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Treatment of motor symptoms in Parkinson's disease

CLINICAL REVIEW

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In recent years, the development of new therapies and improvements in our understanding of older therapies have led to changes in the management of Parkinson's disease. However, current Norwegian and international therapy recommendations present a range of different options as being equally viable. In this clinical review, we propose an updated algorithm for the medical treatment of motor symptoms in Parkinson's disease, based on evidence-based recommendations and our own personal experience and opinions.

The treatment of Parkinson's disease can be complicated. Many different options are available, and deciding how to treat each individual patient can be difficult. The reference group for the Norwegian Centre for Movement Disorders has published treatment recommendations, but these were last updated in 2014 (1). In recent years, many new drugs and treatment methods have become available, and our understanding of the positive and negative effects of both new and older treatments has increased.

New evidence-based recommendations for the treatment of Parkinson's disease have been developed over the last few years in countries including Germany, Sweden and the UK (2–4). These guidelines provide a detailed account of the various treatment options available along with their scientific evidence base; however, they also present a range of different options as being equally viable, even when, in our opinion, there are good clinical reasons to choose one over another. Many treatments have well-established efficacy compared to placebo, but there are few good studies comparing different treatments. These are issues that cannot currently be resolved through evidence-based recommendations, but which can be discussed in a consensus-based process. Based on evidence-based treatment recommendations and our own clinical experience, we present new consensus-based guidance for choosing treatments for motor symptoms at different stages of Parkinson's disease (Figure 1).

