Treatments for progressing Parkinson’s disease: a clinical case scenario study

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On behalf of the study group PARKINSON’S DISEASE: FROM GUIDELINES TO PRACTICE IN BELGIUM – an expert study on the appropriateness of clinical decisions in progressing Parkinson’s disease

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Abstract

Objective: A ‘case scenario’ study on clinical decisions in progressing Parkinson’s disease (PD) was developed to complement scientific evidence with the collective judgment of a panel of experts.

Methods: The opinions of 9 experts in movement disorders on the appropriateness of 9 common pharmacological treatments for 33 hypothetical patient profiles were compared to those of 14 general neurologists. Before rating the case scenarios, all participants received a document integrating European and US guidelines for the treatment of patients with advanced PD. Case scenarios showing disagreement or with inconsistencies in appropriateness ratings were discussed at a feedback meeting. A tool for interactive discussion on the clinical case scenarios included was developed based on the outcome of the study.

Results: Current guidelines are often insufficient to adequately guide the management of patients with progressing PD. The case scenario study did not reveal major differences in opinions between experts in movement disorders and general neurologists about the appropriateness of certain drug choices for specific case scenarios. However, in about 1 out of 5 treatment decisions where experts stated appropriateness or inappropriateness, the general neurologists panel had no or dispersed opinions.

Conclusions: This study reveals more uncertainty about treatment of advanced PD in general neurologists compared with experts in movement disorders and underlines the need for additional support for guiding treatment decisions in clinical practice.

Key words: Clinical case scenario study; expert opinion; guidelines; motor fluctuations; Parkinson’s disease; pharmacological treatment.

Introduction

For decades, levodopa has remained the ‘gold standard’ for managing Parkinson’s disease (PD). Although levodopa is effective, chronic exposure is ultimately challenged by the development of motor complications (Ahlskog and Muehler, 2001). These complications can be disabling and considerably affect the patient’s quality of life in a large number of patients.

Usually the first treatment-related complication of levodopa is the ‘end-of-dose wearing-off’ effect (EODWO), in which symptoms reappear before intake of the next scheduled dose. In addition to the levodopa-induced motor fluctuations, patients may also experience treatment-related fluctuations in non-motor symptoms such as mood changes or symptoms of autonomic dysfunction. However, these non-motor fluctuations are often missed as EODWO symptoms (Witjas et al., 2002; Santens et al., 2006). As PD progresses, the pattern of therapeutic response tends to become more complicated. Patients experience unpredictable fluctuations between periods of improved mobility and response to medication (ON periods) and periods of impaired mobility and non-optimal response to medication (OFF periods). These ON/OFF periods are unpredictable, vary in time and are independent of the timing of the administration of medication.

Another treatment-related complication of chronic levodopa use is the (peak of dose) dyskinesia, which is characterised by drug-induced choreiform or dystonic involuntary movements.
Motor complications are generally believed to develop as a result of the progressive loss of the striatal dopaminergic neurons and terminals and the intermittent oral administration of levodopa. As the disease progresses, the striatal dopaminergic neurons lose their ability to compensate fluctuating dopamine concentration resulting in pulsatile, non physiological stimulation of dopamine receptors (Chase et al., 1989; Olanow et al., 2006). It has been suggested that continuous dopaminergic stimulation of the striatal dopamine receptors may be associated with a reduced risk for motor complications (Chase et al., 1989; Stocchi et al., 2005).

Once dyskinesia have developed, any dopaminergic agent may induce involuntary movements, although the effect remains by far most pronounced for levodopa. Delayed ON response or dose failure may result from a delay in absorption of the medication due to slow gastric emptying or a delay in its crossing of the blood-brain barrier (Nutt et al., 1984; Hardoff et al., 2001).

Since the introduction of levodopa, a wide range of pharmaceutical and surgical therapies that deal with progressing PD have become available. Recently, European and US guidelines have been published with recommendations for the pharmacological treatment of advanced PD. Treatment guidelines are often based on evidence-based medicine and relay on clinical studies available. It does not take into account how a particular patient may be treated, especially if clinical studies are not available. The current paper summarises, compares, and evaluates the European and US guidelines and discusses the outcome of a “clinical case scenario study” that aimed at complementing best available scientific evidence with the collective judgment of experts about the appropriateness of treatment decisions at the “patient-specific” level.

