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Safety of Selegiline (Deprenyl) in the Treatment of Parkinson's Disease

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Abstract

Selegiline (deprenyl), a selective, irreversible inhibitor of monoamine oxidase type B (MAO-B) is widely used in the treatment of Parkinson's disease. As the first MAO-B inhibitor approved for the treatment of Parkinson's disease, concerns were raised about the safety of the drug based on the adverse effect profiles of older, nonselective MAO inhibitors. Unlike the nonselective MAO inhibitors, selegiline does not significantly potentiate tyramine-induced hypertension (the 'cheese effect') at the dosages (5 to 10mg daily) used for the treatment of Parkinson's disease. Selegiline has been well tolerated when given alone. The most frequent adverse events seen during monotherapy have been insomnia, nausea, benign cardiac arrhythmias, dizziness and headache. When combined with levodopa, selegiline can potentiate the typical adverse effects of levodopa, if the dose of levodopa is not reduced sufficiently. Thus, the most common adverse effects associated with this combination are nausea, dizziness, fatigue, constipation and insomnia. At the later stages of Parkinson's disease when fluctuations in disability occur, peak dose dyskinesias, psychiatric complications like hallucinations and insomnia, and orthostatic hypotension are further potentiated by selegiline. Mortality was recently reported to be increased when selegiline and levodopa were given together in comparison with treatment with levodopa alone, but a large meta-analysis of 5 long term studies and 4 separate studies did not support this conclusion. Selegiline seems to be generally well tolerated in combination with other drugs. However, when pethidine (meperidine) has been given to patients who are receiving selegiline therapy, severe adverse effects have been reported. Thus, the concomitant use of these drugs is not recommended. A low tyramine diet is recommended if selegiline is used together with nonselective MAO inhibitors or the selective, reversible MAO-A inhibitor, moclobemide. Several adverse

effects have been reported when fluoxetine and selegiline have been used together. A recent survey revealed that the incidence of a true serotonin syndrome is, however, very low with this combination. Concomitant use of selegiline and other selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs) like citalopram, which have generally less interactions than fluoxetine, seems to be well tolerated. Nevertheless, caution is advised when combining a SSRI or a tricyclic antidepressant and selegiline.

1. Clinical Experience

Selegiline (deprenyl), a selective, irreversible inhibitor of monoamine oxidase type B (MAO-B), is widely used in the treatment of Parkinson's disease. In Western Europe it was first registered in the UK in 1982, later in Germany and France and other European countries; in the US the drug was registered in 1989. Thus, there is over 10 years of clinical experience on the use of the drug in Parkinson's disease. In some centres, where early clinical studies were carried out in the 1960s and 1970s there is actually 20 years' experience of use of this drug. The aim of this article is to review the available data on the safety of selegiline in the treatment of Parkinson's disease, both when used alone in the early phase of the disease and in combination with levodopa in more advanced stages of the disease. The article will also review the issue of mortality, as the matter was brought up by a recent study.[1,2]

2. Selegiline (Deprenyl) Monotherapy

From the time of the seminal findings that selegiline could prevent parkinsonism caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)[3,4] many clinical studies were initiated to investigate the efficacy of the drug as monotherapy, especially studying whether the drug would slow down the progression of the disease.

In the literature we found 16 clinical studies where selegiline had been investigated as monotherapy in the early phase of Parkinson's disease (table I).[5-20] The duration of treatment varied from 1 month to a number of years. Altogether, 919 patients received selegiline in these studies. Some investigators reported data from patients who had been receiving selegiline monotherapy for up to 60 months.[5] There were 8 double-blind, placebo controlled studies, of which 4 long term studies[6-10] had a similar design: the end-point was the need to start levodopa therapy. The largest study, the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) study[7] included 800 patients who were randomised to receive either selegiline, tocopherol (vitamin E), the combination of these 2 drugs or placebo. The study showed clearly that the progression of symptoms of Parkinson's disease was significantly slowed down and the need to start levodopa therapy could be delayed significantly with selegiline. Similar results were shown earlier by Myllylä et al.[21] and Tetrud and Langston,[6] and later confirmed by a Swedish multicentre study.[10] As the symptomatic effect was small in the study by Tetrud and Langston,[6] it was proposed that selegiline would have a bene-

