Utility of tolcapone in fluctuating Parkinson’s disease

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Abstract: Fluctuating Parkinson’s disease (PD) represents a clinical management challenge. The primary utility of levodopa in patients with PD is moderated by the “wearing off” phenomena seen with long-term use. COMT inhibitors slow down the rapid metabolism of levodopa, resulting in a more-sustained response to dopaminergic therapy. Tolcapone is a selective, reversible catechol-O-methyltransferase (COMT) inhibitor, shown to have both peripheral and central effects. In clinical trials, tolcapone has been shown to reduce “off” time, increase “on” time, improve patient and clinician assessments of disease severity, and improve patient quality of life. In a SWITCH study, tolcapone was associated with greater duration of “on” time than remaining on entacapone. Adverse effects of tolcapone are related to the class, with the exception of rare cases of hepatotoxicity. Tolcapone has been recently reintroduced on the European market and recent guidance from the US Food and Drug Administration has reduced the hepatic monitoring requirements for patients initiating tolcapone therapy. With proper monitoring, tolcapone is an effective, well-tolerated drug useful in the management of patients with fluctuating PD.

Keywords: Parkinson’s disease; tolcapone, COMT inhibitors, drug therapy, safety, tolerability

Introduction

Parkinson’s disease (PD) affects about 1% of adults over the age of 60; as industrial societies age, the prevalence of PD is expected to increase (Olanow et al 2001). In the US alone, an estimated 60,000 new cases of idiopathic PD, characterized by resting tremor, rigidity, and bradykinesia, are diagnosed each year.

The dopamine precursor levodopa has been a mainstay of PD treatment for almost 40 years (Cotzias et al 1967). In fact, good response to levodopa helps distinguish idiopathic PD from other, similar movement disorders (Hughes et al 1992). However, levodopa therapy is eventually complicated by motor fluctuations, including “wearing off” and “on-off” phenomena (Fahn 1999). Drug-induced dyskinesias, including chorea and dystonia, also occur with long-term levodopa therapy in most patients, ultimately reducing quality of life and causing significant disability (Chapuis et al 2005).

Levodopa is routinely administered in combination with a decarboxylase inhibitor, many of which are available as co-formulations under a variety of brand names in the US and Europe. Decarboxylase inhibitors prevent conversion of levodopa to dopamine in the peripheral circulation, thereby allowing more levodopa to cross the blood–brain barrier into the central nervous system (CNS) (Olanow et al 2001). Decarboxylase inhibitors also reduce nausea and vomiting that can occur due to stimulation of dopamine receptors in the area postrema that are not protected by the blood–brain barrier.

By blocking the decarboxylase route of metabolism, circulating levodopa is primarily metabolized by catechol-O-methyltransferase (COMT) to 3-O-methyl-dopa (3-OMD) (Kaakkola 2000). COMT inhibitors in combination with levodopa/decarboxylase inhibitor preparations are associated with an increase of CNS...
bioavailability of levodopa. Theoretically, COMT inhibitors that are active in the CNS would also reduce central metabolism of both levodopa and dopamine.

Tolcapone is a potent, selective reversible inhibitor of COMT (Zurcher et al 1990). Preclinical models showed tolcapone effectively inhibited COMT in the gut, brain, and liver (Borgulpya et al 1991; Da Prada et al 1991; Zurcher et al 1991). In clinical trials, it has been shown to be effective adjunctive therapy for patients who are not obtaining optimal response to levodopa-based therapy. In 1998, 3 cases of acute hepatitis leading to mortality among patients receiving tolcapone led to the temporary suspension of availability of tolcapone in the EU (EMEA 2004), as well as stringent monitoring requirements in the US (FDA 1998). Since then, the compound has been returned to the EU approved drugs list, and the US Food and Drug Administration (FDA) requirements for liver monitoring have been eased (FDA 2006). This article will review pertinent research related to appropriate selection of candidates for tolcapone use.