**Pharmacological treatment of advanced PD: clinical evidence**

**BACKGROUND**

Several therapeutic options are available in the management of fluctuating PD patients. Obviously, the major goal of these therapies is to prolong the duration of ON periods while minimising the risk of dyskinesia and to reduce the pulsatility of the exogenous dopamine supply.

Manipulating the levodopa dose may provide clinical benefits for the patient. Shortening the levodopa dose intervals (maintain daily dose of levodopa, but lower individual doses = fractioning) can be a relevant strategy when a more continuous levodopa level is required. However, in some cases, this strategy may induce re-emergence of PD symptoms due to sub-optimal exposure. On the other hand, increasing the levodopa dose may increase the risk for dyskinesia. Oral dispersible levodopa / benserazide, has been suggested to shorten the time to peak plasma levels in patients with fluctuating PD and might be useful for patients with a delayed ON effect (Contin et al., 1999). Controlled release (CR) levodopa can be used as a substitute for immediate-release levodopa to treat the EODWO, but its therapeutic benefit over standard formulations is controversial (Koller et al., 1999). Only a minority of studies showed a significant beneficial effect of CR levodopa on daily ON time. Moreover, this effect was often minor and transient.

Monoamine oxidase type B (MAO-B) inhibitors such as selegiline and rasagiline, increase the concentration of dopamine in the brain by blocking its enzymatic breakdown. Reports on the effect of selegiline on motor fluctuations or dyskinesia are not consistent (Lees et al., 1977; Lieberman et al., 1987; Golbe et al., 1988). Rasagiline has been shown to produce a significant reduction in OFF time in levodopa-treated patients experiencing motor fluctuations (Rascol et al., 2005; Parkinson Study Group, 2005).

Catechol-O-methyltransferase (COMT) inhibitors block the peripheral metabolism of levodopa and thereby extend its half-life, providing a more continuous and consistent delivery of levodopa to the brain (Ruottinen and Rinne, 1996; Jorga et al., 1997). Both entacapone and tolcapone have been shown to significantly reduce OFF time in patients with advanced PD (Deane et al., 2004), but the use of tolcapone has been limited by concerns about its potential hepatotoxicity. A single tablet containing levodopa, carbidopa and entacapone is also available (Brooks et al., 2005).

Dopamine agonists can also be used as adjunctive treatment in progressing PD. These agents improve motor response and decrease OFF time, possibly through direct stimulation of dopamine receptors. Most of the marketed dopamine agonists have similar clinical efficacy and adverse effect profiles (Bonuccelli and Pavese, 2006). In general, they may be associated with cognitive impairment, psychosis and peripheral oedema. Rare cases of restrictive valvular heart disease and pleuropulmonary fibrosis have been observed with bromocriptine, pergolide and cabergoline (Pritchett et al., 2002; Van Camp et al., 2003). There has been discussion about the occurrence of sleep attacks and increased somnolence as well (Frucht et al., 1999). More recently, dopamine agonists have been linked to impulsive
behaviours such as pathological gambling, compulsive eating and hypersexuality (Weintraub et al., 2006). These adverse events have also been described for levodopa, but less frequently. The safety profile of dopamine agonists may be a limiting factor in the use of these drugs, particularly in patients over 70 and those with pre-existing psychiatric illness.

Intermittent subcutaneous apomorphine has been shown to be effective as an acute treatment for OFF episodes. A possible alternative to this intermittent therapy is continuous subcutaneous apomorphine, which has also shown promise in the reduction of dyskinesias (Colzi et al., 1998; Katzenschlager et al., 2005).

The non-competitive N-methyl D-aspartate (NMDA) receptor antagonist amantadine has been suggested to reduce the severity of levodopa-induced dyskinesia in PD patients without worsening parkinsonian symptoms (Verhagen Metman et al., 1998; Snow et al., 2000). Its effect on ON or OFF duration is controversial.