Table I. Clinical studies on selegiline (deprenyl) monotherapy in the early phase of Parkinson's disease

Number of patients (selegiline/placebo)	Duration of treatment	Reference
Open studies		
30	6mo	11
22	7-84mo	12
5	4 wks	13
50	60mo	5
15	2mo	14
28	6-28mo	15
157	2mo	16
Double blind studies		
22/22	24mo	6
399/401	26mo	7,8
20/20	2mo	17
48/45	3mo	18
5/5	4 wks	19
27/25	4-44mo	9
10/10	6 wks	20
81/76	1-43mo	10

ficial effect on disease progression (as suggested by a vast number of animal studies where selegiline was shown to be protective also against other toxins besides MPTP such as DSP-4, 6-hydroxydopamine or AF64A).[22-24] Furthermore, selegiline showed neuronal rescue effects after a lesion-like axotomy, toxin or ischaemia.[25-27] Several studies have suggested that selegiline induces the release of nerve growth factors, anti-apoptotic proteins or enzymes that scavenge free radicals.[28-32] In the DATATOP study[8] and in the study by Myllylä et al.[21] there was, however, a significant symptomatic wash-in effect and a significant wash-out effect in the DATATOP study showing at least partial symptomatic effect. The question of neuroprotection remains, however, clinically unsolved as the presently available methods do not allow a clear separation of symptomatic and neuroprotective effects.

In all studies where selegiline has been used as monotherapy in the treatment of Parkinson's disease the drug has been well tolerated if it is compared with, for example, dopamine agonists. In the DATATOP study[8] the only adverse events that were more frequent in patients receiving either selegiline or a combination of selegiline and tocopherol were nausea (2% *vs* 0.02% in selegiline recipients and non-recipients of selegiline, respectively), musculoskeletal injuries (7.3% *vs* 2.7%) and benign cardiac arrhythmias (2% *vs* 0.2%). Aspartate aminotransferase levels were slightly higher in the selegiline group (7% *vs* 3.2%). When combining the adverse event data from the long term studies with more detailed data available from double-blind studies[6,9,10,18,33] the most common adverse events were insomnia, dizziness, nausea and headache (see table II). There were no statistically significant differences between the selegiline and placebo groups. In the DATATOP study[8] there were no significant differences in the occurrence of insomnia between the selegiline and placebo groups.

It has been suggested that insomnia and the alerting effect sometimes reported by the patients during selegiline treatment are associated with the levoamphetamine metabolites of the drug.[33] However, dopaminergic drugs like levodopa[34] and amantadine, reversible MAO-B inhibitors, such as lazabemide, which are not metabolised to levoamphetamine metabolites,[35] and antidepressant drugs can all cause insomnia. Thus, it is more likely that insomnia during selegiline treatment is associated with enhanced dopaminergic tone than with its levoamphetamine metabolites. According to electroencephalogram studies of patients with Parkinson's disease, selegiline does not seem to affect the structure of sleep in these patients, but may actually improve the quality of sleep.[36]

Table II. Tolerability of selegiline (deprenyl) as monotherapy in Parkinson's disease. The most common adverse events reported in double-blind studies where detailed information was available[6,9,10,18]

Adverse event	Number of patients (%)	
	selegiline (n = 183)	placebo (n = 173)
Insomnia	20 (10.9)	12 (6.9)
Dizziness	17 (9.3)	10 (5.8)
Nausea	11 (6.0)	15 (8.7)
Headache	10 (5.5)	14 (8.1)
Fatigue	3 (1.6)	7 (4.0)
Dry mouth	3 (1.6)	4 (2.3)
Anxiety	1 (0.5)	7 (4.0)

Another way to delay initiation of levodopa is to combine selegiline and a dopamine agonist. There are, however, very few studies using this combination in the early phase of Parkinson's disease.[37,38] One study showed that the dose of lisuride could be reduced by combining it with selegiline.[37] The combination of lisuride and selegiline was well tolerated.

