MAO-inhibitors in Parkinson's Disease

Peter Riederer[1]* and Gerd Laux[2]

[1]Clinic and Policlinic for Psychiatry, Psychosomatic and Psychotherapy,
University of Wuerzburg, 97080 Wuerzburg,
[2]Academic Hospital of Psychiatry, Psychosomatic Medicine, Psychotherapy and
Neurology, Gabersee, 83512 Wasserburg a. Inn, Germany

ABSTRACT

Monoamine oxidase inhibitors (MAO-I) belong to the earliest drugs tried in Parkinson's disease (PD). They have been used with or without levodopa (L-DOPA). Non-selective MAO-I due to their side-effect/adverse reaction profile, like tranylcypromine have limited use in the treatment of depression in PD, while selective, reversible MAO-A inhibitors are recommended due to their easier clinical handling. For the treatment of akinesia and motor fluctuations selective irreversible MAO-B inhibitors selegiline and rasagiline are recommended. They are safe and well tolerated at the recommended daily doses. Their main differences are related to (1) metabolism, (2) interaction with CYP-enzymes and (3) quantitative properties at the molecular biological/genetic level. Rasagiline is more potent in clinical practise and has a hypothesis driven more favourable side effect/adverse reaction profile due to its metabolism to aminoindan. Both selegiline and rasagiline have a neuroprotective and neurorestaurative potential. A head-to head clinical trial would be of utmost interest from both the clinical outcome and a hypothesis-driven point of view. Selegiline is available as tablet and melting tablet for PD and as transdermal selegiline for depression, while rasagiline is marketed as tablet for PD. In general, the clinical use of MAO-I nowadays is underestimated. There should be more efforts to evaluate their clinical potency as antidepressants and antidementive drugs in addition to the final proof of their disease-modifying potential. In line with this are recent innovative developments of MAO-I plus inhibition of acetylcholine esterase for Alzheimer's disease as well as combined MAO-I and iron chelation for PD.

Key words: selegiline, rasagiline, moclobemide, phenelzine, tranylcypromine

INTRODUCTION

Monoamine oxidase (MAO) is an important enzyme to metabolize *in vivo* endogenous and diet-derived biogenic amines via oxidative deamination. Major substrates are noradrenaline, adrenaline, dopamine, β-phenylethylamine (PEA) and serotonin. These substrates are underlying in the biochemical pathology of "depression" and Parkinson's disease (PD). The deficiency of serotonin, noradrenaline and dopamine builds-up the hypothesis of "depression" while a loss of dopamine, noradrenaline and serotonin is the biochemical basis of degenerative processes underlying PD. Therefore, supplementation of deficient biogenic amine neurotransmitters with 3,4-dihydroxy-

phenylalanin (L-DOPA) has been established as early as the late 50th and early 60th of the last century including the use of MAO-inhibitors. This class of psychopharmacological active compounds inhibits the break-down of biogenic amine neurotransmitters and thus increase their concentration in the synaptic cleft and at respective postsynaptic receptor sites. A mood elevating effect in patients with tuberculosis after treatment with iproniazid was first described by Kline (1958). In PD the first reports were published by Sano (1960; Foley et al., 2000) using iproniazid and pheniprazine alone or in combination with D,L-DOPA in a small number of patients, Degkwitz et al. (1960), who used iproniazid in combination with L-DOPA and in reserpin treated patients with schizophrenia and Birkmayer, Hornykiewicz and Bernheimer, who tried a variety of compounds like harmine, isocarboxazid and other MAO-I's (Bernheimer et al., 1961; Birkmayer and Hornykiewicz 1961; 1962; 1964) alone or in combination with L-DOPA in PD. The effects were mild or not existing when these MAO-I were given alone. However all theses early reports agree that MAO-I potentiated the effect of (D), L-DOPA but intensified also adverse reactions. Further examination and post mortem studies gave evidence that MAO-I given shortly before patients deaths were restoring the levels of noradrenaline and serotonin with no significant effect on the concentration of brain dopamine (Bernheimer et al., 1962; 1963). This data pointed to a combination therapy of L-DOPA and MAO-I already in the early 60th of the last century. An extensive description of detailed historical aspects of MAO and its inhibitors is given in the excellent overview on treatment strategies in PD by Foley (2001). A further break-through was the discovery of multiple forms of MAO, MAO-A and MAO-B, by Johnston (1968). MAO-A deaminates especially serotonin, noradrenaline and tyramine and is inhibited selectively at low concentrations (μM) of clorgyline while MAO-B is insensitive to clorgyline and in the human brain desaminates PEA and to a high degree dopamine (Glover et al., 1977). The first selective MAO-B-I was L-deprenyl (E-250, L-deprenyl, selegiline), synthezised by Zoltan Ecseri in 1962, patented as antidepressant in 1965, 1966 and developed by Jozsef Knoll as "psychic energizer (Knoll et al., 1965)." The combination of

