with rasagiline treatment was delayed for 6 months were compared with patients who received rasagiline from the very beginning. After a total of 12 months, patients with initial treatment with 1 or 2 mg of rasagiline performed better than those who received rasagiline treatment only after six months of treatment with a placebo. Hauser et al. (2009) reported that this superiority persisted in a cohort whom they followed for a total of 6 years. These patients had received all kinds of treatment after the 1-year TEMPO study, yet those who had received immediate treatment with rasagiline were still on average 2.5 points better on the UPDRS. This encouraged the performance of a study with a 9 months delayed-start design with rasagiline (ADAGIO study, Olanow et al. 2009). In this study, disease-modification could be demonstrated for 1 mg of rasagiline but not for 2 mg rasagiline, which leads to the decision of the FDA to withhold the label for disease- modification.

The dopamine agonist pramipexole was also tested for disease- modification by use of the delayed-start design (Schapira et al. 2013). Similar to the trial with 2 mg of rasagiline, the trial was negative since all patients who received pramipexole with a delay of 6–9 months caught up with those who had received this treatment from the beginning.

Early motor and non-motor fluctuations

After the so-called honeymoon phase, patients start to develop motor complications. The most abundant and earliest motor complications are wearing-off phenomena such as an increase in bradykinesia, rigidity or tremor before the next regular dose. In the ELLDOPA study, after 40 weeks of treatment with 600 mg levodopa, wearing-off occurred in 30 % of participants and 15 % of participants had dyskinesia. Thus, even after a short period of treatment, at least with levodopa, motor fluctuations do occur. In a recent paper we demonstrated that this is often associated with non-motor complications (Storch et al. 2013b). Typical examples of non-motor fluctuations were anxiety, depression, fatigue, and bladder urgency.

Motor complications and particularly wearing-off can be addressed by various strategies. The addition of a MAO-B inhibitor such as rasagiline (Parkinson Study Group 2005; Rascol et al. 2005) is a rewarding strategy and leads to a decrease in wearing-off, off-time and an increase in on-time without troublesome dyskinesia. The same was shown for the COMT inhibitors. Entacapone reduced the wearing-off and off-time to a similar degree as that shown for MAO-B inhibitors (LARGO study, Rascol et al. 2005). A good strategy to overcome or avoid the advent of peak-dose dyskinesia when entacapone is added to levodopa and

a decarboxylase inhibitor is, according to the NEWSTA study (Ingman et al. 2012), the use of 25 mg more entacapone in the morning than during the rest of the day. The seven doses available for the so-called triple therapy with Stalevo™ make this strategy possible.

The use of a dopamine agonist in addition to levodopa is also a good option as shown by Watts et al. (2010). In particular, combination therapy may not only improve the condition of the patients with motor and non-motor fluctuations but will also guarantee a relatively low dose of both, and because of this, a low occurrence of side effects. In these phases of the disease, long-acting substances with a continuous dopamine replacement and hopefully continuous dopamine receptor stimulation seem to be most efficacious.

Amantadine too, shows good efficacy in patients with dyskinesia (Verhagen Metman et al. 1998). It reduces dyskinesia and improves motor abilities. Side effects may include leg oedema, hyperexcitability, or livedo reticularis.

A new player in the field is safinamide which was licensed for patients with motor complications as add-on to levodopa in Germany in May 2015. Safinamide is unique in that it has a dual mechanism of action, i.e., it acts both as an MAO-B inhibitor and as an anti-glutamatergic substance (Caccia et al. 2006). It is a reversible MAO-B inhibitor and highly specific for the B form and also quite potent with respect to complete inhibition e.g. of platelet MAO-B without affecting MAO-A. In several randomized trials the substance showed a convincing reduction of motor complications (Borgohain et al. 2014a). Particularly in patients receiving levodopa treatment, the addition of safinamide for 6 months increased on-time by about 2 h which was significantly more than with placebo. An extension study was performed in these patients. After an additional treatment phase of 18 months (Borgohain et al. 2014b) this effect was extremely stable using 100 mg of safinamide in the morning. In the so-called SETTLE study the use of 100 mg safinamide not only improved on-time by about 2 h, reduced off-time by 2 h but also improved in a post hoc analysis the occurrence of dyskinesias (data on file, Zambon company) even in those patients who had no reduction in levodopa dose. Thus, this is another once daily preparation, which in addition did not show any specific side effects and was extremely safe. It needs no laboratory tests, has no effect on the ECG, and does not cause hallucinations or impulse control disorders.