Atypical antipsychotics such as clozapine may have a role in treating levodopa-induced dyskinesia (Durif et al., 2004). However, clozapine has been associated with serious adverse events, including agranulocytosis that limits its use in clinical practice.

Continuous duodenal infusion of levodopa / carbidopa enteric gel are suggested to reduce OFF-time without worsening dyskinesia and can be a treatment option for patients with (very) advanced PD (Kurth et al., 1993; Nyholm et al., 2005). However, this therapeutic option is invasive and expensive.

Anticholinergics can be used as symptomatic pharmacotherapy for PD. The anticholinergics used in PD act by blocking muscarinic receptors (Horstink et al., 2006a). Studies have shown that adjunctive anticholinergics in levodopa-treated patients have only a small effect on PD symptoms. Their effect on tremor is inconclusive. The use of anticholinergics is limited by their side effects such as blurred vision, urinary retention, nausea, constipation, dry mouth, reduced sweating, and impaired mental function (Horstink et al., 2006a).

**INTERNATIONAL GUIDELINES**

In 2006, European and US guidelines were published, including recommendations for the management of patients with PD with motor fluctuations and dyskinesia (Pahwa et al., 2006; Horstink et al., 2006b). The US guidelines were developed by the Quality Standards Subcommittee of the American Academy of Neurology (AAN); the European guidelines by a joint task force of the European Federation of Neurological Societies (EFNS). The target population of the European guidelines consists of patients with PD with motor or non-motor complications, either disease-related (e.g. freezing) or treatment-related (e.g. dyskinesias or hallucinations). The US committee prepared guidelines for the management of patients with PD with levodopa-induced motor fluctuations and dyskinesia.

Both committees used ratings for the quality of evidence and recommendations, but differences exist with respect to the definitions used (Table 1). The criteria of the US guidelines for the quality of evidence were more stringent than those of the European guidelines (drop in class level if the study does not include ≥ 20 patients followed for > 3 months). In addition, level A, B, and C recommendations required a higher level of evidence in the US guidelines than in the European guidelines.

The European guidelines distinguish between patients with EODWO and unpredictable ON-OFF motor fluctuations and between patients with peak-dose dyskinesia, biphasic dyskinesia, and OFF-period and early morning dystonia. Specific recommendations are only given for patients with EODWO and for those with peak-dose dyskinesia. In contrast, the US guidelines include recommendations for patients with PD with motor fluctuations and patients with dyskinesia, without distinguishing between different subtypes. Medications for the treatment of motor fluctuations were specifically evaluated for their effect on OFF time.

Table 2 summarises the recommendations of the European and US committees for the treatment of patients with PD with (wearing-off) motor fluctuations and (peak-dose) dyskinesia. References to drugs that are currently not available on the Belgian market or to invasive therapies, such as deep brain stimulation and ablative procedures, are not included in the summary. The European and US guidelines do not give specific recommendations on combination therapy due to insufficient evidence. The European guidelines also include recommendations for the symptomatic control of freezing and non-motor problems. These are not specifically discussed in the current US guidelines and therefore not included in the comparative summary.

The European and US guidelines for the treatment of advanced PD with motor fluctuations seem to be rather comparable. Both give A recommendations for the use of COMT and MAO-B inhibitors and B to C recommendations for the use of dopamine agonists. Whereas the European guidelines provide global recommendations for the use of COMT inhibitors, MAO-B inhibitors, and dopamine agonists, the US guidelines distinguish between
different components of these drug classes. Treatment options for dyskinesia appear to be limited. Both guidelines recommend the use of amantadine (Europe: A recommendation, US: C recommendation), but they disagree on the use of atypical antipsychotics. Although both guidelines are built on strong evidence from well-performed clinical trials, they do not always provide a sufficient basis for guiding treatment decisions at the “patient-specific” level due to the wide range of patients seen in everyday clinical practice.

