REVIEW ARTICLE

Drugs 2000 Jun; 59 (6): 1233-1250
0012-6667/00/0006-1233/$25.00/0

Clinical Pharmacology, Therapeutic Use and Potential of COMT Inhibitors in Parkinson's Disease

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Abstract

When peripheral decarboxylation is blocked by carbidopa or benserazide, the main metabolic pathway of levodopa is *O*-methylation by catechol-*O*-methyltransferase (COMT). Entacapone and tolcapone are new potent, selective and reversible nitrocatechol-type COMT inhibitors. Animal studies have demonstrated that entacapone mainly has a peripheral effect whereas tolcapone also inhibits *O*-methylation in the brain. In human volunteers, both entacapone and tolcapone dose-dependently inhibit the COMT activity in erythrocytes, improve the bioavailability and decrease the elimination of levodopa, and inhibit the formation of 3-*O*-methyldopa (3-OMD). Entacapone is administered with every scheduled dose of levodopa whereas tolcapone is administered 3 times daily. The different administration regimens for these agents are based on their different pharmacokinetic and pharmacodynamic profiles.

Both entacapone and tolcapone enhance and extend the therapeutic effect of levodopa in patients with advanced and fluctuating Parkinson's disease. They prolong the duration of levodopa effect. Clinical studies show that they increase the daily ON time by an average 1 to 3 hours, improve the activities of daily living and allow daily levodopa dosage to be decreased. Correspondingly, they significantly reduce the daily OFF time. No comparative studies between entacapone

and tolcapone have been performed. Tolcapone also appears to have a beneficial effect in patients with nonfluctuating Parkinson's disease.

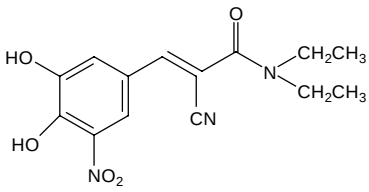
The main adverse effects of the COMT inhibitors are related to their dopaminergic and gastrointestinal effects. Enhancement of dopaminergic activity may cause an initial worsening of levodopa–induced adverse effects, such as dyskinesia, nausea, vomiting, orthostatic hypotension, sleep disorders and hallucinations. Levodopa dose adjustment is recommended to avoid these events. Tolcapone is associated with diarrhoea in about 16 to 18% of patients and entacapone in less than 10% of patients. Diarrhoea has led to discontinuation in 5 to 6% of patients treated with tolcapone and in 2.5% of those treated with entacapone. Urine discoloration to dark yellow or orange is related to the colour of COMT inhibitors and their metabolites. Elevated liver transaminase levels are reported in 1 to 3% of patients treated with tolcapone but very rarely, if at all, in patients treated with entacapone. The descriptions of acute, fatal fulminant hepatitis and potentially fatal neurological reactions, such as neuroleptic malignant syndrome and rhabdomyolysis, in association with tolcapone led to the suspension of its marketing authorisation in the European Community and Canada. In many other countries, the use of tolcapone is restricted to patients who are not responding satisfactorily to other therapies. Regular monitoring of liver enzymes is required if tolcapone is used. No such adverse reactions have so far been described for entacapone and no laboratory monitoring has been proposed.

COMT inhibitors added to levodopa therapy are beneficial, particularly in patients with fluctuating disease. They may be combined with other antiparkinsonian drugs, such as dopamine agonists, selegiline and anticholinergics without adverse interactions. They provide a new treatment possibility in patients with Parkinson's disease who have problems with their present levodopa therapy.

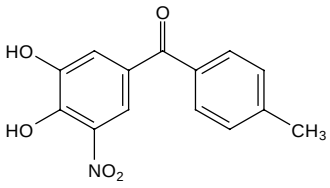
Catechol *O*-methyltransferase (COMT) is an intracellular enzyme that is widely distributed in the body. COMT catalyses the transfer of the methyl group of S-adenosyl-L-methionine to one of the hydroxyl groups of a catechol substrate.[1] The physiological substrates include dopa, dopamine, noradrenaline, adrenaline, their hydroxylated metabolites and catecholestrogens.[2] In addition, several medicinal substances with a catechol structure are substrates, for example, apomorphine, benserazide, carbidopa, dobutamine, isoprenaline, methyldopa and rimiterol. The general function of COMT is the elimination of biologically active or toxic catechols and some other hydroxylated metabolites.

The first COMT inhibitors were described in 1960s.[2] Several of these compounds, for example, the gallates, U-0521 and tropolone, have been used as *in vitro* tools. Since they are unselective, nonpotent and quite toxic they were not particularly suitable for clinical purposes. However, butylgallate and U-0521 were tested in a few patients with Parkinson's disease in combination with levodopa but the results were not very promising.[3,4]

The interest in COMT inhibitors revived in 1980s when new, potent and selective inhibitors were developed.[5-7] Nearly all of them have a nitrocatechol structure. The exception is CGP-28014 which is a pyridine derivative. Two of them, namely entacapone and tolcapone (fig. 1), have been widely studied in Parkinson's disease and are now available for clinical use in many countries (see section 9 for details of the suspension of and restrictions for the use of tolcapone). Their properties will be described in detail in this article. Some clinical data are also available on nitecapone[8,9] and CGP-28014.[10,11] Apparently they were not further developed for Parkinson's disease or other neurological indications and therefore are not discussed here.



Entacapone



Tolcapone

Fig. 1. Chemical structures of entacapone and tolcapone.

1. Rationale for the Use of Catechol-*O*-methyltransferase (COMT) Inhibitors in Parkinson's Disease

The main clinical application of COMT inhibitors is as adjuncts in levodopa therapy, which is still the most effective agent for treating patients with Parkinson's disease. Levodopa is extensively metabolised in the periphery (fig. 2) and therefore less than 1% of the dose reaches the brain. The most important metabolic pathway for levodopa is decarboxylation by dopa decarboxylase (DDC) or L-aromatic amino acid decarboxylase to dopamine. The introduction of the peripheral DDC inhibitors benserazide and carbidopa has largely eliminated this pathway allowing the effective dose of levodopa to be reduced by about 75%. *O*-methylation to 3-*O*-methyldopa (3-OMD) becomes the predominant metabolic pathway for eliminating levodopa when DDC is inhibited. The main formation of 3-OMD occurs in the peripheral organs, such as liver, kidney and gut, where the highest COMT activities are found. During chronic levodopa therapy, 3-OMD accumulates as its elimination half-life ($t_{½\beta}$) is long, about 15h, compared with about 1h for levodopa. This metabolite has no therapeutic value. On the contrary, it has been associated with fluctuations in levodopa treatment[12-14] and may compete with levodopa for transport across intestinal mucosa and the blood-brain barrier.[15]

When a COMT inhibitor is coadministered with levodopa/DDC inhibitor the following potential benefits may be anticipated:

- decreased elimination of levodopa or prolonged levodopa $t_{½\beta}$
- increased area under the concentration time curve (AUC) of levodopa
- reduced formation of 3-OMD
- improved delivery of levodopa to the brain
- reduced levodopa dose and administration frequency
- improved and prolonged clinical response to levodopa

These advantages can be obtained by peripheral COMT inhibition only. Central COMT inhibition might further potentiate the effect of levodopa by inhibiting its conversion to 3-OMD and the metabolism of dopamine to 3-methoxytyramine (fig. 2).

