Ch. 4: Movement Disorders

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Parkinson’s Disease and DOPA


**Background:** At the time of the writing of this article, it was known that Parkinson’s disease consisted of a biochemical abnormality defined as a decrease of melanin pigment in the substantia nigra and a decrease of some biogenic amines in the substantia nigra and corpus striatum. It was hypothesized that these two abnormalities may be related given that in both melanocytes and sympathetic cells there exists a common precursor in the synthesis of melanin and catecholamine: tyrosine is hydroxylated to dihydroxyphenylalanine (D.L-DOPA) as well as the fact that both types of cells originate from the neural crest. Melanocyte-stimulating hormone was initially investigated with the hope that as it was observed to increase melanin deposition in melanocytes in the skin, a similar effect would be seen in the pigmented cells of the brain. (Also, in animal studies in the spinal cord of the cat, the peptide increased the amplitude of evoked monosynaptic potentials.) However, administration of MSH reversibly worsened the Parkinsonian state; investigators postulated that the hormone was shifting DOPA from the brain to the skin. Therefore, they set out to investigate the potential therapeutic potential of D,L-DOPA.

**Methods:** Seventeen patients with Parkinsonism were entered into the study along with three controls. All had been tried on ‘standard medications’ prior to this trial and 2 had cryopallidectomy. Melanocyte-stimulating hormone was administered intramuscularly. D,L-DOPA was administered in doses of 100, 200 or 500 mg in capsules. The patients were studied as inpatients for several to many months.

**Results:** MSH was given to 6 patients in addition to D,L-DOPA. All patients initially had abdominal cramps and diarrhea, which resolved in all but one subject after a few days. The subjects experienced increased pigmentation of the skin, particularly of the face and arms. Progressive increments of MSH administration induced increased manifestation of Parkinsonism (increased tremor, worsened strength, posture, gait and movements). In repeated trials of D,L-DOPA 8 of the 16 patients showed either complete, sustained disappearance or marked improvement of their Parkinsonian symptoms. The dose required for improvement was thought to be possibly a function of body mass. Clinical improvement in symptoms was observed in the following order: rigidity followed by tremor. Side effects that were observed included euphoria with exaggerated facial expression, intermittent athetoid movements, and gesticulation, these effects were reversible. One subject became pale, apathetic and immobile and D,L-DOPA was discontinued (likely a result of orthostasis). The control patients had no effect of D,L-DOPA – mental or physical. Athetoid movements were only observed in those with PD. Some receiving D,L-DOPA developed a granulocytopenia and had morphological changes in the bone marrow (increased vacuoles).

**Take home points:**

- D,L-DOPA provided a sustained beneficial effect.
- MSH was observed to worsen the parkinsonian state.
- D,L-DOPA provided relief of rigidity and tremor with incremental administration of the drug.
- Transient granulocytopenia was a side effect along with vacuolization of immature cells
- Reversible athetoid movements were caused only in patients with PD when a therapeutic effect was observed
- D,L-DOPA administration caused a temporary GI toxicity (abdominal cramps and nausea) that abated with time as well as faintness
- Improvement when D,L-DOPA was given was rapid (within 2-3 hours), though after withdrawal of D,L-DOPA, there was clinical improvement (over the baseline state) that persisted for 4-14 days
- Interestingly, oral-buccal dyskinesias were described in a patient – perhaps this patient actually had an atypical parkinsonian syndrome (like CGBD)


**Background:** This paper addressed the induction and maintenance of the therapeutic effects of dopamine. It was observed that the effective doses of DOPA were large and a large fraction of DOPA would become decarboxylated into dopamine (which would cause its effects in peripheral tissues as well as the brain). For that reason, the investigators sought to examine the effects of a peripheral decarboxylase inhibitor as well as further clarify the therapeutic effects of DOPA.

**Methods:** Twenty-eight patients with Parkinsonism were referred for study for several months and up to 2 years in the metabolic wards. L-DOPA was administered in capsules of 5, 10, 50, 100 and 500 mg. L-DOPA was administered according to the following protocol: 100 mg given three times a day and increased by 200 to 300 mg every 2-4 days. Increments were stopped when an optimum dose was reached (the dose bringing on maximum improvement with tolerable side effects), typically after 5-7 weeks. When involuntary movements, nausea or faintness resulted, or any toxicity was suspected, or a total of 8gm a day was reached, the increments were also stopped.

