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Movement disorders

Initial treatment of Parkinson's disease in 2016: The 2000 consensus conference revisited

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INFO ARTICLE

Article history:
Received 1st March 2016
Accepted 8 July 2016
Available online 29 July 2016

Keywords:
Parkinson's disease
Levodopa
Dopamine agonist
Monoamine oxidase B inhibitors
Cathecol-O-methyltransferase inhibitors
Anticholinergics
Amantadine

ABSTRACT

In 2000, a French consensus conference proposed guidelines for the treatment of Parkinson's disease (PD). Since then, new drugs have been concocted, new studies have been published and clinicians have become aware of some drug-induced adverse effects that were little known in the past. This has led us to reconsider the recommendations published 16 years ago. Thus, the aim of the present review is to present the recent data related to the different medications and non-pharmacological approaches available for PD, with a special focus on early-stage PD. Levodopa (LD), dopamine agonists (DAs), catechol-O-methyltransferase inhibitors (COMT-Is), anticholinergics, monoamine oxidase inhibitors (MAOB-Is) and amantadine have been considered, and their efficacy and safety for both motor as well as non-motor aspects are reported here. This has led to our proposal for a revised therapeutic strategy for the initiation of treatment in newly diagnosed PD patients, based on the available literature and the relative benefits/side effects balance.

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disease that affects about 1% of the population over 60 years of age and represents the second most common cause of neurological motor disability in the elderly. With aging of the population, the management of PD is likely to become an increasingly important part of neurological practice [1,2]. In the early stage of PD, many factors can guide the choice of treatment strategy: the patient's clinical phenotype and age; the severity of motor and also non-motor symptoms; and the risk of side effects. The final aim is to restore the patient's quality of life as much as possible. In addition, the neurologist's challenge is to find the best compromise between the need for rapid efficacy and avoidance of delayed motor complications, but also between drug benefits and adverse effects, through a constant dialogue with patients and their

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http://dx.doi.org/10.1016/j.neurol.2016.07.007
0035-3787/

families. Therefore, the timing and choice of treatment initiation represent major decisions, with both short- and long-term consequences, that take place at the difficult moment of announcing the diagnosis [3].

In 2000, a consensus conference was held in France to provide guidelines for PD management throughout the course of the disease, but notably for treatment initiation [4]. More recently, the French National Authority for Health (*Haute Autorité de santé* [HAS]) published its recommendations on how PD patients should be managed [5]. However, in the 16 years since the French consensus conference, new antiparkinsonian drugs have entered the market and new data have been collected regarding the risk of side effects with some of these drugs. Thus, there is now a need for reappraisal of the recommendations made in 2000 for treatment initiation in PD. This is the aim of the present review.

In this evidence-based review of the initial management of PD, the available data regarding the efficacy (for motor and also non-motor aspects) and safety of the various pharmacological treatments, as well as non-pharmacological approaches, are summarized, followed by a proposal for a modified therapeutic strategy.

2. Methods

Data sources include studies published in English and in French identified *via* the PubMed database. The research terms were ''Parkinson's disease treatment'', ''Dopamine agonist'', ''Levodopa'', ''Monoamine oxidase inhibitors'', ''Catechol-O-methyltransferase inhibitors'', ''Anticholinergics'', ''Amantadine'', ''Dyskinesia'', ''Physiotherapy'' and ''Physical exercise''.

Randomized clinical trials, meta-analyses and published guidelines were also systematically included. Controlled but non-randomized trials were included if reporting new information. Open-label studies and case reports were excluded.

3. Results

3.1. *Current recommendations based on the 2000 consensus conference*

The most recent French guidelines for PD treatment were proposed in 2000, with a reappraisal in 2012 [4,5]. In patients with minimal functional impairment and according to age, the recommendations were to use monoamine oxidase inhibitors (MAOB-Is), dopamine agonists (DAs), amantadine or anticholinergics (for tremor-dominant presentations only). In cases of greater disability, DA monotherapy treatment was recommended for as long as possible in patients aged $\leq$ 65 years. Use of levodopa (LD) was justified in cases of intolerability or inadequate therapeutic responses. For patients $>$ 65 years of age, LD was proposed as the first-line treatment.

3.2. *Developments in PD treatment since 2000*

3.2.1. *Levodopa*

Since the 1970s, LD has remained the most prescribed and effective medical treatment for PD [6,7]. In randomized trials comparing LD and DAs, activities of daily living and the motor aspects of PD were improved with LD by around 40–50% compared with around 30% with DAs [7–11]. Acute side effects associated with LD include nausea, vomiting and hypotension, although the drug is generally well-tolerated [12].

However, the question of its potential neurotoxicity has been debated ever since some in vitro studies suggested that LD could be neurotoxic [13–15]. However, convergent data coming notably from cell cultures [16,17], and histopathological [18] and clinical [7] studies, have ruled out that hypothesis [19]. Furthermore, it has been suggested that early treatment with LD might reduce striatal dopamine turnover [20], which can be deleterious [21], whereas some authors have argued that early treatment with LD could correct the increased turnover and delay the progression of PD [22]. The ELLDOPA study [7] showed results that supported such assertions, but the hypothesis could not be confirmed due to the long-lasting symptomatic effects of LD and the study's too-short washout period.

Nevertheless, this multicenter double-blind, placebo-controlled study, involving 361 early PD patients treated by either LD at three different doses or a placebo, confirmed the major efficacy of LD, but also added some new information regarding its pharmacokinetics and the risk of LD-induced dyskinesias [7]. The Unified Parkinson's Disease Rating Scale (UPDRS) motor score at week 42 (2 weeks after washout of the study medication) was 6.0 ± 7.6 in the placebo group vs 3.2 ± 6.4 in the group treated with 150 mg/day of LD, 3.0 ± 6.4 for those treated with 300 mg/day and 0.6 ± 7.7 in those treated with 600 mg/day ($P < 0.001$), demonstrating a dose–response effect. The maximum clinical benefit was obtained after 24 weeks of treatment, thereby suggesting that once LD treatment is started, it should be given for at least 3 months with a slow daily dose increment before concluding that a patient does or does not respond to LD [8,7].

On the other hand, the ELLDOPA study also showed that dyskinesias, nausea and headaches were more common with the highest LD dose regimen, which fits well with animal studies [23]. This is a key issue, as the incidence of motor complications (dyskinesias and motor fluctuations) represents the most important factor limiting the use of LD. More precisely, in the ELLDOPA study after 9 months of treatment, 13% of patients exposed to a high LD dose developed dyskinesia vs 3% with a low dose [7]. These data indicate that, to prevent motor complications, the LD prescribed dosage should be the minimum dose providing effective symptom control and that, whenever possible, it should remain $<$ 300–400 mg/day in the early stages of PD.

Other studies have confirmed that the LD dose and duration of exposure were two major factors predicting the occurrence of dyskinesias and motor fluctuations [24,25]. In the Schrag and Quinn study [24], 87 patients were treated by LD and, among them, 40% had motor fluctuations. The main factors predicting the prevalence of motor fluctuations were disease duration and dose of LD. Indeed, the prevalence of motor fluctuations with a disease duration $\leq$ 5 years was 14%, while the prevalence with disease durations of 6–9 years was 39% [24].

However, the question of the role of LD exposure duration remains a matter of debate as a recent study demonstrated