selegilines selective MAO-B-I properties and the short-lasting stimulant effect of one of its metabolites, metamphetamine, (later proved to be also a reversible MAO-inhibitor see also Foley 2001 for details of such early developments) was indeed a concept to put forward new antidepressant agents (Varga and Tringer, 1967). Knoll mentioned in his 1965 publication that selegiline does not increase motility and lowers blood pressure in experimental animals. Using tyramine (a MAO-A and -B substrate) it became evident that selegiline antagonizes the socalled "cheese-effect" (increase of blood pressure noteable especially after consumption of larger amounts of cheese in patients treated with unselective or MAO-A-inhibitors) (Knoll and Magyar, 1972). As dopamine in rodent brain is s preferred MAO-A substrate an effect of MAO-inhibitors on motility (see above) has not been observed. PD, therefore, was not the focus for using MAO-B-I as therapeutic strategy. The suggestion in late 1974 for selegilines use in PD and especially in treating ON-OFF symptoms by one of use (PR) was based on (1) the early and in principle beneficial effects of MAO-I when combined with L-DOPA (see above), (2) the effects of selegiline in antagonizing the cheese-effect and (3) the possibility that dopamine in humans might well be a substrate for MAO-B. Convincing Moussa Youdim about using selegiline for a first trial in PD patients in PD he agreed to provide Walther Birkmayer and myself (P.R.) with some grams of selegiline that he had obtained from Josef Knoll. The trial was showing a beneficial effect in the symptomology of PD (Birkmayer et al., 1975; 1977; Foley, 2001; for historical notes see Riederer 2004; Youdim, 2006). Later (Birkmayer et al., 1983; 1985) we provided evidence for selegiline having neuroprotective action, a concept that is still followed and seems to be proven by the follow-up propargylaminoderivative rasagiline as shown recently in the ADAGIO-study (Olanow et al., 2008; 2009).

The innovating basic research and beneficial actions of selegiline in PD were responsible for intensive MAO-I drug developments for both PD and "depression". In this review we present the major compounds currently being used as well as an outlook of further such developments.

Table 1. Monoamine oxidase inhibitors

Drug	Metabolites	Trials in humans	Galenic forms
Selegiline	Desmethylselegiline p-Hydroxydesmethylselegiline Selegiline-N-oxide L-Amphetamin L-Metamphetamin p-Hydroxyamphetamine p-Hydroxymetamphetamine	AD, DEP, PD	Tablet, transdermal, melting tablet
Rasagiline	Aminoindan	PD	Tablet

As reviewed by Magyar et al., 2010; Weinreb et al., 2010; Naoi and Maruyama, 2010.

MAO-I in clinical practise

Monoamine oxidase (MAO) inhibitors (MAOIs) at present can be classified into 3 types:

- Older, irreversible nonselective agents such as phenelzine and tranylcypromine
- Irreversible, selective drugs (MAO-B-I's) such as selegiline and rasagiline
- Reversible, selective MAO-A inhibitors (RIMAs = reversible inhibitors of MAO-A) such as moclobemide (Overviews: Szelenyi 1993; Laux et al., 1995)

Overview of   MAOIs:

Iproniazid	Non-selective, irreversible
Isocarboxazid	Non-selective, irreversible
Moclobemide	MAO-A selective, reversible (RIMA)
Nialamide	Non-selective, irreversible
Pargyline	MAO-B selective, irreversible
Phenelzine	Non-selective, irreversible
Rasagiline	MAO-B selective, irreversible
Safrazine	Non-selective, irreversible
Selegiline	MAO-B selective, irreversible
Toloxatone	MAO-A selective, reversible (RIMA)
Tranylcypromine	Non-selective, irreversible

The clinical indications and efficacy of the MAOIs are established for disorders as follows:

- Parkinson's disease (PD)
- Depressive disorders
- Anxiety disorders (social phobia, panic disorder, PTSD)

Other potential therapeutic uses and indications can be smoking cessation, attention deficit hyper-activity disorder and cognitive deficits in dementia for moclobemide (Chan-Palay, 1992; Berlin et al., 1995).

INDICATIONS IN PARKINSON'S DISEASE

Treatment of motor symptoms

Both, **selegiline** and **rasagiline** (Table 1) are beneficial in treating motor symptoms in PD as monotherapy and in combination with L-DOPA and a decarboxylase inhibitor. Rasagiline is more effective in this regard as shown also in the daily dosis necessary for a symptomatic effect: $5 \sim 10$ mg/day selegiline, 1 mg/day rasagiline. Long-term trials with selegiline point to the fact that $30 \sim 40\%$ of the daily L-DOPA dosis can be spared when combined with the MAO-B-I (Szeleny, 1993; Lees et al., 1995; Myllylä et al., 1997). It is not far-fetched to assume, that PEA, which increases after selegiline treatment in brain tissue (Reynolds et al., 1978) and by this exerts dopamine release-promoting properties, contributes to dopamine's behavioural effects including improvement of motility (Foley, 2001; Gerlach et al., 2007; Riederer, 2009).

There is overwhelming evidence that selegiline has beneficial effects on motoricity and motorfluctuations as shown already in the first clinical trial (Birkmayer et al., 1975) and in follow-up clinical studies as summarized by Gerlach et al. (2007).

Rasagiline effects on motoricity are even stronger as shown by the TEMPO-(Parkinson Study Group, 2002; 2004), PRESTO- (Parkinson-Study-Group, 2005), LARGO- (Rascol et al., 2005) and ADAGIO- (Olanow et al., 2008; 2009) studies.

In all these and additional clinical studies (eg Rabey et al., 2000; Thebault et al., 2004; Rascol,

2005; Biglan et al., 2006; Siderowf and Stern, 2006) it could be shown that rasagiline is well tolerated, safe, improves motor symptoms, prevents motor complications in PD, has beneficial effects on quality of life parameters, is effective as mono-therapy or in adjunctions to L-DOPA-therapy, is beneficial in early and late stages of PD, is safe when combined with all other PD-relevant therapies including COMT-inhibitors and may have disease-modifying properties.