**Results:** Slowly increasing oral doses of L-DOPA induced improvement of parkinsonian symptoms in 28 patients which was modest (4 patients), moderate (4), marked (10), and dramatic (10) and sustained for up to 2 years. There was a time lag to improvement in symptoms in some. Symptoms responded typically in the following order: akinesia, rigidity, tremor. Mental effects included: improved memory, sleeplessness, nervousness, nausea and vomiting (avoided by gradual increases in doses). A peripheral dopamine decarboxylase inhibitor (alpha methyl dopa hydrazine) lowered the required dose of L-DOPA to produce therapeutic effect and avoided nausea and anorexia (in one case). Neurologic side effects observed were primarily of involuntary movements.

**Take home points:**
- Granulocytopenia was eliminated by substitution of L-DOPA.
- Several patients experienced the ‘awakening effect’ – improved memory.
- Necessary for treatment was the following: slow titration, sufficient dose, distribution of daily dose to fit the patient.
- L-DOPA resulted in lower doses, diminished toxicity and increasing the proportion of improved patients.
- A peripheral dopamine decarboxylase inhibitor lowered the required dose of L-DOPA.
Parkinson’s Disease and MAO-inhibitor


**Background:** Various oxidative mechanisms (and free radicals) were postulated to contribute to neuronal degeneration in the substantia nigra. Consequently, in 1987, a multicenter controlled clinical trial of a monoamine oxidase inhibitor (irreversible, type B) (deprenyl or Selegeline) and a free radical trapping vitamin E component (tocopherol) was initiated.

**Methods:** 800 patients with Stage 1 or 2 PD were randomly assigned to placebo, one of the active drugs (deprenyl or tocopherol) or both active drugs. Tocopherol was administered as 2000 IU per day and deprenyl was administered as 10 mg per day. The subjects were followed for 24 months of follow up at 3 month intervals. The primary end point was to be the decision to begin L-DOPA therapy.

**Results:** There was no benefit of tocopherol. Deprenyl (MAO-I) was beneficial after 12 months of treatment and significantly delayed the onset of disability requiring L-DOPA therapy (HR = 0.50, 95% CI 0.41-0.62, p < 0.001). The duration of time was 9 months (disability delayed by 9 months). Parkinson's disease clinical ratings improved after 3 months and there was a slower decline in total UPDRS scores in those taking deprenyl. Motor performance worsened after Deprenyl was withdrawn. Deprenyl treatment in PD patients, especially when they were also treated with L-DOPA, was associated with nausea, dizziness, confusion, hallucinations, insomnia and cardiovascular changes (arrhythmias) that are potentially related to active amphetamine metabolites. Deprenyl likely acts partly by symptomatic treatment of PD as well as a protective influence (though the latter was not confirmed by this trial).

**Take home points:**

- Deprenyl (10 mg/day) reduces the risk of disability requiring L-DOPA therapy by 50%.
- Deprenyl delays the onset of disability of early, untreated PD and therefore should be utilized as initial treatment of early PD.
- Deprenyl is well tolerated.


**Background:** DATATOP established that Deprenyl delays the need for levodopa in patients with early PD, but the long term benefits were unclear. This paper documented the second, independent randomization that was carried out in early 1993 for 368 subjects who required levodopa and consented to continuing deprenyl or placebo. This was a study of re-randomization of selegiline and placebo after the subjects had end-pointed and were on levodopa.

**Methods:** 368 subjects on levodopa therapy were randomized to continue deprenyl or change to placebo. The primary end point was the first development of wearing off, dyskinesias, or motor fluctuations. Subjects were followed at 3 month intervals for approximately 2 years.

**Results:** There was no difference between PD patients treated with levodopa and deprenyl compared to levodopa alone in reaching the primary end point. 34% of patients treated with deprenyl developed
dyskinesias (compared to 19% of controls). 16% of Deprenyl treated patients developed freezing of gait compared to 29% of controls.

