



# Selegiline orally disintegrating tablet in the treatment of Parkinson's disease

Anthony Clarke &  
Joseph Jankovic†

†Author for correspondence  
Parkinson's Disease Center  
and Movement Disorders  
Clinic, Baylor College of  
Medicine, Department of  
Neurology, The Smith Tower,  
Suite 1801  
6550 Fannin, Houston,  
TX 77030, USA  
Tel.: +1 713 798 5998  
Fax: +1 713 798 6808  
josephj@bcm.tmc.edu

Mono- and adjunctive therapy with the oral monoamine oxidase B inhibitor selegiline has been used to treat motor complications resulting from long-term treatment of Parkinson's disease. However, oral selegiline undergoes extensive first-pass metabolism resulting in low bioavailability and production of amphetamine and other metabolites, as well as compromised efficacy and tolerability. An orally disintegrating tablet of selegiline utilizing Zydys® technology undergoes markedly reduced presystemic metabolism, thus providing higher plasma concentrations and lower levels of amphetamine metabolites. As an adjunct to levodopa, selegiline orally disintegrating tablet has been found to significantly reduce 'off' time, increase 'on' time, and improve motor function in Parkinson's disease patients experiencing 'wearing off' episodes. This article provides an overview of the Zydys technology, the rationale for its application in delivering selegiline, and results from clinical trials of selegiline orally disintegrating tablet in patients with Parkinson's disease.

Although conventional oral administration is the preferred and more convenient route of drug delivery, it has some disadvantages. Pharmacokinetic limitations to conventional oral administration can include poor absorption and enzymatic degradation of the drug within the gastrointestinal tract. Also, reduced bioavailability may result from the intestinal Phase I metabolism and the active extrusion of absorbed drug by cytochrome P450 enzymes and P-glycoprotein. Bioavailability is also limited by hepatic first-pass metabolism, which gives rise to metabolites that do not contribute greatly to clinical benefit and may even produce substantial toxicity [1–7]. In some patients, conventional oral delivery is not possible because of gastric mucosal irritation, bowel obstruction, frequent emesis, or severe dysphagia [8]. In addition, an estimated 50% of the general population reports difficulty swallowing tablets and hard gelatin capsules, which results in a high incidence of noncompliance and the consequent compromises in efficacy [9]. This is most common among pediatric and geriatric patients, but also occurs in those who are ill or who are busy or traveling and do not have convenient access to water [9].

The monoamine oxidase type B (MAO-B) inhibitor selegiline has been shown to be clinically effective for the treatment of patients with Parkinson's disease (PD) [10–16]. Laboratory experiments have also shown that selegiline provides protection against apoptosis and may have neuroprotective properties [17]. The DATATOP

study was carried out in part to evaluate potentially neuroprotective effects of selegiline in patients with early PD. While results demonstrated that selegiline conferred some clinical benefit, they did not permit any conclusions regarding the medication's neuroprotective effects [18]. Selegiline has been used most extensively for the treatment of wearing-off symptoms, and several studies have demonstrated modest decreases in symptoms, duration of 'wearing-off' and 'on-off' episodes, levodopa dose, and disability [10–15]. The benefit of selegiline in reducing motor fluctuations has also been demonstrated in a meta-analysis of clinical trial results for this MAO-B inhibitor [14]. However, it is important to note that some studies have shown minimal or no benefit long-term from adjunctive selegiline in patients with PD [19]. The role of selegiline as adjunctive therapy in the treatment of patients with PD has also been controversial because of results reported by the Parkinson's Disease Study Group of the United Kingdom indicating that long-term exposure to this agent was associated with increased mortality risk, particularly in patients with a history of dementia or falls [20]. While these results may be troubling, it is important to note that long-term follow-up of selegiline-treated patients in other studies has failed to detect any mortality [21,22].

