Acta Med. Okayama, 2002
Vol. 56, No. 1, pp. 1-6

Acta Medica Okayama

http://www.lib.okayama-u.ac.jp/www/acta/

Review

Catechol-*O*-methyltransferase and Parkinson's Disease

Chun-Hwi Tai[a] and Ruey-Meei Wu[b]*

[a]*Department of Neurology, National Taiwan University Hospital, and*
[b]*Department of Neurology, College of Medicine, National Taiwan University and National Taiwan University Hospital, Taipei 100, Taiwan*

Parkinson's disease (PD) is one of the main causes of neurological disability in the elderly. Levodopa is the gold standard for treating this disease, but chronic levodopa therapy is complicated by motor fluctuation and dyskinesia. The catechol-*O*-methyltransferase (COMT) inhibitors represent a new class of antiparkinsonian drugs. When coadministered with levodopa/decarboxylase inhibitor, 2 COMT inhibitors, tolcapone and entacapone have been shown to improve the clinical benefit of levodopa. COMT activity is genetically polymorphic, and individuals with the low activity ($COMT^{L/L}$) genotype have a thermolabile COMT protein; studies suggest that this genotype is less common in Asians than in Caucasians. Differences in COMT activity may determine the individual response to levodopa and result in ethnic differences in PD susceptibility. Our recent study suggests that the COMT*L* allele can interact with the MAOB gene to increase the occurrence of PD in Taiwanese. In order to understand this new class of antiparkinsonian drugs, we review their basic properties, pharmacology, and clinical efficacy. The frequency distribution of COMT genetic polymorphisms among different populations and its implications in the etiology and drug response is also discussed.

Key words: Parkinson's disease, catechol-*O*-methyltransferase, catechol-*O*-methyltransferase inhibitors, genetic polymorphism, susceptibility

I. Introduction

Parkinson's disease (PD) is one of the most common neurogenerative disorders in the elderly. The clinical manifestations of this disease, which was first described by James Parkinson in 1817, consist of progressive tremor, rigidity, bradykinesia, and postural instability. Pathologically, it is characterized by the degeneration of dopaminergic neurons and the presence of Lewy bodies in the substantia nigra. Degeneration of the nigrostriatal pathway results in reduced striatal concentrations of dopamine and thus the characteristic motor symptoms, but the cause of the cell death is unknown.

The current mainstay of PD treatment is dopamine replacement therapy with levodopa, the natural precursor of dopamine [1]. Levodopa was introduced in the 1960's after the discovery of the underlying pathology of dopamine depletion. For the past 3 decades, it has been the single most effective antiparkinsonian drug available [2]. However, despite its efficacy, levodopa can lose its effectiveness with time [3]. Most patients develop a fluctuating response to levodopa and/or levodopa-related involuntary movements with disease progression [4]. In our previous study in PD patients, 40% or 15%, respectively, of our PD patients developing motor fluctuation or dyskinesia after 5 years of levodopa treat-

Received August 8, 2001; accepted August 21, 2001.
*Corresponding author. Phone: +886-2-2312-3456; Fax: +886-2-2341-8395
E-mail: rmwu@ha.mc.ntu.edu.tw (RM. Wu)

ment [5]. The appearance of these complications is termed the "end-of-dose deterioration" or "wearing-off" phenomenon, with affected patients experiencing a shorter duration of the therapeutic effect of levodopa [6, 7]. Patients experience "ON/OFF" fluctuations between states of mobility (ON-time) and states of disabling parkinsonism (OFF-time). Moreover, with very advanced disease, some patients may experience unexpected swings in, or loss of, response to levodopa or complicated involuntary movements, such as diphasic dystonia or dystonic cramp, during "on" and "off" periods [4, 8].

The underlying mechanisms for the response variation in PD patients on levodopa therapy are not clear [4, 9]. Clinically, several risk factors, including age at onset, disease severity at levodopa initiation, duration of illness prior to levodopa therapy, and the daily dose of levodopa, have been shown to influence the development of these adverse effects during levodopa therapy [5, 10, 11]. Our previous study showed that patients with a younger age at onset have a higher risk of developing these complications; this result is in agreement with those of previous studies showing that delaying the use of levodopa can prevent the early occurrence of response variance and adverse effects of levodopa in young-onset PD patients [12, 13].