Neuroprotection and disease-modification

Selegiline and rasagiline are "suizide-inhibitors" which inhibit the enzyme irreversibly and for a rather long time. Therefore only newly synthesized enzyme will recover MAO activity sufficient to meta-bolize its substrates in an adequate amount. Positron-emission tomography (PET) studies have shown a biological half-life time (HLT) of MAO-B recovery after selegiline - (Fowler et al., 1994) or rasagiline-(Freedman et al., 2005) induced blockade of about $30 \sim 40$ days. As described earlier (Riederer and Lachenmayer, 2003; Gerlach et al., 2007) PET-studies are only in part suitable to detect the HLT of MAO-inhibitors as they only detect the distri-bution of radiolabeled inhibitor and its metabolites. In addition the exact kinetic properties underlying these PET-studies have been described only at random (Arnett et al., 1987). In contrast, measure-ment of PEA, the pure MAO-B substrate, in the urine of healthy individuals after selegiline dosing showed recovery (decline) of this amine concentration to normal values already $2 \sim 3$ days after withdrawal of selegiline (Clarke et al., 2001). Such data agree with other pharmacological studies as described by Riederer and Lachenmayer (2003) and point to the

Table 2. Nueroprotection in Parkinson's disease by selegline (prospective, randomized, double-blind, placebo-controlled studies)

Autuors (year)	Name of the study	N	Result
Tetrud and Langston (1989)	Pilot study for DATATOP	44	Endpoint (levodopa) Placebo 312.1 d Selegiline 548.9 d
Parkinson Study Group (1989a, b, 1993)	DATATOP	800	Endpoint (levodopa) After 12 months: Placebo 47% Selegiline 26%
Myllylä et al. (1992)	Finnish trial	47	Endpoint (levodopa) Placebo 372±28 d Selegiline 545±94 d
Allain et al. (1993)	French Selegiline multicenter trial	93	Endpoint (levodopa) After 3 months: Placebo 18.4% Selegiline 4.5%
Olanow et al. (1995)	SINDER	101	Deterioration in UPDRS between baseline and final visit (14 months) Placebo −5.8±1.4 points Selegiline −0.4±1.3 points
przuntek et al. (1999)	SELEDO	116	Primary end point: need for >50% increase in levodopa dose Placebo 2.6 years Selegiline 4.9 years
Larsen et al. (1997, 1999)		163	Patients treated with levodopa+selegiline developed markedly less severe parkinsonism (not statistically significant) and required lower doses of levodopa+placebo.
Myllylä et al. (1992)		52	Endpoint (levodopa) after two years Placebo 545±90 d Selegiline 372±28 d
Myllylä et al. (1997)		44	Levodopa dose (5 years): Placebo 725±78 mg/d Selegiline 405±59 mg/d

From Riederer and Lachenmayer 2003.

Table 3. Datatop follow-up-clinical studies

	N
Parkinson Study Group (1996a)	· 310 of originally 800
	· No levodopa necessary for the first 21±4 month
	· Patients remained blind regarding selegiline and tocopherol and received 10 mg selegiline per day
	189 on selegiline, earlier need for levodopa
	121 without selegiline, later need for levodopa
	Result: loss of selegilines efficacy?
Shoulson et al. (2002)	Patients of DATATOP with levodopa plus selegiline treatment for seven years were included
	Patients that received placebo after three to five years treatment with selegiline were included
	Results: improvement of ON-OFF fluctuations and motoricity in the selegiline's treated group
	Less dyskinesias in the placebo group

conclusion that the HLT of MAO-B recovery after irreversible inhibition by selegiline is about 7 days. According to Green et al. (1977) an 80% inhibition of MAO-isoenzymes is necessary to increase concentration of biogenic amines significantly. This means that newly synthesized enzyme in the range of 20 to 30% is sufficient to lose any symptomatic behavioural effect after withdrawal of any MAO-inhibitor. In line with this are studies by Youdim and Tipton (2002) who could not detect selegiline-induced stereotyped behaviour due to PEA increase 4 days after withdrawal of selegiline. At this time MAO-B recovery was already 20%. Taking these findings into account a wash-out phase of two weeks or after selegiline/rasagiline withdrawal is sufficient to avoid any symptomatic effect of these MAO-I's. Therefore, the interpretations of the DATATOP-study and other follow-up trials to demonstrate a "neuroprotective" effect have to be reconsidered. If so, a neuroprotective effect of selegiline cannot be excluded (Riederer and Lachenmayer, 2003; Gerlach et al., 2007). Table 2 (taken in part from Riederer and Lachenmayer 2003 with permission) illustrates the major outcomes of the most important clinical long-term trials with selegiline. While treatment of patients in an early phase of PD with selegiline shows sufficient results regarding motoricity and disease-modification the unconclusive results of the DATATOP-follow-up clinical trials may demonstrate a bias in severity of patients grouping as given in the first follow-up study (Parkinson Study Group, 1996a) or that the patients have non-response based on disease-progression and/or accompanying diseases (Table 3). As there were no final conclusions about the neuroprotective effect of selegiline the development

of more efficient clinical trial designs have been investigated including PET-controlled studies as shown with dopaminergic agonists. More recently the "delayed-start study design" has been developed as discussed by D'Agostino (2009). Rasagiline has been the first drug tested in such clinical trial. In fact the ADAGIO-study has given profound evidence for a disease-modifying effect of 1 mg/day rasagiline, while there was not such benefit at a 2 mg/day dosis (Table 4). Although - and in comparison to the negative outcome of a delayed-start-study with pramipexol (Schapira et al., 2009) - there is ample evidence for a significant disease-modification with low dosis rasagiline this clinical outcome has been questioned recently (Ahlskog and Uitti, 2010; Sampaio and Ferreira, 2010; Schwarzschild, 2010). Caslake et al. (2009) conclude in their Cochrane Database report: "MAO-B inhibitors are one option for the early treatment of PD although they have weaker symptomatic effects than levodopa and dopamine agonists. They may reduce the rate of motor fluctuations compared with initial levodopa therapy and may have fewer significant adverse effects than the older agonists but data are too few to provide reliable conclusions".