COMT inhibitors could also potentiate or prolong the action of other compounds with a catechol structure. One such drug is apomorphine, an effective dopaminergic agent with antiparkinsonian activity. It is *O*-methylated although it has also other metabolic pathways.[16] Animal studies indicate

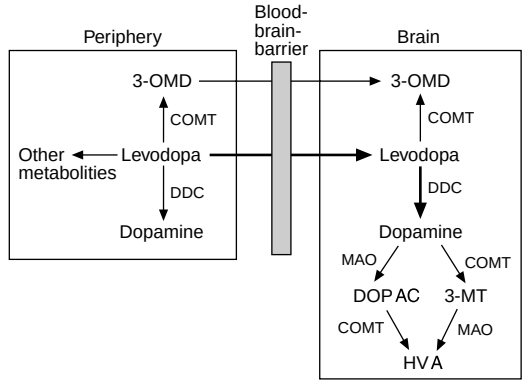


Fig. 2. Metabolic pathways of levodopa. **3-MT** = 3-methoxytyramine; **3-OMD** = 3-*O*-methyldopa; **COMT** = catechol-*O*-methyltransferase; **DDC** = dopa decarboxylase; **DOPAC** = 3,4,-dihydroxyphenylacetic acid; **HVA** = 3-methoxy-4-hydroxyphenylacetic acid or homovanillic acid; **MAO** = monoamine oxidase.

that a COMT inhibitor increases the bioavailability and dopaminergic effects of apomorphine.[17,18] However, no clinical results of the combination of apomorphine and a COMT inhibitor are so far available. Another compound with a catechol structure is the very potent dopamine D1 receptor agonist, dihydrexidine.[19] It has antiparkinsonian efficacy in animal studies and a COMT inhibitor would possibly enhance its efficacy.

2. Human Pharmacokinetics of COMT Inhibitors

Both entacapone and tolcapone are rapidly and dose-proportionally absorbed after oral administration, with maximum plasma concentrations (C_{max}) usually reached within 0.5 to 2h.[20,21] Oral bioavailability of tolcapone (60%) is about double that of entacapone (35%). Clearly higher C_{max} and AUC values are obtained with tolcapone than with entacapone, mainly because of the better bioavailability and lower clearance of tolcapone (fig. 3; table I).

The volume of distribution at steady state is small, 10 to 20L for both compounds. Tolcapone is more highly bound to plasma proteins (99.9%) than entacapone (98%). This may indicate more interactions in protein binding with tolcapone. At therapeutic doses, the COMT inhibitors are rapidly eliminated, with an apparent half-life ($t_{½}$) of 1.5 to 3h after oral administration. After intravenous administration, entacapone has shorter $t_{½\beta}$, about 0.5h, than tolcapone, about 1.3h (table I).

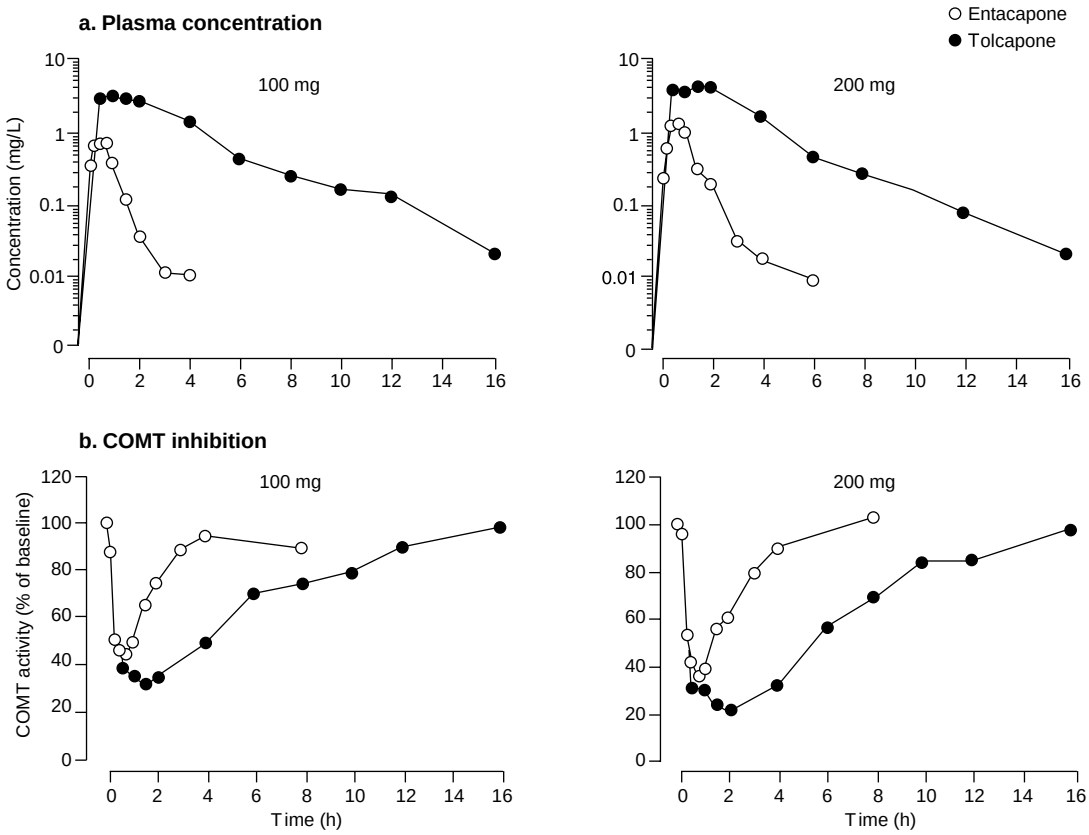


Fig. 3. Plasma concentrations (**a**) and catechol-*O*-methyltransferase (COMT) inhibition in erythrocytes (**b**) after administration of entacapone[20] and tolcapone[21] as a single 100 or 200mg dose in healthy volunteers.