**Clinical pharmacology of tolcapone**

**Pharmacokinetics**

Tolcapone displays linear pharmacokinetics, independent of levodopa/carbidopa administration, and independent of sex, age, weight, or race (Tasmar PI 2006). Oral tolcapone is rapidly absorbed, with a tmax of about 2 hours and an elimination half-life (t1/2) of about 2 to 3 hours in both single doses and at the recommended dosing frequency of three times a day, both alone and in combination with levodopa and a decarboxylase inhibitor (Table 1) (Dingemanse, Jorga, Schmitt, et al 1995; Dingemanse, Jorga, Zurcher, et al 1995; Dingemanse et al 1996; Jorga et al 1997). Tolcapone displays high plasma binding (>99.9%), mainly to serum albumin, leading to a limited volume of distribution at steady state (9L). The oral bioavailability of tolcapone is approximately 65%, which is decreased by about 10% to 20% if taken 1 hour before or 2 hours after a meal. Tolcapone can be taken without regard to meals (Tasmar PI 2006).

Tolcapone is extensively metabolized, primarily by glucuronidation into an inactive conjugate, with only 0.5% of the administered dose excreted unchanged in urine (Jorga et al 1999). In patients with moderate cirrhotic liver disease (Child-Pugh Class B), clearance and volume of distribution of unbound tolcapone was reduced by almost 50% (Jorga et al 1998). However, no clinically significant changes in pharmacokinetics were noted among patients with noncirrhotic liver disease. Tolcapone therapy should not be initiated in patients with active liver disease or who have elevated transaminase values (Tasmar PI 2006). Tolcapone pharmacokinetics are not altered by renal impairment, although caution is warranted among patients with severe renal dysfunction.

**Pharmacodynamics**

At clinically relevant concentrations, tolcapone inhibited COMT activity in in vitro assays of human liver, duodenum, kidney, and lung tissue (De Santi et al 1998). Tolcapone also inhibited COMT activity in erythrocytes among healthy volunteers receiving single or multiple doses of the drug (Dingemanse, Jorga, Schmitt, et al 1995; Dingemanse, Jorga, Zurcher, et al 1995; Dingemanse et al 1996; Jorga et al 1997). This dose-dependent inhibition was rapid, occurring within 2 hours of administration, and reversible, with ≥80% inhibition occurring with a single 200 mg dose.

Tolcapone may also block COMT activity in the CNS (Ceravolo et al 2002). A study of 12 patients with PD using positron emission tomography and radiolabelled fluorodopa showed evidence of central blockade of central COMT activity compared with placebo.

<table>
<thead>
<tr>
<th>Table 1 Pharmacokinetic parameters (mean values) of oral tolcapone (TOL) in healthy volunteers.</th>
<th>TOL alone</th>
<th>TOL + L-Dopa/Ben</th>
<th>TOL + L-Dopa/Car</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetic parameter</td>
<td>100 mg sd (n=5–6)</td>
<td>200 mg sd (n=5–6)</td>
<td>100 mg sd (n=6)</td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>4.6</td>
<td>6.3</td>
<td>4.5</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>1.7</td>
<td>1.8</td>
<td>0.7</td>
</tr>
<tr>
<td>AUC∞ (mg • h/L)</td>
<td>12.2</td>
<td>18.5</td>
<td>10.2</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>2.0</td>
<td>2.1</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Notes: a volunteers were aged 18–40 y, 19–35 y, or 55–75 y; b values given are those for day 7; c AUC from 0–6 h.

Abbreviations: AUC∞, area under the plasma concentration-time curve from time zero to infinity; Cmax, maximum plasma concentration; sd, single dose; t1/2, elimination half-life; tid, three times daily; tmax, time to Cmax.
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Mechanism of action – impact on levodopa pharmacokinetics

The mechanism of action of tolcapone is based on altering levodopa pharmacokinetics, as well as reducing the levodopa metabolite 3-OMD. Tolcapone prolongs the $t_{1/2}$ of levodopa from approximately 2 to 3.5 hours (Davis et al 1995a; Tasmar PI 2006). This results in an approximate doubling of levodopa relative bioavailability (area under curve). However, $C_{\text{max}}$ or $t_{\text{max}}$ of levodopa are unaffected. Studies in healthy volunteers and Parkinson’s disease patients have confirmed that the maximal effect occurs with 100 mg to 200 mg tolcapone. Plasma levels of 3-OMD are markedly and dose-dependently decreased by tolcapone when given with levodopa/carbidopa.

