

## Catechol-O-Methyltransferase in Parkinson's Disease

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The introduction of levodopa therapy for Parkinson's disease (PD), initially by Birkmayer and colleagues in 1961 and Barbeau and colleagues in 1962, and in its ultimately successful form by Cotzias and colleagues in 1967, still represents the defining landmark in the treatment of PD (1–3). This dramatic advance was preceded by methodical basic laboratory research in the late 1950s and early 1960s, which formed a groundwork documenting the presence of striatal dopamine deficiency in PD (4–8) and paved the road for the application of this knowledge in the clinical arena.

These developments took place against a broader backdrop in which both the role of catecholamines and their metabolic pathways in body and brain were being unraveled (9). As part of this panorama, Axelrod, in 1957, first suggested that one of the metabolic pathways for catecholamines might be via O-methylation (9–11), and in the same year Shaw and colleagues proposed that catechol-O-methyltransferase (COMT) might be important in the inactivation of dihydroxyphenylalanine (DOPA) and dopamine (12). By 1964 the metabolic pathways for DOPA and dopamine had been delineated and the involved enzymes identified. Aromatic amino acid decarboxylase (AAAD) and COMT were identified as being responsible for converting

DOPA to dopamine and 3-O-methyldopa (3-OMD), respectively, while monoamine oxidase (MAO) and COMT were documented as being responsible for converting dopamine to 3,4-dihydroxyphenylacetic acid (DOPAC) and 3-methoxytyramine (3-MT), respectively. As early as 1964 it was suggested that agents inhibiting COMT might potentiate the effects of DOPA (13).

COMT is found throughout the body, with highest concentrations in the liver, kidneys, gastrointestinal tract, spleen, and lungs (14–17). It is also present in the brain, where it resides primarily in nonneuronal cells, such as glia. There is little COMT in neurons, and none has been identified in nigrostriatal dopaminergic neurons (18). It is principally a cytoplasmic enzyme, although a membrane-bound component has also been identified (11). A number of substrates are acted upon by COMT, including catecholamines such as epinephrine, norepinephrine, and dopamine and their hydroxylated metabolites, but all known substrates have a catechol configuration (11). COMT mediates the transfer of a methyl group from S-adenosylmethionine to a hydroxyl group on the catechol molecule. Its actions, especially in peripheral structures such as intestinal mucosa, seem to be primarily directed toward protecting the body by inactivating biologically active or toxic catechol compounds (11,18,19). Both levodopa and dopamine are examples of such biologically active compounds.

Recognition of the wretched bioavailability of orally administered levodopa in the treatment of PD, with perhaps only 1% of the levodopa actually reaching the brain because of extensive peripheral metabolism by both AAAD and COMT (18,20), fueled the search for drugs that might inhibit the two enzymes and improve levodopa therapeutic efficacy. This led relatively quickly to the introduction of two inhibitors of AAAD, carbidopa and benserazide, as adjunctive agents administered concomitantly with levodopa to PD patients (21,22). This approach of administering levodopa in conjunction with an AAAD inhibitor remains the standard today. However, use of these agents only expands the amount of levodopa reaching the brain to an estimated 10% of an administered dose, primarily because blocking AAAD simply shunts levodopa into the COMT metabolic pathway, with increased peripheral formation of 3-OMD (20).

## **FIRST-GENERATION COMT INHIBITORS**

During the 1960s and 1970s a number of COMT inhibitors were identified and studied. Pyrogallol (1,2,3-trihydroxybenzene) was perhaps the first COMT inhibitor to be identified (23,24), but its short duration of action, toxicity (methemoglobinemia and renal impairment), and probable lack of COMT specificity precluded its clinical use (11). The list of additional “first-

generation” COMT inhibitors that were studied and subsequently abandoned as potential therapeutic agents is long. Catechol itself, adnamine and noradnamine, various flavonoids, tropolone and its derivatives, 8-hydroxyquinolines, S-adenosylhomocysteine, sulfhydryl binding agents, pyrones and pyridones, papaveroline, methylspinazarin, 2-hydroxylated estrogens, and 3-mercaptotyramine represent only a partial listing of such compounds (11). Even the two agents that are primarily recognized as inhibitors of AAAD, carbidopa and benserazide, have some modest COMT-inhibiting properties, although not enough to be clinically relevant (11).

Several of these early COMT inhibitors did undergo pilot testing in humans. *N*-Butyl gallate (GPA 1714), a derivative of gallic acid, was found to be effective in alleviating signs and symptoms of PD when administered to 10 patients in a pilot study (25). The dose of levodopa was reduced by an average of 29%, and the drug was also noted to alleviate nausea and vomiting in affected patients. No significant adverse effects were noted in this initial study, but testing was eventually abandoned because of toxicity (26). Another compound, 3,4-dihydroxy-2-methylpropiophenone (U-0521), demonstrated significant COMT inhibition in animal studies in the laboratory, but when it was administered orally to a single human in progressively increasing doses it demonstrated no effect on erythrocyte COMT activity (26).