Table I. Pharmacokinetics of catechol-*O*-methyl transferase (COMT) inhibitors (mean values) in healthy volunteers after oral and intravenous administration

	Entacapone[20,22]		Tolacapone[21,23]	
Oral	100mg	200mg	100mg	200mg
C_{max} (mg/L)	1.1	1.8	4.6	5.7
t_{max} (h)	0.6	0.7	1.7	1.8
$AUC_{0-\infty}$ (h • mg/L)	0.7	1.6	12.2	17.5
$t_{½\beta}$ (h)	1.6	3.4	2.0	1.8
F (%)	32	36	na	60
Intravenous	25mg		50mg	
$t_{½\beta}$	0.4		1.3	
V_{ss} (L)	19.9		8.6	
CL (L/h)	51.8		7.1	
Unbound fraction (%)	2		0.1	

$AUC_{0-\infty}$ = area under the plasma concentration time curve from zero time to infinity; **C_{max}** = maximum (peak) plasma concentration; **CL** = total body clearance; **F** = fraction of administered dose systemically available; **na** = not available; **$t_{½}$** = plasma half-life; **$t_{½\beta}$** = elimination half-life; **t_{max}** = time to reach C_{max}; **V_{ss}** = apparent volume of distribution at steady state.

Entacapone and tolcapone are highly metabolised, mainly in the liver. Most of the absorbed entacapone is eliminated via the biliary route[22,24] whereas a smaller amount of tolcapone, about 40% of the dose, is excreted in the faeces.[25] Only 0.5% or less of an oral dose of both compounds is excreted unchanged in the urine. The main urinary metabolite is the glucuronide of the parent compound, representing 70% and 30% of the metabolites of entacapone and tolcapone, respectively.[24,26] Entacapone (the E-isomer of the molecule) has one active metabolite, the Z-isomer, which accounts for only 5% of the total plasma AUC of both isomers.[20,24] Entacapone is not *O*-methylated in humans, whereas about 3% tolcapone is converted to 3-*O*-methyltolcapone. This metabolite has a long $t_{½\beta}$ of 35h,[21] which may suggest that accumulation could occur. However, during long term administration only minor accumulation of 3-*O*-methyltolcapone was detected due to the suppression of its formation by tolcapone itself (by COMT inhibition).[27] In contrast to entacapone, about 3% of tolcapone is oxidised by cytochrome P-450 (CYP) isoenzymes (CYP3A4 and CYP2A6) to active alcohol and carboxyl acid metabolites.[26] Tolcapone did not change the pharmacokinetics and pharmacodynamics of tolbutamide, an agent metabolised by CYP2C9, suggesting that a clinically relevant interaction between tolcapone and this isoenzyme is unlikely.[28]

As expected, during chronic administration at therapeutic doses neither entacapone nor tolcapone accumulate in plasma.[27,29,30] The combination of levodopa and a DDC inhibitor with entacapone or tolcapone does not significantly affect entacapone and tolcapone pharmacokinetics.[29,31] A dosage reduction for entacapone and tolcapone is recommended in patients with liver impairment because of increased bioavailability and reduced clearance of the COMT inhibitors.[32,33] In fact, entacapone is not recommended for patients with liver impairment since there is currently only a 200mg tablet available which cannot be halved.[34]

3. COMT Inhibition

Nitrocatechols are so called tight-binding inhibitors of COMT, although their binding to COMT is fully reversible when studied *in vitro*.[35-37] In addition, *in vivo* they reversibly and dose-dependently inhibit the COMT activity in human erythrocytes.[20,21] Tolcapone appears to be more potent than entacapone, as evaluated by both maximum inhibition and duration of inhibition. After a single dose of entacapone 200mg, the COMT activity has fully recovered within 8h whereas the corresponding time is about double after tolcapone administration (fig. 3b). During repeated administration of entacapone or tolcapone, no tolerance develops to their inhibitory activities.[27,29]

4. Levodopa Pharmacokinetics

Entacapone and tolcapone dose-dependently increase the AUC of levodopa in healthy volunteers, without significantly changing the C_{max} value[31,38-40] (table II). Higher than therapeutic doses (400mg) may retard the absorption of levodopa, as observed in prolonged time to reach C_{max} (t_{max}).[31,38,39]

At single doses of 100 to 200mg, tolcapone appears to be more potent than entacapone in increasing the AUC of levodopa in line with its higher plasma concentration (fig. 4a). Multiple administration of entacapone or tolcapone does not alter their effects on levodopa pharmacokinetics.[27,29,30] The type of DDC inhibitor (carbidopa or benserazide) used with levodopa does not essentially affect the pharmacokinetic effects of COMT inhibitors.[40-42] Both entacapone and tolcapone are also effective in combination with controlled release levodopa preparations.[40,42,43] In combination with a controlled release levodopa preparation, entacapone appears to slightly increase the C_{max} of levodopa whereas tolcapone increases the t_{max} value of levodopa.[42,43]

When studied in patients with Parkinson's disease both entacapone and tolcapone significantly increase the AUC and $t_{½\beta}$ of levodopa. The increase in AUC and $t_{½\beta}$ after tolcapone 200mg has been equal or slightly greater than after entacapone 200mg (table III). However, there are no published data on levodopa pharmacokinetics in patients with Parkinson's disease after a single dose of tolcapone 100mg, which is the recommended initial dose for tolcapone.

After 8 weeks treatment with tolcapone up to 200mg 3 times daily, AUC values of levodopa increase by 33%.[51] The corresponding figure after 8-weeks treatment with entacapone (1200 mg/day) was slightly better at 43%.[47] The latter study is notable because repeated plasma samples were taken throughout the day. This study demonstrated that during entacapone treatment, the mean daily levodopa concentration increases despite the reduction of levodopa dose (-27%) and the daily variation in plasma levodopa concentrations significantly decreases. This would indicate less fluctuation in clinical disability in patients with Parkinson's disease, as was also found by Nutt et al.[47] As was noted in the study in volunteers,[43] entacapone (200mg 3 or 4 times daily) for 10 days led to a significant increase in the AUC of levodopa in patients with Parkinson's disease receiving either standard or controlled release levodopa formulations.[52] In this study, entacapone increased levodopa C_{max} in patients receiving a controlled release levodopa preparation but not in those receiving a standard levodopa preparation. No pharmacokinetic data for levodopa are available when tolcapone is administered in combination with a controlled release levodopa preparation in patients with Parkinson's disease.