Pharmacologically, factors determining the delivery of levodopa to the brain [14-16] or regulating dopamine receptor functions [6] can contribute to the pathogenesis of the motor fluctuations and dyskinesias. It is generally believed that the response to levodopa reflects the ability of intact nigro-striatal neurons to convert levodopa to dopamine and store it in pre-synaptic vesicles for physiological release [7, 9, 14]. With disease progression, dopamine storage in the striatum is reduced and gradually loses its function as a buffer. At this stage, patients may be susceptible to fluctuations in plasma levodopa concentrations [6, 7]. Delayed absorption may retard the onset of the effect, while a reduced peak plasma levodopa concentration may result in a brief, or even no response to the drug [17]. Thus, therapeutic strategies to improve the pharmacokinetics of levodopa become important in optimizing its efficacy and minimizing adverse reactions [14-18]. The use of oral controlled-release levodopa addresses the need for greater constancy of levodopa effects [19, 20]. More recently, the second generation COMT inhibitors proved effective in reducing such situations in PD patients on levodopa [21-23].

Since the 1990's, second generation COMT inhibitors have been introduced [24]. These selective COMT inhibitors block the peripheral metabolism of levodopa and therefore enhance the bioavailability of levodopa in the brain, prolonging the "on" time and decreasing the "wearing off" phenomenon [25]. Because these new COMT inhibitors are becoming more widely used in the treatment of parkinsonian patients, it is essential to have more information about them [26]. Moreover, the level of COMT enzyme activity is genetically polymorphic in human tissues. This polymorphism has ethnic differences and may be associated with PD susceptibility in the Japanese population [27, 28]. It also influences the clinical response to levodopa in different populations [29]. In this review article, we therefore first review the properties of the COMT gene and the 2 types of COMT enzyme, then briefly summarize the important pharmacological properties and clinical effects of the new COMT inhibitors. The distribution of genetic polymorphisms of the COMT gene in different ethnic populations and its impact on both the treatment and etiology of PD are also addressed.

II. The COMT gene and enzyme

COMT, the enzyme responsible for the *O*-methylation of catecholamines, was first characterized and purified in 1958 [30], but it was not until the 1990's that the structures of the 2 isoforms of the COMT enzyme [31] and the COMT gene [32] were determined. The human COMT gene is found at chromosome 22, band q11.2, and consists of 6 exons. Its expression is regulated by 2 distinct promoters located in exon 3. Two mRNA species with sizes of 1.5 kb and 1.3 kb are synthesized and are translated to give, respectively, membrane-bound (MB-COMT) and soluble (S-COMT) forms of COMT [33-34]. COMT is a cellular enzyme that occurs throughout the body and is present at high concentrations in peripheral organs, such as the liver, kidney, and intestines [35]. Most human tissues contain both types of COMT, usually with a preponderance the S-COMT, but the situation is reversed in the brain, in which MB-COMT accounts for 70% of the total. MB-COMT contains an additional 20 amino acids, which function as an hydrophobic membrane anchor [36].

The principle function of COMT is the inactivation of biologically active or toxic catechols and some hydroxylated metabolites. In the presence of Mg^{2+}, it catalyzes the

transfer of the methyl group of S-adenosyl-L-methionine to one of the hydroxyl groups of the catechol substrate [37]. Physiological substrates of COMT include levodopa, catecholamines (dopamine, noradrenaline, and adrenaline), their hydroxylated metabolites, and ascorbic acid. COMT can act as an enzymatic defense in the blood and other tissues against toxins and xenobiotics. In the kidney and intestine, it may also play an indirect role in modulating dopaminergic function. In the brain, it may regulate the amounts of active dopamine and norepinephrine in different regions and could therefore be associated with mental and mood processes [36].

Levels of COMT activity show a trimodal distribution, described as low ($COMT^{L/L}$), intermediate ($COMT^{L/H}$), and high ($COMT^{H/H}$) [38, 39]. This polymorphism is caused by paired autosomal dominant alleles. In human erythrocytes, there is an up to 3- to 4-fold difference in COMT activity between the low and high activity enzymes [39]. In fact, the catalytic activity of both variants is the same, the main cause of the observed difference being related to the thermolability of the enzyme [40, 41], which is determined by a single nucleotide change at nucleotide 1947 of exon 4, if this nucleotide is a guanine, coding for valine, the enzyme is thermostable (high activity), whereas if it is an adenine, coding for methionine, the enzyme is thermolabile (low activity).