Neuroprotective, neurorestaurative and disease-modifying effects of selegiline and rasagiline are substantiated by in vitro-as well as in vivo experimental studies (Table 5). There is ample evidence that compounds attached to a propargylamino group induce molecular processes which act against cell death mechanisms like apoptosis, excitotoxicity and oxidative stress. These are non-MAO based mechanisms and they act not only on a functional level but rather on influencing gene expression and

Table 4. Summary of rasagiline clinical studies

Study	Design*	Duration	Rasagiline therapy	No. patients	Primary outcome	Principle secondary outcomes
Monotherapy for early Parkinson's disease (Hoehn &Yahr stage≤3)						
Stern et al. (2004) (Phase II)	Placebo-controlled	10 weeks	1, 2 or 4 mg/day	56	Safety and tolerability	UPDRS, CGI
Parkinson Study Group (2002) (TEMPO) (Phase III)	Placebo-controlled	6 months	1 or 2 mg/day	404	Efficacy (UPDRS-Total)	UPDRS subscales (Mental, ADL, motor)
Parkinson Study Group (2004) (TEMPO delayed-start, active-treatment phase) (Phase III)	Delayed-start (see adove row for initial 6 month placebo-controlled phase)	12 months	1 or 2 mg/day (12 months), or 2 mg/day after 6 months placebo	380	Efficacy (UPDRS-Total)	UPDRS subscales (Mental, ADL, motor)
Adjunct therapy for advanced Parkinson's disease (Hoehn & Yahr stage<5)						
Rabey et al. (2000) (Phase II)	Placebo-controlled	12 weeks	0.5, 1 or 2 mg/day	70	Safety and tolerability	UPDRS, CGI, levodopa dose
Parkinson Study Group (2005) (PRESTO) (Phase III)	Placebo-controlled	6 months	0.5 or 1 mg/day	472	Efficacy (Total daily OFF time)	CGI, UPRDS-ADL OFF, UPRDS-Motor ON, PD-QUALIF
Rascol et al. (2005) (LARGO) (Phase III)	Placebo-controlled plus an active comparator (entacapone 200 mg with each levodopa dose)	18 weeks	1 mg/day	687	Efficacy (total daily OFF time)	CGI, UPDRS-ADL OFF, UPDRS-Motor On

*All studies were randomised, multi-centre, parallel-group and double-blind.
ADL: activities of daily living, CGI: clinical global impressions scale, LARGO: lasting effect in adjunct therapy with rasagiline given once daily, OFF: poor symptom response, ON: good symptom reponse, PD-QUALIF: parkinson's disease quality of life, PRESTO: Parkinson's rasagiline efficacy and safety in the treatment of OFF, TEMPO: trial of etanercept and methotrexate with radiographic patient outcomes, UPDRS-ADL: unified parkinson's disease rating scale-activities of daily living. From Rascol 2005.

Table 5A. Actions of propargylamine derived MAO-B-I

Antagonise	MPTP, MPP$^+$, 6-OHDA
	DSP4
	AF64 A
	Excito toxins
	Ischemia
Antiapoptotic eg. Bcl-2 increase	
Prevention of mPT in isolated mitochondria	
Gene induction of Bcl-2, NFT's	
APP processing inhibition	
SEL RAS potentiate PEA behavioural response	

As reviewed by Magyar et al 2010, Weinreb et al 2010, Naoi and Maruyama 2010.

Table 5B. Non-MAO related actions of selegiline and rasagiline on molecular paramters *in vitro*

SEL	CNTF-, NGF-, BDNF-, GDNF-mRNA
	Bcl-2-, Trx-1-, Prx1-, HO-1-, TrxRx1-, γ-GCS
	DAT increase (but not after rasagiline, nomifensine, clorgyline and amphetamine)
	Suppression of Aβ aggregation
RAS	Bcl-2-, BDNF-, GDNF-, BcL-xL-, Bcl-w-, PKCα and ε-mRNA
	Bcl-2-, Bcl-xL-, GDNF-protein

As reviewed by Magyar et al 2010, Weinreb et al 2010, Naoi and Maruyama 2010.

protein synthesis. These more recent discoveries are in line with the earlier assumption of neuroprotective/neurorestaurative/disease-modifying properties especially of this chemical class of compounds.

Depression in PD

With a prevalence of approximately 40% depression is considered to be the most frequent psychiatric manifestation in PD (Burn, 2002; McDonald and DeLong, 2003; Veazey et al., 2005). Particular clinical features of the depressive symptom profile in patients with PD have been described (Wermuth and Bech, 2006; Brand et al., 2007) and recommendations towards better recognition given (Burn 2002). About 50% of the patients meet the criteria for major depressive disorder (MDD), 50% have

minor depression or dysthymia (Chaudhuri et al., 2006). Depression in PD is associated with increased disability and reduced quality of life, the impact of depressive symptoms in early PD especially should not be underestimated (Ravina et al., 2007).

