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Efficacy and Tolerability of Tolcapone Compared With Bromocriptine in Levodopa-Treated Parkinsonian Patients

The Tolcapone Study Group*

Summary: The catechol-O-methyltransferase inhibitor tolcapone was compared with the dopamine agonist bromocriptine in an open-label, randomized trial involving 146 levodopa-treated parkinsonian patients with end-of-dose deterioration of efficacy. Tolcapone was given at a dosage of 200 mg three times daily; bromocriptine was titrated from 1.25 mg once daily at baseline to, at most, 10 mg three times daily by day 24 (mean final dose 22.4 mg/day). After 8 weeks, the tolcapone group had a significant reduction in daily levodopa dose compared with the bromocriptine group ($p < 0.05$). No significant differences in the ''on/off'' time and motor disability were seen between the tolcapone and bromocriptine treatment groups. Bromocriptine induced more hallucinations, orthostatic hypotension, and nausea, whereas tolcapone therapy was associated with more muscle cramps and dystonia. These results suggest that when added to levodopa therapy, the two drugs have a different side effect profile, with the advantages for tolcapone being absence of titration and quicker efficacy. **Key Words:** Tolcapone—Bromocriptine—Parkinson's disease—Motor fluctuations—Levodopa.

The ''gold standard'' treatment for Parkinson's disease is dopamine replacement with levodopa (3,4-dihydroxy-l-phenylalanine), which is converted to dopamine in the brain by aromatic amino acid decarboxylase. Levodopa is normally given with a peripheral dopa decarboxylase inhibitor (benserazide or carbidopa) to prevent excessive peripheral dopamine formation.[1] Although such treatment is highly effective in relieving parkinsonian symptoms, within 5 years 50% of patients experience predictable fluctuations in response to levodopa, the so-called ''wearing-off'' phenomenon.[2,3]

These motor fluctuations result when levodopa repeatedly enters and leaves an optimal therapeutic range (the ''therapeutic window''), which becomes increasingly narrow with time. The peripheral pharmacokinetics of levodopa thus become important determinants of its central nervous system (CNS) effects, especially in the context of limited CNS dopamine storage capacity. Plasma levodopa concentrations rise abruptly (within 15 min in some instances) and fall within less than 2 hrs (elimination half-life approximately 90 min).[4]

Some evidence indicates that the efficacy of levodopa is reduced by peripheral methylation of levodopa to form 4-hydroxy-3-methoxy-l-phenylalanine, also called 3-O-methyldopa (3-OMD)[5]; this process is mediated by catechol-O-methyltransferase (COMT), which plays an important role in the inactivation of catecholamine neurotransmitters such as dopamine and norepinephrine. Methylation of levodopa appears to reduce its therapeutic effect in two ways: the amount of levodopa available for conversion to dopamine in the brain is decreased, and, more speculatively, 3-OMD competes with levodopa for transport across the blood–brain barrier.[6,7] Thus, inhibition of COMT, both in the periphery and in the

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CNS, could result in more stable plasma concentrations of levodopa and improve efficacy.

Tolcapone (3,4-dihydroxy-4′-methyl-5-nitrobenzophenone) is a potent, selective, and reversible inhibitor of COMT.[8] In animal studies, it has been shown to inhibit COMT in both brain and peripheral tissues such as the gut and liver.[9–11] Preliminary clinical studies in healthy volunteers treated with levodopa and a peripheral decarboxylase inhibitor showed that when tolcapone was added to the regimen, the area under the plasma concentration-time curve and elimination half-life of levodopa approximately doubled with no change in peak levodopa concentrations[12]; moreover, the area under the curve of 3-OMD was reduced by up to 80%. In parkinsonian patients, the increased bioavailability of levodopa, with the concomitant reduction in 3-OMD levels, resulted in reduced ''wearing-off'' in the tolcapone-treated group without aggravating the risk of peak-dose dyskinesias (associated with high concentrations of levodopa).[13]

Dopamine agonists are widely used as adjuncts to levodopa treatment in parkinsonian patients with motor fluctuations.[14] Therefore, a comparative study was performed to compare the new COMT inhibitor tolcapone with that of the widely used dopamine agonist bromocriptine in parkinsonian patients with the ''wearing-off'' phenomenon. The preliminary results of this study have been published as a letter in *Lancet*.[15]

METHODS

This 8-week, open-label, randomized, comparative trial was conducted in 19 centers in France in accordance with the Declaration of Helsinki and its revisions and French laws and regulations. Local ethics committee approval was received before the start of the study. Written informed consent to participate was obtained from all patients.