Clinical trials of tolcapone

Effects of COMT inhibition are seen shortly after administration, allowing for clinical efficacy of tolcapone to be investigated in single-dose trials where patients were observed in a controlled setting for several hours after acute administration. In a dose-ranging study, single doses of tolcapone were found to extend the time antiparkinsonian effects of levodopa/carbidopa by about 70% (Roberts et al 1994). A separate study using levodopa/benserazide concurred with this finding, with tolcapone-treated patients displaying approximately 1 hour of extra “on” time versus placebo (Limousin et al 1995). A dose-ranging study of levodopa/carbidopa plus the monoamine oxidase inhibitor selegiline found that the addition of a single dose of tolcapone, ranging from 50 mg to 800 mg, prolonged the antiparkinsonian effects of levodopa/carbidopa (Davis et al 1995b). In a study of tolcapone pharmacokinetics following 6 weeks of open-label therapy, improvements were seen in the Unified Parkinson's Disease Rating Scale (UPDRS) at 7 time points following administration (Yamamoto et al 1997).

The approval of tolcapone in the US and Europe was based on evidence from 2 multicenter, randomized, double-blind, placebo-controlled clinical trials in patients with levodopa-induced motor fluctuations (Baas et al 1997. Rajput et al 1997).

In the pivotal trial conducted in Europe, 177 patients were randomized 1:1:1 to receive tolcapone 100 mg or 200 mg three times daily (tid), or placebo (containing riboflavin to mimic urinary discoloration seen as a harmless side effect of tolcapone) (Baas et al 1997). Levodopa could be adjusted according to patient response and adverse effects up until 2 weeks prior to the 3-month efficacy endpoint determination. Levodopa could not be increased above baseline prior to the 3-month time point. “On” time increased by 21.3% and 20.6% from baseline with 100 mg and 200 mg tolcapone (p<0.01 versus placebo). “Off” time decreased by 31.5% with the 100 mg dose (p<0.5) and 26.2% with the 200 mg dose (p=NS). Tolcapone 200 mg tid was superior to placebo in UPDRS motor function score during “on” time. Tolcapone therapy was also associated with a statistically significant reduction in levodopa doses, with larger dose reductions seen with the 200 mg tid dose.

There were 202 patients enrolled in a similarly designed study conducted in North America (Rajput et al 1997). Total levodopa doses were significantly reduced in both tolcapone dose arms (p<0.01), as well as number of mean daily levodopa doses. In this trial, patients receiving tolcapone showed decreases in “off” time; however only tolcapone 200 mg tid reached statistical significance (p<0.01). At 3 months, a mean reduction in “off” time of 3.25 hours was noted with tolcapone 200 mg tid. Investigators’ global assessment (IGA) indicated that 68% of patients receiving tolcapone 100 mg tid, and 95% of those receiving tolcapone 200 mg tid displayed a reduced “wearing off” effect, compared with 37% of patients receiving placebo (p<0.01). Patients were allowed to continue on their assigned therapy for up to 12 months after randomization. For those that reached the 12-month time point, the IGA of overall efficacy showed improvement in 80% of patients receiving tolcapone 100 mg tid, and 88% of patients receiving tolcapone 200 mg tid, compared with 37% of patients receiving placebo. In addition, reductions in levodopa dosages noted at 3 months were maintained through the 12-month completion of the trial (Figure 1).

The above trials were included in an analysis of treatment for levodopa-induced motor fluctuations recently completed by a committee of the American Academy of Neurology (AAN) (Pahwa et al 2006). The committee recognized tolcapone as having utility in reducing “off” time. Additional clinical trials of tolcapone that were not reviewed by the AAN committee have also been completed in patients with fluctuating PD, including a head-to-head study with the COMT inhibitor entacapone, as well as studies in patients with stable PD.

Tolcapone substantially increased “on” time and decreased “off” time in a study of 215 patients with fluctuating PD (Adler et al 1998). Patients were randomized to tolcapone 100 mg, 200 mg, or matching placebo. The
onset of response to tolcapone was rapid; improvements were seen at the first study visit 2 weeks after initiation of therapy. By week 6, on time had increased by more than 2 hours, and off time had decreased to a similar extent in both tolcapone groups (Figure 2) (p<0.001 versus placebo). The improvement noted represented an approximately 38% improvement in off time. The total daily dose of levodopa required for patients receiving tolcapone 100mg tid was reduced by 23% (p<0.01 versus placebo). Patients receiving tolcapone 200 mg tid reduced their levodopa requirements by 29% (p<0.001 versus placebo). The total number of daily doses of levodopa was reduced significantly in both tolcapone groups.