MAOIs in depression

While early studies suggested that MAOIs were not as effective as other antidepressants, more recent studies have demonstrated that, when prescribed in adequate dosages, phenelzine and tranylcypromine are as effective as other antidepressants (Pare, 1985). Table 6 gives a summary

of important controlled studies with tranylcypromine. In a recent study tranylcypromine, 60 mg daily, was found effective in the treatment of panic disorder and social anxiety disorder comorbidity (Nardi et al., 2010).

The main indications for the classical irreversible MAOIs are subgroups of depression such as atypical depression, dysthymia or for patients who do not respond to reuptake inhibitors, so-called therapy resistant depressions (Nolen et al., 1994; Paykel, 1995; Bauer et al., 2002).

The therapeutic efficacy of moclobemide has been assessed in numerous controlled studies comparing it with placebo and established antidepressants (for reviews see Laux, 1989; Fitton et al., 1992; Fulton and Benfield, 1996; Laux et al., 2002). An overview of the most relevant trials is given in Table 7.

Large trials in patients with major depression have generally confirmed that the efficacy of moclobemide is equivalent to that of TCAs beside some negative studies. Moclobemide treatment was usually fixed up to 300, 400 or 600 mg/day. It should be noted, however, that the use of dosages of up to 900 mg/d has been established due to clinical experience nowadays particularly in patients with refractory depression (Guentert et al., 1995). A meta-analysis of inpatient studies indicated that higher dosages (>450 mg/day) of moclobemide are needed for full therapeutic effect in patients with severe depression (Angst et al., 1995).

Subgroup analyses of patients revealed moclo-

Table 5C. Non-MAO related actions of selegiline and rasagiline on molecular parameters *in vivo*

SEL	Increase of GDNF-, BDNF-, CDNF mRNA
	Increase of GPx-, SOD-, catalase activities,antioxidative capacity, thioredoxin
	Increase of s APPα secretion
	Decreases cell-cell adhesion
	Antagonizes hyperpermeability of vascular endothelial cells
	Increase of life span in low dosis
	Re-uptake inhibitor Increase in dopamine release after chronic treatment
	Dopamine potentiation
RAS	BDNF-, 14-3-3 γ mRNA and protein
	Rin-, Ras-, AF6-, SOS-, ShcC-mRNA
	Aβ-processing activities, inhibition of holo APP protein increase
	PRDX2, 14-3-3γ mRNA
	Dopamine release (chronic rasagiline)

As reviewed by Magyar et al 2010, Weinreb et al 2010, Naoi and Maruyama 2010.

Table 6. Randomised, double-blind controlled studies with tranylcypromine (TCP) in the treatment of depressive disorders (from Laux et al., 2002)

Study/Reference	N	TCP-Dosage (mg/day)	Duration (wk)	Results
vs. Imipramin (I)				
Freyhan (1960)	147	30~150	2~13	TCP>I
Spear et al. (1964)	78	30	3	TCP=I
Himmelhoch et al (1991)	56	37	6	TCP>I
Thase et al. (1992)	16	39	6	TCP>I
vs. Amitriptylin (A)				
Razani et al. (1983)	53	40	4	TCP=A
vs. Nortriptylin (N)				
White et al. (1984)	183	44	4	TCP=N>Pl
vs. Moclobemid (M)				
Heinze et al. (1993)	160	10~30	4	TCP>M

Legend: =indicates equivalent to, >indicates more effective than references in this table are given in detail in Laux et al., 2002.

Table 7. Randomised, double-blind controlled studies with moclobemide (M) in the treatment of depressive disorders (selection; references see Fulton and Benfield 1996; Laux et al., 2002)

Study/Reference	N	M-Dosage (mg/day)	Duration	Response-rate (%) M	Response-rate (%) C	Adverse effects
vs. Amitriptylin (A)						
Bakish et al. (1992)	82	200~600	6	56	60	M=PL<A
Evans et al. (1992)	48	300~400	4	49	59	M<A
vs. Clomipramin (C)						
Dierick et al. (1990)	53	300~600	4	43	38	M<C
Larsen et al. (1991)	80	300~600	6	46	72	M<C
Guelfi et al. (1992)	103	75~450	6	66	72	M<C
DUAG (1993)	107	400	6	19	33	M<C
Kragh-Sorensen et al. (1995)	142	400	6	51	36	M<C
Lecrubier et al. (1995)	191	400~600	12	63	65	M<C
Jouvent et al. (1998)	124	450	4	C>M		M<C
vs. Doxepin (D)						
Philipp et al. (1993)	183	400	6	52	44	M<D
vs. Imipramin (I)						
Baumhackl et al. (1989)	325	300~600	4	58	58	M<I
Versiani et al. (1989)	273	300~600	6	63	68	PI<M<I
Lecrubier & Guelfi (1990)	291	300~600	6	M=I		M<I
Rimon et al. (1993)	113	150~525	4	71	64	M<I
UK Study Group (1994)	106	300~450	6	M=I=PI		M<I
vs. Maprotilin (M)						
Gachoud et al. (1994)	109	300~400	4	55	59	
vs. Nortriptylin (N)						
Nair et al. (1995)	35	100~400	7	23	33	M=PI<N
vs. Fluoxetin (F)						
Williams et al. (1993)	92	300~600	6	72	59	M=F
Lonnqvist et al. (1994)	169	300~450	6	67	57	M=F
Reynaert et al. (1995)	80	300~600	6	47	48	M=F
Lapierre et al. (1997)	121	200~600	6	M=F		M=F
vs. Sertraline	63	300~600	13	73	42	
Turkcapar et al. (1998)				50	82*	
Sogaard et al. (1999)	197	300~450	12	68	78	

C: comparator, =indicates equivalent to, >indicates more effective/better tolerated than. *melancholic subtype.

bemide to be effective in patients with dysthymia or atypical depression especially (Lonnqvist et al., 1995).