Patients and Randomization

Patients were eligible for inclusion if they were at least 30 years of age at the onset of parkinsonian symptoms and satisfied the clinical criteria for Parkinson's disease from the United Kingdom Parkinson's Disease Brain Bank. They had to be taking at least three daily doses of levodopa plus a decarboxylase inhibitor (carbidopa or benserazide) and be experiencing clinical fluctuations, such as the ''wearing-off'' phenomenon or predictable ''on/off'' fluctuations. They were required to be able to keep reliable ''on/off'' charts, alone or with the help of a family member.

The planned total sample size for this study was 150 patients (75 patients in each group). This sample size was chosen primarily from a practical point of view using clinical estimates of enrollment rates. In fact, 162 patients were screened, of whom 146 were randomized using a centralized randomization procedure. Randomization was stratified by previous use of dopamine agonists and weighted every two patients in each stratum. To randomize a given patient, the investigator called a vocal computer that reviewed his or her most important selection criteria and assigned treatment accordingly.

Exclusion criteria included the following: nonidiopathic parkinsonism, progressive supranuclear palsy, or multiple system atrophy; unpredictable fluctuations or prolonged, severe dyskinesias that could interfere with daily activities; treatment with a dopamine agonist during the previous 4 weeks before randomization, apomorphine during the previous 6 months, or a monoamine oxidase inhibitor (other than selegiline) during the previous 2 months; a Mini-Mental State Examination score of 24 or less; a history of psychotic illness or major depression during the previous 6 months; unstable medical problems; and a history of alcohol or drug abuse.

Women were required to be sterile or to be using effective contraception. Patients treated with dopamine agonists (up to 20 mg/day bromocriptine, up to 1.2 mg/day lisuride, or up to 150 mg/day piribedil) could be included after a 4-week washout period.

Treatment

Patients were randomized to receive either 200 mg tolcapone three times daily or titrated doses of bromocriptine. The first daily dose of tolcapone was taken with the first daily dose of levodopa; the second and third doses of tolcapone were taken at 6-hr intervals thereafter. The dose of bromocriptine was titrated from 1.25 mg once daily at baseline to 10 mg three times daily on day 24 or to a dose that produced an adequate response. The titration was performed in steps of 2.5 mg/day every 2 days starting on day 2; titration could be extended over 28 days at the discretion of the investigator. Treatment with either drug was continued for 8 weeks.

In the tolcapone group, the dosage of levodopa and decarboxylase inhibitor was adjusted during the study as needed to manage levodopa-related adverse events. In bromocriptine-treated patients, the dosage of levodopa was reduced to manage motor adverse events. When other dopaminergic adverse events occurred, bromocriptine titration was stopped and the bromocriptine dose subsequently adjusted as necessary. No increase in levodopa dose above the baseline dose was permitted.

Other antiparkinsonian medication was allowed, provided the dosage had been stable for 1 month before entry to the study and remained unchanged during the study. Patients could receive medication for ad-

verse events during the study, including the peripheral dopamine antagonist domperidone to treat nausea and vomiting.

Assessments

Patients were screened for eligibility in the 4 weeks before randomization. During this time, they were given ''on/off'' diary charts and instructions on how to complete them. For each 30-min period during an 18-hr day, patients were required to rate their condition as ''asleep,'' ''on'' (good to excellent mobility), ''off'' (bad mobility to complete blockade), or ''intermediate'' (not ''on'' and not ''off''). To be eligible for inclusion, patients had to complete at least three daily diaries each week during the past 2 weeks before randomization and have at least two ''off'' periods each day. ''On'' and ''off'' times were recorded just before baseline and at the end of the 8-week treatment period. Patients were also asked to rate the degree of nocturnal disability or immobility on a four-point scale from 1 (no difficulty) to 4 (severe).