A 6-week placebo-controlled trial of tolcapone 50mg, 200 mg, and 400 mg tid reported results from 151 patients (Kurth et al 1997). In this trial, investigators also conducted 10-hour evaluations of motor fluctuations at baseline and at the 6-week study visit. During this evaluation, patients were scored every 30 minutes for “off” time, “on” time, and “on” time with dyskinesia. The primary endpoints were changes in investigator-rated measurements of “on/off” time at the 6-week evaluation from baseline, as well as changes in the UPDRS motor subscale score. All three dosages of tolcapone reduced “off” time by about 40% from baseline (p<0.01 for all tolcapone arms vs placebo). Tolcapone also significantly increased “on” time for the 50 mg (p<0.05), 200 mg (p<0.01) and 400 mg (p<0.01) groups compared with placebo. In this study, there was no difference between the three tolcapone arms in “on” time. Patient diaries completed during the 6-week study supported the 10-hour evaluation finding of decreased “off” time and increased “on” time. The change in the area under the curve of mean UPDRS motor subscale scores favored all tolcapone doses (p<0.05). Patients receiving tolcapone also reported significant decreases in total levodopa dosing (p<0.01); reduction in the number of daily levodopa doses was statistically significant for patients receiving tolcapone 200 mg and 400 mg tid.

A European-Australian collaborative group reported a 6-week placebo-controlled trial of tolcapone 50mg, 200 mg, and 400 mg tid versus placebo among 154 patients in a study that included a 2-week single-blind placebo run-in phase.
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(45) The primary efficacy analysis was patient diary assessments of "on" and "off" time. In this study, improvements were seen in both primary efficacy variables. All tolcapone doses were statistically significantly more effective than placebo in increasing "on" time; however, only tolcapone 200 mg tid reached statistical significance versus placebo in reducing "off" time. The tolcapone 200 mg tid dose resulted in a 34% increase in "on" time and a 42% reduction on "off" time from baseline values. The greatest reduction in total levodopa daily dosage was also greatest in the tolcapone 200 mg tid group (p<0.01 versus placebo). The IGA for "wearing off" and symptom severity were both statistically significant for all tolcapone doses (p<0.05 versus placebo).

The UPDRS motor scores during off-period and the percentage of off time improved significantly using tolcapone in a small study of 40 patients (Shan et al 2001). However gait analysis did not confirm these findings in this trial. Secondary analyses of other UPDRS subscales of total scores in the above studies did not demonstrate statistically significant improvements over placebo (Kurth et al 1997; Myllyla et al 1997; Rajput et al 1997; Adler et al 1998; Shan et al 2001). Other secondary analysis of health-related quality of life found an improvement in one study (Baas et al 1997), but not another (Adler et al 1998).

Comparator trials

One other COMT inhibitor, entacapone, is approved for use in the US and Europe for patients with symptoms of levodopa "wearing off" (Comtan PI 2006). Recently, data were presented from the SWITCH study aimed at determining if switching from entacapone to tolcapone might improve patient outcomes (SWITCH 2006). This was a double-blind, active-control study conducted at 32 centers in Europe and the US, enrolling 150 individuals who had 3 or more hours of "off" time despite optimized entacapone therapy. Patients were randomized to receive either entacapone 200 mg with each levodopa dose, or tolcapone 100 mg tid. Treatment duration was 3 weeks. In the per protocol analysis, a statistically significant greater proportion of patients switched to tolcapone had at least 3 hours a day of additional "on" time (p=0.018). Both groups saw an increase in "on" time; however, the tolcapone had a mean increase of 0.86 hours more than the entacapone group (p=0.042). More patients on tolcapone were judged to have a moderate or marked improvement on the IGA (27% for entacapone vs 40% for tolcapone; p=not significant). More patients responded to tolcapone, as defined by both at least 1 hour/day improvement in "on" time and an IGA rating of moderate or marked improvement (p=0.051). There was no difference between groups in the frequency or severity of adverse events, including dyskinesia, or in the incidence of liver enzyme abnormalities.

Other evidence in favor of the increased efficacy of tolcapone over entacapone was reported in a case study series of 40 patients who were switched from tolcapone to entacapone (Onofrj et al 2001). Patients had been switched either due to intolerability or due to the temporary suspension of tolcapone availability in Europe. After 3 to 6 months of levodopa therapy adjustments, all patients received entacapone for 3 months. The authors reported that levodopa daily dosage was significantly reduced by both tolcapone and entacapone. "On" time was increased by 15% during tolcapone treatment (p<0.05), and by 8% during entacapone treatment. "Off" time was decreased by 16% during tolcapone and by 7% during entacapone treatment.