3. Early Combination of Selegiline and Levodopa

We have recently written a comprehensive review on the efficacy of selegiline in combination with levodopa in various stages of Parkinson's disease.[39] There were 10 open and 8 double-blind studies of the early combination of selegiline and levodopa. In these studies levodopa was either added to the pre-existing selegiline monotherapy or the placebo group when the severity of symp-

toms so warranted or therapy was initially started with the combination of levodopa and selegiline (or placebo). In all these studies the dose of levodopa could be maintained at a significantly lower level without compromising the clinical efficacy of levodopa in patients receiving selegiline compared with those not receiving selegiline. In two double-blind studies[40,41] there was a tendency for the time that fluctuations in disability occurred to be delayed in the selegiline groups compared with placebo groups, although the differences did not reach statistical significance. In two open studies,[42,43] one of which was retrospective,[42] no such tendencies were reported. As the progression of the disease was compensated for by increasing the daily levodopa dose and administration frequency, no differences were seen in clinical disability in any of the studies. In the Sinemet-Deprenyl-Parlodel (SINDEPAR) study,[44] patients were randomised to receive either levodopa or bromocriptine in combination with either selegiline or placebo.[44] The patients received these medications for 12 months. This was followed by a wash-out period of 2 months when they did not receive either selegiline or placebo. After this wash-out period, all antiparkinsonian medication was stopped for 1 week. The disability of those patients who had not received selegiline progressed significantly faster than that of patients who had received selegiline. This study suggests that selegiline could slow down the progression of Parkinson's disease when it is given together with levodopa or a dopamine agonist.

In general, the combination of selegiline and levodopa seems to be relatively well tolerated. Combining the available safety data from 2 double-blind studies,[40,41] the most common adverse events seen with the combination were nausea, dizziness, fatigue, constipation and insomnia (table III). These adverse events were also common in patients receiving levodopa plus placebo and no significant differences in incidences of these adverse events were seen between either patient group. There were, however, more withdrawals because of adverse events in the selegiline plus levodopa group than in the levodopa plus placebo group in 1 of the studies.[40] Most of these adverse events causing withdrawals were hallucinations. Cases have been described in the literature where psychiatric adverse events like hypomania or paranoia have persisted even after a considerable reduction in the levodopa dose with continued selegiline treatment.[45-47] In these cases it has been suggested that treatment should be discontinued and slowly reintroduced, starting with 2.5mg of selegiline daily and increasing the dose up to 10mg daily over a period of 10 to 15 days.

The incidence of orthostatic hypotension did not differ significantly between the selegiline plus levodopa groups and the levodopa plus placebo groups in the 2 studies when orthostatic hypotension was measured by the conventional method of having the patient first lie down for 5 minutes and then stand up. However, when the tilt table test was used the mean values for blood pressure became significantly lower in the selegiline group over the 5 years of follow-up.[48] Selegiline also diminished the heart rate responses to normal breathing and Valsalva manoeuvre, but did not affect heart rate response to deep breathing in the same study. The authors concluded that selegiline might have a sympatholytic effect similar to that induced by β-

Table III. The most common adverse events with the combination of selegiline (deprenyl) plus levodopa or placebo plus levodopa[40,41]

Adverse event	Number of patients	
	selegiline + levodopa (n = 96)	placebo + levodopa (n = 102)
Vertigo/dizziness	20	22
Nausea	18	13
Insomnia	17	16
Fatigue	17	15
Depression	13	19
Constipation	13	15
Orthostatic hypotension	11	11
Dry mouth	9	11
Sweating	8	9
Hallucinations	8	3
Musculoskeletal system disorders	6	12
Palpitations	4	4

blockers. The heart rate tended to be higher in the selegiline group, possibly as a compensation for the subclinical orthostatic hypotension.[40] Hypotension is a usual symptom in Parkinson's disease especially in patients with autonomic dysfunction,[49] and is a common adverse effect of levodopa,[34,50] dopamine agonists,[51,52] MAO inhibitors and tricyclic antidepressants.[53] Pargyline, an irreversible MAO inhibitor which is chemically very similar to selegiline, has been used as a medication for hypertension.[54] Thus, the orthostatic hypotension caused by selegiline is likely to be partly caused by inhibition of MAO-B and partly caused by potentiation of the effect of levodopa. If patients have orthostatic symptoms already before starting selegiline, it is probable that the hypotension will get worse when selegiline is added to their treatment regimen.