Scores for the Unified Parkinson's Disease Rating Scale (UPDRS)[16] were calculated at baseline and at the end of treatment. In addition to total scores, Subscales I (mentation, behavior, and mood), II (activities of daily living during ''on'' periods), III (motor symptoms during ''on'' periods), and IV (dyskinesia and clinical fluctuations) were used to assess specific aspects of efficacy.

Information about adverse events was collected throughout the study. In particular, dopaminergic adverse events were recorded at baseline, after 1 and 4 weeks, and at the end of the study. A 12-lead electrocardiogram was performed during the screening period and at the end of the study. Vital signs (supine and standing blood pressure and heart rate) and clinical laboratory tests (hematology, blood chemistry, urine analysis) were recorded during the screening period, at baseline, and after 1, 4, and 8 weeks. The adverse events data were summarized by incidence and intensity, using crude incidence rates, calculated by dividing the number of patients experiencing a specific adverse event by the number of patients initially exposed to the treatment regardless of duration of treatment and of whether or not the event was attributable to the study treatment.

TABLE 1. *Patient characteristics at baseline*

	Bromocriptine	Tolcapone
Patients (no.)	74	72
Male:female ratio (no.)	40:34	40:32
Age (yrs)	65 ± 9	61 ± 11
Duration of disease (yrs)	9.9 ± 4.3	9.2 ± 5.0
Total daily levodopa dose (mg)*	779 (42)	750 (45)
Hoehn & Yahr stage: ''on'' (% patients)		
0–1.5	17.5	22.2
2–2.5	41.9	61.1
3	19.0	9.7
>3	8.1	6.9
Unified Parkinson's Disease Rating Scale		
Subscale I (mentation)	1.8 ± 1.3	1.8 ± 1.5
Subscale II (activities of daily living during ''on'' phase)	7.8 ± 5.5	6.8 ± 5.7
Subscale III (motor function during ''on'' phase)	19.9 ± 11.2	16.1 ± 11.7

Data are means ± standard deviation, except for *total daily levodopa dose, in which case data are means (SEM). No significant differences were found between the groups.

Statistics

Patients were included in the intention-to-treat analysis if they had been randomized to treatment, had taken at least one dose of study medication, and were subsequently observed at least once. Analyses of last-observation-carried-forward data were performed.

The trial was designed primarily to assess safety and tolerability. Because the study was not adequately powered to compare the efficacy of the two drugs, no primary efficacy variable was selected. Nonetheless, statistical analyses were performed on ''on/off'' time, levodopa dosage, and UPDRS scores regarded as continuous variables and analyzed by analysis of covariance.

RESULTS

Of the 146 patients randomized to treatment, 74 received bromocriptine and 72 tolcapone. The bromocriptine dose (1.25 mg/day on day 1 for all 74 patients) was 22.4 ± 9.0 mg/day (mean ± standard deviation) by the end of the study. Sixteen patients, eight (11%) in each group, withdrew because of adverse events or intercurrent illness; one patient in the bromocriptine group withdrew because of protocol violations. Patient characteristics and Parkinson's disease history are shown in Table 1.

By the end of week 8, the total daily levodopa dose decreased by a mean of 124 mg (16.5%) in the tolcapone-treated patients compared with 30 mg (4%) in the bromocriptine-treated patients (difference between the groups $p < 0.01$). In the tolcapone group, the total daily levodopa dose had decreased by a mean of 92 mg by the end of the first week of treatment, and the decrease was virtually complete after 4 weeks (124-mg reduction). In both groups, levodopa dose reduction was achieved by a reduction in the number of daily doses of levodopa; in the tolcapone group, 24 patients (33%) had at least one intake reduction compared with eight patients in the bromocriptine group (11%). However, the difference in the reduction of the mean number of daily intakes between treatment groups was not significant.