Several trials have evaluated moclobemide alone or in combination with TCAs or SSRIs in the treatment of refractory depression (Bakish et al., 1995) reporting positive results. These data are limited and great caution is necessary because of the potential to induce the serotonin syndrome when combining moclobemide with serotoninergic drugs.

Uncontrolled long term follow-up studies demonstrated continued effectiveness of moclobemide over the treatment period of 1 year with more than 60% of patients having continued response (Fulton and Benfield, 1996). The role of MAOIs in mainte-

nance treatment of depression still has to evaluated (Kennedy, 1997).

MAO-B inhibitors like selegiline in high dosage have been used in therapy-refractory depressions probably due to non-selective MAO effects (see review Laux, 1993). Recently, transdermal selegiline has been approved and released in the USA for treatment of major depression with a target dose of 6 mg/24 hours. This dosage and application overcomes the MAO-B selectivity and leads to MAO-A inhibition, seen to be necessary for antidepressive effects. In several controlled studies selegiline transdermal system exhibited significant treatment effects on MDD including core depression symptoms, vegetative symptoms and motor retardation (Frampton and Plosker, 2007; Robinson et al., 2007). A combi-

nation of selegiline and 5-hydroxytryptophan has been tested in a pilot study and proved antidepressant efficacy (Mendlewicz and Youdim, 1978).

Treatment with antidepressants and MAOIs in PD

The scientific knowledge about the treatment with antidepressant drugs among PD patients is nearly missing. A pharmaco-epidemiological study in Danmark showed that persons treated with antiparkinson drugs have higher frequency of antidepressant drug treatment than have controls (Brandt-Christensen et al., 2007). Most authors conclude, that recommendations for the optimal drug treatment of depression in PD are difficult to give (Burn, 2002). Serotonin selective reuptake inhibitors (SSRIs) are given frequently, the benefit of SSRI treatment in PD has not been established, however (Wermuth and Bech, 2006).

Thirty-seven patients with early PD have been treated successfully with tranylcypromine (TCP), parkinsonian symptoms improved slightly, follow-up after 1.5 years on average revealed only slight worsening (Fahn and Chouinard, 1998). No other studies have been reported with TCP so far.

Ten patients with PD have been treated successfully with moclobemide vs. moclobemide with selegiline under tyramine restriction (Steuer and Ballering, 1997). Sufficient data allowing conclusions are missing.

Dosage and administration

The recommended initial dosage of tranylcypromine is $10 \sim 20$ mg/day, of moclobemide 300 to 450 mg/day, given in 2 to 3 divided doses. Subsequent dosage increase to a maximum of 60 mg/day, 900 mg/day respectively, are made as clinically indicated (Beckmann and Laux, 1991; Fitton et al., 1992). Clinical experience and studies in the last years clearly have shown the necessity of higher dosage of moclobemide pointing out the lack of early sufficient dose-finding studies. Recommended daily doses of phenelzine are 30 to 90 mg, of isocarboxazid 30 to 60 mg, respectively.

Dietary restrictions are essential for tranylcypromine (tyramine-rich food), unnecessary for moclobemide taken at the end of a meal. A 2 week wash-out period is required for switching between tranylcy-

promine and other classes of antidepressants, not between moclobemide and other antidepressants.

In patients with severe hepatic impairment, tranylcypromine and moclobemide dosages should be reduced by one-third to one-half in such patients (Atkinson and Ditman, 1965; Fitton et al., 1992).

The target dose of selegiline transdermal (not released in Europe so far) is 6 mg/24 hours.

Tolerability and safety

The most frequent adverse effects of irreversible MAOIs are orthostatic hypotension, sleep disturbances and nervousness/agitation (Remick et al., 1989). The mostly limiting factor in the use of these MAOIs is the potential for dangerous interactions with tyramine-rich foods and sympathomimetic and serotoninergic substances. Therefore, prescription is only possible to patients being strongly compliant with dietary restrictions. In the case of RIMAs like moclobemide there is no need for dietary restrictions. For "selegiline transdermal system" tyramine dietary restrictions are not needed. The incidence of the most frequently reported adverse effects from patients receiving MAOIs are summarised in Table 7.

Insomnia and impotency in men have been the most frequent side effects of TCP in patients with early PD (Fahn and Chouinard, 1998).

Unlike nonselective, irreversible MAOIs and tricyclics, moclobemide has little effect on the cardiovascular system and lacks anticholinergic properties associated with TCAs (Moll et al., 1994; Fulton and Benfield, 1996). In almost all controlled clinical studies comparing moclobemide with TCAs moclobemide showed clearly superior tolerability (Versiani et al., 1990; Fitton et al., 1992; Fulton and Benfield, 1996). Headache, insomnia and agitation were the only one side effects being reported more frequently with moclobemide compared to re-uptake inhibiting antidepressants. Dizziness and nausea have been noticed additionally. No systematic changes in blood pressure were observed with moclobemide, whereas increases in both blood pressure and pulse were recorded for tranylcypromine (Laux et al., 1996). Body weight gain has been observed with phenelzine and isocarboxazid, no clearcut cases with tranylcypromine or moclobemide have been reported (Cantu and Korek, 1988). Compared to SSRIs

moclobemide showed fewer gastrointestinal adverse effects and sexual dysfunction have not been reported with moclobemide (Philipp et al., 1999).

