Management of Parkinson’s Disease: An Evidence-Based Review*

Although Parkinson’s disease is still incurable, a large number of different treatments have become available to improve quality of life and physical and psychological morbidity. Numerous journal supplements have appeared in recent years highlighting one or more of these and disparate treatment algorithms have proliferated. Although these are often quite useful, this “mentor analysis” approach lacks the scientific rigor required by modern evidence-based medicine standards. The Movement Disorder Society, with generous but unrestricted support from representatives of industry, have, therefore, commissioned a systematic review of the literature dealing with the efficacy and safety of available treatments. The accompanying treatise is the result of a scrupulous evaluation of the literature aimed at identifying those treatments for which there is sound scientific support to justify their application (or avoidance) and to highlight where a lack of evidence points to the need for future clinical trials. The introductory chapter reviews the study methodology while subsequent chapters deal with specific interventions subdividing the evidence under the categories of: prevention of disease progression; symptomatic control of Parkinson’s disease; prevention of motor complications; control of motor complications; and control of non-motor features. Based on a systematic review of the data, efficacy conclusions are provided. On the basis of a narrative non-systematic approach, statements on safety of the interventions are given and finally, a qualitative approach is used to summarize the implications for clinical practice and future research.

This mammoth task has taken two years to complete and the task force members, principal authors and contributors are to be congratulated for their outstanding work. Physicians, the Parkinson’s disease research community and most of all patients themselves should welcome and embrace the salient findings of this report as an effort to improve clinical practice. It is hoped that this supplement will serve as a landmark in the treatment of Parkinson’s disease, not only encouraging ongoing excellence in patient care but also providing guidance in the development of future research studies designed to fill the identified gaps in our current knowledge base.

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*Produced by a task force commissioned by The Movement Disorder Society
sustained release Levodopa and followed patients up for 5 years. Primary endpoint in this trial was defined as the presence of motor fluctuations defined in three different ways: based on 24 hour diaries filled in on two consecutive days per week for a total of 8 days over a one month period after each quarterly visit patients had to exhibit a minimum of 10% on-time with dyskinesias or 20% of off-time during the waking day to reach endpoint. Alternatively, 5 of 10 questions in a motor fluctuation questionnaire specially designed for the trial had to be scored positive by the investigator. A third definition of endpoint was that both the diary and the questionnaire criterion were met. All three criteria had to be met on at least two consecutive visits for an “event” to be coded for the survival analysis. After 5 years of treatment the mean daily dose of standard Levodopa in this trial was 426 mg. 21% of patients had fluctuations or dyskinesias by the diary criterion while only 16% had reached the event by questionnaire definition. The paper does not quote percentages of patients meeting both criteria. This study had an overall quality score of 80%.

CONTROL OF MOTOR COMPLICATIONS

It is common practice to modify dose size and dose frequency of standard Levodopa preparations to improve motor response oscillations and/or dyskinesias but no Level-I trials assessing such strategies were identified. Studies assessing alternative pharmacokinetic formulations of delivery routes of Levodopa will be reviewed below.

REVIEW OF SAFETY

Treatment of PD with standard Levodopa causes a number of typical dopaminergic adverse events including nausea, vomiting, and hypotension. Central dopaminergic adverse reactions include hallucinosis and paranoid psychosis as well as drug-induced dyskinesias. From the available Level-I studies the risk of drug-induced psychosis with Levodopa monotherapy appears low with less than 5% of de novo patients being affected after 3 to 5 years. The incidence of Levodopa-induced dyskinesias in prospective randomized long-term trials varies between less than 20% to more than 50% at 5 years.

There have been a number of retrospective and prospective cohort studies assessing mortality in Levodopa treated patients with PD. All but one have found excess mortality over the general population by factors between 1.5 and 2.5.35-39 However, the impact of Levodopa treatment itself on the mortality of PD has only been inferred from comparisons with historical controls and this approach is obviously flawed by confounding changes in life expectancy, levels of general medical care, uncontrolled factors of comorbidity and co-medication. Given these limitations a number of such studies have demonstrated associations of improved survival after initiation of Levodopa treatment in PD.35,40-44 While it is commonly accepted that Levodopa treatment by virtue of its symptomatic efficacy improves disability and survival early in the disease advancing disability in later stages along with age associated comorbidity still accounts for excess mortality.

Because of the role of oxidative stress as a pathogenetic factor of nigral cell death in PD and the theoretical possibility that the oxidative metabolism of Levodopa itself might accelerate this process there has been an intense debate of possible nigral toxicity induced by Levodopa treatment.45 Although a number of in vitro experiments in neuronal and non-neuronal cell cultures have indeed demonstrated toxic effects of Levodopa results from in vivo studies are controversial.46 In addition to the conflicting evidence from experimental studies there is currently no clinical indication of detrimental effects of Levodopa in terms of accelerating disease progression.47 However, the mechanisms leading to potentially irreversible dyskinesias following prolonged Levodopa exposure may be viewed as a type of drug-related “toxicity”.

CONCLUSIONS

PREVENTION OF DISEASE PROGRESSION

There is INSUFFICIENT EVIDENCE to conclude on the effects of Levodopa on the progression of PD. Evidence from a single Level-I trial designed to assess the effects of deprenyl on disease progression when added to bromocriptine or Levodopa for a period of 12 months suggests that Levodopa and bromocriptine are not different regarding impact on progression of motor impairment as assessed after appropriate washout periods following 12 months of treatment. Recently concluded studies have employed surro-gate markers (18FD-PET/Beta-CIT-SPECT) to assess the relative impact of Levodopa versus dopamine agonists but such studies do not allow conclusions on the impact of Levodopa treatment on disease progression in relation to untreated PD. Again the only available Level-I trial showed similar outcomes regarding decline of striatal b-CIT binding as assessed by SPECT after two years of treatment with Levodopa or pramipexole.

SYMPTOMATIC CONTROL OF PARKINSONISM

Although there are no Level-I placebo-controlled trials available, the efficacy of Levodopa regarding symptomatic control of parkinsonism is clearly established. Levodopa monotherapy is LIKELY MORE EFFICACIOUS than monotherapy with anticholinergics or amantadine, but the two Level-I studies identified in this review are insufficient for methodological reasons to unequivocally prove superiority of Levodopa.

Similarly, based on 8 Level-I studies, Levodopa monotherapy is LIKELY MORE EFFICACIOUS than monotherapy with bromocriptine, but methodological quality, designs (Levodopa supplementation to bromocriptine in case of clinical need in several trials) and reported study results are too heterogeneous to make this a firm conclusion.

There is INSUFFICIENT EVIDENCE to conclude on the relative efficacy of Levodopa versus lisuride monotherapy since a single Level-I trial eventually lost power for meaningful comparisons between Levodopa and lisuride monotherapy due to Levodopa add-on in the majority of lisuride patients.

A single trial assessing pergolide versus Levodopa monotherapy only included 20 de novo patients and provides INSUFFICIENT EVIDENCE to conclude on the relative efficacy of these two types of treatment, but a larger long-term randomized controlled trial has been completed and awaits full publication.

Based on one high quality long-term prospective double-blind trial each there is sufficient evidence to conclude that Levodopa monotherapy is MORE EFFICACIOUS than monotherapy with ropinirole, pramipexole or cabergoline in improving symptomatic control in de novo patients with PD.

PREVENTION OF MOTOR COMPLICATIONS

Efficacy conclusions related to the prevention of motor complications are not applicable to standard Levodopa therapy.