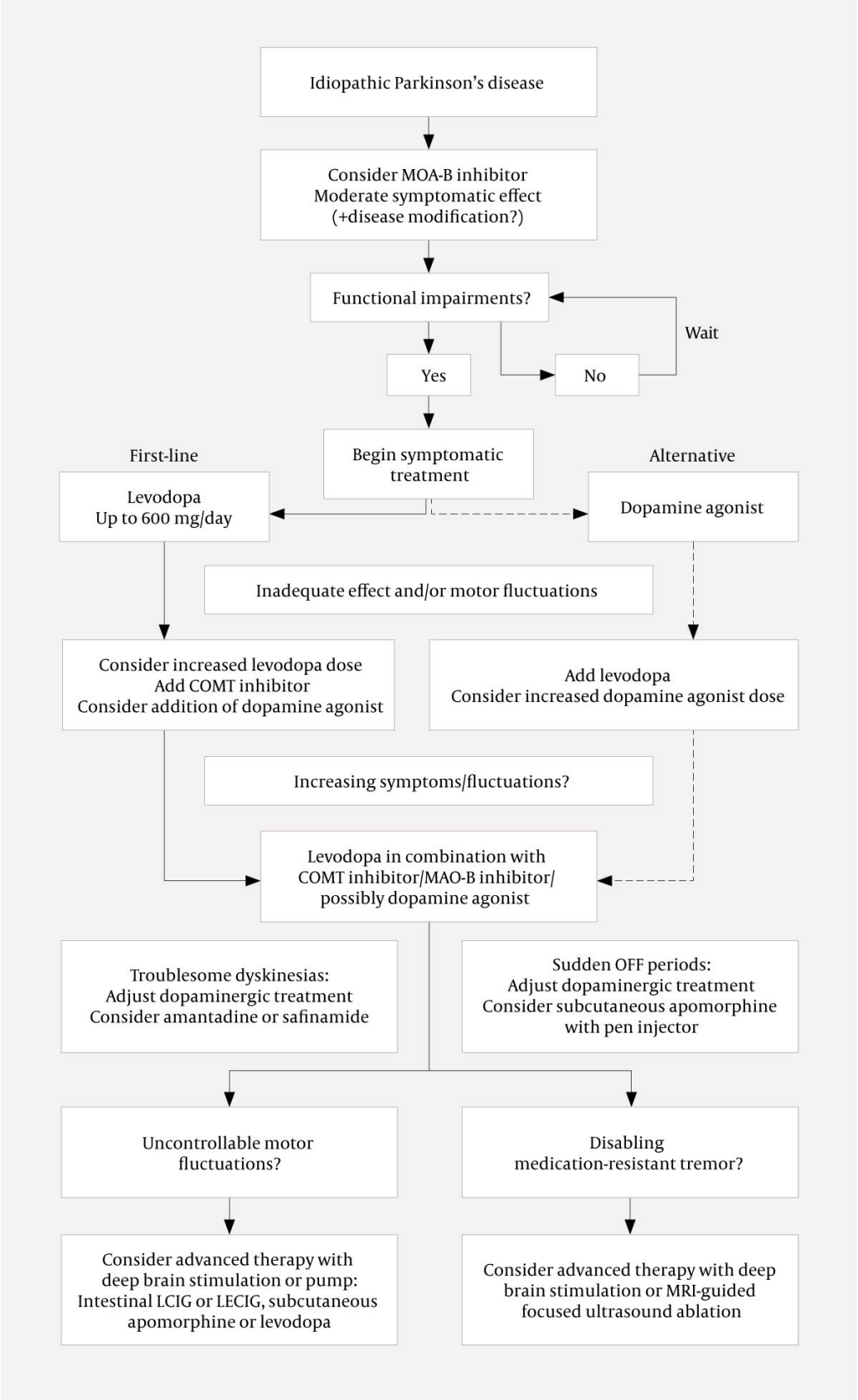

Figure 1 Our proposed treatment algorithm for motor symptoms in Parkinson's disease. COMT = catechol-O-methyltransferase, LCIG = levodopa/carbidopa intestinal gel, LECIG = levodopa/entacapone/carbidopa intestinal gel, MAO-B = monoamine oxidase B. An OFF period is a period of limited medication effectiveness and increasing parkinsonian symptoms/pronounced rigidity.

Parkinson's disease

Parkinson's disease is a neurodegenerative disorder characterised by motor symptoms in the form of hypokinesia/bradykinesia, plus rigidity and/or resting tremor (5). Many patients also have non-motor symptoms such as sleep problems, autonomic dysfunction, exhaustion/fatigue, pain, depression, and cognitive impairment (6). Motor symptoms result from the loss of dopaminergic neurons in the substantia nigra. Dopaminergic agents therefore play a key role in the treatment of motor symptoms and can also help to some extent with non-motor symptoms.

Our proposed treatment algorithm applies to idiopathic Parkinson's disease, which is by far the most common form of parkinsonism, and which can usually be diagnosed with considerable certainty (5). However, it can occasionally be difficult to distinguish Parkinson's disease from rarer forms of neurodegenerative parkinsonism (7). A symmetrical clinical profile without tremor, as well as early onset of falls, cognitive impairment, and pronounced autonomic dysfunction are red flags that should raise suspicion of atypical parkinsonism.

Dopaminergic treatment is usually much less effective in these disorders than in idiopathic Parkinson's disease. The response to dopaminergic medication thus provides important additional information that can be used in diagnosis, and it may be necessary to escalate treatment with levodopa at an early stage to higher doses than those described in the algorithm for idiopathic Parkinson's disease. In cases where the diagnosis is uncertain, treatment with levodopa at doses of 600–800 mg/day for several months may be required to test medication response.

Initial treatment

There are currently no treatments available that are guaranteed to slow disease progression. Several studies, including a double-blind Norwegian-Danish study (8), have provided evidence for a disease-modifying effect of monoamine oxidase B inhibitors (MAO-B inhibitors), but the interpretation of the results is disputed. MAO-B inhibitors do, however, have a symptomatic effect since they inhibit dopamine metabolism in the brain, thereby increasing dopamine availability in the synaptic cleft. Although the effect is modest, MAO-B inhibitors (selegiline or rasagiline) are included in all evidence-based treatment recommendations as one of several equally valid options for newly diagnosed patients without major functional impairment (2–4).

Symptomatic treatment

Dopaminergic agents (levodopa and dopamine agonists) constitute the most effective symptomatic treatment. There is no evidence to suggest that delaying treatment is beneficial, but there is some uncertainty related to the choice of agent. Levodopa is undoubtedly the most potent oral treatment, but most patients who use levodopa will go on to develop motor fluctuations over time (9,10). Several studies have shown that such fluctuations occur later in patients who are started on dopamine agonists, with levodopa added when the effect of dopamine agonists alone is no longer sufficient, compared to patients who are started on levodopa monotherapy at gradually increasing doses (11). It has therefore been common practice to recommend dopamine agonists as first-line therapy in younger patients, due to the increased likelihood that these patients will eventually develop motor fluctuations (1,12).

However, we now propose that levodopa should be used as first-line therapy for most symptomatic patients, irrespective of age. Several factors have led to this change of view. First, levodopa provides faster and better symptomatic relief. This is particularly important

for younger patients with respect to maintaining quality of life and ability to work. It has also been shown that the risk of motor fluctuations is very small at doses of levodopa under 600 mg/day (9).

In addition, the use of dopamine agonists increases the risk of non-motor side effects such as visual hallucinations, sleep attacks, and impulse control disorders (gambling addiction, compulsive shopping, eating disorders, hypersexuality). A Norwegian study showed that the odds ratio for having an impulse control disorder was 7.4 in patients with Parkinson's disease who were using only dopamine agonists, 4.6 in those who were using both levodopa and dopamine agonists, and 1.2 in those on levodopa alone (13). Dopamine agonists must therefore be used with caution. Patients should be informed about the risk of impulse control disorders prior to beginning treatment with a dopamine agonist, and it is important to follow up with patients as well as their family to identify any reduction in impulse control during treatment.