In Table 1 a summary of the use of medication in early fluctuators is given.

Advanced phase

After a rather broad range of years of suffering from PD and receiving adequate treatment, patients still develop more severe motor and non-motor complications. These are mostly dyskinesia, on–off fluctuations, and biphasic or dystonic motor symptoms which need more invasive treatment (Table 2).

Both the use of pumps and deep brain stimulation (DBS) aims at a more continuous dopamine replacement or silencing of over-stimulation (DBS). There are many patients who need an apomorphine pump, the intrajejunal

Table 1 Treatment of patients with wearing-off or mild fluctuations/dyskinesia

	Wearing-off	Mild dyskinesia
1st choice	Add entacapone	Long-acting dopamine agonist
2nd choice	Increase dopamine agonist dose	Amantadine
	Shorten-dopa intervals	Safinamide
3rd choice	Rasagiline	Rasagiline

Table 2 Invasive treatment for patients with major motor fluctuations who cannot be controlled by oral medication

	Apomorphine Pump	LCIG	Deep brain stimulation
Age	No limitation	No limitation	Patients should not be older than 70–75 years
Cognitive impairment	No severe cognitive impairment	No limitation	No cognitive impairment (MMSE >24 points)
Psychiatric symptoms	Do not use in patients with hallucinations and psychosis	No limitation	No depression of cognitive impairment allowed
Co-morbidities	Careful evaluation	No limitation	Not recommended
Follow-up treatment	Application and dose modification by patient or caregiver according to physician	Application and dose modification mostly by caregiver according to treating physician	Technical adjustments only by physician

infusion of levodopa and carbidopa or DBS. As pointed out in Table 2, patients with cognitive impairment or major depression may gain benefit from the LCIG (levodopa, carbidopa, intestinal gel) and should not be treated with the apomorphine pump or DBS. Patients older than 70 years can be treated with pumps, especially with LCIG. Thus, LCIG seems to be the treatment of choice in patients who have a high comorbidity, especially with hallucinations, cognitive decline and major depressive symptoms. Some patients want to buy time before they are ready to undergo surgery. Most of them opt for the apomorphine pump which is the least invasive method of all three. Over recent years, the needle and the apomorphine solution have become more tolerable than previously. These improvements much reduce the risk of skin irritation and furuncles.

A recent double-blind study with LCIG and regular levodopa (both cohorts had a percutaneous endoscopic gastrostomy) demonstrated a convincing superiority for LCIG (Olanow et al. 2014). This may come from the achievement of a relatively continuous receptor stimulation in the brain as indicated by previous work from Stocchi et al. (2005) and Syed et al. (1998). LCIG improved the on-time, and reduced off-time without causing troublesome dyskinesia. It has to be stated, however, that some dyskinesia was even recorded with the use of LCIG.

The apomorphine pump is usually saved for advanced patients, when a patient's symptoms do not respond to oral drug treatment any more. It serves to counteract unpredictable motor complications, severe off-phases or on-time with troublesome dyskinesia. Usually during the day apomorphine is applied via a small portable, battery-driven pump using a pre-filled syringe. The syringe has a fine needle that is inserted subcutaneously. Over the last years progress has been gained with respect to skin irritability by improving the needles but also the solution in which apomorphine is kept in the syringe. If nodules occur they can be treated by ultrasound and certainly hygiene is important when inserting the needle under the skin. In Germany, the UK and other countries Parkinson-nurses assist such patients. Unfortunately, apomorphine causes nausea and vomiting. In previous times domperidone could be used (with the exception of the U.S.A.) but in 2014 restrictions on its use due to QTc-time prolongation and the rare occurrence of torsades de pointes make the use difficult. In Germany domperidone use should not exceed 30 mg/day and not last longer than 1 week.