Regarding cognitive functions data in favour of moclobemide compared to other antidepressants are available: Behavioural toxicity assessed by choice reaction time is very low or missing, psychomotor functions seem not be influenced negatively perhaps even improved (Hindmarch et al., 1992).

The principal side effects of selegiline transdermal were local dermal reactions and (dose-related) insomnia (Robinson and Amsterdam, 2008).

After ingestion of up to 20 g of moclobemide no fatalities were observed, so moclobemide can be considered as a 'safe' antidepressant (DeJonghe and Swinkels, 1992; Chen and Ruch, 1993). Several fatal overdoses have been reported when moclobemide was combined with serotoninergic antidepressants like citalopram, clomipramine or fluoxetine due to occurrence of a serotonin syndrome (Neuvonen et al., 1993). In contrast, irreversible MAOIs like tranylcypromine must be regarded as less safe regarding to the fatal toxicity index (Henry et al., 1995).

Side effects of selegiline and rasagiline

Selegiline is well tolerated. Side effects/adverse reactions like sleeplessness, nausea, vomiting, dizziness, dry mouth, orthostatic hypotension and dyskinesias have been all observed in the range of 2~5% of PD patients (Parkinson-Study-Group, 1993; Reichmann et al., 2002) which is comparable to placebo. Other side effects like headache, heart beating, dyspnoe, edema, confusion, micturition dysfunction, loss of appetite and anxiety are even more rare and below 2% (Reichmann et al., 2002).

Rasagiline

Adverse reactions as seen with other dopaminergic drugs, like nausea, vomiting, orthostatic hypotension, somnolence, hallucinations and dyskinesias are tolerable in most cases. Vomiting was noteable at 1 mg/day in the PRESTO-study, as was the occurrence of dyskinesias but such adverse reactions have not been described in other clinical trials like the LARGO-trial. Cognitive and behavioural symptoms of PD are not changed/worsened at 1 mg/day rasagiline (Elmer et al., 2006).

Although interactions may be suggested when MAO-B inhibitors are combined with COMT-inhibitors, such adverse reactions have not been reported to be of relevance. In fact rasagiline is effective and well tolerated in PD patients with L-DOPA induced motor fluctuations receiving entacapone (Elmer et al., 2006).

The cardiovascular risk in selegiline and rasagiline treated PD

Selegiline is metabolized mainly to desmethyl-selegiline, L-amphetamine and L-metamphetamine. Given these facts there was always a profound discussion about the contribution of these metabolites to selegiline's clinical symptomatic effects (Reynolds et al., 1978; Elsworth et al., 1982) and selegilines adverse reactions, predominantly of cardiovascular origin (Churchyard et al., 1997). L-Amphetamine has about a ten times lower activity on the peripheral sympathetic system compared to D-amphetamine. On the other hand, both are equipotent in blocking striatal dopamine uptake (Coyle and Snyder, 1969). A clinical trial of daily 10 mg selegiline vs. the calculated dosis and ratio of L-amphetamine and L- metamphetamine in PD patients came to the conclusion that selegiline did show antiakinetic efficacy while the metabolites did not (Elsworth et al., 1982). Therefore, selegiline is not acting via the amphetamine metabolites. Also, from the side effect profile as reported in the large selegiline based trials there is no evidence for enhanced cardiovascular risk (eg. Parkinson Study Group, 1989; 1993). This holds true also when selegiline is compared to treatment based on L-DOPA and dopaminergic receptor agonists. However, head-to head comparison is missing.

Nevertheless, to avoid further such discussion a sublingual galenic form of selegiline treatment has been developed named Zydis-selegiline (Clarke et al., 2003a; 2003b). This "melting-tablet" avoids a first-pass effect and therefore a significant break-down to L-amphetamine and L-metamphetamine in the range of 90%. A reduction of the daily dosis of 10 mg selegiline to 1, 25 mg selegiline is advised. The bioavailability of selegiline when given as "melting-tablet" is more homogene and better reproduceable compared to the peroral type of application (Clarke et al., 2003a; 2003b). In addition a transdermal

galenic form of selegiline has been developed for the treatment of major depression again reducing seligilines first-pass biotransformation (Frampton and Plosker, 2007; Robinson et al., 2007).

Melting tablet and transdermal selegiline avoid first-pass metabolism, cause higher drug availability in MAO-B preferring organs and reduce the concentration of metabolites. Increased drug concentration may cause significant inhibition of both MAO-B and $-A$ in brain but not in the periphery. This explains seligilines antidepressant activity when combined with 5-hydroxytryptophan without the cheese-effect and without the serotonin syndrome (Mendlewicz and Youdim, 1978).

Under clinical conditions selegiline is not more "toxic" than other dopaminergic treatment strategies. In fact the side effect and adverse reaction profile of selegiline has been evaluated as being well tolerated and "mild" compared to other PD treatment strategies, eg. orthostatic reactions have been noteable in only 3, 7% of patients (Reichmann et al., 2002).

It should be mentioned that L-amphetamine is in clinical use for the treatment of attention-deficit-hyperactivity syndrome (ADHD) without major side effects. In line with this are several studies as summarized by Reidenberg (1994) showing no abuse liability of selegiline.

The contribution of desmethylselegiline (DMS) to the effects of selegiline has been underestimated so far. DMS is a weak inhibitor of MAO-B and seems to have glutathione related properties (Heinonen, 1997; Heinonen et al., 1997).