**Using clinical expertise to guide treatment decisions: a case scenario study**

The goal of the study was to explore the applicability of general guidelines to the specific level of treatment decisions to be taken in daily practice. A clinical case study, including 33 scenarios, was set up to apply the available scientific evidence about the appropriateness of treatment decisions and to complement it with the collective judgment of a panel of experts at the patient-specific level. The ultimate objective was to develop a format and a tool for interactive discussion on selected individual clinical case scenarios during educational meetings.

**METHODS**

Using modified Delphi techniques (Kahn et al., 1988), the opinions of nine experts in movement disorders (patient population and clinical expertise focused on PD) on the appropriateness of nine common pharmacological treatments for 33 hypothetical patient profiles (indications or clinical case scenarios) were evaluated and compared to the treatment decisions of a sample of 14 “general neurologists” (seeing patients with all types of neurological disorders).

The study was restricted to hypothetical profiles of patients diagnosed with PD with initially satisfactory dopaminergic treatment and subsequent development of motor complications, non-motor symptoms and/or side effects. Each of the profiles was built using a combination of variables that were considered relevant for taking treatment decisions according to the experts. Variables included age, treatment history, and current symptoms (Table 3). Two Belgian general neurologists ultimately selected 33 patient profiles of the defined patient population that were most commonly seen in the general neurology setting. Via a web-based rating program all panellists expressed individually the extent of appropriateness of 9 treatment decisions (Table 4) for each of the 33 profiles (total of 297 treatment decisions) on a 9-point scale in which 9 means extremely appropriate, 1 extremely inappropriate, and 5 uncertain. A treatment decision was considered appropriate if its expected benefits outweigh its potential negative consequences by a sufficiently wide margin that the procedure is worth doing. Financial costs were not considered. All participants received a document integrating the European and US guidelines before rating the case scenarios.

For each treatment decision, the dispersion of the ratings was determined first. The term “agreement” was given to a decision for which at maximum 2 (for a panel of 9 experts) or 4 (for a panel of 14 general neurologists) of the individual scores were lying outside the section in which the median score fell.

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**Table 1**

<table>
<thead>
<tr>
<th>Europe</th>
<th>US</th>
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<tbody>
<tr>
<td><strong>Level A recommendation</strong></td>
<td>Established as effective, ineffective or harmful. Requires at least one convincing class I study or at least two consistent, convincing class II studies</td>
</tr>
<tr>
<td><strong>Level B recommendation</strong></td>
<td>Probably effective, ineffective, or harmful. Requires at least one convincing class II study or overwhelming class III evidence</td>
</tr>
<tr>
<td><strong>Level C recommendation</strong></td>
<td>Possibly effective, ineffective, or harmful. Requires at least two convincing class III studies</td>
</tr>
<tr>
<td><strong>Good practice points</strong></td>
<td>In cases where there is insufficient scientific evidence, a consensus statement (“good practice point”) is made</td>
</tr>
<tr>
<td><strong>Level U recommendation</strong></td>
<td>Studies not meeting criteria for class I to class III</td>
</tr>
</tbody>
</table>
“Disagreement” was used for decisions with at least 3 (for expert panel) or 5 (for general neurologist panel) of the individual scores lying in each of the opposite sections 1-3 and 7-9. All other outcomes had “indeterminate” dispersion.

Appropriateness statements were designated as follows: all treatment decisions with disagreement were considered “uncertain”; if there was no disagreement, median ratings by the panel of 7, 8 or 9 were designated as “appropriate” and median ratings of 1, 2 or 3 as “inappropriate”; median ratings by the panel of 4, 5 or 6 were always designated “uncertain”. The intra-group agreement among experts was analysed to measure consensus and disagreement and to yield statements of appropriateness for different decisions. The inter-group agreement between movement disorder experts and general neurologists was evaluated to assess any competence gap at general neurology level.

Based on the results of the study, an educational tool was developed containing the appropriateness outcome for each of the included case scenarios. The
scenarios with expert disagreement and those with wide variation between the general neurology ratings and expert ratings were discussed in depth at an expert feedback meeting.

**Outcome and Discussion of Individual Case Scenarios**

Figure 1 shows an example of the rating procedure for one of the clinical case scenarios and the outcome showing median appropriateness scores for each treatment decision and intra-group agreement among experts and general neurologists.