III. COMT Inhibitors

After the partial purification and characterization of COMT in 1958 [30], the first generation of COMT inhibitors was developed, but they are no longer used because of their low efficacy, lack of selectivity, and toxicity [37]. The newly-developed second generation COMT inhibitors, introduced in the late 1980's and including tolcapone, entacapone, and nitecapone, are highly potent, selective, and reversible COMT inhibitors in which the key chemical structure is nitrocatechol [35, 36].

Entacapone and nitecapone are effective in peripheral COMT inhibition, whereas tolcapone also inhibits COMT in the brain. However, peripheral COMT inhibition would be more important in assisting the effect of levodopa treatment in PD patients [36]. The underlying rationale for using COMT inhibitor as an adjunct to levodopa therapy is the optimization of the pharmacokinetic profile of levodopa and hence its access to the brain [26]. Before levodopa is delivered to the brain, it can be metabolized by either aromatic L-amino acid decarboxylase (AADC) or COMT. So, when a peripheral inhibitor of AADC, such as benserazide (Madopar®) or carbidopa (Sinemet®), are co-administered with levodopa, the main metabolic pathway of levodopa in the peripheral is the conversion into 3-*O*-methyldopa (3-OMD) by COMT. The 3-OMD, which has no therapeutic effect in PD, has a long elimination half-life and thus accumulates in the plasma, and has been suggested to compete with levodopa for transport into the brain and thus impairs its therapeutic effect. COMT inhibitors reduce the conversion of levodopa to 3-OMD, resulting in an increased area under the concentration curve (AUC) for plasma levodopa [42, 43] and therefore improve the bioavailability of levodopa in the brain.

In several large clinical studies in PD patients, tolcapone and entacapone, the 2 currently marketed new COMT inhibitors, have proved effective in prolonging the daily "on" time by 1-2 hours, alleviating the symptoms of motor fluctuations, and potentiating the effect of levodopa [21-23]. They are also reported to be well tolerated. The main adverse events include gastrointestinal problems, such as diarrhea, and an hyperdopaminergic effect. Diarrhea occurs in 16% or less than 10%, respectively, of patients treated with tolcapone [21, 22, 44] or entacapone [23, 43, 45]. Symptoms of hyperdopaminergic activity, especially the initial worsening of levodopa-induced dyskinesia, occur in approximately 40% or 30%, respectively, of patients receiving tolcapone or entacapone, and include nausea, vomiting, orthostatic hypotension, hallucination, and sleep disorders [21-23, 43-46]. Abnormal liver function has been reported in 1-3% of patients treated with tolcapone [46], and is rarely observed in entacapone-treated patients [23, 45]. Although tolcapone was generally well tolerated in clinical trials, 4 cases of serious hepatic dysfunction have been described in postmarketing surveillance reports, with 3 of these resulting in death [47]. These reports have led to the drug being withdrawn from the market in Europe and Canada, and the introduction of more intensive monitoring requirements and a black box warning in the United States [48].

IV. The association between COMT genetic polymorphism and PD susceptibility

Many studies have been performed to investigate the relationship between COMT genetic polymorphism and

Table I Correlation studies of COMT polymorphism and Parkinson's disease

References	Ethnic group	Subjects (N)	Genotype frequency			Association with PD
			H/H	*H/L*	*L/L*	
Wu, 2000	Taiwanese	C = 191	0.61	0.33	0.06	No.
		PD = 222	0.56	0.36	0.08	
Xie, 1997	Chinese, HK	C = 62	0.60	0.30	0.10	No.
		PD = 70	0.63	0.30	0.07	
Kunugi, 1997	Japanese	C = 153	0.48	0.46	0.06	Yes, *L/L* is higher in PD
		PD = 109	0.42	0.43	0.15	
Yoritaka, 1997	Japanese	C = 156	0.44	0.49	0.07	Yes, *H/H* is higher in PD
		PD = 176	0.57	0.35	0.08	
Hodal, 1996	Caucasian, UK	C = 173	0.23	0.51	0.26	No.
		PD = 139	0.23	0.50	0.27	