In contrast to selegiline, **rasagiline** is not metabolized to amphetamine. The main metabolite of rasagiline is aminoindan. Therefore any cardiovascular responses of rasagiline are neglectible as shown in animal studies (Finberg et al., 2006) and in all clinical trials including the TEMPO- (Parkinson Study Group, 2002), PRESTO- (Parkinson Study Group, 2005), LARGO- (Rascol et al., 2005) and ADAGIO-study (Olanow et al., 2008; 2009).

In the recommended therapeutic dosis of 1 mg/day rasagiline does not potentiate the tyramine induced cheese-effect (de Marcaida et al., 2006). This is in agreement with earlier findings in rats and cats (Finberg et al., 1981; Chen and Swope, 2005; Finberg et al., 2006).

Drug interactions

Coadministration of SSRIs and other serotoninergic substances to tranylcypromine is contraindicated due to the risk of serotonin syndrome. With moclobemide great caution should be exercised with this combination. Severe, sometimes fatal, interactions between nonselective, irreversible MAOIs, moclobemide as well as selegiline and pethidine and dextromethorphan have been reported. Indirectly acting sympathomimetics (tyramine, ephedrine, pseudoephedrine) should be administered with caution in patients treated with MAOIs (Dingemanse, 1993).

The elimination of moclobemide is significantly reduced by cimetidine making dose adjustment necessary.

Although selegiline has been reported to have antidepressant actions when combined with 5-hydroxytryptophan (Mendlewicz and Youdim, 1978) MAO-B-inhibitors may not be safe enough to avoid the "serotonin-syndrome" when given in adjunct to serotonin-reuptake inhibitors (SSRIs) to treat depression and anxiety in PD patients. However, there is a low risk (0, 24%) to develop the "serotonin-syndrome" in selegiline treated patients (Richard et al., 1997). Also the results of a small number of PD patients treated with tricyclics and SSRIs plus rasagiline in the TEMPO-, PRESTO- and LARGO-studies do not give evidence for the "serotonin-syndrome", the population incidence of serotonin toxicity in those patients has a 9, 5% probability of being less than 1, 2% (Pannisset et al., 2007; Montgomery and Panisset, 2009). However, a clinical trial with a biostatistic power relevant to give a definite answer to the problem is missing. Therefore MAO-B inhibitors have not to be combined with drugs stimulating the serotoninergic system.

Meperidin plus selegiline has been reported to be dangerous as it causes severe hypertension (Zornberg et al., 1991).

Selegiline transdermal without tyramine restriction revealed no acute hypertensive reactions in trials, until more data are available, foods that are rich sources of tyramine should be avoided, however.

As described by Chen and Swope (2005) CYP1A2 inhibitors (cimetidine, fluvoxamine, ciprofloxacin) increase the area under curve of rasagiline,

while CYP1A2 inducers like omeprazol decrease it, as it may decrease in heavy smokers.

Minor time-dependent mechanism-based inhibition of CYP2D6 has been described for selegiline and moclobemid in experimental designs; the significance in human beings remains to be investigated (Polasek et al., 2006). For selegiline interactions with CYP 3A4 and CYP 2E1 may be relevant too.

Expert commentary

While selective MAO-B-inhibitors demonstrate a significant benefit in PD and improve motoricity and motor fluctuations eventually causing disease-modification in general MAOIs to date play a subordinate therapeutic role in the treatment of depression in PD compared to SSRIs or reboxetine, a selective noradrenergic reuptake inhibitor. This attitude is primarily due to the risk of adverse effects and compliance problems (e.g. dietary restrictions, interaction problems) with MAOIs. Moclobemide according to its favourable adverse effect, interaction and toxicity profile can be used in depressed Parkinson patients when activating properties are necessary, especially.

Overall, the clinical use of MAOIs may be limited by the possible adverse effects of restlessness and insomnia - but see rasagiline. As far as long term and prophylactic treatments are concerned, the place of MAOIs still has to be verified as antidepressant or antidementive drugs in PD (Tariot et al., 1987; Sano et al., 1997; Filip and Kolibas, 1999; Sterling et al., 2002; Elmer et al., 2006; Carageorgiou et al., 2008). Controlled studies are urgent needed for final evaluation and recommendations.

Five-year view

It would be worthwile to perform clinical studies to demonstrate the capacity of MAO-B inhibitors as antidepressants and antidementive drugs. New substances like ladostigil (MAOA/B inhibitor; AchE-inhibitor) or M30 and HLA-20 (MAO-A/B inhibitor, iron-chelator) and M30P (MAO-A/B inhibitor, carbonate cholinesterase inhibitor) give future aspects of using MAO-I's in a variety of clinical indications (Weinreb et al., 2010). The pharmacological properties of aminoindan have to be elucidated as they may be neuroprotective (Bar-Am et al., 2010).

Key issues

Head-to-head clinical trials are necessary to demonstrate disease-modification using improved delayed-start-study designs with selegiline and rasagiline. Otherwise no objective comparison can be made between the neuroprotective/neurorestaurative properties of selegiline and rasagiline.

Aminoindan has to be tested in vivo in order to get insight into its anti-parkinsonian efficacy.

The many molecular biological and -genetic data evolved from in-vitro studies have to be confirmed in in-vivo experiments to prove relevance in human beings. That other MAO-Is, even reversible ones might well be important in neuroprotection/disease modification is a just ongoing important issue. In addition, the respective role of MAO-A has to be elucidated in more detail.

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