**Take home points:**

- Selegiline was superior compared to placebo – they had slower motor decline (measured by UPDRS) and delay of freezing. (Subjects had access to unlimited open-label levodopa and still selegiline was effective.)
- Selegiline was superior compared to placebo when considering risk of motor fluctuations.
- PD subjects treated with selegiline and levodopa were more likely to develop dyskinesias than those treated with levodopa and placebo.
- One caveat – the subjects in this trial were selected on the basis of prior exposure in the DATATOP trial, perhaps identifying those that are
- Deprenyl had no adverse effect on mortality


**Background:** The purpose of the study was to examine the long-term effects of selegiline in monotherapy and combination with levodopa in early PD. It had been previously established that selegiline could be used as monotherapy in the early phase of disease, and as combination therapy with levodopa in the early and late phase of PD. Selegiline monotherapy was shown to slow progression of symptoms and delay levodopa therapy in double-blind, placebo-controlled trials. In early phase therapy, selegiline reduced the required dose of levodopa while maintaining/enhancing the efficacy of levodopa. In long term studies, selegeline delayed the time to wearing-off fluctuations. The current paper was a continuation of a previous trial looking at whether selegiline could delay levodopa therapy initiation by comparing subjects taking levodopa + selegiline to those taking levodopa alone (without re-randomization).

**Methods:** 157 untreated patients with PD were randomized in a double-blind, placebo-controlled study of 7 years duration. 140 patients received selegiline or placebo in addition to individualized levodopa therapy. There were three phases: a selegiline monotherapy phase, an 8-week washout phase, and a levodopa-selegiline combination phase. Monotherapy with selegiline continued until the patient was at a level of disability requiring levodopa treatment. At that point, experimental treatments were withdrawn for 8 weeks. Then, either selegiline or placebo was restarted in addition to levodopa therapy. The two end points were: time until the occurrence of fluctuations in disability (wearing off) and progression of clinical disability (measured by the UPDRS, modified Hoehn and Yahr, and visual analog scale).

**Results:** There was no difference in the percentage of patients reaching the termination point. The percentage of fluctuation patients tended to be higher in the placebo group compared to the selegeline groups (34% vs. 20%, p =0.053). There was no difference in incidence of dyskinesia or time to onset of dyskinesia between the two groups. Selegiline slowed the progression of disease disability as measured by the UPDRS total score (or by motor or ADL scores). Specifically, those treated with selegiline had better mean scores for tremor, bradykinesia and rigidity. Patients treated with placebo required higher doses of levodopa than patients treated with selegeline. After 5 years, the mean dose of levodopa was 19% higher with placebo than with selegiline. There was a trend for selegiline to delay the start of wearing-off fluctuations (HR 0.55, p=0.08).
Take home points:

- Selegiline delays the progression of the signs and symptoms of PD.
- In monotherapy, selegiline slows progression of symptoms and delays time to initiation of levodopa therapy.
- In combination with levodopa, selegiline offers better symptom control, slower progression of symptoms, and lower doses of levodopa required for clinical efficacy.
- Selegiline treated patients have a lower frequency of fluctuations as well as a delay to the start of fluctuations.
- There are benefits of selegiline as both monotherapy and in combination with levodopa; selegiline was superior to placebo despite open-label levodopa when looking at ON scores.


Background: Neuroprotective therapies remain an unmet need in PD. Delayed-start trial designs were introduced to address this issue. In phase 1, subjects are randomly assigned to active drug or placebo, at the end of this phase, differences between the two groups could be related to effects on symptoms, disease-modifying effects or both. In phase 2, both groups are treated with active drug. At the end of this phase, persistent differences should represent disease-modifying effect.

Methods: This was a double-blind placebo-controlled multi-center trial conducted over 18-months using a delayed-start design. 1176 subjects with untreated PD were assigned to receive rasagiline (1mg or 2mg per day) for 72 weeks (early-start group) or placebo for 36 weeks followed by rasagiline (1mg or 2mg) for 36 weeks (delayed-start group). A positive result with either dose required meeting the following end points: superior to placebo in rate of change in UPDRS between weeks 12 and 36, superior to delayed-start in the change of score between baseline and week 72, and noninferiority to delayed-start treatment in the rate of change in the score between weeks 48 and 72.

Results: Early-start treatment with rasagiline at a dose of 1mg met all end points: smaller mean rate of worsening in the UPDRS between weeks 12 and 36, less worsening in the score between baseline and week 72, and noninferiority to delayed-start treatment in the rate of change in UPDRS between weeks 48 and 72.