No significant differences were seen between the two groups in changes in ''on/off'' time or UPDRS Subscales II (activities of daily living) and III (motor function) scores (Table 2). By the end of the study, ''on'' time had increased by 2.8 hr/day in patients treated with tolcapone compared with 2.1 hr/day in patients receiving bromocriptine, and ''off'' time had decreased by 3.0 hr/day in the tolcapone group and 2.4 hr/day in the bromocriptine group.

Changes in disability or immobility were assessed from the average ratings in the last three daily diaries at baseline and week 8. Both groups had a mean baseline score of 1.8 on the four-point scale of nocturnal disability. The mean decrease in score between baseline and week 8 was 0.4 in the tolcapone group compared with 0.1 in the bromocriptine group (not significant).

The adverse events that occurred most often in the two treatment groups are listed in Table 3; the most frequent of these were considered to be dopaminergic. The dopaminergic events of nausea, orthostatic hypotension, and hallucinations occurred more often in the bromocriptine group as did peripheral edema, a nondopaminergic event. Muscle cramps and dystonia (both dopaminergic) were more frequent in the tolcapone group as was xerostomia (nondopaminergic).

The two treatment groups had differing time courses of dyskinesia. The tolcapone group showed an immediate increase followed by a progressive decrease in the number of patients with dyskinesia, whereas a progressive increase in the number of dyskinetic patients was observed in the bromocriptine group (Fig. 1), so that the prevalence of dyskinesia was roughly the same in the two groups after 8 weeks of treatment.

In the bromocriptine group, 22 patients (30%) received the peripheral dopamine antagonist domperidone for the treatment of nausea compared with five (7%) in the tolcapone group.

In the tolcapone group, 22 patients (31%) had clinically relevant abnormalities in heart rate and blood pressure compared with 33 (45%) in the bromocriptine group. The incidence of orthostatic hypotension was 4% in the tolcapone group (three patients) and 7% in the bromocriptine group (five patients).

The effect of previous dopamine agonist treatment on the tolerability of current therapy was also analyzed, although relatively few patients previously had not received such treatment (Table 4). Significantly more patients in the bromocriptine group (30%) than in the tolcapone group (7%) had received domperidone ($p < 0.05$). In the bromocriptine group, 11 of the 15 most frequently

TABLE 2. *Changes in fluctuations of motor performance and functional disability between baseline and week 8 of treatment in patients receiving bromocriptine or tolcapone*

	Bromocriptine (n = 74)	Tolcapone (n = 72)
''On''-time (% waking day)	+13.4 (2.7)	+17.6 (2.9)
''Off''-time (% waking day)	−14.9 (2.7)	−18.8 (3.0)
Unified Parkinson's Disease Rating Scale		
Subscale II (activities of daily living during ''on'' phase)	−0.1 (0.4)	−0.9 (0.5)
Subscale III (motor function)	−3.3 (1.0)	−3.1 (1.0)

Data are means (SEM). No significant differences were found between the groups.

TABLE 3. *Adverse events occurring in at least 5% of patients*

	Bromocriptine (n = 74)	Tolcapone (n = 72)
Dopaminergic		
Dyskinesia	28 (38)	37 (51)
Nausea	27 (37)*	12 (17)
Sleep disorders (insomnia)	11 (15)	20 (28)
Orthostatic complaints (for example, hypotension)	17 (23)*	4 (6)
Muscle cramps	5 (7)	15 (21)*
Somnolence	7 (10)	12 (17)
Anorexia	9 (12)	7 (10)
Dystonia	1 (1)	10 (14)*
Excessive dreaming	6 (8)	3 (4)
Hallucinations	7 (10)*	1 (1)
Vomiting	5 (7)	3 (4)
Nondopaminergic		
Abdominal pain	4 (5)	8 (11)
Peripheral edema	6 (8)*	0 (0)
Falling	2 (3)	4 (6)
Xerostomia	0 (0)	5 (7)*
Urine discoloration	0 (0)	4 (6)

Data are numbers of patients, with percentages in parentheses.
* Difference between groups $p < 0.05$.