4. Selegiline in Combination with Levodopa in Fluctuating Parkinson's Disease

There is a multitude of clinical studies assessing the efficacy and safety of selegiline in patients with fluctuations in disability in later stages of Parkinson's disease. In our recent review,[39] we found 42 studies including 14 open short term (≤ 6 months), 12 open long term (over 6 months) and 16 double-blind, placebo controlled studies.[39] In these studies selegiline was added to an existing levodopa regimen. In most of these studies the addition of selegiline alleviated the main symptoms of the disease, i.e. tremor, rigidity and bradykinesia. Also, the severity and frequency of motor fluctuations, especially of end-of-dose type fluctuations could be reduced. In some studies where the reduction in levodopa dose was the main efficacy criteria, the reduction in levodopa dose was significantly greater in the selegiline group than in the placebo group.[55-57]

The most common adverse events in patients with fluctuating Parkinson's disease who were receiving combined treatment with levodopa and selegiline were an increase of dyskinesias followed by nausea, dizziness, confusion, orthostatic hypotension, vivid dreams and insomnia (see table IV).[58] These adverse events are dopaminergic, and there are usually no significant increase in their incidence if the levodopa dose has been adjusted properly.[59] In 1 study, comparing the addition of selegiline or bromocriptine to the regimens of patients already receiving levodopa, selegiline appeared to be better tolerated than bromocriptine in the treatment of patients with fluctuating disease.[60]

Activation of a pre-existing gastric ulcer[61,62] and urinary disturbances[63] have been reported in some patients who had selegiline added to their levodopa regimen. Laboratory values for haematological parameters and liver and renal function tests have been followed in many clinical studies that have assessed the combination of selegiline and levodopa[40,41,64-68] and these values have usually remained within normal limits. In some studies, slight increases in serum liver enzyme levels (up to 3 times the normal limits in some patients) have been reported with combined levodopa and seleigiline therapy,[69] but usually the values have been well within the normal range of the reference population. Hyperglycaemia has been reported in only a few patients during selegiline treatment.[67] On the other hand, hypoglycaemia has also been reported,[70] but the prevalence of hyper- or hypoglycaemia during selegiline treatment would seem to be low in clinical studies and few adverse event reports of hyper- or hypoglycaemia have

Table IV. The most common adverse events of the selegiline (deprenyl) and levodopa combination. Summary of data from 21 clinical studies (n = 971 patients; most of whom had fluctuations in disability)[58]

Adverse events	Number of patients (%)
Increased dyskinesias	119 (12.2)
Nausea	64 (6.6)
Dizziness	48 (4.9)
Confusion	38 (3.9)
Hypotension	35 (3.6)
Insomnia, vivid dreams	33 (3.4)
Anxiety	33 (3.4)
Hallucinations	30 (3.1)
Dry mouth	26 (2.7)

been received by the manufacturer.[58] Selegiline may aggravate pre-existing cardiac arrhythmias,[71] but generally cardiac arrhythmias do not seem to be more frequent in patients receiving the combination of levodopa and selegiline than in patients receiving levodopa alone.

The combination of selegiline and dopamine agonists is relatively well tolerated by patients in the later stages of Parkinson's disease. However, selegiline may potentiate the adverse reactions of some dopamine agonists, e.g. piribedil, if the dosage of the dopaminergic medication is not reduced sufficiently.[72] Because selegiline is metabolised to levomethamphetamine (l-MA) and levoamphetamine (l-A),[73] during the early days of the agent's development there was concern that addiction might occur with selegiline use. The preclinical findings, however, show that l-A is clearly a less potent CNS stimulant than the corresponding dextroform.[74,75] In clinical trials there have been no signs of addiction during selegiline treatment or withdrawal effects after treatment discontinuation.

5. Selegiline and Mortality

A report by Lees et al.[1] suggested that combined therapy with levodopa and selegiline was associated with increased mortality compared with treatment with levodopa alone. They reported that after 5.6 years of treatment, approximately 28% patients treated with selegiline and levodopa had died compared with 17% of patients treated with levodopa alone. The risk ratio was 1.57 [95% confidence intervals (CI) 1.09 to 2.3, $p = 0.015$]. These results contrast with the results of a meta-analysis of 5 long term, randomised studies, where the mortality rate was found to be 4.7% (14/297 patients) in patients treated with levodopa and selegiline and 5.8% (17/292) in patients treated with levodopa.[76] The risk ratio was 1.05 (95% CI 0.46 to 2.43, $p = 0.91$) and the ratio adjusted to baseline factors (age, gender and severity of disease was 0.90 (95% CI 0.38 to 2.17, $p = 0.82$).