Take home points:

- Early treatment with rasagiline at a dose of 1mg per day provided benefits consistent with possible disease-modifying effect.
- Early treatment with rasagiline at a dose of 2mg did not meet the end points.
- Given results with different doses, this was a controversial trial and results should be interpreted with caution.

Parkinson’s Disease and Dopamine Agonists

**Background:** The best way to initiate dopaminergic therapy for early Parkinson disease was still unclear. The PSG sought to compare initial treatment with pramipexole (a nonergot dopamine agonist) with levodopa in early PD.

**Methods:** This trial took place from 1996-2001. It was a multicenter double-blind randomized controlled trial with 301 patients with early PD who required dopaminergic therapy (to treat disability). Subjects were assigned to pramipexole (+ levodopa placebo) or Sinemet (+ pramipexole placebo) with dosage escalation taking place over 10 weeks. All subjects initially were escalated to a daily dosage of 1.5 mg of pramipexole or 75/300 mg of Sinemet. If subjects required additional therapy, they could escalate further. Following, investigators could add open-label levodopa or other antiparkinsonian medications to treat disability. The main outcome measure was the time to dopaminergic complications, changes in the UPDRS and quality of life scales, and adverse events.

**Results:** 52% of subjects assigned to pramipexole treatment reached the primary end point of developing dyskinesias, wearing off, or on-off fluctuations compared with 74% of the levodopa group (HR, 0.48, 95% CI, 0.35-0.66, P<0.001). Initial pramipexole treatment resulted in a reduction in the risk of developing dyskinesias (24.5% vs. 54%, HR 0.37, 95% CI, 0.25-0.56, p<0.001) and wearing off (47% vs. 62.7%, HR, 0.68, 95% CI, 0.49-0.63, p=0.02). Pramipexole tended to be particularly effective in risk reduction of dyskinesia among subjects with Hoehn and Yahr scores less than 2. Initial levodopa treatment resulted in reduction in the risk of freezing (25.3% vs. 37.1%, HR, 1.7, 95% CI, 1.11-2.59, p=0.01). By 48 months, disabling dyskinesias were uncommon and did not differ between the 2 groups. The mean improvement in the total UPDRS score was greater in the levodopa group. Somnolence and edema was more common in pramipexole treated subjects. Quality of life scores did not differ between the groups. A subset of the cohort (82 subjects), patients treated with pramipexole demonstrated 40% lower rate of loss of striatal I-beta-CIT uptake (marker of dopamine transporter receptor) compared to those treated with levodopa.

**Take home points:**

- Initial treatment with pramipexole -> lower incidences of dyskinesias and wearing off (compared to L-DOPA) and higher incidences of somnolence and edema.
- Initial treatment with L-DOPA -> lower incidences of freezing, as well as improved symptomatic control (by UPDRS).
- Initial dopaminergic treatment can reasonably be pramipexole or levodopa – they are associated with different efficacy and side effect profiles.
- This study does not take into account cost effectiveness (dopamine agonists are more expensive than Sinemet).


**Background:** A previous publication of a 5-year trial of ropinirole and levodopa in early PD showed that ropinirole is associated with reduced incidence of dyskinesias, supporting the principle of initial treatment of PD with dopamine agonists. This analysis was done post hoc to determine if this benefit (dyskinesia sparing) of ropinirole is lost when levodopa is added to the regimen.

**Methods:** This was a 5-year, prospective, randomized, controlled study, comparing subjects treated with initial ropinirole or initial levodopa monotherapy. 268 patients were randomized – 179 to ropinirole, 89 to levodopa. Subsequently the patient could receive open-label levodopa supplementation. The main endpoint was incidence of dyskinesias.
Results: 20% of those in the ropinirole group and 45% of those in the levodopa group developed dyskinesias, (HR 2.56, 95% CI 1.64-4.00, p<0.001). The ropinirole group was more likely to receive open levodopa supplementation. Patients receiving levodopa had a significantly higher risk of dyskinesia compared to those taking ropinorole monotherapy (HR, 6.67, 95% CI 3.23-14.29, p<0.001). Age at baseline (younger age increasing the risk), baseline disease stage (greater stage increasing the risk), treatment in the UK and levodopa dose (higher dose increasing the risk) were significant predictors of time to develop dyskinesia. When patients on ropinorole monotherapy were treated with supplementary levodopa, the incidence of dyskinesia was not different from those previously being treated with levodopa though onset was delayed by 3 years. There is no subsequent rapid ‘catch up’ period of preventive effect.