Table 5a shows the overall intra-group levels of agreement among movement disorder experts and general neurologists. The agreement among experts was larger than among general neurologists (57% versus 46%). Inter-group analysis showed 66% accordance (kappa value of 0.39; \( p < 0.001 \)). Table 5b shows the overall inter-group appropriateness statements. Analysis of the overall inter-group accordance of these appropriateness statements was 78% (kappa value of 0.67; \( p < 0.001 \); from the 100 clinical decisions considered as appropriate by the experts, 31 were felt to be uncertain by the general neurologists (31%). Conversely, from the 120 clinical decisions rated inappropriate by the experts, 14 were felt to be uncertain by the general neurologists (12%).

These results show that the general neurologists were more often uncertain about the appropriateness of treatments for specific case scenarios and, therefore, rated to the middle (no opinion) compared to
the experts. Of course, it is not a surprise that experts had more pronounced opinions.

Eight of the case scenarios rated with disagreement or with inter-group inconsistencies in appropriateness ratings were discussed at the feedback meeting. Based on the discussion, the experts re-rated all cases scenarios to formulate final statements of appropriateness for treatment decisions. These statements were included in the educational tool.

First, the experts stressed that the patient’s age and his/her pattern of daily activities can be important variables when choosing an appropriate treatment for PD. While dopamine agonists are often used in younger patients as a levodopa-sparing strategy, these agents may be associated with more adverse events and reduced symptom control compared to levodopa. It was discussed that the middle age-category of the case scenarios, ranging from 50 to
70 years was too large leading to different opinions.
Nevertheless, it was felt that no optimal age cut-off
between young and old patients can be given and that
this problem is rather artificial and would not lead to
discussion in real patients.

Another point of disagreement was when fraction-
ation of levodopa is indicated. It became clear that
some experts were more in favour of applying
fractionation than others, and that the potential
advantages for a particular patient were weighed
against the risk for insufficient compliance. The
experts underlined that fractionation is mainly
recommended for patients with dyskinesia. Although
fractionation can reduce fluctuations, the pharma-
koetic profile of levodopa is still characterised by
deep troughs, leading to intermittent stimulation of
postsynaptic dopaminergic receptors. Moreover,
taking more frequent doses of levodopa can be
impractical, which might lead to sub-optimal com-
pliance with the medication (Grosset et al., 2005).
Overall, the experts and general neurologists agreed
that treatment change to levodopa sustained release
is not recommended in the present case scenarios.

There was limited discussion on the use of
COMT-inhibitors. By extending the levodopa half-
life, the addition of a COMT-inhibitor may provide
more stable levodopa plasma levels and, conceivably,
more sustained brain dopaminergic stimulation.
Triple combination therapy (levodopa + carbidopa +
entacapone) allows optimising the levodopa therapy
without the need to increase the number of pills
taken daily.

Some experts prefer a stepwise approach, starting
with adding COMT-inhibitor to levodopa and
switching to the combination pills at a next consul-
tation as soon as the corresponding dose is achieved
giving higher rates to adding COMT-inhibitor),
while other experts prefer a direct switch (giving
higher rates to the combination pills). It was
concluded that the different ratings did not reveal
different opinions, and resulted from differences
in timing. Patient ability and preference are also
considered.

In contrast to all other treatment options, there
was no clear consensus among the experts about
the use of MAO-B inhibitors for any of the case
scenarios that were evaluated. The appropriateness
of treatment with MAO-B inhibitors was either rated
as uncertain, or there was disagreement or inter-
mediate agreement among the experts about the
appropriateness of treatment.