## **SECOND-GENERATION COMT INHIBITORS**

Little literary attention was devoted to the subject of COMT inhibitors for the treatment of PD during the mid-1980s, but the dawning of the 1990s ushered in renewed interest in the potential clinical usefulness of these compounds. This attention was prompted by the development of a “second generation” of COMT inhibitors, substances that were more potent, more selective, and less toxic than their predecessors. Several nitrocatechol compounds, eventually bearing the names nitecapone, entacapone, and tolcapone, became the favored subjects of laboratory, and eventually clinical, focus.

### **Nitecapone**

Nitecapone (OR 462) was demonstrated to be well tolerated and modestly effective when administered to mice, rats, and monkeys (27–29). Its actions were confined to the periphery since it did not cross the blood-brain barrier (30), and, in fact, its primary action appeared to be in the intestinal mucosa (31,32). In subsequent human studies it was noted to “slightly but

significantly” increase the relative bioavailability of levodopa and to reduce plasma 3-OMD (33), but it eventually ceded its place in clinical PD development to entacapone (OR 611), which was judged to be the more effective compound.

## Entacapone

Entacapone is readily absorbed across the intestinal mucosa and does not seem to be significantly affected by first-pass metabolism in the liver. The bioavailability of an oral dose of entacapone ranges from 30 to 46% (18,34–37). It is highly (98%) protein bound and metabolized via glucuronidation. The elimination half-life of entacapone is generally reported to be 0.4–0.7 hours (18,34–36). Entacapone does not cross the blood-brain barrier to any significant extent and is generally considered to exert its action exclusively in the periphery (38), although some inhibition of striatal COMT activity following entacapone administration in rats has been described (38,39). When administered to humans, the inhibition of COMT activity by entacapone is dose dependent. Soluble COMT is reduced by 82% with an entacapone dose of 800 mg, the maximum amount that has been administered (40). In multiple dose studies, 100 mg of entacapone given 4–6 times daily with levodopa reduced COMT activity by 25% compared to placebo, while 200 mg produced a 33% reduction and 400 mg generated a 32% diminution in COMT activity (35).

Entacapone also has a dose-related effect on both levodopa and 3-OMD pharmacokinetics. In the same group of patients noted above, the elimination half-life ( $T_{1/2}$ ) of levodopa was prolonged by 23, 26, and 48% at entacapone doses of 100, 200, and 400 mg, respectively, while the area under the levodopa plasma curve (AUC) was increased by 17, 27, and 37% (35). Investigators in two earlier studies, however, had noted a leveling off of the levodopa AUC increase between entacapone doses of 200 and 400 mg and suggested that this might be due to interference with carbidopa absorption by entacapone at the higher dose (41,42). In other studies utilizing an entacapone dose of 200 mg, increases in the levodopa AUC ranged between 23 and 48%, and prolongation of the levodopa  $T_{1/2}$  hovered around 40% (18). Despite these rather dramatic alterations, no significant increase in the time to reach the maximum plasma levodopa concentration ( $T_{max}$ ) or the maximum plasma levodopa concentration itself ( $C_{max}$ ) is seen following concomitant administration of levodopa and entacapone. The  $T_{max}$  remains between 30 and 60 minutes (18,31,43–46). Nutt notes that the absence of an effect on the levodopa  $T_{max}$  and  $C_{max}$  is, strictly speaking, true only for the initial dose of the day and that some modest progressive elevation of the levodopa  $C_{max}$  develops with repeated doses during the day (47). This does

not carry over to the next day and progressive escalation of COMT inhibition does not occur (18,43). Concomitant with these changes in levodopa pharmacokinetics, entacapone also induces a significant reduction in the plasma AUC of 3-OMD, reflecting reduced COMT-mediated peripheral metabolism of levodopa to 3-OMD (18,35,37). It was predicted that the clinical correlate of these pharmacokinetic alterations would be extended efficacy of a levodopa dose. This is due to a combination of the prolonged  $T_{1/2}$  and increased AUC of levodopa and the reduced AUC of 3-OMD, possibly without an increase in levodopa-related toxicity, in light of the absence of change in levodopa  $C_{max}$ . Subsequent full-scale clinical trials have largely validated these predictions and confirmed the safety and efficacy of entacapone.

The SEESAW study, a double-blind, placebo-controlled trial conducted by the Parkinson Study Group, evaluated the safety and efficacy of entacapone over a 6-month period in 205 PD patients on levodopa with motor fluctuations (48,49). A statistically significant 5% increase in “on” time per day (translating to approximately 1 hour) was documented in patients receiving entacapone, compared to the placebo group. Motor function, as measured by the Unified Parkinson’s Disease Rating Scale (UPDRS) (50), improved slightly in the entacapone-treated group, while it deteriorated during the 6 months of the trial in the placebo group. Average daily levodopa dosage diminished by 12% (from 791 to 700 mg/day) in the entacapone-treated group but did not change in the placebo group. Adverse effects were generally mild and manageable, consisting primarily of symptoms consistent with enhanced dopaminergic activity, such as dyskinesia, nausea, and dizziness. Dyskinesia was reported as an adverse effect by 53% (55/103) of patients on entacapone, compared to 32% (33/102) of individuals on placebo. Yellow discoloration of the urine also occurred in 37% of those receiving entacapone, but diarrhea was infrequent (7%).