Table II. The effect of catechol-*O*-methyl transferase (COMT) inhibitors on levodopa pharmacokinetics and metabolism in healthy volunteers after single dose administration in combination with levodopa/carbidopa 100/25mg

Parameter	Entacapone[38]		Tolcapone[39]	
	100mg	200mg	100mg	200mg
t_{max}	no change	no change	no change	no change
C_{max}	no change	no change	no change	no change
Levodopa $AUC_{0-\infty}$	+29%	+42%	+50%	+88%
Levodopa $t_{½\beta}$	no change	no change	+32%	+60%
3-OMD $AUC_{0-\infty}$	–35%[a]	–46%[a]	–64%	–64%
DOPAC $AUC_{0-\infty}$	+149%[b]	+214%[b]	+175%	+253%
HVA $AUC_{0-\infty}$	no change	no change	–52%	–54%

a AUC_{0-10h}.

b $AUC_{0\text{-last determinable concentration}}$.

3-OMD = 3-O-methyldopa; **AUC** = area under the plasma concentration time curve; **C_{max}** = maximum (peak) plasma concentration; **DOPAC** = 3,4,-dihydroxyphenylacetic acid; **HVA** = 3-methoxy-4-hydroxyphenylacetic acid or homovanillic acid; **t_{max}** = time to C_{max}.

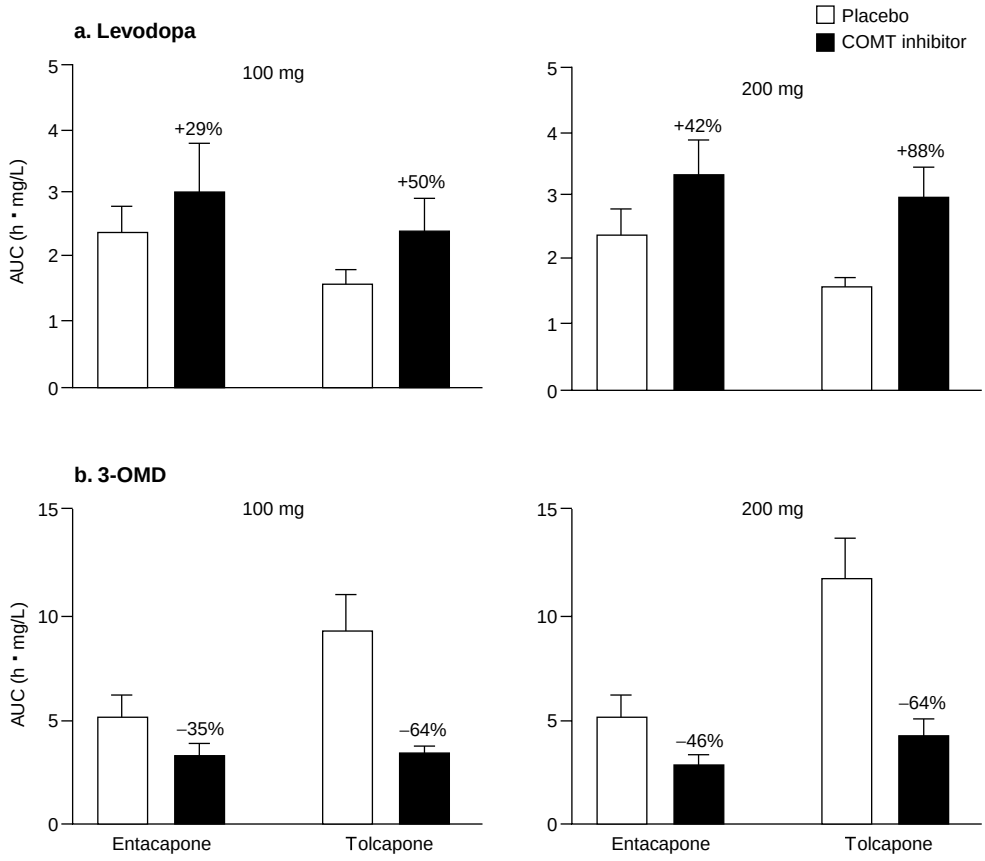


Fig. 4. Increase in area under the plasma concentration time curve (AUC) of levodopa (**a**) and decrease in the AUC of 3-*O*-methyldopa [3-OMD] (**b**) after administration of entacapone 100 or 200mg[38] and tolcapone 100 or 200mg[39] in combination with levodopa/carbidopa 100/25mg in healthy volunteers. **COMT** = catechol-*O*-methyltransferase.

5. 3-*O*-Methyldopa Levels

As would be expected, the COMT inhibitors reduce the formation of 3-OMD both in healthy volunteers and patients with Parkinson's disease. Since 3-OMD has a long $t_{1/2}$, about 15h,[53] the inhibition of 3-OMD formation in patients with Parkinson's disease can only be observed after chronic treatment with COMT inhibitors. In healthy volunteers, single doses of entacapone and tolcapone dose-dependently suppress the formation of 3-OMD[31,38,39] (table II, fig. 4b). A similar inhibition of 3-OMD formation has also been observed after entacapone and tolcapone in combination with controlled release levodopa formulations.[42,43] One to 2 months' treatment with entacapone at recommended clinical doses (200mg with each levodopa dose) inhibits the formation of 3-OMD by 45 to 63%.[45,47,54] The corresponding figure after 2-months of tolcapone (200mg 3 times daily) was 79%.[51] There are no data available on changes in 3-OMD pharmacokinetics after administration of tolcapone 100mg 3 times daily.

6. Peripheral Catecholamine Metabolism

Since the COMT enzyme is involved in the metabolism of dopamine, noradrenaline and adrenaline, it is possible that COMT inhibitors affect peripheral catecholamine metabolism. Treatment with

Table III. The effect of a single 200mg dose of entacapone and tolcapone on levodopa AUC and $t_{½β}$ in patients with Parkinson's disease

COMT inhibitor	AUC (%)	$t_{½β}$ (%)	Reference
Entacapone	+23[a]	+39	44
	+29[a]	+17	45
	+46[b]	+32	46
	+48[c]	+75	47
Tolcapone	+32	+77	48
	+53[c,d]	+32[d]	49
	+58[c]	+79	50

a $AUC_{0\text{-}4h}$.

b $AUC_{0\text{-}6h}$.

c $AUC_{0\text{-}\infty}$.

d 400mg.