Tolcapone also appears to have greater long-term benefits compared with entacapone, according to an analysis conducted of data collected from 2 groups of patients enrolled in parallel long-term tolerability and efficacy studies of tolcapone and entacapone (Factor et al 2001). The entry criteria, efficacy and tolerability analyses, and data collection points for the two trials were similar. In this analysis, tolcapone was more effective in lowering UPDRS motor and complication subscores, as well as duration of "off" time, and total levodopa doses. Improvements seen in UPDRS motor scores and change in levodopa dose remained below baseline level for 36 months in the tolcapone group; those same scores climbed above baseline in the entacapone group from the 6-month study visit onward.

Tolcapone 100 mg tid was compared with add-on therapy with the dopamine agonist pergolide (Koller et al 2001). There was no placebo-controlled arm in this trial; however, both therapies showed similar efficacy in reducing "off" time, increasing "on" time, reducing total daily levodopa dosage, or in UPDRS scores, and IGAs. Tolcapone was more effective than pergolide in improving a quality of life measure, the PDQ-39 scale, at 12 weeks (p=0.0005).

An open-label comparative trial of tolcapone 200 mg tid versus the dopamine agonist bromocriptine was conducted in 146 PD patients (TSG 1999). At the end of 8 weeks, both treatment groups showed similar results in "on" time, "off" time, and UPDRS subscale scores. Because bromocriptine must be titrated upward over a period of time, patients assigned to tolcapone showed greater improvements early in the course of therapy. The mean total daily levodopa
dosage decreased by 16.5% in the tolcapone-treated patients, compared with 4% among patients receiving bromocriptine (p<0.01). In the tolcapone group, this reduction was achieved as early as week 1 and was almost complete by week 4.

Trials in stable PD
All of the trials reviewed above were conducted among patients with fluctuating PD associated with the levodopa “wearing off” syndrome. Tolcapone is approved for this indication in the US and Europe. Additional studies have been conducted to determine if tolcapone can provide benefits for patients with stable PD on levodopa therapy.

Tolcapone 100 mg and 200 mg tid were evaluated in patients on stable levodopa therapy in a 12-week crossover study (Suchowersky et al 2001). All patients received tolcapone 100 mg tid for 4 weeks, then were randomly assigned to either continue on that dosage or to receive tolcapone 200 mg tid. At week 8, therapy was switched to the alternate dosage level in a double-blind fashion. During the 4-week open-label run-in, tolcapone 100 mg tid resulted in improvements in IGAs among 76% of patients. In addition, the mean total daily levodopa dose and mean UPDRS subscale scores decreased significantly (p<0.001 for all measures compared with baseline). During the double-blind treatment period, 61% of patients showed improvements in their IGA at either or both dosages. Other efficacy variables changed minimally; there was no difference between tolcapone dosages.

A double-blind, placebo-controlled trial investigated the effect of tolcapone 100 mg or 200 mg tid on activities of daily living and motor function in 298 patients with PD receiving levodopa but without motor fluctuations (Waters et al 1998). At 6 months, both dosages of tolcapone produced significant reductions in the UPDRS subscales II and III and in the total score for subscales I to III. These improvements were maintained up to 12-months. At 6 months, both tolcapone groups had significant decreases in levodopa dosage compared with placebo. Both tolcapone groups reported decreases in mean total daily dose of levodopa, while the placebo group had a mean increase.

Tolcapone 200 mg and 400 mg tid were studied in patients whose “wearing off” symptoms had been stabilized by increasing their levodopa dosing (Dupont et al 1997). After a 1-week placebo run-in, patients were assigned to placebo or one of the tolcapone dosages. Levodopa dosage was reduced by 35% on day 1, then titrated upward as required. After 6 weeks, the study was unblinded and the tolcapone groups crossed over to the other dose for exploratory purposes. Although not statistically different, both tolcapone groups showed greater reductions in levodopa dosage requirements compared with placebo. Tolcapone 200 mg tid showed statistically significant improvement in the UPDRS subscale II (p<0.05 versus placebo).