A second, large multicenter study, NOMECOMT, had a trial design similar to the SEESAW study with similar results (47,49,51). This trial, also 6 months in duration, included 171 PD patients on levodopa who were experiencing motor fluctuations. In the entacapone-treated group, mean “on” time increased by 1.4 hours, compared to an increase of 0.2 hours in the placebo group. This relative increase of 13% in the treatment group was statistically significant. The mean benefit from an individual levodopa dose increased by 24 minutes in the group receiving entacapone. Average daily levodopa dosage diminished by 12% in the entacapone group, compared to a 2% increase in the placebo group. Adverse effects in this study were similar to those in the SEESAW study, except that worsening of dyskinesia was reported by only 8.2% of entacapone-treated participants (vs. 1.2% of those on placebo), while diarrhea was reported by 20%.

More recent studies have augmented the findings of the SEESAW and NOMECOMT studies. Two additional large multicenter trials have investigated the safety and efficacy of entacapone in PD patients (52,53). In an open-label study of 8 weeks duration 489 patients were administered entacapone in conjunction with each dose of levodopa up to a maximum of 10 doses per day (52). Some reduction in “off” time was experienced by approximately 41% of patients and quality of life, as measured by the Parkinson’s Disease Questionnaire (PDQ-39), was also improved. In a double-blind study of 301 PD patients, most of whom were experiencing motor fluctuations, significant improvement in both motor function and activities of daily living was documented in the group receiving entacapone compared to the placebo group (53). Concerns that the efficacy of entacapone might be reduced when used in conjunction with controlled-release levodopa preparations, because of a potential “mismatch” in absorption and metabolism of the two drugs, led several groups of investigators to address the issue (42,53,54). The effect of entacapone was, for the most part, found to be comparable between standard and controlled-release levodopa preparations.

Drug interactions are not a prominent problem with entacapone, although the capability of entacapone to chelate iron in the GI tract has been noted (55), and it has been suggested that a 2- to 3-hour interval be allowed between entacapone and iron ingestion (18).

Genetic polymorphism has been demonstrated with COMT. The gene on chromosome 22 is regulated by two co-dominant alleles, one of which codes for a high-activity thermostable COMT and one for a low-activity thermolabile COMT (56,57). It appears, however, that this dichotomy has little or no effect on the clinical response to entacapone (56).

## **Tolcapone**

Tolcapone (Ro 40-7592), like entacapone, is rapidly absorbed after oral administration and reaches  $T_{max}$  in approximately 1.5–2 hours (18,58,59). The bioavailability of an oral dose is about 60% (60). Tolcapone is very highly (99.9%) protein bound (61). Metabolism of tolcapone is primarily, but not exclusively, via glucuronidation (62) since both methylation and oxidation also occur (63). The elimination  $T_{1/2}$  of tolcapone is between 2 and 3 hours, which is distinctly longer than that of entacapone (58). At doses above 200 mg three times per day (TID), some accumulation of tolcapone can occur, but this appears to be of no practical significance since levels, even at doses of 800 mg TID, remain well below those associated with toxicity in animals (58).

Unlike entacapone, tolcapone is sufficiently lipophilic to cross the blood-brain barrier to some degree (64). While tolcapone-induced inhibition of COMT within the brain has clearly been demonstrated in animal experiments (63,65), it has been less convincingly demonstrated that similar central COMT inhibition takes place in humans receiving tolcapone in clinically relevant doses. Fluorodopa position emission tomography (PET) studies have provided some evidence that such central COMT inhibition does, indeed, take place with tolcapone doses of 200 mg (66). Tolcapone has also been identified in the cerebrospinal fluid (CSF) of patients with PD 1–4 hours after oral intake of 200 mg, concentrations sufficient to reduce CSF COMT activity by 75% (67). Inhibition of COMT within both peripheral and CNS structures provides some theoretical advantages over peripheral inhibition alone since, in addition to the peripheral levodopa-sparing capability, concomitant central COMT inhibition would not only reduce metabolism of levodopa to 3-OMD within the striatum, but would also block one route of metabolism of dopamine itself.

Single-dose studies demonstrated tolcapone to be a noticeably more potent COMT inhibitor than entacapone. At a dose of 200 mg, tolcapone increases the levodopa AUC by anywhere from 50 to 100%, prolongs the levodopa  $T_{1/2}$  by 60–80%, and reduces the AUC of 3-OMD by 64% (18,47,68,69). No appreciable increase in  $C_{max}$  or  $T_{max}$  is seen with 200 mg of tolcapone, although some delay in the  $T_{max}$  becomes evident at higher doses (68).

A number of double-blind, placebo-controlled clinical trials have confirmed the efficacy of tolcapone in reducing motor fluctuations in individuals with PD (70–73). In each of these multicenter trials, which varied in length from 6 weeks to 6 months, significant increases in “on” time and reductions in “off” time were documented in the tolcapone-treated groups compared to the placebo groups. Reduction in both total daily levodopa dosage and number of levodopa doses taken was often evident in the tolcapone-treated groups.