AUC = area under the plasma concentration time curve; **COMT** = catechol-*O*-methyl transferase; $t_{½β}$ = elimination half-life.

a single dose (up to 200mg) or repeated doses (400 or 800mg 3 times daily for 1 week) of entacapone has no effect on plasma catecholamine levels at rest or during exercise but significantly changes the metabolic profile of catecholamines.[55,56] After entacapone administration, plasma concentrations of the monoamine oxidase (MAO)-dependent metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and 3,4-dihydroxyphenyl glycol (DHPG), increase, whereas those of the COMT-dependent metabolite, 3-methyl 4-hydroxyphenylethylene glycol (MHPG), decrease. COMT inhibitors substantially increase the plasma levels of DOPAC and generally decrease the levels of HVA, when studied in healthy volunteers[38,39,43,57] (table II).

In patients with Parkinson's disease, a single dose of entacapone 200mg in combination with levodopa and benserazide does not alter the plasma levels of dopamine or noradrenaline but decreases those of MHPG.[58] In contrast to entacapone, tolcapone has been reported to significantly elevate plasma dopamine levels.[59] Treatment with entacapone or tolcapone decreases plasma HVA levels and increases DOPAC levels in patients with Parkinson's disease.[46,54,58,60]

The results suggest that the free plasma levels of catecholamines are probably not substantially increased by COMT inhibitors. This is an important safety aspect for the use of COMT inhibitors. The results also suggest that the combination of a COMT inhibitor with the present fixed ratio levodopa/DDC inhibitor formulations may lead to some peripheral levodopa being converted to dopamine and further to DOPAC, since the extent of DDC inhibition may not be sufficient. It should be noted that neither entacapone nor tolcapone increase plasma carbidopa concentrations despite the fact that carbidopa is a weak substrate for COMT *in vitro*.[34,61] Oechsner et al.[59] have suggested that the dose of the DDC inhibitor should be increased when combined with tolcapone to avoid the peripheral adverse effects of dopamine. Different dose ratios of COMT inhibitor, levodopa and DDC inhibitor are worth testing to identify the optimum dose ratios.

7. Positron Emission Tomography (PET) Studies

6-[^{18}F]-fluorodopa (6-FD) is an analogue of levodopa. It is widely used in positron emission tomography (PET) studies as a tracer of the dopaminergic system. Like levodopa, it is decarboxylated by DDC to [^{18}F]-dopamine and *O*-methylated by COMT to 3-*O*-methyl-[^{18}F]-dopa (3-OMFD). In routine PET studies 3-OMFD represents a considerable proportion of the radioactivity in both plasma and brain.[62,63] Various kinetic models have been used to differentiate the specific from nonspecific activity. Selective COMT inhibition would reduce the formation of 3-OMFD, simplify PET modelling, and improve the quality of PET images. In addition, PET provides an *in vivo* method to test whether peripheral COMT inhibition actually increases the availability of 6-FD (a marker of levodopa) to the brain.

Both entacapone and tolcapone when given in combination with 6-FD and a DDC inhibitor, significantly reduce the plasma levels of 3-OMFD in monkeys.[64-68] The decreased peripheral metabolism of 6-FD after COMT inhibition is reflected as an increased striatal uptake of 6-FD and significantly better PET image contrast.

The human PET studies with COMT inhibitors have been performed either with entacapone or nitecapone, another peripherally acting COMT inhibi-

tor.[69] No published data on PET studies with tolcapone in humans are available. Entacapone has significantly improved the ratio of the activity in the striatum versus the occipital lobe or cerebellum both in normal volunteers and in patients with Parkinson's disease. The improvement has varied from 2 to 41%.[70-73] The patients with a short history of Parkinson's disease have shown better striatal uptake of 6-FD than those with advanced disease. The probable explanation is that the 6-FD storage capacity in striatum decreases with degenerating dopaminergic neurons.

To conclude, PET studies with 6-FD demonstrate that the peripheral COMT inhibitors substantially improve the brain entry of 6-FD. Consequently, it is likely that such an effect is also obtained in clinical practice with the combination of a levodopa/DDC inhibitor and a COMT inhibitor.

8. Clinical Efficacy

Both entacapone and tolcapone have been effective in several non-blind and double-blind clinical studies. Because of differences in patient materials, study designs, treatment periods, medications and statistical analyses, comparing the results achieved with these two inhibitors is complicated. With these reservations, some of the clinical results are collated in tables IV and V. All studies with entacapone and most of the studies with tolcapone have been conducted in patients with Parkinson's disease who were experiencing clinical fluctuations, that is, end-of-dose deterioration (wearing off) and dyskinesias.

The dose of entacapone 200mg with each levodopa and DDC inhibitor dose up to 10 times per day has been selected for clinical use, mainly based on the results of a dose-response study.[44] The compatible pharmacokinetic profiles of levodopa and entacapone also favour this administration regimen. The dose-response relationship for tolcapone has not been very consistent in single-dose studies.[50,60,83,84] In long term studies, the daily dosages of tolcapone have varied from 50 to 400mg 3 times daily. Even in these studies, the differences between 4 dose levels have been ambiguous (see table V). At present, the manufacturer recommends that tolcapone should be initiated at a dosage of 100mg 3 times daily together with the first levodopa dose, then at 6-hourly intervals with a 12–hour night-time break.[25] The dosage can be increased to 200mg 3 times daily but dopaminergic adverse reactions may be a limiting factor.

Both entacapone and tolcapone as single doses with levodopa and DDC inhibitor prolong the motor response (the so-called ON time) to levodopa (table IV). The conclusion from these results is that there are apparently no marked differences between the two compounds.

The efficacy of entacapone in patients with fluctuating Parkinson's disease has been elucidated in 2 double-blind studies of 6 months duration[76,77] and that of tolcapone in several double-blind studies of 6 weeks and 3 months formal duration[78-82] (table V). Both entacapone and tolcapone significantly increase the ON time and correspondingly decrease the OFF time in patients with advanced Parkinson's disease. The net increase (placebo effect deducted) in daily ON time has varied from about 1 to 2h with entacapone and from about 0 to 2.5h with tolcapone (table V). The clinical efficacy of COMT inhibitors is observed within a few days after treatment initiation, as would be expected as even a single dose of a COMT inhibitor increases the AUC and $t_{1/2}$ of levodopa. In line with their effect on levodopa pharmacokinetics, COMT inhibitors permit a reduction in daily levodopa dose. The average daily dose reduction has been about 100 to 200mg. The intensification of dyskinesias by COMT inhibitors is the most important reason for dose reduction. In case the patient has pronounced peak-dose dyskinesia it is advisable to reduce the amount of single doses of levodopa. In other patients it may be more reasonable to increase the levodopa administration interval.