Additional studies did not find an increase in mortality rate associated with selegiline use either. In an Italian multicentre study, 475 patients with early Parkinson's disease were randomised to receive levodopa, selegiline or a dopamine agonist.[77] Levodopa was added to the 2 latter groups when clinically necessary. There was no difference in the mortality rates between the 3 groups after 5 years of follow-up. Di Rocco et al.[78] analysed retrospectively 176 patients treated with either levodopa or the combination of selegiline and levodopa. Again, there were no differences in mortality between the 2 groups. The Parkinson Study Group analysed mortality in the patient population of the DATATOP[79] study, when the majority of patients were receiving levodopa with or without selegiline. After a follow-up time of 8.2 years, there were no significant differences between those treated with or without selegiline; the overall mortality was 17.1%. Furthermore, Fuell et al.[80] analysed the database of clinical studies carried out with ropinirole, a novel dopamine agonist. Among 2164 patients treated with ropinirole there were less deaths in patients taking selegiline than in patients not taking selegiline. On the other hand, these studies could not confirm the finding of Birkmeyer et al.[81] that selegiline enhanced survival when given together with levodopa.

The group of Lees et al.[1] recently published a follow-up report of their study[2] with a mean follow-up time of 6.8 years. There was no significant difference in mortality rate between the levodopa and levodopa plus selegiline groups in terms of patients who had died since the last interim analysis was performed and the risk ratio was 1.05. Neither were there differences between the groups in terms of mortality in those patients who had been randomised from the bromocriptine group to either levodopa or the combination group. Analysis of mortality in those patients who had actually received the randomised treatment (on-treatment analysis) did not reveal any significant increase in mortality rate. Only when all patients were included in the analysis (without making any correction for multiple interim analysis) was the increase in mortality rate significant, but the risk ratio (adjusted for baseline factors) had decreased since the previous analyses to 1.30 (95% CI 0.99 to 1.72).

We believe that something particular must have happened at around 2.5 years into the study as the mortality curves of the 2 groups before and after this point are parallel.[2]

One of the problems with the study was the fact that the patients were allowed to be rerandomised to another group after the original randomisation. In addition, a large proportion of patients were switched from one group to another during the study because of withdrawal from treatment, etc. The analysis of patients' survival was, however, based on the original randomisation of the patients, although the investigators did not often know what medication the patients had been taking before death. Information on death was based on patient records flagged from the UK National Health Service Central Register, not on the information obtained from the investigators. These problems in design and lack of individual patient data may explain the differences in the survival data between the study of Lees et al.[1] and the other long term studies. It also reflects the difficulties in undertaking reliable survival studies in a disease which is progressive, where medication may change many times during the course of the disease and other concurrent diseases may appear.

Churchyard et al.[82] suggested later that selegiline could be cardiotoxic after finding that the drug caused orthostatic hypotension in a tilt test. This study was not randomised, there was an unequal number of patients in the 2 groups (9 in the levodopa group and 16 in the selegiline plus levodopa group) and the patients were selected for participation. As noted in section 3, selegiline may cause orthostatic hypotension,[48] in the same way as other dopaminergic agents,[53] but this does not mean that the drug is cardiotoxic.

6. Interactions with Other Compounds

Only a few interactions between selegiline and other drugs have been described. In the early days of the development of selegiline, one of the most important questions needed to be investigated was whether selegiline would cause the so called 'cheese effect', which is related to ingestion of tyramine. Tyramine is an indirectly acting sympathomimetic amine which evokes its pharmacological action by releasing intraneuronal noradrenaline (norepinephrine).[83] It is normally rapidly metabolised by MAO-A or -B and dopamine-β-hydroxylase. Tyramine is present in relatively large quantities (200 to 1000 mg/kg) in fermented and aged food like cheese, salami and yeast extracts.[84] When the nonselective MAO inhibitors were used for the treatment of depression the patients sometimes developed hypertensive periods as tyramine accumulated resulting in the release of excess amounts of noradrenaline.[85] Similarly, when nonselective MAO inhibitors and levodopa were combined, increases of blood pressure were reported.[86] In animal experiments it was shown that unlike, for example, clorgiline, the selective MAO-A inhibitor selegiline did not potentiate the effects of tyramine, but actually diminished them.[87] In humans, the 10 mg/day oral dose of selegiline that is usually used in the treatment of Parkinson's disease does not cause significant potentiation of tyramine sensitivity.[88-90] This is most likely because of the selectivity of inhibition caused by selegiline: MAO-B is inhibited almost totally, but MAO-A in, for example, the intestines and liver, is active and able to metabolise tyramine. The sensitivity factor for an increase in blood pressure after intravenous tyramine challenge was less after 10mg of selegiline than after 400mg of moclobemide, a reversible MAO-A inhibitor used for the treatment of depression.[91] Hypertension has been reported in very few patients receiving selegiline therapy and the causal relationship has not been very clear.[60]