If levodopa provides inadequate symptomatic relief, it is often necessary to increase both the total dose and the frequency of levodopa intake. When a patient begins to experience fluctuations that require dosing more than three times a day, it may be appropriate to add a catechol-O-methyltransferase (COMT) inhibitor, such as entacapone or opicapone, to increase the bioavailability of levodopa. Combination therapy with levodopa and dopamine agonists may help counteract motor fluctuations while allowing a lower dose of levodopa to be used than would otherwise be the case, but again it is important to be aware of the risk of impulse control disorders and other non-motor side effects.

Motor fluctuations

After a number of years of treatment with levodopa, many patients experience motor fluctuations in the form of end-of-dose deterioration ('wearing off') and dyskinesias. The first step in addressing these is usually to adjust the dose and frequency of dopaminergic medication, or to begin combination therapy if this has not already been initiated. Patients with troublesome dyskinesias may benefit from amantadine or safinamide (an MAO-B inhibitor, any other MAO-B inhibitor must therefore be discontinued).

Some patients can experience major problems as a result of motor fluctuations, such as rapid-onset episodes of severe bradykinesia (OFF periods). Subcutaneous administration of the dopamine agonist apomorphine via a pen injector works quickly and can be a useful treatment option. Apomorphine has a slightly different receptor profile to other dopamine agonists and is associated with a lower risk of impulse control disorders.

Advanced treatment

As Parkinson's disease progresses, the capacity of the brain to store dopamine gradually decreases. The therapeutic window for levodopa therefore narrows and the risk of motor fluctuations increases. If motor fluctuations become disabling and can no longer be controlled with standard Parkinson's disease medications, advanced therapies using medical technical devices should be considered. The options here are continuous infusion of dopaminergic drugs through a pump or neurosurgical implantation of electrodes for deep brain stimulation (12).

The advantage of pump-delivered therapy is that medication can be administered at a uniform rate, largely avoiding variations in serum concentration and the resulting motor fluctuations. The dopamine agonist apomorphine can be infused subcutaneously, such that no surgical intervention is required at all. Levodopa can be delivered continuously to the small intestine through a percutaneous endoscopic jejunostomy (PEJ) tube, in the form

of an intestinal gel containing levodopa and the decarboxylase inhibitor carbidopa (LCIG), or as an intestinal gel containing levodopa, carbidopa and the COMT inhibitor entacapone (LECIG).

Several companies are now testing levodopa for subcutaneous infusion, and such preparations are likely to become available in Norway in the near future (14).

Deep brain stimulation is the most invasive of the advanced therapies, as electrodes must be implanted in the brain – usually in the subthalamic nucleus of the midbrain — and connected to a pulse generator implanted subcutaneously, either in the chest or the abdomen. Deep brain stimulation is also effective against motor fluctuations, and most patients are able to reduce their dopaminergic medication postoperatively (15).

All forms of advanced therapy help to reduce motor fluctuations and thus have overlapping indications. However, due to differences in their risk profiles, the suitability of the various options differs between patients. Specific algorithms can be used to assess which advanced therapy is best suited to an individual patient (12). Where there are several viable alternatives, it is the patient who must ultimately decide which treatment option they would prefer.

More patients should probably be offered advanced therapy than is currently the case. However, not all patients are suitable candidates. Both physical and mental comorbidities can be contraindications, increasing the associated risks and reducing the benefits. For patients with advanced disease and a history of complications and side effects from multiple drugs, levodopa as monotherapy will often be the best option.

Inadequate tremor suppression

In some patients with tremor-dominant Parkinson's disease, it can be difficult to achieve adequate tremor suppression with medication alone. In specific cases where tremor is disabling, neurosurgical treatment may be indicated, usually deep brain stimulation. Electrodes implanted in the subthalamic nucleus can be effective against tremor (15). Another option is to implant electrodes in either the ventral intermediate nucleus (VIM) of the thalamus or the posterior subthalamic area. The latter is often preferred when the indication for surgery is tremor (16), but stimulating this area is not effective against the other motor symptoms of Parkinson's disease.

MRI-guided focused ultrasound ablation can reduce tremor by creating a permanent lesion in the brain (17). This method is most relevant when there are contraindications for deep brain stimulation. The equipment required is not currently available in Norway, and eligible patients must be referred for treatment abroad.

Discussion

This article represents our proposed algorithm for the treatment of the motor symptoms of Parkinson's disease. However, it is essential to keep in mind that symptoms can vary significantly from patient to patient. The top priority must therefore be to treat each patient individually, focusing on whichever symptoms – motor or non-motor – are considered most problematic by the patient themselves.

Given the complex nature of Parkinson's disease and the many treatment options available, we recommend that diagnostics and treatment are carried out mainly in the specialist health service, but in close collaboration with general practitioners and other healthcare providers in the primary care service. It is important to keep in mind that medical treatment is only one aspect of managing the disorder. Education, exercise, social and practical support, and a range of other interdisciplinary activities and measures are also crucial.

This article has been peer-reviewed.

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