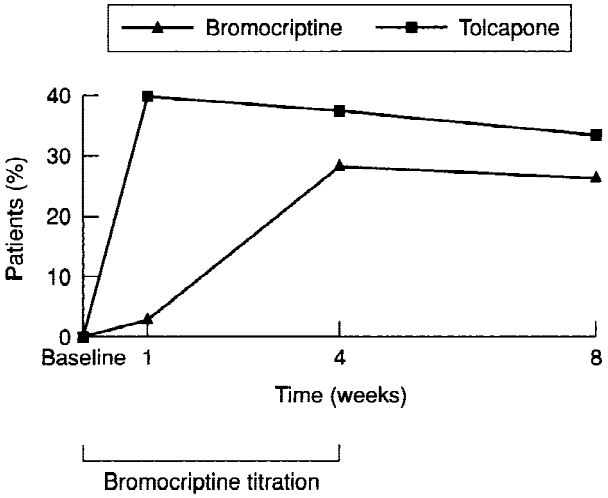

FIG. 1. Prevalence of increased dyskinesia between baseline and week 8 of treatment in patients receiving tolcapone or bromocriptine.

TABLE 4. *Adverse events in patients with and without previous dopamine agonist treatment*

	Bromocriptine		Tolcapone	
	DA+ (n = 59)	DA– (n = 15)	DA+ (n = 57)	DA– (n = 14)
Dyskinesia	36	47	51	50
Nausea	32	53	19	7
Sleep disorders (insomnia)	14	20	25	43
Muscle cramps	7	7	23	14
Orthostatic complaints (for example, hypotension)	20	33	5	7
Somnolence	9	13	16	21
Anorexia	9	26	11	7
Dystonia	2	0	18	0
Abdominal pain	5	7	11	14
Excessive dreaming	9	7	5	0
Peripheral edema	10	7	0	0
Hallucinations	9	13	2	0
Constipation	2	13	2	0
Dizziness	2	13	4	0
Visual disturbances	0	13	0	0

Data are percentages of patients in each subgroup. Data were not analyzed for statistical significance because of the small numbers of agonist-naive patients.

DA+, previous dopamine agonist treatment; DA–, no previous dopamine agonist treatment.

reported adverse events occurred in more patients without previous dopamine agonist treatment than with previous treatment (Table 4). In the subgroup of bromocriptine-treated patients with no previous dopamine agonist treatment, 60% (n = 9) had worsened tolerability compared with 34% (n = 20) of the bromocriptine patients who had received dopamine agonists previously. Little difference was found in the proportion of tolcapone-treated patients experiencing worsened tolerability between those who had previously been treated with dopamine agonists (25% [n = 14] had worsened tolerability) and those who were dopamine agonist-naive (28% [n = 4] had worsened tolerability).

DISCUSSION

The present study had an open-label design because of the marked differences between tolcapone and bromocriptine in dosage regimens and management of adverse events. Tolcapone was administered at a fixed dose from the start of treatment, and the therapeutic effect was detectable immediately, whereas titration to an optimal dose was needed with bromocriptine to achieve a balance between efficacy and adverse events. If dopaminergic adverse events occurred during tolcapone treatment, the dosage of levodopa was reduced, allowing tolcapone treatment to be maintained at the fixed dosage. During bromocriptine treatment, however, a distinction had to be made between motor adverse events (dyskinesia, motor fluctuations) and non-motor adverse events (psychiatric disturbances, peripheral side effects). The dose of levodopa was reduced only if motor adverse events were seen, because levodopa is known to induce more motor than non-motor events. With non-motor events by contrast, bromocriptine was reduced or withdrawn if hallucinations or confusion were seen.

Two reasons led us to consider that a blinded study was not justified: first, the different adverse events in the two groups, namely immediate adverse motor events in tolcapone-treated patients and delayed psychiatric adverse events in the bromocriptine group, necessitated different management; second, the titration of bromocriptine was difficult to obtain in contrast to the fixed tolcapone dosage. We think these problems would have biased the design of a double-blind study in such a way that we favored an open-label study.