C, controls; PD, Parkinson's disease; HK, Hong Kong; UK, United Kingdom

various neuropsychiatric diseases, such as Parkinson's disease and schizophrenia [27, 49–51]. Previous studies on the correlation between COMT polymorphism and PD risk are summarized in Table 1. The low COMT activity allele ($COMT^{L}$) is less common in Asians than in Caucasians, the allele frequency being approximately 25% in oriental, and 45% in white, populations [52]. In studies on Britain [53], Finnish [54] and Chinese [55] populations, no significant difference was found in the distribution of the genetic polymorphism in PD patients and normal controls. One study showed that the homozygous low activity allele ($COMT^{L/L}$) was more common in Japanese PD patients than in normal controls [27], whereas another study, again in Japanese, found a significant higher percentage of the homozygous high activity ($COMT^{H/H}$) allele in PD patients [56]. In our study on Taiwanese, there was no correlation between $COMT^{L}$ genotype and PD when COMT genetic polymorphism was considered in isolation, but, when MAOB genotype polymorphism was taken into account, a significant synergistic enhancement was found in PD patients possessing both the $COMT^{L}$ and MAOB *G* genotypes [57]. Thus, an interaction between these 2 dopamine-metabolizing enzymes may be correlated with the pathogenesis of sporadic PD. Further studies on COMT polymorphism, its effect on COMT activity, and its interaction with MAOB enzyme activity are being undertaken to enhance our understanding of the pathogenesis of sporadic PD.

V. Ethnic differences in the response to levodopa and COMT inhibitors

As already mentioned, the level of COMT enzyme activity is genetically polymorphic. Some ethnic differences have been recognized and may explain variations in the individual response to levodopa therapy [29, 58, 59]. Whether the variations in COMT activity can influence the clinical response to COMT inhibitors in levodopa-treated patient is another interesting issue. One recent report from Canada showed that COMT genetic polymorphism did not influence the clinical response to tolcapone in PD patients [60]. However, in our recent study of the clinical effect of tolcapone in PD patients with the "wearing-off" phenomenon, we observed that patients with the $COMT^{L/L}$ alleles had a less favorable response to tolcapone than those with $COMT^{H/L}$ or $COMT^{H/H}$ [61, and manuscript in preparation]. These different results may be due to the ethnic groups studied and/or differences in the methodology used to evaluate the end-point of drug efficacy.

Conclusion

Levodopa is the gold standard in the treatment of PD. In advanced PD patients who have received chronic levodopa treatment, motor fluctuation and drug-induced dyskinesia complicate the treatment course and also result in a poorer quality of life for the patient. The newly developed COMT inhibitors can improve the potency of levodopa and reduce motor fluctuations. Polymorphism

of the COMT gene is ethnically determined and associated with the different thermostabilities of the variant COMT enzymes. The study of COMT genetic polymorphism has opened up a new field of research on the pharmacogenetics of COMT inhibitors in different ethnic groups and has also improved our understanding of the etiology of PD.