The use of dopamine agonists for patients with
mood disturbances, psychiatric disorders (hallucina-
tions / psychosis), cognitive dysfunction or au-
tonomic disorders was also discussed. It was stated
that, whereas psychiatric disturbances, especially
psychosis, may be a side effect of dopamine ago-
 
 

Table 5a
Intra-group agreement about treatment decisions among experts in movement disorders and general neurologists

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<th>Experts (N = 9)</th>
<th>General neurologists (N = 14)</th>
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<tbody>
<tr>
<td></td>
<td># decisions</td>
<td>%</td>
</tr>
<tr>
<td>Agreement</td>
<td>170</td>
<td>57</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>101</td>
<td>34</td>
</tr>
<tr>
<td>Disagreement</td>
<td>26</td>
<td>9</td>
</tr>
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</table>

Table 5b
Intra-group accordance of appropriateness statements about treatment decisions between experts in movement disorders and general neurologists

<table>
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<th>Experts (N = 9)</th>
<th>General neurologists (N = 14)</th>
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<tbody>
<tr>
<td></td>
<td># decisions</td>
<td>%</td>
</tr>
<tr>
<td>Appropriate</td>
<td>120</td>
<td>40</td>
</tr>
<tr>
<td>Uncertain</td>
<td>77</td>
<td>26</td>
</tr>
<tr>
<td>Inappropriate</td>
<td>100</td>
<td>34</td>
</tr>
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evaluated, experts rated adding or increasing the dose of a dopamine agonist as inappropriate, whereas the neurologists rated the appropriateness of this treatment change as uncertain. The experts generally agreed that dopamine agonists are neither preferred for patients with autonomic disorders, nor for patients with cognitive or psychiatric disorders. Anticholinergics should also be avoided if cognitive disturbances are present.

**Limitations of the Study**

It should be emphasised that the recommendations formulated by the experts cannot be considered as the “gold standard” for taking treatment decisions in clinical practice. They are the result of a scientific approach and combine scientific evidence with collective judgments. Rather, these recommendations should be used as an educational tool for neurologists to compare their own decisions with those of a panel of experts in movement disorders and as a starting point for discussion of the relative risks and benefits of applying a procedure to a particular patient.

The comparison of the general neurologist and expert panel is probably hampered by some selection bias. Though the expert panel was selected based on their academic curriculum, publications in the domain, and the fact that their main patient population consisted of Parkinson patients, the so-called randomly selected general neurologists were probably more experienced in PD than initially intended. The fact that about 2 out of 3 contacted general neurologists were not willing to perform the electronic rating of about 300 hypothetical decisions within the given short time frame, suggests that those neurologists who accepted were those with a higher affinity for the area of PD and important study-mindedness.

Due to the nature of the clinical case scenario development process, important patient information might be missing or interpretation bias of the described clinical variables might be present, which may lead to flaws in the recommendations. The clinical case scenarios selected for the programme do not cover the total population seen in routine clinical practice. In addition, reimbursement conditions were not considered for the ratings.

**Conclusions**

Current guidelines lack clear directions and recommendations on a systematic approach to the management of patients with progressing PD, and are therefore believed to exert limited effect on

| Table 6 | Intra-group agreement (# decisions) and Inter-group (% decisions) accordance by treatment among experts in movement disorders (EXP; N = 9) and general neurologists (GN; N = 14) |
|---|---|---|---|---|
| | Intra-group (# decisions) | Inter-group accordance |
| | Agreement | Indeterminate | Disagreement | % |
| Add or increase dose of levodopa | EXP 9 GN 3 | 18 28 | 6 2 | 58 |
| Add or increase dose of dopamine agonist | EXP 15 GN 9 | 15 22 | 3 2 | 48 |
| Fractionate levodopa dose | EXP 8 GN 8 | 20 25 | 5 0 | 70 |
| Switch to levodopa sustained release | EXP 33 GN 18 | 0 15 | 0 0 | 55 |
| Add MAO-B inhibitor | EXP 1 GN 18 | 28 15 | 4 0 | 76 |
| Add COMT inhibitor | EXP 24 GN 2 | 6 30 | 3 1 | 36 |
| Switch to combination drug | EXP 21 GN 23 | 10 8 | 2 2 | 70 |
| Add amantadine | EXP 30 GN 29 | 2 4 | 1 0 | 94 |
| Add anticholinergics | EXP 29 GN 27 | 2 5 | 2 1 | 89 |
physician behaviour today. Although expert recommendation is the reflection of experience-based opinions, it might be a valuable contribution to the decision-making process. This study underlines the importance of additional support for guiding treatment decisions in clinical practice.

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