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Effects of monoamine oxidase Type B inhibitors on motor and non-motor symptoms in Parkinson's disease: A systematic comparison of rasagiline and selegiline

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ABSTRACT

During recent decades, clinical research has provided a variety of pharmacological substances that can effectively ameliorate the symptoms of Parkinson's disease (PD), among them selective monoamine oxidase type B inhibitors such as selegiline and rasagiline. Although the latter two substances are nowadays broadly used in clinical practice for monotherapy in early PD and for adjunct therapy to levodopa in advanced PD, there is still uncertainty amongst neurologists whether selegiline or rasagiline should be preferred for antiparkinsonian therapy, since clinical studies directly comparing the efficacy of both compounds on motor and non-motor symptoms are lacking. This article aims to systematically compare the effects of selegiline and rasagiline as monotherapy in early PD and as adjunct treatment in advanced PD with motor fluctuations that have been measured in previous placebo-controlled, double-blind clinical trials and provides an overview about their potential benefits on non-motor symptoms of the disease. In early PD, monotherapy with selegiline and rasagiline provides similar symptomatic efficacy and can be classified as clinically useful for amelioration of emerging motor symptoms. Whereas rasagiline has also demonstrated symptomatic efficacy in patients with advanced PD and can moreover be regarded as efficacious for the treatment of motor fluctuations, the scientific evidence for selegiline in these indications is still insufficient. The available data for both compounds are insufficient to provide a clear picture of their effects on NMS, but recent studies and *post hoc* analyses provide first evidence for positive actions of rasagiline on fatigue and some aspects of attention and executive functions in non-demented PD patients.

Introduction

Parkinson's disease (PD) is a common neurodegenerative disease, which historically has been described for the first time in 1871 by James Parkinson in his "essay on the shaking palsy" [1] and pathologically is characterized by a progressive loss of dopaminergic neurons of the nigrostriatal pathway [2]. While primarily defined by the presence of motor symptoms such as bradykinesia, rigidity, rest tremor and postural imbalance, PD is known to be also associated with non-motor symptoms, such as dementia, depression and sleep problems. In recent decades, clinical research has provided a variety of pharmacological substances that can effectively ameliorate the symptoms of the disease, among them levodopa, dopamine agonists and monoamine oxidase type B inhibitors.

Non-selective monoamine oxidase inhibitors initially emerged into clinical medicine during the early 1950s with the discovery of their antidepressant effects [3] and rapidly became the most widely used antidepressant agents in that decade. The situation dramatically changed in the 1960s with the observation that hydrazine-like MAO inhibitors like iproniazid were associated with a risk for hepatic cell damage [4,5]. Simultaneously, non-hydrazine derivatives such as tranylcypromine, which were devoid of hepatotoxicity, were reported to lead to an increased incidence of hypertensive crisis [6], which had been initially observed in patients after the consumption of cheese [7]. This "cheese reaction" could later been linked to an increased crossover of dietary sympathomimetic amines, such as tyramine, into the systemic circulation due to MAO-A inhibition in the gut [8] and eventually also led to the development of selective MAO-B inhibitors that are nowadays used to treat PD, such as selegiline and rasagiline.

The antiparkinsonian effect of selegiline and rasagiline is based on inhibition of monoamine oxidase type B (MAO-B), which is the predominant enzyme isoform in the human brain, where it is responsible for the breakdown of dopamine to 3,4-dihydroxyphenylacetic acid and homovanillic acid, as well as for the deamination

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of β-phenylethylamine, which stimulates the release of dopamine and inhibits its neuronal reuptake [9]. The development of the first-generation MAO-B inhibitor selegiline was closely linked to the work of Joseph Knoll in Hungary, who published the first paper about the compound in 1965 [10] and subsequently reported that this propargylamine derivate of methamphetamine is able to selectively and irreversibly block MAO-B activity in the brain [11]. Selegiline undergoes extensive hepatic first-pass metabolism to the metabolites to L-methamphetamine and L-amphetamine, which may contribute to the cardiac and psychiatric side effects seen in patients with PD [12,13]. In contrast, the second-generation propargylamine rasagiline is mainly metabolized to aminoindan, which is not based on an amphetamine-like chemical scaffolding and thus considered not to have vasoactive properties [14]. Moreover, rasagiline has been found to be about ⩽10-fold more potent than selegiline [15] and due to its potential neuroprotective properties has become a strong competitor for selegiline on the market.

Although both compounds are nowadays broadly used for the treatment of patients with early and advanced PD, there is still uncertainty amongst physicians whether selegiline or rasagiline should be preferred for specific indications since clinical studies directly comparing the efficacy of these two substances are lacking. Our article therefore aims to systematically compare the symptomatic effects of both substances as monotherapy in early PD and as adjunct therapy to levodopa in advanced PD with motor fluctuations in comparison to placebo and will furthermore provide an overview about their potential benefits on non-motor symptoms of the disease.