In these four multicenter studies, in which 517 patients (out of 745 enrolled), received tolcapone in various doses ranging from 50 to 400 mg TID, adverse effects were generally mild and most often felt to be dopaminergic in character (70–73). In the three studies where the treatment groups consisted of placebo vs. 100 mg TID vs. 200 mg TID, dyskinesia was reported as an adverse event in 19–21%, 37–62%, and 53–66%, respectively (71–73). Diarrhea, at times unresponsive to medication and of sufficient severity to warrant drug discontinuation, was reported in a relatively small percentage of individuals receiving tolcapone, possibly in a dose-related pattern (47,72,73). The mechanism of the diarrhea is uncertain, although tolcapone has been noted to trigger intestinal fluid and electrolyte secretion,

albeit not actual diarrhea, in dogs (18,74). As with entacapone, yellowish urine discoloration also occurred in some individuals.

In these initial multicenter trials, elevation of liver transaminase levels occurred in a small number of individuals, but all were clinically asymptomatic and the laboratory abnormalities sometimes returned to normal despite continued treatment. In all clinical trials of tolcapone the reported incidence of transaminase elevations greater than three times the upper limit of normal was approximately 1% at a dose of 100 mg TID and 3% at a dose of 200 mg TID (75). However, following introduction of tolcapone into routine clinical use, three cases of fulminant hepatic failure with a fatal outcome occurred, which led regulatory agencies in Europe and Canada to withdraw tolcapone from the market and the Food and Drug Administration in the United States to severely limit its use to situations in which other drugs have not provided sufficient benefit. Baseline liver function tests must be normal, and monitoring of liver function studies must be performed on a regular basis in patients receiving tolcapone. Similar hepatotoxicity has not occurred with entacapone.

## **CURRENT STATUS OF COMT INHIBITORS**

Two COMT inhibitors are currently available for use as adjunctive therapy in PD, to be used in conjunction with levodopa and an AAAD inhibitor in patients who have developed motor fluctuations with end of dose failure. Tolcapone is the more potent of the two and, with its longer  $T_{1/2}$ , can be given on a TID basis. However, its potential to produce hepatic failure has severely restricted its clinical utility. Because of this, the field has largely been ceded to entacapone, which is a somewhat less potent, but a safer alternative. Because of its short  $T_{1/2}$ , entacapone must be administered with each dose of levodopa. The additional 1–2 hours of “on” time per day a COMT inhibitor typically affords to a fluctuating patient can be beneficial. A recent cost-effectiveness analysis of entacapone concluded that the additional drug costs when entacapone is employed are offset by reductions in other costs and improvement (6%) in “quality-adjusted life years” (76).

While it is clear that COMT inhibitors provide quantifiable improvement in function for PD patients with motor fluctuations, their potential benefit in stable PD patients who have not yet developed motor fluctuations has received much less attention. Two clinical trials have addressed this question with tolcapone (77,78). In the larger of the two trials (77), statistically significant improvement in both Part II (activities of daily living) and Part III (motor exam) of the UPDRS were documented. Improvement was most evident in more severely affected patients. Fewer patients in the tolcapone-treated group developed motor fluctuations during the duration

of the trial, which extended to a maximum of 12 months for some participants (average 8.5 months). Adverse events were similar to those encountered in earlier trials described above. The second, smaller trial actually did not examine nonfluctuating PD patients, but rather evaluated individuals who had previously experienced wearing-off of levodopa efficacy, which had been successfully controlled by levodopa dosage adjustment (78). A greater reduction of levodopa dosage was achieved in the tolcapone-treated group, but this did not achieve statistical significance. A single tolcapone trial in levodopa-untreated patients demonstrated no clinical benefit (79). Studies in nonfluctuating patients have not yet been reported with entacapone. Therefore, at the present time the adjunctive role for COMT inhibitors still seems most appropriate.

## **THE FUTURE OF COMT INHIBITORS**

The pathogenesis of motor fluctuations in individuals with PD receiving levodopa has been the subject of much speculation, but little certainty, over the years. Both peripheral and central mechanisms have been hypothesized. Both may actually be active, but it appears that most often the predominant mechanisms driving the pathogenic process are within the CNS. Evidence has begun to accumulate that with PD progression the dwindling number of surviving nigrostriatal dopaminergic neurons are unable to maintain the normal synaptic atmosphere of constant dopaminergic stimulation; instead, the environment becomes one in which dopamine receptor stimulation is intermittent, characterized by pulses of dopaminergic stimulation coincident with levodopa administration. It appears that this pulsatile stimulation, in turn, incites a cascade of changes within the postsynaptic striatal spiny neurons that produces sensitization of glutamate receptors and altered motor responses (80,81).

If this is correct, providing and maintaining a synaptic environment of more constant dopaminergic stimulation from the beginning of treatment might forestall the development of the postsynaptic alterations and delay or prevent the appearance of motor fluctuations. This has led to the proposal that a COMT inhibitor, such as entacapone, be administered along with levodopa and carbidopa right from the initiation of therapy (82). To bolster this hypothesis, Jenner and colleagues recently reported that in marmosets with MPTP-induced parkinsonism, initiation of treatment with levodopa combined with entacapone resulted in less frequent and less severe dyskinesia than that which developed in animals treated with levodopa alone (83). If a reduction or delay in the development of motor fluctuations with such treatment is demonstrated, in humans the role for COMT inhibitors in the treatment of PD may expand dramatically.