In comparative trials such as this, patients who have previously been treated with either of the drugs under investigation, or with other drugs from the same classes, should ideally be excluded to avoid selection bias. For example, patients who had previously shown poor tolerance to a dopamine agonist might be less likely to be included than patients who had previously tolerated such treatment well. Although patients who had previously received tolcapone were excluded from this study, excluding patients who had previously received dopamine agonists was not practical because these agents are widely used in France in the treatment of Parkinson's disease.

The scores for the UPDRS activities of daily living and motor scales and ''on/off'' state in the two groups were not significantly different. In the tolcapone group, the significant decrease in the levodopa dosage, with fewer intakes, reflects the tolcapone-induced inhibition of COMT on the levodopa pharmacokinetics, namely a

twofold increase in levodopa bioavailability and half-life without a change in peak concentration.[12] This modification in the levodopa pharmacokinetics profile has a tendency toward a smoothing of the fluctuations in levodopa concentration. This could explain the improvement in the ''wearing-off'' phenomenon (related to the rapid fall in levodopa blood concentration) and may mitigate in the long term the pharmacodynamic changes of the striatal dopaminergic receptors, which may play a role in the worsening of the motor fluctuations.[17]

Although tolcapone was given from the start at the therapeutic dosage, it was well tolerated, the most frequent adverse events being the expected dopaminergic events, such as dyskinesia, associated with levodopa treatment. These adverse effects may appear from the start of tolcapone treatment and tend to decrease thereafter. The management of these events rests logically on a decrease in levodopa dosage. This dosage reduction could be made preventively just before the initiation of tolcapone treatment in patients who have periods of severe dyskinesia. Bromocriptine induced more hallucinations, symptoms of orthostatic hypotension, and nausea, which are adverse events known to occur more often with dopamine agonists than with levodopa. The hallucinations and orthostatic symptoms are often difficult to manage; a decrease in bromocriptine dosage or stopping dopamine agonist treatment completely is usually advocated. Diarrhea, which has previously been reported as a frequent adverse event in patients receiving tolcapone,[18,19] was rarely noted in the present trial; it was reported by one patient in the bromocriptine group and by two patients in the tolcapone group. This is probably because our study was shorter than the other studies in which diarrhea usually began 2–4 months after the start of treatment. Bromocriptine patients more often required the dopamine antagonist domperidone to treat nausea and vomiting.

Most of the patients enrolled in the two groups had already received dopamine agonists. This selection bias was clearly shown by the higher occurrence of almost all adverse events in the patients in the bromocriptine group who had never taken bromocriptine or any other dopamine agonist previously. Thus, the tolerability problems associated with bromocriptine treatment in agonist-naive patients may have been an underestimation, which strengthens the results indicating the good acceptability of tolcapone in comparison with bromocriptine.

Dystonia was the most clinically important adverse event, occurring in significantly more tolcapone patients than bromocriptine patients ($p < 0.05$). This is inconsistent with previous reports in which tolcapone was not found to increase dystonia compared with placebo.[20,21] Table 4 shows that all 10 cases of dystonia in the tolcapone group occurred in patients with previous dopamine agonist treatment. Many of these patients had stopped dopamine agonist therapy shortly before the present trial (as little as 4 weeks before randomization), raising the possibility that dystonia may be a long-term consequence of discontinuing dopamine agonist therapy, and this may have biased the results.

Although further study is needed to compare the efficacy of tolcapone and bromocriptine, this study shows that the two drugs have a different side effect profile, tolcapone being easier and quicker to titrate compared with bromocriptine.