After withdrawal of entacapone or tolcapone, a rapid worsening of Parkinson's disease symptoms is observed and a levodopa dose adjustment upwards is needed.[61,76,77]

COMT inhibitors have also had a beneficial effect on other efficacy parameters. For instance, en-

Table IV. Clinical efficacy of entacapone and tolcapone in single dose studies compared with placebo

COMT inhibitor	N	Dose (mg)	Method	Increase in ON time (min)	Increase in ON time (%)	Reference
Entacapone	19	50	motor UPDRS	≈20	≈12	44
	19	100	"	≈23	≈14	
	19	200	"	33	21	
	19	400	"	≈28	≈17	
	19	200	tapping test	62	81	
	19	400	"	51	66	
	12	200	tapping test	35	27	74
	10	800	"	39	30	
	13	200	tapping test	36	40	47
	8	200	walking test	72	75	
	12	200	motor UPDRS	54	39	45
Tolcapone	10	50	motor UPDRS	57	75	49
	5	100	"	54	69	
	10	200	"	15	15	
	9	400	"	63	70	
	10	50	motor UPDRS	16	11	75
	4	100	"	62	42	
	9	200	"	51	38	
	9	400	"	59	43	
	6	800	"	137	122	
	10	200	motor UPDRS	62	65	50
	10	400	"	72	77	

COMT = catechol-*O*-methyl transferase; **N** = no of patients; **UPDRS** = Unified Parkinson's Disease Rating Scale.

tacapone has potentiated the magnitude of the levodopa effect, that is, the motor part of Unified Parkinson's Disease Rating Scale (UPDRS) has significantly improved,[76,77] even though the patients were tested in ON phase. A similar tendency has been observed in long term studies with tolcapone.[78,80-82] Tolcapone has clearly decreased the motor scores of UPDRS when evaluated every 30 minutes for 10 hours after 42-days treatment.[79] The activities of daily living (ADL) score has also improved in most of these studies, indicating significant subjective benefit for patients. Furthermore, investigators' global measures of disease severity indicate that both entacapone and tolcapone have positive effects on Parkinson's disease symptoms. The patients' self-reported global evaluations demonstrate similar positive results in long term studies with entacapone.

The clinical efficacy of tolcapone has also been investigated in patients with nonfluctuating Parkinson's disease. One of these studies included patients with Parkinson's disease whose fluctuations were controlled by more frequent levodopa administration.[85] At 6 weeks, the tolcapone groups (200 and 400mg 3 times daily) had a moderately greater levodopa dose reduction than the placebo group (about 180mg for tolcapone and 110mg for placebo). The only statistically significant clinical benefit of tolcapone over placebo was observed in UPDRS subscale II (ADL) with the 200mg dose. In another study, patients with wearing off phenomena were excluded. Thus, the patients in this study represent those with true nonfluctuating Parkinson's disease.[86] At 6 months, tolcapone (100 or 200mg 3 times daily) produced a significant improvement in disability, as assessed by UPDRS part II (ADL) and part III (motor) and quality of life measures. Levodopa dosages were slightly but significantly decreased in the tolcapone groups (by about 30 mg). The beneficial effects of tolcapone were still maintained at 12 months.

One open-label study has been performed to compare the effects of tolcapone and bromocript-

ine.[87] Tolcapone 200mg 3 times daily or bromocriptine titrated up to 10mg 3 times daily in combination with levodopa was administered to 146 patients with fluctuating Parkinson's disease for 8 weeks. The mean levodopa dose reduction was greater in tolcapone group (120mg) than the bromocriptine group (30mg). Both treatments increased ON time, decreased OFF time, and improved UPDRS ADL and motor scores with tolcapone being slightly more effective than bromocriptine. No comparative data between entacapone and dopamine agonists are available.

The efficacy studies with COMT inhibitors demonstrate that their beneficial effects on levodopa pharmacokinetics and metabolism are also reflected on a patient level as an improved therapeutic effect. However, since there have been no studies performed directly comparing entacapone and tol-

Table V. Clinical efficacy of catechol-*O*-methyl transferase (COMT) inhibitors in long term placebo-controlled double-blind studies in patients with fluctuating Parkinson's disease. Entacapone (200mg) was administered with each levodopa dose whereas tolcapone was given three times daily. An overall treatment effect is given, that is, placebo effect has been deducted (for tolcapone, no overall treatment effects are given in original publications, thus approximate results were calculated)

COMT inhibitor	N (agent)	Dosage (mg/day)	Duration/design	Method	ON time increase (h)	OFF time decrease (h)	Decrease in levodopa dose (mg)	Reference
Entacapone	23	800-2000	4 weeks cross-over	patient diary (18h)	2.1	NA	140	54
	102 (P)		6 months parallel	patient diary (24h)				76
	103 (E)	800-2000			≈1	≈1	100	
	86 (P)		6 months parallel	patient diary (18h)				77
	85 (E)	800-2000			1.2	1.3	100	
Tolcapone	72 (P)		6 weeks parallel	patient diary (16h)				78
	69 (T)	300			1.8	1.7	190	
	74 (T)	600			2.0	2.3	250	
	42 (P)		6 weeks parallel	patient diary (16h)				79
	41 (T)	150			0.5	1.3	110	
	40 (T)	600			±0	0.9	170	
	38 (T)	1200			1.4	2.8	140	
	37 (P)		6 weeks parallel	patient diary (16h)				80
	34 (T)	150			2.2	1.1	60	
	31 (T)	600			2.4	1.7	80	
	31 (T)	1200			2.1	1.1	10	
	58 (P)		3 months	patient diary (16h)				81
	60 (T)	300			1.8	1.3	80	
	59 (T)	600			1.8	0.9	90	
	66 (P)		3 months	patient diary (16h)				25, 82
	69 (T)	300			0.6	0.9	180	
	67 (T)	600			1.5	1.8	220	

E = entacapone; **N** = no of patients; **na** = not available; **P** = placebo; **T** = tolcapone.

capone it is not possible to conclude whether there are any significant differences in their clinical efficacy.