## REFERENCES

1. Birkmayer W, Hornykiewicz O. Der 1-3,4-Dioxyphenylalanin (=DOPA)-Effekt bei der Parkinson-Akinese. *Wien J Klin Wochenschr* 1961; 73:787-788.
2. Barbeau A, Sourkes TL, Murphy CF. Les catecholamines dans la maladie de Parkinson. In: Ajuriaguerra J de, ed. *Monoamines et Systeme Nerveux Central*. Geneva: Gerog, 1962:247-262.
3. Cotzias GC, Van Woert MH, Schiffer LM. Aromatic amino acids and modification of parkinsonism. *N Engl J Med* 1967; 276:374-379.
4. Carlsson A, Lindquist M, Magnusson T. 3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. *Nature* 1957; 180:200.
5. Bertler A, Rosengren E. Occurrence and distribution of catecholamines in brain. *Acta Physiol Scand* 1959; 47:350-361.
6. Ehringer H, Hornykiewicz O. Verteilung von Noradrenalin und Dopamin (3-Hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des extrapyramidalen Systems. *Wien Klin Wochenschr* 1960; 38:1236-1239.
7. Anden NE, Carlsson A, Dahlstrom A, Fuxe J/K, Hillarp N-A, Karlsson K. Demonstration and mapping of nigrostriatal dopamine neurons. *Life Sci* 1964; 3:523-530.
8. Poirier LJ, Sourkes TL. Influence of the substantia nigra on the catecholamine content of the striatum. *Brain* 1965; 8:181-192.
9. Axelrod J. Catecholamine neurotransmitters, psychoactive drugs, and biological clocks. *J Neurosurg* 1981; 55:669-677.
10. Axelrod J. The O-methylation of epinephrine and other catechols in vitro and in vivo. *Science* 1957; 126:1657-1660.
11. Guldberg HC, Marsden CA. Catechol-O-methyl transferase: pharmacological aspects and physiological role. *Pharmacol Rev* 1975; 27:135-206.
12. Shaw KNF, McMillan A, Armstrong MD. The metabolism of 3,4-dihydroxyphenylalanine. *J Biol Chem* 1957; 226:255-266.
13. Carlsson A. Functional significance of drug-induced changes in brain monoamine levels. In: HE Himwich, WA Himwich, eds. *Biogenic Amines*. Amsterdam: Elsevier, 1964:9-27.
14. Nissinen E, Tuominen R, Perhoniemi V, Kaakkola S. Catechol-O-methyltransferase activity in human and rat small intestine. *Life Sci* 1988; 42:2609-2614.
15. Schultz E, Nissinen E. Inhibition of rat liver and duodenum soluble catechol-O-methyltransferase by a tight-binding inhibitor OR-462. *Biochem Pharmacol* 1989; 38:3953-3956.
16. Mannisto PT, Ulmanen I, Lundstrom K, Taskinen J, Tenhunen J, Tilgmann C, Kaakkola S. Characteristics of catechol-O-methyltransferase (COMT) and properties of selective COMT inhibitors. *Prog Drug Res* 1992; 39:291-350.
17. Ding YS, Gatley SJ, Fowler JS, Chen R, Volkow ND, Logan J, Shea CE, Sugano Y, Koomen J. Mapping catechol-O-methyltransferase in vivo: initial studies with [18F] Ro41-0960. *Life Sci* 1996; 58:195-208.