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REFERENCES

1. Cedarbaum JM. Clinical pharmacokinetics of anti-parkinsonian drugs. *Clin Pharmacokinet* 1987;13:141–178.
2. Mouradian MM, Chase TN. Levodopa response fluctuations in Parkinson's disease. *Clin Neuropharmacol* 1988;11:378–385.
3. Rinne UK. Problems associated with long-term levodopa treatment of Parkinson's disease. *Acta Neurol Scand Suppl* 1983;95: 19–26.
4. LeWitt PA. Treatment strategies for extension of levodopa effect. *Neurol Clin* 1992;10:511–526.
5. Reilly DK, Rivera-Calimlim L, van Dyke D. Catechol-O-methyltransferase activity: a determinant of levodopa response. *Clin Pharmacol Ther* 1980;28:278–286.
6. Wade LA, Katzman R. 3-O-Methyldopa uptake and inhibition of L-dopa at the blood–brain barrier. *Life Sci* 1975;17:131–136.
7. Männistö PT, Ulmanen I, Lundström K, et al. Characteristics of catechol-O-methyltransferase (COMT) and properties of selective COMT inhibitors. *Prog Drug Res* 1992;39:291–350.
8. Männistö PT. Clinical potential of catechol-O-methyltransferase (COMT) inhibitors as adjuvants in Parkinson's disease. *CNS Drugs* 1994;1:172–179.
9. Zürcher G, Colzi A, Da Prada M. Ro 40-7592: inhibition of COMT in rat brain and extracerebral tissues. *J Neural Transm Suppl* 1990; 32:375–380.
10. Da Prada M, Zürcher G, Kettler R, Colzi A. New therapeutic strategies in Parkinson's disease: inhibition of MAO-B by Ro 19-6327 and of COMT by Ro 40-7592. *Adv Behav Biol* 1991;39:723–732.
11. Borgulya J, Da Prada M, Dingemanse J, Scherschlicht R, Schläppi B, Zürcher G. Ro 40-7592: catecholamine-O-methyltransferase (COMT) inhibitor. *Drugs Future* 1991;16:719–721.
12. Dingemanse J, Jorga K, Zürcher G, et al. Pharmacokinetic-pharmacodynamic interaction between the COMT inhibitor tolcapone and single-dose levodopa. *Br J Clin Pharmacol* 1995;40: 253–262.
13. Anonymous. Levodopa. In: Dollery C, ed. *Therapeutic Drugs,* vol 2. Edinburgh: Churchill Livingstone, 1991:L10–L15.
14. Montastruc J-L, Rascol O, Senard JM. Current status of dopamine agonists in Parkinson's disease management. *Drugs* 1993;46:384–393.
15. Agid Y, Destée A, Durif F, Montastruc JL, Pollak P, on behalf of the French Tolcapone Study Group. Tolcapone, bromocriptine, and Parkinson's disease. *Lancet* 1997;350:712–713.
16. Lang AE, Fahn S. Assessment of Parkinson's disease. In: Munsant TL, ed. *Quantification of Neurological Deficit.* Woburn, MA: Butterworths, 1989:285–309.

17. Mouradian MM, Heuser IJE, Baronti F, Chase TN. Modification of central dopaminergic mechanisms by continuous levodopa therapy for advanced Parkinson's disease. *Ann Neurol* 1990;27: 18–23.
18. Baas H, Beiske AG, Ghika J, et al. Catechol-O-methyltransferase inhibition with tolcapone reduces the 'wearing off' phenomenon and levodopa requirements in fluctuating parkinsonian patients. *J Neurol Neurosurg Psychiatry* 1997;63:421–428.
19. Rajput AH, Martin W, Saint-Hilaire MH, Dorflinger E, Pedder S. Tolcapone improves motor function in parkinsonian patients with the 'wearing-off' phenomenon: a double-blind, placebo-controlled, multicenter trial. *Neurology* 1997;49:1066–1071.
20. Kurth MC, Adler CH, Saint Hilaire M-H, et al. Tolcapone improves motor function and reduces levodopa requirements in patients with Parkinson's disease experiencing end-of-dose motor fluctuations. *Neurology* 1997;48:81–87.
21. Myllylä VV, Jackson M, Larsen JP, Baas H. Efficacy and safety of tolcapone in levodopa-treated Parkinson's disease patients with 'wearing-off' phenomenon: a multicentre, double-blind, randomized, placebo-controlled trial. *Eur J Neurol* 1997;4:333–341.