However, at higher oral dosages (≥ 20 mg/day) selegiline starts to lose its selectivity and tyramine sensitivity is enhanced.[90] Therefore, when high dosages of selegiline are used, for example, in the treatment of depression or narcolepsy, a diet low in tyramine is recommended and, in this way, the high dosage is well tolerated.[92,93] In a study where selegiline 10 to 40 mg/day was given to 17 patients with narcolepsy, the most common adverse events were dry mouth, headache, insomnia, sweating, muscle twitching, dizziness, irritability, restless-

ness, tremor and visual disturbances.[92] If selegiline is combined with a selective, even reversible, MAO-A inhibitor, like moclobemide, potentiation of tyramine sensitivity has been described[91] as both types of MAO are inhibited. Although the combination has been reported to be well tolerated, a tyramine low diet is, nevertheless, advisable, as is the case if a reversible MAO-B inhibitor, like lazabemide, and moclobemide are combined.[94] On the contrary, severe orthostatic hypotension has been reported when selegiline and a nonselective MAO inhibitor have been combined.[95] With this combination there is again a risk of the cheese effect, especially as the inhibition of MAO-A is also irreversible.

Pethidine (mependine) is contraindicated in combination with MAO inhibitors because of reports of serious, sometimes fatal interactions. Although animal studies have shown no interaction between selegiline and pethidine,[96,97] agitation, delirium, irritability, hyperpyrexia, restlessness, rigidity, stupor and sweating were reported in one patient who was concomitantly taking selegiline, pethidine, a dopamine agonist and a noradrenaline uptake inhibitor.[98] In addition, various other serious, even lethal, adverse events, such as confusion, hyperthermia, tremor, hypertension, seizures and coma, have been reported when using selegiline together with pethidine.[99] The interaction between pethidine and MAO-inhibitors has been associated with elevation of hypothalamic serotonin (5-hydroxytryptamine; 5-HT) levels and is thus more likely to take place with MAO-A inhibitors, and especially if both forms of MAO are inhibited.[96] Although some inhibition of MAO-A activity takes place during selegiline therapy with 10 mg/day dosage, this is not enough to increase the brain serotonin levels as shown in a post mortem study.[100] Inhibition of *N*-demethylation of pethidine has also been suggested to account for the interaction. However, the mechanism of the interaction is not well understood and the concomitant use of selegiline and pethidine should be avoided.

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) widely used in the treatment of depression. A great number of interactions have been described with fluoxetine with various drugs possibly caused by competition at the level of metabolism. These drugs include tricyclic antidepressants (TCAs), nonselective MAO inhibitors, antipsychotics, benzodiazepines, carbamazepine, phenytoin, lithium, some β-blockers, antihistamines and opioids.[101-103] Some instances of an interaction between selegiline and fluoxetine have been described. The adverse effects seen have included agitation, ataxia, hypertension, mania, tachycardia, sweating and shivers.[47,58,104-106] Some instances of interactions between selegiline and other SSRIs, for example sertraline and paroxetine[58] have also been described. On the other hand, instances of successful concomitant use of selegiline and fluoxetine or other SSRIs without significant interactions have been reported.[107,108]

There have also been some reports of interactions when selegiline and TCAs have been given together.[58] The adverse events seen as a result of these interaction have included tremor, agitation, restlessness, hyper/hypotension, dizziness, seizures and changes in behavioural and mental status. In one case, hypertension was reported when selegiline was given together with maprotiline, levodopa, lisuride, theophylline and ephedrin.[109]