18. Teravainen H, Rinne U, Gordin A. Catechol-O-methyltransferase inhibitors in Parkinson's disease. In: Calne D, Calne S, eds. *Parkinson's Disease*. Philadelphia: Lippincott Williams Wilkins, 2001:311–325.
19. Huotari M, Gogos JA, Karayiorgou M, Koponen O, Forsberg M, Raasmaja A, Hyttinen J, Mannisto PT. Brain catecholamine metabolism in catechol-O-methyltransferase (COMT)-deficient mice. *Eur J Neurosci* 2002; 15:246–256.
20. Olanow CW, Schapira AHV, Rascol O. Continuous dopamine-receptor stimulation in early Parkinson's disease. *Trends Neurosci* 2000; 23(suppl):S117–S126.
21. Rinne UK, Sonninen V, Siirtola T. Treatment of parkinsonian patients with levodopa and extracerebral decarboxylase inhibitor, Ro 4-4602. In: Calne D, ed. *Progress in the Treatment of Parkinsonism*. New York: Raven Press, 1973:59–71.
22. Porter CC. Inhibitors of aromatic amino acid decarboxylase—their biochemistry. In: Yahr MD, ed. *Treatment of Parkinsonism—The Role of Dopa Decarboxylase Inhibitors*. New York: Raven Press, 1973:37–58.
23. Bacq AM, Gosselin L, Dresse A, Renson J. Inhibition of O-methyltransferase by catechol and sensitization to epinephrine. *Science* 1959; 130:453–454.
24. Axelrod J, LaRoche MJ. Inhibitor of O-methylation of epinephrine and norepinephrine in vitro and in vivo. *Science* 1959; 130:800.
25. Ericsson AD. Potentiation of the L-Dopa effect in man by the use of catechol-O-methyltransferase inhibitors. *J Neurol Sci* 1971; 14:193–197.
26. Reches A, Fahn S. Catechol-O-methyltransferase and Parkinson's disease. In: Hassler RG, Christ JF, eds. *Parkinson-Specific Motor and Mental Disorders*. New York: Raven Press, 1984:171–179.
27. Linden IB, Nissinen E, Etemadzadeh E, Kaakkola S, Mannisto P, Pohto P. Favorable effect of catechol-O-methyltransferase inhibition by OR-462 in experimental models of Parkinson's disease. *J Pharmacol Exp Ther* 1988; 247:289–293.
28. Tornwall M, Mannisto PT. Acute toxicity of three new selective COMT inhibitors in mice with special emphasis on interactions with drugs increasing catecholaminergic neurotransmission. *Pharmacol Toxicol* 1991; 69:64–70.
29. Cedarbaum JM, Leger G, Reches A, Guttman M. Effect of nitecapone (OR-462) on the pharmacokinetics of levodopa and 3-O-methyldopa formation in cynomolgus monkeys. *Clin Neuropharmacol* 1990; 13:544–552.
30. Marcocci L, Maguire JJ, Packer L. Nitecapone: a nitric oxide radical scavenger. *Biochem Mol Biol Int* 1994; 34:531–541.
31. Nissinen E, Linden IB, Schultz E, Kaakkola S, Mannisto PT, Pohto P. Inhibition of catechol-O-methyltransferase activity by two novel disubstituted catechols in the rat. *Eur J Pharmacol* 1988; 153:263–269.
32. Schultz E, Tarpila S, Backstrom AC, Gordin A, Nissinen E, Pohto P. Inhibition of human erythrocyte and gastroduodenal catechol-O-methyltransferase activity by nitecapone. *Eur J Clin Pharmacol* 1991; 40:577–580.
33. Kaakkola A, Gordin A, Jarvinen M, Wikberg T, Schultz E, Nissinen E, Pentikainen PJ, Rita H. Effect of a novel catechol-O-methyltransferase

- inhibitor, nitecapone, on the metabolism of L-Dopa in healthy volunteers. *Clin Neuropharmacol* 1990; 13:436–447.
34. Najib J. Entacapone: a catechol-O-methyltransferase inhibitor for the adjunctive treatment of Parkinson's disease. *Clin Ther* 2001; 23:802–832.
  35. Heikkinen H, Nutt JG, LeWitt PA, Koller WC, Gordin A. The effects of different repeated doses of entacapone on the pharmacokinetics of L-Dopa and on the clinical response to L-Dopa in Parkinson's disease. *Clin Neuropharmacol* 2001; 24:150–157.
  36. Keranen T, Gordin A, Karlsson M, Korpela K, Pentikainen PJ, Rita H, Schultz E, Seppala L, Wikberg T. Inhibition of soluble catechol-O-methyltransferase and single-dose pharmacokinetics after oral and intravenous administration of entacapone. *Eur J Clin Pharmacol* 1994; 46:151–157.
  37. Keranen T, Gordin A, Harjola V-P, Karlsson M, Korpela K, Pentikainen PJ, Rita H, Seppala L, Wikberg T. The effect of catechol-O-methyl transferase inhibition by entacapone on the pharmacokinetics and metabolism of levodopa in healthy volunteers. *Clin Neuropharmacol* 1993; 16:145–156.
  38. Nissinen E, Linden I-B, Schultz E, Pohto P. Biochemical and pharmacological properties of a peripherally acting catechol-O-methyltransferase inhibitor entacapone. *Naunyn Schmiedebergs Arch Pharmacol* 1992; 346:262–266.
  39. Brannan T, Prikhojan A, Yahr MD. Peripheral and central inhibitors of catechol-O-methyl transferase: effects on liver and brain COMT activity and L-DOPA metabolism. *J Neural Transm* 1997; 104:77–87.
  40. Keranen T, Gordin A, Karlsson M, Korpela K, Pentikainen P, Schultz E, Seppala L, Wikberg T. Effect of the novel catechol-O-methyltransferase inhibitor OR-611 in healthy volunteers. *Neurology* 1991; 41(suppl):213.
  41. Ruottinen HM, Rinne UK. A double-blind pharmacokinetic and clinical dose-response study of entacapone as an adjuvant to levodopa therapy in advanced Parkinson's disease. *Clin Neuropharmacol* 1996; 19:283–296.
  42. Ahtila S, Kaakkola S, Gordin A, Korpela K, Heinavaara S, Karlsson M, Wikberg T, Tuomainen P, Mannisto PT. Effect of entacapone, a COMT inhibitor, on the pharmacokinetics and metabolism of levodopa after administration of controlled-release levodopa-carbidopa in volunteers. *Clin Neuropharmacol* 1995; 18:46–57.
  43. Rouru J, Gordin A, Huupponen R, Huhtala S, Savontaus E, Korpela K, Reinikainen K, Scheinin M. Pharmacokinetics of oral entacapone after frequent multiple dosing and effects on levodopa disposition. *Eur J Clin Pharmacol* 1999; 55:461–467.
  44. Heikkinen H, Saraheimo M, Antila S, Ottoila P, Pentikainen PJ. *Eur J Clin Pharmacol* 2001; 56:821–826.
  45. Kaakkola S, Teravainen H, Ahtila S, Rita H, Gordin A. Effect of entacapone, a COMT inhibitor, on clinical disability and levodopa metabolism in parkinsonian patients. *Neurology* 1994; 44:77–80.
  46. Schapira AHV, Obeso JA, Olanow CW. The place of COMT inhibitors in the armamentarium of drugs for the treatment of Parkinson's disease. *Neurology* 2000; 55(suppl 4):S65–S68.