Amongst the invasive methods, DBS seems to be the most reliable and longest lasting. In various trials, best medical treatment was compared with DBS and in all studies DBS was superior (Deuschl et al. 2006). It has to be noted, however, that modern long-lasting dopamine agonists were not used in this study (Deuschl et al. 2006). Nonetheless, a significantly better quality of life was achieved by the use of DBS than by medication, which encouraged a consortium of German and French DBS centers to analyze DBS in patients with early motor complications (Schuepbach et al. 2013). While the patients in the Deuschl study were on average 62 years of age, the patients in the so-called Early Stim Study were 53 years old and had suffered from PD for 7–8 years and only presented with dyskinesia during the previous 12–15 months. Again, a very significant positive result was seen in patients who received DBS compared to those who were treated with oral medication. An important bias is the fact that all of these patients had given consent for DBS, and it may well be that this lead to a worse rating in the patients who took pills. The question as to which surgical procedure, stimulation of the subthalamic nucleus or globus pallidus, is the better one cannot be decided when efficacy is taken into account. A major difference between the two options lies, however, in the fact that only patients with DBS of the subthalamic nucleus can decrease their medication by about 50 % (Weaver et al. 2009) which is not the case in patients with globus pallidus stimulation. Thus, stimulation of the subthalamic nucleus buys time during which oral medication can be increased step by step again. DBS is potent in patients with off-drug dystonia, diphasic dyskinesia and peak-dose dyskinesia as shown by Weaver et al. (2009). We have more and more patients that were followed for more than 10 years and for this reason it is undisputable that DBS shows benefit for many years.

Non-motor symptoms

This article concentrates on the treatment of motor symptoms. It should be noted however that non-motor symptoms may impair quality of life of patients with PD even more (Schrag et al. 2000). Besides motor complications patients rated cognitive impairment and depression to impair their quality of life the most. So-called non-motor symptoms impair mood, cognition, the autonomic nervous system, pain and sleep to name the most important ones (Martinez-Martin et al. 2007; Chaudhuri and Odin 2010; Reichmann 2010). Non-motor symptoms such as hyposmia (Haehner et al. 2009), constipation (Abbott et al. 2001; Cerosimo et al. 2013), depression (Leentjens et al. 2003) and REM-sleep behavior abnormalities (Iranzo et al. 2005) may precede the motor symptoms and give rise to pre-motor diagnosis (Sommer et al. 2004; Stiasny-Kolster et al. 2005). Also, in the advanced phases, non-motor symptoms such as hallucinations, dementia, anxiety, sleep-wake dysregulation, psychosis play a major part with respect to quality of life (Martinez-Martin et al. 2011). Treatment of these symptoms often causes major problems (Chaudhuri and Schapira 2009; Ziemssen and Reichmann 2010).

What does the future hold?

Many patients are still eagerly waiting for what they call a more sustained or even permanent improvement of their condition. Thus, enzyme replacement strategies, administration of neurotrophic factors, stem cell therapy or alpha-synuclein accumulation inhibitors may be new options. Unfortunately, the results so far available are not very encouraging. In particular, stem cell therapy, even when using induced pluripotent stem cells, still holds so many problems such as purity of the material injected, risk of brain tumors and especially since PD is a spreading disease, independent progression of the disease. In my view, a much better strategy would be to prevent the spread of abnormally accumulated alpha-synuclein and luckily there are many groups working on this new option.

In summary, PD patients have to accept that this neurodegenerative disease or diseases requires an escalation therapy and only by using many options can the motor control of patients be guaranteed for many years, especially if the patients don't develop early falls, gait disturbances in general or cognitive decline.

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