It has been suggested that the interaction between selegiline and SSRIs and TCAs would fall under the definition of 'serotonin syndrome', which according to Sternbach[110] should include at least 3 of the following: mental status changes (confusion, hypomania), agitation, myoclonus, hyper-reflexia, diaphoresis, shivering, tremor, diarrhoea, inco-ordination and fever. In addition, other causes have to be ruled out and an antipsychotic drug should not have been started or the dosage of one increased before the onset of the signs and symptoms. Richard et al.[111] investigated the occurrence of the serotonin syndrome among 4568 patients who were treated with the combination of selegiline and antidepressants. The frequency of a possible serotonin syndrome was extremely low (0.24%) and the frequency of serious symptoms was even lower (0.04%). They also analysed 48

cases reported to the US Food and Drug Administration (FDA) as a possible interactions between selegiline and antidepressants and only 2 cases satisfied the criteria of serotonin syndrome. Often the adverse events seen could be explained by the adverse event profile of either selegiline and levodopa or by the antidepressants. Thus, the symptoms were more likely to be a sum effect of the adverse effects of 2 drugs than a true interaction. On the other hand, serotonin syndrome fulfilling the Sternbach criteria has been described in a patient who received a combination of levodopa and bromocriptine, but not selegiline or an antidepressant.[112] Yu and Zweig[113] performed a retrospective analysis of patients who had been taking selegiline and an antidepressant drug. Of 11 patients treated with selegiline and an SSRI, 10 benefited from the combination; adverse events included increased tremor and hallucinations. Of 28 patients treated with selegiline and a TCA, 17 definitely and 6 possibly benefited from the combination. Adverse events were minor and included constipation, bodyweight gain, increased tremor, worsening of orthostatic hypotension and fluctuations in disability.

It is probable that many of the interactions between selegiline and fluoxetine and other drugs are caused by interference of metabolism of the drugs in the liver. Fluoxetine inhibits, at least to some degree, the cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2C19, CYP2D6, CYP2C9 and CYP3A3/4.[114] There are differences in the ability of various SSRIs to inhibit different P450 isoenzymes. Thus CYP2D6, for example, is inhibited, in order of potency, by paroxetine, norfluoxetine (a metabolite of fluoxetine), fluoxetine, sertraline, citalopram and fluvoxamine.[115] Fluoxetine has also been shown to be a weak competitive inhibitor of MAO-A, which may further contribute to interactions.

Laine et al.[116] performed a detailed interaction study on the combination of selegiline and citalopram. Healthy volunteers were randomised to receive either citalopram 20 mg/day or placebo for 14 days and selegiline was added to both groups from day 11 to 14. There were no pharmacodynamic or pharmacokinetic interactions between selegiline and citalopram. This is in line with the fact that there have been no interaction reports sent to the manufacturer (Orion Corporation) on this combination, although citalopram is a widely used antidepressant drug in Europe. Furthermore, there are some reports that fluoxetine might actually worsen the motor symptoms in Parkinson's disease or induce parkinsonian features in patients with concomitant depression possibly because of its antidopaminergic effects.[102,117,118]

Nevertheless, one should be cautious when combining selegiline with antidepressant drugs and the patient should be monitored carefully. When selecting the antidepressant, it is advisable to choose drugs that generally have shown to cause less interactions.

7. Conclusions

There is clinical experience with selegiline since the 1960s. Overall, the number of patients that have been involved in published clinical studies assessing the efficacy and safety of selegiline in the treatment of Parkinson's disease is over 4000. As monotherapy in the early phase of the disease, selegiline is well tolerated, adverse effects are mild and mostly dopaminergic. When combined with levodopa, the dopaminergic adverse effects (dizziness, dyskinesias, orthostatic hypotension, nausea, hallucination and insomnia) caused by levodopa may be potentiated by selegiline, but these adverse effects can usually be managed by reducing the dosage of levodopa. One recent study suggested an increase in mortality associated with the combination of selegiline and levodopa in comparison with treatment with levodopa alone, but 10 other studies did not support this finding. It is therefore probable that selegiline does not increase mortality and that the earlier findings were a result of problems in study design.[119]

In general, selegiline has been relatively well tolerated when given in combination with other drugs. The combination of pethidine and selegiline should, however, be avoided. Caution should be

taken when combining SSRIs or TCAs with selegiline, as some severe adverse effects have occurred with these combinations.

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