References

1. Calne DB: Treatment of Parkinson's disease. N Engl J Med (1993) **329**, 1021–1027.
2. Marsden CD: Parkinson's disease. J Neurol Neurosurg Psychiatry (1994) **57**, 672–81.
3. Jankovic J: Natural course and limitations of levodopa therapy. Neurology (1993) **43** (Suppl 1), S14–S17.
4. Hurtig HI: Problems with current pharmacologic treatment of Parkinson's disease. Exp Neurol (1997) **144**, 10–16.
5. Wu RM, Chiu HC, Wang M and Chen RC: Risk factors on the occurrence of response fluctuations and dyskinesias in Parkinson's disease. J Neural Transm [Park Dis Dement Sec] (1993) **5**, 127–133.
6. Chase TN, Mouradian MM and Engber TM: Motor response complications and the function of striatal efferent systems. Neurology (1993) **43** (Suppl 6), S23–S27.
7. Harder S, Baas H and Rietbrock S: Concentration-effect relationship of levodopa in patients with Parkinson's disease. Clin Pharmacokinet (1995) **29**, 243–256.
8. Obeso JA, Grandas F, Vaamonde J, Luquin MR, Artieda J and Lera G: Motor complications associated with chronic levodopa therapy in Parkinson's disease. Neurology (1989) **39** (Suppl 2), S11–S19.
9. Mouradian MM, Juncos JL, Fabbrini G and Chase TN: Motor fluctuations in Parkinson's disease: Pathogenetic and therapeutic studies. Ann Neurol (1987) **22**, 475–479.
10. De Jong GJ, Meerwaldt JD and Schmitz PI: Factors that influence the occurrence of response variations in Parkinson's disease. Ann Neurol (1987) **22**, 4–7.
11. Caraceni T, Scigliano G and Musicco M: The occurrence of motor fluctuations in parkinsonian patients treated long-term with levodopa: Role of early treatment and disease progression. Neurology (1991) **41**, 380–384.
12. Kostic V, Przedborski S, Flaster E and Sternic N: Early development of levodopa-induced dyskinesias and response fluctuations in young-onset Parkinson's disease. Neurology (1991) **41**, 202–205.
13. Golbe LI: Young-onset Parkinson's disease: A clinical review. Neurology (1991) **41**, 168–173.
14. Fabbrini G, Juncos J, Mouradian MM, Serrati C and Chase TN: Levodopa pharmacokinetic mechanisms and motor fluctuations in Parkinson's disease. Ann Neurol (1987) **21**, 370–376.
15. Contin M, Riva R, Albani F and Baruzzi A: Pharmacokinetic optimization in the treatment of Parkinson's disease. Clin Pharmacokinet (1996) **30**, 463–481.
16. Ogawa N: Factors affecting levodopa effects in Parkinson's disease. Acta Med Okayama (2000) **54**, 95–101.
17. Nutt JG, Woodward WR, Hammerstad JP, Carter JH and Anderson JL: The "on-off" phenomenon in Parkinson's disease: Relation to levodopa absorption and transport. N Engl J Med (1984) **310**, 483–488.
18. Wu RM, Tai CH and Chen RC: Monitoring of the levodopa concentration-response relationship in Parkinson's disease. Kaohsiung J Med Sci (2000) **16**, 117–125.
19. Quinn N, Parkes JD and Marsden CD: Control of on/off phenomenon by continuous intravenous infusion of levodopa. Neurology (1984) **34**, 1131–1136.
20. LeWitt PA: Treatment strategies for extension of levodopa effect. Neurol Clin (1992) **10**, 511–526.