Safety and tolerability of tolcapone
Hepatotoxicity
During post-marketing surveillance, 3 cases of fatal hepatotoxicity were reported in patients who were not properly monitored. As a result, new FDA guidelines for liver testing were established. This also prompted the sponsor to conduct a review of the tolcapone safety database, representing approximately 100000 patient-years of therapy (Watts and Kricorian 2005). Although underreporting of adverse events may have occurred, a total of 219 cases of hepatobiliary events were recorded. Most of these cases were mild transient elevations in liver function tests <3 times the upper limit of normal (ULN). Most cases were either asymptomatic or resolved without treatment interruption. Only 21 cases (0.001%) reported elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times ULN; the median time to this adverse event was 81 days. After new monitoring guidelines were in place, no deaths related to hepatotoxicity occurred. In addition, asymptomatic elevations in liver function tests did not progress to acute hepatitis if treatment was withdrawn.

As a result of this analysis, the FDA has recently reduced the liver monitoring requirements for tolcapone use (FDA 2006). The newly approved labeling states that serum glutamic pyruvic transaminase (SGPT)/ALT and serum glutamic oxaloacetic transaminase (SGOT)/AST levels should be determined at baseline, as well as periodically (ie, every two to four weeks) for the first six months of therapy. Periodic monitoring is recommended at intervals deemed clinically relevant after the first 6 months of therapy. In addition, patients can remain on tolcapone therapy if liver enzymes are below 2 times ULN and/or do not display symptoms of liver toxicity.

Other adverse events
New or worsening dyskinesia is the most common adverse event associated with tolcapone therapy. Worsening of dyskinesia most commonly occurs at the start of tolcapone
therapy, and may be moderated by optimizing levodopa dosages (Baas et al 1997; Rajput et al 1997; Adler et al 1998). Dyskinesia and other dopaminergic adverse events are most likely due to the increase in levodopa concentrations that provide the rationale for tolcapone use.

Diarrhea is the most commonly reported nondopaminergic adverse event reported in clinical trials (Rajput et al 1997; Waters et al 1997; Adler et al 1998). Table 2 lists the common adverse events reported by the manufacturer in clinical trials.

In the comparative trial with entacapone, the frequency and severity of adverse events was similar between the two medications (SWITCH 2006). In the trial comparing tolcapone with pergolide, tolcapone was associated with reduced risk of nondyskinesia adverse events (59% vs 77% for pergolide; p=0.001) (Koller et al 2001). Dyskinesia occurred in 34% of tolcapone recipients and 25% of pergolide recipients. Incidence of nausea was also substantially higher with pergolide therapy (35%) compared with tolcapone (20%). In the trial comparing tolcapone with bromocriptine, nausea, orthostatic complaints, hallucinations, and peripheral edema were reported more often among bromocriptine patients, while muscle cramps, dystonia, and dry mouth were reported more often among tolcapone recipients (TSG 1999).

**Discussion**

Tolcapone is an effective agent that can help improve the efficacy of levodopa-based therapy in patients with PD. It is especially useful, and indicated for, patients who are experiencing “wearing off” motor fluctuations from their levodopa therapy. Benefits of tolcapone have also been demonstrated among patients on stable levodopa therapy who have not yet begun to display motor fluctuations. There is also increasing interest in determining whether early administration of a COMT inhibitor (ie, at the first use of levodopa) might reduce the risk of eventual motor complications (Olanow et al 2001). The primary adverse effect of tolcapone is dyskinesia, which is more of a problem among patients who present with dyskinesia prior to initiation of tolcapone therapy. Immediate reductions in levodopa dosages between 15% and 30% may be warranted to obviate this concern.

The goal of providing clinical benefits for PD patients over the longest period of time without undue adverse events remains elusive at best. The determination of when to begin levodopa-based therapy in patients with PD is complex. It is generally recommended that any pharmacotherapy not be initiated until patients begin to show functional deterioration (Olanow et al 2001). Levodopa therapy may be delayed with early use of dopamine agonists in younger patients; however, eventually all patients receiving dopamine agonist therapy will require levodopa supplementation. Levodopa has the advantage of being almost universally efficacious among patients with idiopathic PD. However, the long-term outcome of levodopa-based therapy is clouded by the “wearing off” phenomena. Future clinical research is warranted to determine whether early use of COMT inhibitors like tolcapone can delay the onset of levodopa-associated adverse effects.

**References**