Selegiline and rasagiline as monotherapy in early PD

Selegiline

One of the first double-blind, placebo-controlled clinical trials investigating the efficacy of selegiline as monotherapy in early PD was conducted by Tetrud and Langston [16]. This study enrolled 54 patients with early, untreated PD to test the hypothesis whether selegiline treatment would be able to delay the need for levodopa treatment by slowing the rate of progression of PD. Patients were randomized to treatment with placebo or 5 mg selegiline twice a day, re-examined 1 month after initiation of the study drug and then followed up at 5-month intervals or until the end point was reached (need for levodopa therapy). The study was able to demonstrate that selegiline treatment is capable to significantly delay the need for levodopa, since selegiline-treated patients reached the end point about 237 days later than placebo-treated individuals. When study participants were assessed for symptomatic effects one month after the start of study treatment, there were no significant differences in the outcome on the activities of daily living (ADL) and on motor disability as measured by part 3 of the Unified Parkinson's Disease Rating Scale (UPDRS) between placebo and selegiline treatment in the corresponding scores (Table 1). However, comparison of annualized rates of disease progression showed significant benefits in ADL and motor disability for selegiline treated patients in comparison to the placebo group.

A similar study was conducted in Finland, where Myllylä et al. investigated the efficacy and safety of selegiline in 54 patients with early PD, who were randomized to treatment with placebo or selegiline 5 mg twice a day [17]. The endpoint of the study was again the need for levodopa, whereas motor disability and ADL were measured with the Columbia University Rating Scale (CURS) and the Northwestern University Disability Scale (NUDS), respectively. The Finnish study confirmed that selegiline treatment is capable to significantly delay the need for supplementary levodopa treatment. In comparison to individuals in the placebo group, selegiline treated patients had a significantly better outcome on the CURS and the NUDS for up to one year after the initiation of the treatment.

The largest clinical trial into selegiline effects in early PD was the Deprenyl And Tocopherol Antioxidative Therapy Of Parkinsonism (DATATOP) study [18], in which 800 untreated patients with early PD were randomized into four groups: (1) tocopherol placebo and selegiline placebo, (2) 2000 IU tocopherol per day and selegiline placebo, (3) tocopherol placebo and 10 mg selegiline per day and (4) 2000 IU tocopherol and 10 mg selegiline per day. Primarily designed to investigate putative disease-modifying effects of α-tocopherol, the biologically active component of vitamin E, and selegiline in early PD, the primary endpoint of this trial was the onset of disability prompting the clinical decision to begin administering levodopa. Study participants were evaluated with the UPDRS at baseline and reevaluated 1 month and 3 months after randomization and approximately every 3 months thereafter, for a planned maximum of 24 months of follow-up. While there was no beneficial effect of tocopherol in comparison to placebo, selegiline treatment significantly delayed the onset of disability requiring levodopa therapy by about nine months [18]. During the initial three months of treatment, selegiline moreover led to a significant symptomatic effect on ADL, motor disability and the total UPDRS score in comparison to the placebo treatment (Table 1). These advantageous effects were also apparent when the authors analyzed the average annual rates of decline in the UPDRS ratings in all four groups.

The French Selegiline Multicenter Trial investigated whether disability of *de novo* PD patients could be improved by monotherapy with selegiline during the first 3 months [19]. In this double-blind, randomized, placebo-controlled clinical trial 93 patients with previously untreated PD were randomized to placebo or 5 mg selegiline twice daily and followed up with examinations at 1, 2 and 3 months with various clinical scales. In comparison to placebo treatment, selegiline treatment within 3 months led to a significant improvement of mood, motor disability and of the total UPDRS score, whereas ADL and other global scores remained unchanged (Table 1). The authors have argued that ADL and global scores may not be as sensitive as other scales to assess the small improvements caused by selegiline treatment [19].

Results of another randomized, placebo-controlled, double-blind, parallel trial investigating the efficacy of selegiline as monotherapy in early PD were reported by the Swedish Parkinson Group in 1998 [20]. In this study, 157 *de novo* PD patients were randomized to receive either 10 mg selegiline or matching placebo once in the morning and were investigated at baseline and 6 weeks, 3 months and 6 months after treatment and at 6-month intervals thereafter. The primary efficacy variable was the time until the initiation of levodopa therapy became necessary, whereas secondary efficacy variables included the UPDRS, Schwab and England Activities of Daily Living, Hoehn and Yahr staging, Visual Analogue Scale for the assessment of tremor and motor function, Mini-Mental State Examination and the Hamilton Depression Scale. The median time from inclusion until time to the need for additional levodopa therapy was 12.7 months in the selegiline group and 8.6 months in the placebo group, demonstrating that treatment with selegiline was capable to significantly delay the need for levodopa therapy. At the first assessment after 6 weeks, selegiline treatment showed a significant benefit on ADL, motor disability and total UPDRS score in comparison to placebo, which was still apparent after 3 months of treatment except for the ADL (Table 1). Comparison of the semiannual rates of disease progression showed a significant advantage for selegiline treatment on motor disability and the total UPDRS, which however could not be confirmed after 12 months, possibly due to the low number of patients reaching this time point [20].