47. Nutt JG. Effect of COMT inhibition on the pharmacokinetics and pharmacodynamics of levodopa in parkinsonian patients. *Neurology* 2000; 55(suppl 4):S33–S37.
48. Parkinson Study Group. Entacapone improves motor fluctuations in levodopa-treated Parkinson's disease patients. *Ann Neurol* 1997; 42:747–755.
49. Kieburtz K, Hubble J. Benefits of COMT inhibitors in levodopa-treated parkinsonian patients: results of clinical trials. *Neurology* 2000; 55(suppl 4):S42–S45.
50. Fahn S, Elton RL, Members of the UPDRS Development Committee. Unified Parkinson's disease rating scale. In: Fahr S, Marsden CD, Goldstein M, Calne DB, eds. *Recent Developments in Parkinson's Disease, Vol 2*. New York: Macmillan, 1987:153–163.
51. Rinne UK, Larsen JP, Siden A, Worm-Petersen J, and the Nomecomt Study Group. Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. *Neurology* 1998; 51:1309–1314.
52. Durif F, Devaux I, Pere JJ, Delumeau JC, Bourdeix I, F-01 Study Group. Efficacy and tolerability of entacapone as adjunctive therapy to levodopa in patients with Parkinson's disease and end-of-dose deterioration in daily medical practice: an open, multicenter study. *Eur Neurol* 2001; 5:111–118.
53. Poewe WH, Deuschl G, Gordin A, Kultalahti ER, Leinonen M, the Celomen Study Group. Efficacy and safety of entacapone in Parkinson's disease patients with suboptimal levodopa response: a 6-month randomized placebo-controlled double-blind study in Germany and Austria (Celomen Study). *Acta Neurol Scand* 2002; 105:245–255.
54. Piccini P, Brooks DJ, Korpela K, Pavese N, Karlsson M, Gordin A. The catechol-O-methyltransferase (COMT) inhibitor entacapone enhances the pharmacokinetic and clinical response to Sinemet CR in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2000; 68:589–594.
55. Orama M, Tilus P, Taskinen J, Lotta T. Iron (III)-chelating properties of the novel catechol O-methyltransferase inhibitor entacapone in aqueous solution. *J Pharm Sci* 1997; 86:827–831.
56. Lee MS, Kim HS, Cho EK, Lim JH, Rinne JO. COMT genotype and effectiveness of entacapone in patients with fluctuating Parkinson's disease. *Neurology* 2002; 58:564–567.
57. Tai CH, Wu RM. Catechol-O-methyltransferase and Parkinson's disease. *Acta Med Okayama* 2002; 56:1–6.
58. Jorga KM. Pharmacokinetics, pharmacodynamics, and tolerability of tolcapone: a review of early studies in volunteers. *Neurology* 1998; 50(suppl 5):S31–S38.
59. Dingemans J, Jorga K, Zurcher G, Schmitt M, Sedek G, Da Prada M, Van Brummelen P. Pharmacokinetic-pharmacodynamic interaction between the COMT inhibitor tolcapone and single-dose levodopa. *Br J Clin Pharmacol* 1995; 40:253–262.
60. Jorga K, Fotteler B, Heizmann P, Zurcher G. Pharmacokinetics and pharmacodynamics after oral and intravenous administration of tolcapone,