9. Tolerability

The COMT inhibitors have been generally well tolerated.[34,61] The most frequent adverse events are presented in table VI. The main adverse effects experienced by patients during entacapone and tolcapone therapy are related to their dopaminergic and gastrointestinal effects. The most commonly observed dopaminergic adverse event with both drugs is dyskinesia. The COMT inhibitors may either worsen pre-existent dyskinesia or cause new dyskinesias. The risk of dyskinesia is highest during the first weeks of therapy. To reduce the severity of dyskinesia it is necessary to adjust the levodopa dosage within the first days after initiating treatment with a COMT inhibitor. In particular, a dose reduction has to be considered in patients with high daily levodopa doses (≈600mg or more). A dose reduction of 10 to 30% is recommended.[34,88] In controlled studies, the dose adjustment appears to have been successful since premature termination rate due to dyskinesia was low, being 1.7% with entacapone and 0.3 to 1.0% with tolcapone.[34,61] The combination of a COMT inhibitor (+levodopa/DDC inhibitor) with a dopamine agonist and/or selegiline increases the possibility of dyskinesia.

Nausea, anorexia, vomiting, orthostatic hypotension, sleep disorders and hallucinations are other dopaminergic events, which may be potentiated by a COMT inhibitor. Nausea appears to be the most frequent adverse event with tolcapone in patients with stable disease.[86] Regarding psychiatric symptoms, hallucinations developed in 8 to 10% of tolcapone-treated and in 3% of entacapone-treated patients (table VI). Three elderly patients (68, 79 and 87 years of age) with severe Parkinson's disease developed acute confusion with tolcapone treatment which was reversed after its withdrawal.[89]

Table VI. The most frequent adverse events (% of patients) occurring in placebo-controlled, double-blind studies (events occurring >5% in any group are presented)[34,61]

Adverse event	Entacapone (n = 406)	Placebo (n = 296)	Tolcapone 100mg tid (n = 296)	Tolcapone 200mg tid (n = 298)	Placebo (n = 298)
Dyskinesia	27.3	13.9	41.9	51.3	19.8
Nausea	11.1	6.4	30.4	34.9	17.8
Insomnia	4.4	3.7	23.6	24.8	18.1
Anorexia	<2	<2	18.9	22.8	12.8
Dystonia	2.7	2.4	18.6	22.1	17.1
Excessive dreaming	2.0	1.4	21.3	16.4	17.1
Diarrhoea	8.4	3.0	15.5	18.1	7.7
Somnolence	4.2	2.4	17.9	14.4	13.4
Orthostatic symptoms	2.0	2.0	16.6	16.8	13.8
Dizziness	7.4	5.4	13.2	6.4	9.7
Urine discoloration	12.6	0	2.4	7.4	0.7
Headache	2.5	2.7	9.8	11.4	7.4
Confusion	2.0	1.0	10.5	10.4	8.7
Hallucination	3.4	2.4	8.4	10.4	5.4
Vomiting	<2	<2	8.4	9.7	3.7
Constipation	3.0	2.0	6.4	8.4	5.0
Upper respiratory tract infections	<2	<2	4.7	7.4	3.4
Excessive sweating	2.7	1.7	4.4	7.4	2.3
Abdominal pain	7.1	2.7	4.7	5.7	2.7
Xerostomia	4.2	0	4.7	6.4	2.3

tid = 3 times daily.

The authors recommend that in some frail patients with severe disease, tolcapone should be started with a daily dose of 100mg only.

The most common nondopaminergic adverse event is diarrhoea. Tolcapone has been associated with diarrhoea in about 16 to 18% of patients and entacapone in about 8% (table VI). It is also the most common cause of treatment discontinuation. Five to 6% of patients receiving tolcapone discontinued the treatment because of diarrhoea.[61] A considerably lower discontinuation rate of 2.5% has been reported in patients receiving entacapone.[34] The incidence of diarrhoea is independent of levodopa/DDC inhibitor therapy, since it was experienced by 24% of patients treated with tolcapone 200mg 3 times daily plus selegiline 5mg twice daily without levodopa for one month.[90] It usually occurs within the first 6 to 16 weeks of the treatment. Diarrhoea may be related to tolcapone dose but probably not with entacapone dose. Diarrhoea can be severe with tolcapone[81] whereas it is usually milder with entacapone.[77] The mechanism by which the diarrhoea is caused is currently unknown.

Patients should be warned that their urine might become coloured to dark yellow or reddish-brown because of the presence of COMT inhibitors and their metabolites. This harmless event appears to be more common in entacapone– than tolcapone–treated patients (table VI).

The most serious adverse event associated with tolcapone treatment is liver failure. In phase III studies, significantly elevated liver transaminase levels were reported in 1 to 3% of patients treated with tolcapone but no cases of liver failure were observed. However, after marketing authorisation, acute, fatal fulminant hepatitis was reported in 3 patients from approximately 60 000 patients who had received tolcapone therapy.[91,92] At least one of the deaths occurred despite adequate liver monitoring. It seems that a few additional cases of serious liver injury during tolcapone therapy were reported to authorities. According to the summary of product characteristics for entacapone,[34] rare reports of clinically significant increases in liver enzyme levels have been reported. No cases of hepatitis or other serious liver failure have been reported with entacapone treatment, however, clinical experience with this agent is still limited.

In addition to liver problems, potentially fatal neurological adverse reactions, including neuroleptic-like malignant syndrome and rhabdomyolysis, have been described in relation to tolcapone treatment. These symptoms have been associated with withdrawal or rapid lowering of the dose of tolcapone and other antiparkinsonian drugs. Serum creatine kinase activity is typically elevated and hyperpyrexia may occur.[25,92] To avoid these adverse reactions the dosage of tolcapone should be decreased gradually and concurrently the levodopa dosage should be titrated upwards. The same administration recommendation is also relevant to entacapone.

Because of these serious adverse drug reactions, the regulatory authorities in the European Union and Canada decided that marketing of tolcapone should be suspended. In many other countries, including the US, the use of tolcapone has now been restricted to patients experiencing symptom fluctuations and who are not responding satisfactorily to or are not appropriate candidates for other adjunctive therapies.[93] In these patients, liver function tests should be taken at baseline and regularly every 2 weeks for the first year of therapy, then every 4 weeks for the next 6 months and every 8 weeks thereafter. Tolcapone therapy should not be initiated if the patient has liver disease or abnormal liver function tests.