21. Kurth MC, Adler CH, Hilaire MS, Singer C, Waters C, LeWitt P, Chernik DA, Dorflinger EE and Yoo K: 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. Tolcapone Fluctuator Study Group I. Neurology (1997) **48**, 81–87.
22. Rajput AH, Martin W, Saint-Hilaire MH, Dorflinger E and 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.
23. Rinne UK, Larsen JP, Siden A and Worm-Petersen J: Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. Nomecomt Study Group. Neurology (1998) **51**, 1309–1314.
24. Männistö PT and Kaakkola S: New selective COMT inhibitors: Useful adjuncts for Parkinson's disease? Trends Pharmacol Sci (1989) **10**, 54–56.
25. Nutt JG, Woodward WR, Beckner RM, Stone CK, Berggren K, Carter JH, Grancher ST, Hammerstad JP and Gordin A: Effect of peripheral catechol-*O*-methyltransferase inhibition on the pharmacokinetics and pharmacodynamics of levodopa in parkinsonian patients. Neurology (1994) **44**, 913–919.
26. Davis LT: Catechol-*O*-methyltransferase inhibitors in Parkinson's disease: guidelines for effective use. CNS drugs (1998) **10**, 239–246.
27. Kunugi H, Nanko S, Ueki A, Otsuka E, Hattori M, Hoda F, Vallada HP, Arranz MJ and Collier DA: High and low activity alleles of catechol-*O*-methyltransferase gene: Ethnic difference and possible association with Parkinson's disease. Neurosci Lett (1997) **221**, 202–204.
28. Yoritaka A, Hattori N, Yoshino H and Mizuno Y: Catechol-*O*-methyltransferase genotype and susceptibility to Parkinson's disease in Japan. J Neural Transm (1997) **104**, 1313–1317.
29. Rivera-Calimlim L and Reilly DK: Difference in erythrocyte catechol-*O*-methyltransferase activity between Orientals and Caucasians: Difference in levodopa tolerance. Clin Pharmacol Ther (1984) **35**, 804–809.
30. Axelrod J, Senoh S and Witkop B: *O*-Methylation of catechol amines *in vivo*. J Biol Chem (1958) **233**, 697–701.
31. Salminen M, Lundstrom K, Tilgmann C, Savolainen R, Kalkkinen N and Ulmanen I: Molecular cloning and characterization of rat liver catechol-*O*-methyltransferase. Gene (1990) **93**, 241–247.
32. Grossman MH, Emanuel BS and Budarf ML: Chromosomal mapping of the human catechol-*O*-methyltransferase gene to 22q11.1-q11.2. Genomics (1992) **12**, 822–825.
33. Roth JA: Membrane-bound catechol-*O*-methyltransferase: A reevaluation of its role in the *O*-methylation of the catecholamine neurotransmitters. Rev Physiol Biochem Pharmacol (1992) **120**, 1–29.
34. Tenhunen J and Ulmanen I: Production of rat soluble and membrane-bound catechol *O*-methyltransferase forms from bifunctional mRNAs. Biochem J (1993) **296**, 595–600.
35. Männistö PT, Ulmanen I, Lundström K, Taskinen J, Tenhunen J, Tilgmann C and Kaakkola S: Characteristics of catechol-*O*-methyltransferase (COMT) and properties of selective COMT inhibitors. Prog Drug Res (1992) **39**, 291–350.
36. Männistö PT and Kaakkola S: Catechol-*O*-methyltransferase (COMT): Biochemistry, molecular biology, pharmacology, and clinical efficacy of the new selective COMT inhibitors. Pharmacol Rev (1999) **51**,