- a novel adjunct to Parkinson's disease therapy. *Eur J Clin Pharmacol* 1998; 54:443–447.
61. Dingemans J. Issues important for rational COMT inhibition. *Neurology* 2000; 55(suppl 4):S24–S27.
  62. Jorga K, Fotteler B, Heizmann P, Gasser R. Metabolism and excretion of tolcapone, a novel inhibitor of catechol-O-methyltransferase. *Br J Clin Pharmacol* 1999; 48:513–520.
  63. Da Prada M, Borgulya J, Napolitano A, Zurcher G. Improved therapy of Parkinson's disease with tolcapone, a central and peripheral COMT inhibitor with an S-adenosyl-L-methionine-sparing effect. *Clin Neuropharmacol* 1994; 17(suppl 3):S26–S37.
  64. Dingemans J. Catechol-O-methyltransferase inhibitors: clinical potential in the treatment of Parkinson's disease. *Drug Dev Res* 1997; 42:1–25.
  65. Zurcher G, Dingemans J, Da Prada M. Potent COMT inhibition by Ro 40-7592 in the periphery and in the brain. Preclinical and clinical findings. In Narabayashih H, Nagatsu T, Yanagisawa N, Mizuno Y, eds. *Parkinson's Disease. From Basic Research To Treatment*. New York: Raven Press, 1993:641–647.
  66. Ceravolo R, Piccini P, Bailey DL, Jorga KM, Bryson H, Brooks DJ. 18F-dopa PET evidence that tolcapone acts as a central COMT inhibitor in Parkinson's disease. *Synapse* 2002; 43:201–207.
  67. Russ H, Muller T, Woitalla D, Rahbar A, Hahn J, Kuhn W. Detection of tolcapone in the cerebrospinal fluid of parkinsonian subjects. *Naunyn Schmiedebergs Arch Pharmacol* 1999; 360:719–720.
  68. Sedek G, Jorga K, Schmitt M, Burns RS, Leese P. Effect of tolcapone on plasma levodopa concentrations after coadministration with levodopa/carbidopa to healthy volunteers. *Clin Neuropharmacol* 1997; 20:531–541.
  69. Kurth MC, Adler CH. COMT inhibition: a new treatment strategy for Parkinson's disease. *Neurology* 1998; 50(suppl 5):S3–S14.
  70. Kurth MC, Adler CH, St. Hilaire M, Singer C, Waters C, LeWitt P, Chernik DA, Dorflinger EE, Yoo K, and the Tolcapone Fluctuator Study Group I. Tolcapone improves motor function and reduces levodopa requirement in patients with Parkinson's disease experiencing motor fluctuations: a multicenter, double-blind, randomized, placebo-controlled trial. *Neurology* 1997; 48:81–87.
  71. Adler CH, Singer C, O'Brien C, Hauser RA, Lew MF, Marek KL, Dorflinger E, Pedder S, Deptula D, Yoo K, for the Tolcapone Fluctuator Study Group III. Randomized, placebo-controlled study of tolcapone in patients with fluctuating Parkinson's disease treated with levodopa-carbidopa. *Arch Neurol* 1998; 55:1089–1095.
  72. Rajput AH, Martin W, Saint-Hilaire M-H, 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.

73. Baas H, Beiske AG, Ghika J, Jackson M, Oertel WH, Poewe W, Ransmayr G, on behalf of the study investigators. 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.
74. Larsen KR, Dajani EZ, Dajani NE, Dayton MT, Moore JG. Effects of tolcapone, a catechol-O-methyltransferase inhibitor, and Sinemet on intestinal electrolyte and fluid transport in conscious dogs. *Dig Dis Sci* 1998; 43:1806–1813.
75. Watkins P. COMT inhibitors and liver toxicity. *Neurology* 2000; 55(suppl 4):S51–S52.
76. Nuijten MJ, van Iperen P, Palmer C, van Hilten BJ, Snyder E. Cost-effectiveness analysis of entacapone in Parkinson’s disease: a Markov process analysis. *Value Health* 2001; 4:316–328.
77. Waters CH, Kurth M, Bailey P, Shulman LM, LeWitt P, Dorflinger E, Deptula D, Pedder S, and the Tolcapone Stable Study Group. Tolcapone in stable Parkinson’s disease: efficacy and safety of long-term treatment. *Neurology* 1997; 49:665–671.
78. Dupont E, Burgunder J-M, Findley LJ, Olsson J-E, Dorflinger E, and the Tolcapone in Parkinson’s Disease Study Group II (TIPS II). Tolcapone added to levodopa in stable parkinsonian patients: a double-blind placebo-controlled study. *Mov Disord* 1997; 12:928–934.
79. Hauser RA, Molho E, Shale H, Pedder S, Dorflinger EE, and the Tolcapone De Novo Study Group. A pilot evaluation of the tolerability, safety and efficacy of tolcapone alone and in combination with oral selegiline in untreated Parkinson’s disease patients. *Mov Disord* 1998; 13:643–647.
80. Chase TN. Levodopa therapy: consequences of the nonphysiologic replacement of dopamine. *Neurology* 1998; 50(suppl 5):S17–S25.
81. Chase TN, Oh JD. Striatal dopamine- and glutamate-mediated dysregulation in experimental parkinsonism. *Trends Neurosci* 2000; 23(suppl):S86–S91.
82. Olanow CW, Obeso JA. Pulsatile stimulation of dopamine receptors and levodopa-induced motor complications in Parkinson’s disease. Implications for the early use of COMT inhibitors. *Neurology* 2000; 55(suppl 4):S72–S77.
83. Jenner P, A1-Barghouthy G, Smith L, Kuoppamaki M, Jackson M, Rose S, Olanow W. Initiation of entacapone with L-dopa further improves antiparkinsonian activity and avoids dyskinesia in the MPTP primate model of Parkinson’s disease. *Neurology* 2002; 58(suppl 3):A374–A375.