It is not currently considered essential to monitor liver enzymes during entacapone therapy. It should be noted, however, that entacapone is contraindicated in patients with liver impairment, since it is not possible to decrease the dose with the currently available single tablet formulation. Neither neuroleptic-like malignant syndrome nor rhabdomyolysis have been reported in association with entacapone treatment.[34] As in case of tolcapone, entacapone should not been initiated if the patient has a history of neuroleptic malignant syndrome or nontraumatic rhabdomyolysis.

10. Drug Interactions

There is no pharmacological evidence for interactions between the COMT inhibitors and dopamine agonists, selegiline, amantadine or anticholinergics, since these drugs and their metabolites are not substrates for COMT. In several clinical trials, their combinations have been used without any apparent true interactions, although dopaminergic effects may be intensified. A single high dose of entacapone (400 or 800mg) seems to decrease the absorption of carbidopa in studies in healthy volunteers,[43] whereas the therapeutic dose (200mg) does not affect carbidopa pharmacokinetics. Tolcapone may inhibit the *O*-methylation of benserazide, which is a substrate of COMT.[94] The elevation in benserazide plasma concentrations increases the risk of this agent crossing into the brain. If this should occur, then benserazide can start to inhibit dopamine synthesis in the striatum. Some evidence of brain penetration has been found in animals but not in humans.[95]

COMT inhibitors can potentiate the effects of catechol drugs, such as adrenaline, dopamine, noradrenaline and isoprenaline. The interaction may be clinically significant if such a compound is administered parenterally in patients treated concurrently with a COMT inhibitor. Entacapone has potentiated the effects of intravenously administered isoprenaline and adrenaline. The risk for cardiac arrhythmias is increased.[96] If the patient uses a COMT inhibitor the recommendation is that the dose of a catechol drug should be decreased. In cases where it is necessary to discontinue a COMT inhibitor, for example, before an elective surgery, tolcapone should probably be discontinued 2 days and entacapone 1 day before based on their pharmacokinetic and pharmcodynamic data.

COMT inhibitors do not potentiate the cardiovascular effects of endogenous catecholamines, not even when the peripheral release has been induced by exercise or drugs. Entacapone did not alter cardiovascular responses or haemodynamics in healthy volunteers or patients with Parkinson's disease at rest or during exercise.[46,55,56,97] Tolcapone did not modify the action of ephedrine, an indirectly acting sympathomimetic drug.[98] There are no significant interactions between entacapone or tolcapone and moclobemide, a reversible MAO-A inhibitor, selegiline, an irreversible MAO-B inhibitor, or imipramine or desipramine, catecholamine uptake inhibitors.[34,61,99-101] The administration of a COMT inhibitor concomitantly with a MAO-A inhibitor and a MAO-B inhibitor (selegiline) or with a nonselective MAO inhibitor may be unsafe as in this case three elimination pathways of catecholamines will be blocked simultaneously. The same may also happen with the combination of a COMT inhibitor concomitantly with a MAO inhibitor and a catecholamine uptake inhibitor.

Although both tolcapone, in particular, and entacapone are highly protein bound, *in vitro* they do not significantly displace other drugs from their binding sites at therapeutic concentrations.[34,61]

All catechol drugs can form chelates with iron. It is well known that iron preparations significantly reduce the absorption of levodopa because of chelation.[102] *In vitro* studies have shown that entacapone can also chelate iron.[103] There is no definite evidence that chelation occurs also *in vivo* in humans. Entacapone (+levodopa/DDC inhibitor) and iron preparations should be taken at least 2 to 3 hours apart. No data concerning the ability of tolcapone to chelate iron have been published. However, chelation is possible, since tolcapone has a catechol structure.

11. Present Status

The main clinical indication of COMT inhibitors is as adjuncts to levodopa/DDC inhibitor therapy in patients with fluctuating Parkinson's disease. Entacapone is currently indicated as an adjunct to standard levodopa/DDC inhibitor in patients with Parkinson's disease and end-of-dose motor fluctuations, who cannot be stabilised on those combinations.[34] Because of serious adverse reactions, the use of tolcapone is suspended in many countries. In some other countries, such as the US, it is indicated only in patients with Parkinson's disease who are experiencing symptom fluctuations and are not responding satisfactorily to or are not appropriate

candidates for other adjunctive therapies.[93] Regular monitoring of liver enzymes is required with tolcapone but not with entacapone. Tolcapone is given every 6 hours 3 times daily with a 12h break at night, whereas entacapone is given with each levodopa/DDC inhibitor dose up to 8 to 10 times daily.

There are several ways to manage fluctuations in advanced Parkinson's disease, including the addition of a dopamine agonist or selegiline to levodopa treatment, replacement of a standard levodopa preparation with a controlled release levodopa preparation, or more frequent administration of standard levodopa with lower doses. The introduction of COMT inhibitors now provides an additional effective way to manage end-of-dose deterioration with levodopa therapy. A COMT inhibitor need not necessarily be used as an alternative to these other management regimens since it can be used in combination with other antiparkinsonian drugs without adverse interactions. In fact, most of the long term clinical studies with COMT inhibitors have been performed in patients with Parkinson's disease who are receiving other antiparkinsonian drugs. Nutt has recently reviewed the pros and cons of these treatment alternatives in an excellent brief article.[104]

Entacapone has been shown to improve the quality of 6-FD PET studies and may be used also in this indication.

12. Future Aspects

The potential benefit of COMT inhibitors in patients with stable Parkinson's disease and also *de novo* patients should be elucidated and subsequently the indication for their use may be broadened. The efficacy and tolerability profile of COMT inhibitors should also be compared with other antiparkinsonian drugs, first of all with dopamine agonists. Because of the serious adverse effects seen with tolcapone, comparative studies between entacapone and tolcapone may be no longer possible. As in case of any new drug, rare adverse drug reactions can be excluded only after long term and more extensive clinical usage and this is still the case for COMT inhibitors.

Centrally acting COMT inhibitors may have cognition-enhancing and antidepressive effects. Tolcapone has been shown to affect several phases of learning in a simple passive avoidance paradigm and to have antidepressant activity in rat models.[105,106] Tolcapone has increased S-adenosyl-L-methionine levels in brain,[107,108] which may explain its antidepressive and cognition-improving effects. One report has described improved cognition during tolcapone therapy in patients with Parkinson's disease.[109] Consequently, a new centrally active COMT inhibitor would be needed to further test these interesting effects of COMT inhibition in humans.

In conclusion, COMT inhibitors do not revolutionise the therapy of Parkinson's disease but they do help, in particular, those patients with moderate to advanced Parkinson's disease who have problems in their present levodopa therapy.

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