593–628.
37. Guldberg HC and Marsden CA: Catechol-*O*-methyl transferase: Pharmacological aspects and physiological role. Pharmacol Rev (1975) **27**, 135–206.
38. Weinshilboum R and Raymond F: Variations in catechol-*O*-methyltransferase activity in inbred strains of rats. Neuropharmacology (1977) **16**, 703–706.
39. Boudikova B, Szumlanski C, Maidak B and Weinshilboum R: Human liver catechol-*O*-methyltransferase pharmacogenetics. Clin Pharmacol Ther (1990) **48**, 381–389.
40. Scanlon PD, Raymond FA and Weinshilboum RM: Catechol-*O*-methyltransferase: Thermolabile enzyme in erythrocytes of subjects homozygous for allele for low activity. Science (1979) **203**, 63–65.
41. Lotta T, Vidgren J, Tilgmann C, Ulmanen I, Melen K, Julkunen I and Taskinen J: Kinetics of human soluble and membrane-bound catechol *O*-methyltransferase: A revised mechanism and description of the thermolabile variant of the enzyme. Biochemistry (1995) **34**, 4202–4210.
42. Dingemanse J, Jorga K, Zürcher G, Schmitt M, Sedek G, Da Prada M and Van Brummelen P: Pharmacokinetic-pharmacodynamic interaction between the COMT inhibitor tolcapone and single-dose levodopa. Br J Clin Pharmacol (1995) **40**, 253–262.
43. Ruottinen HM and Rinne UK: Effect of one month's treatment with peripherally acting catechol-*O*-methyltransferase inhibitor, entacapone, on pharmacokinetics and motor response to levodopa in advanced parkinsonian patients. Clin Neuropharmacol (1996) **19**, 222–233.
44. Baas H, Beiske AG, Ghika J, Jackson M, Oertel WH, Poewe W, Ransmayr G, Auff E, Volc D, Dupont E, Mikkelsen B, Wermuth L, Worm-Petersen J, Benecke R, Eichhom T, Kolbe H, Oertel W, Schimrigk K, Olsson JE, Palhagen S, Burgunder JM, Ghika A, Regli F, Steck A and Medcalf P: COMT inhibition with tolcapone reduces the "wearing-off" phenomenon and levodopa requirements in fluctuating parkinsonian patients. J Neurol Neurosurg Psychiatry (1997) **63**, 421–428.
45. Parkinson Study Group: Entacapone improves motor fluctuations in levodopa-treated Parkinson's disease patients. Ann Neurol (1997) **42**, 747–755.
46. Goetz CG: Highlights of the North America and European experiences. Neurology (1998) **50**, (Suppl 5) S15–S16.
47. Assal F, Spahr L, Hadengue A, Rubbia-Brandt L, Burkhard PR, and Rubbici-Brar: Tolcapone and fulminant hepatitis. Lancet (1998) **352**, 958.
48. Olanow CW and the Tasmar Advisory Pane: Tolcapone and hepatotoxic effects. Arch Neurol (2000) **57**, 263–267.
49. Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL and Weinshilboum RM: Human catechol-*O*-methyltransferase pharmacogenetics: Description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics (1996) **6**, 243–250.
50. Chen CH, Lee YR, Wei FC, Koong FJ, Hwu HG and Hsiao KJ: Association study of NlaIII and MspI genetic polymorphisms of the catechol-*O*-methyltransferase gene and susceptibility to schizophrenia. Biol Psychiatry (1997) **41**, 985–987.
51. Tan EK, Khajavi M, Thornby JI, Nagamitsu S, Jankovic J and Ashizawa T: Variability and validity of polymorphism association studies in Parkinson's disease. Neurology (2000) **55**, 533–538.
52. McLeod HL, Syvanen AC, Githang'a J, Indalo A, Ismail D, Dewar K, Ulmanen I and Sludden J: Ethnic differences in catechol *O*-methyltransferase pharmacogenetics: Frequency of the codon 108/158 low activity allele is lower in Kenyan than Caucasian or South-west Asian individuals. Pharmacogenetics (1998) **8**, 195–199.
53. Hoda F, Nicholl D, Bennett P, Arranz M, Aitchison KJ, al-Chalabi A, Kunugi H, Vallada H, Leigh PN, Chaudhuri KR and Collier DA: No association between Parkinson's disease and low-activity alleles of catechol *O*-methyltransferase. Biochem Biophys Res Commun (1996) **228**, 780–784.
54. Syvanen AC, Tilgmann C, Rinne J and Ulmanen I: Genetic polymorphism of catechol-*O*-methyltransferase (COMT): Correlation of genotype with individual variation of S-COMT activity and comparison of the allele frequencies in the normal population and parkinsonian patients in Finland. Pharmacogenetics (1997) **7**, 65–71.
55. Xie T, Ho SL, Li LS and Ma OC: G/A1947 polymorphism in catechol-*O*-methyltransferase (COMT) gene in Parkinson's disease. Mov Disord (1997) **12**, 426–427.
56. Yoritaka A, Hattori N, Yoshino H and Mizuno Y: Catechol-*O*-methyltransferase genotype and susceptibility to Parkinson's disease in Japan. J Neural Transm (1997) **104**, 1313–1317.
57. Wu RM, Cheng CW, Chen KH, Lu SL, Shan DE, Ho YF and Chern HD: The COMT L allele modifies the association between MAOB polymorphism and PD in Taiwanese. Neurology (2001) **56**, 375–382.
58. Reilly DK, Rivera-Calimlim L and Van Dyke D: Catechol-*O*-methyltransferase activity: A determinant of levodopa response. Clin Pharmacol Ther (1980) **28**, 278–286.
59. Lee MS, Lyoo CH, Ulmanen I, Syvanen AC and Rinne JO: Genotypes of catechol-*O*-methyltransferase and response to levodopa treatment in patients with Parkinson's disease. Neurosci Lett (2001) **298**, 131–134.
60. Chong DJ, Suchowersky O, Szumlanski C, Weinshilboum RM, Brant R and Campbell NR: The relationship between COMT genotype and the clinical effectiveness of tolcapone, a COMT inhibitor, in patients with Parkinson's disease. Clin Neuropharmacol (2000) **23**, 143–148.
61. Wu RM: COMT inhibition: A new therapeutic strategy for Parkinson's disease. Bull Taiwan Neurol Soc (1999) **24**, 95.