Take home points:
- The risk of developing dyskinesias during initial ropinorole monotherapy is very low and delays the onset of dyskinesias possibly extending the ‘honeymoon period’.
- The risk of developing dyskinesias substantially changes when levodopa is added to initial ropinorole monotherapy.
- Once levodopa is initiated to those on initial ropinirole, there was NO evidence that the cumulative risk of developing subsequent dyskinesias catches up in the first years of follow-up.

Parkinson’s Disease and Dementia


Background: Parkinson’s disease is now recognized to be a disorder that has both motor and non-motor features. Though principally affecting the dopaminergic system resulting in bradykinesia, tremor and rigidity (which consequently tend to respond to dopaminergic therapy), PD has widespread involvement of the CNS with other features like autonomic failure, hypersomnolence, imbalance, dysarthria and dysphagia which do not respond to first line dopaminergic therapy. These non-motor features as well as dementia often cause the most concern as the disease progresses and were recognized in James Parkinson’s initial Essay on the Shaking Palsy. Dementia prevalence is debated, anywhere from 10-80% in those with PD. As age of patient increases and with longer duration of disease, prevalence of dementia among PD patients increases as well. Young onset PD patients also have a high prevalence of dementia (19% after 18 years of disease duration).

Methods: A cohort of 149 community-dwelling newly diagnosed patients with PD were followed over the period of 20 years, beginning in 1984.

Results: 30 patients survived to be included in the 20-year follow-up. Dementia is present in 83% of 20-yr survivors. Dementia correlates with increasing age. Brain only postmortems were performed for 17 patients who died with dementia and 4 who died without dementia early in their course. All had brainstem Lewy body pathology consistent with the diagnosis of PD. Additional large vessel disease and hippocampal sclerosis were found. Limbic and or neocortical Lewy bodies were found in 8/17 of those with dementia.

Take home points:
- Dementia is very common among those with PD.
- Unless dementia is actively sought and excluded, it should not be assumed to be absent.
It is essential to perform serial brief regular assessments to detect cognitive decline.

The neuropathology of dementia in PD is heterogeneous.

**Parkinson’s Disease and Deep Brain Stimulation**


**Background:** Neurostimulation of the subthalamic nucleus is known to reduce levodopa-related motor complications (dyskinesias) and improve mobility in advance PD in open follow-up studies for up to 5 years.

**Methods:** This was a randomized-pairs trial conducted in Germany and Austria. Randomized pairs refers to the fact that one patient randomly assigned to neurostimulation would be followed by enrollment of another subject within 6 weeks to best medical treatment. 156 patients under 75 years of age with advanced PD and severe motor symptoms were enrolled. Those undergoing neurostimulation underwent bilateral stereotactic surgery targeting the subthalamic nucleus (Kineta, Medtronic devices were utilized). The primary end points were the changes from baseline to six months in quality of life, severity of symptoms without medication (measured by the UPDRS).

**Results:** Neurostimulation was superior to medication alone in terms of quality of life and severity of symptoms. Neurostimulation led to improvement in mobility, ADL, emotional well-being, stigma and discomfort. Serious adverse events were more common with neurostimulation when compared to medication alone (13% vs. 4%, p<0.04) and there was one case of fatal intracerebral hemorrhage. One patient committed suicide 5 months after randomization and one patient died from pneumonia 6 weeks after randomization. In the medication arm, one patient died in a motor vehicle accident because he was driving during a psychotic episode. Overall rates of adverse events was higher in the medication group (64% vs. 50%, p=0.08).

**Take home points:**
- Neurostimulation was superior to medication alone when considering severe motor complications and quality of life.

**Dystonia and Artane**


**Background:**

**Methods:** This was a prospective, double-blind crossover protocol. Thirty-one patients completed the protocol.

**Results:** Twenty-two (71%) had a clinically significant response. After a mean follow-up of 2.4 years, 68% of patients continued to take trihexyphenidyl, and 42% continued to show a considerable or dramatic benefit. The 30-mg dose used was generally well tolerated.

**Take home points:**
- High-dosage trihexyphenidyl therapy is effective in the management of torsion dystonia.