The maximum dose of selegiline is limited because the drug undergoes extensive hepatic first-pass metabolism, which leads to high levels of amphetamine metabolites and ultimately compromises efficacy and tolerability [23,24]. To

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overcome these problems, selegiline was formulated in an orally disintegrating tablet (ODT) using Zydis® technology. This new formulation is awaiting approval by the US FDA for use as adjunctive therapy to levodopa in the management of PD.

This article describes the Zydis fast-dissolve drug delivery system, introduced more than a decade ago [9], which eliminates many of the problems associated with traditional oral drug formulations. The article also presents the rationale for its application in the formulation of selegiline for the treatment of PD, and discusses the results of clinical trials of selegiline ODT.

### Alternatives to conventional oral drug delivery

Limitations of conventional oral drug administration have prompted intensive exploration of alternative delivery vehicles that use transdermal administration or transmucosal drug delivery through the nasal, rectal, vaginal, ocular, and oral cavities [1,7]. Drug preparations that permit absorption through the oral mucosa have a number of potential advantages over conventional oral preparations. Pharmacokinetic and pharmacodynamic benefits may include more rapid onset of action, avoidance of presystemic metabolism to provide higher and steadier drug levels than standard formulations, and decreased levels of unwanted metabolites that may result from hepatic first-pass metabolism. Benefits may also include reduced risk of interaction with food and

decreased dosing restrictions with respect to meals, which can potentially improve the balance of efficacy and safety of orally delivered medications, increase tolerability and compliance, and enhance therapeutic outcomes [1,25,26].

Two distinct types of preparations that permit absorption of medication through the oral mucosa are in relatively wide clinical use: rapidly disintegrating tablets and soft gelatin capsules filled with liquid drug [1]. The current discussion focuses on the Zydis fast-dissolve drug delivery system (Cardinal Health Oral Technologies, NJ, USA) and its application to improve delivery of selegiline given as adjunctive therapy with levodopa in patients with PD.

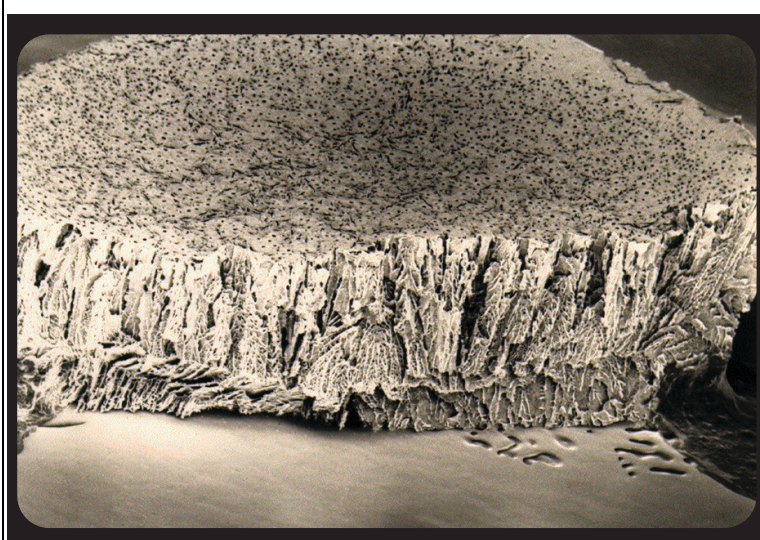
### Zydis formulation for oral drug delivery

Zydis technology is used to create a rapidly disintegrating dosage form in a freeze-dried medicinal tablet that differs qualitatively from conventional oral dosage forms [9]. The production sequence begins with the bulk preparation of an aqueous drug solution or suspension into preformed blisters in the shape of the tablet. The filled blisters are rapidly frozen and transferred to large-scale freeze dryers for a sublimation process, during which the remaining moisture is removed. This leaves a matrix composed of microspindles of gelatin and large spaces (where the ice once resided) and allows for rapid disintegration on contact with moisture (Figure 1). Finally, tablets are heat sealed in the blisters to ensure the product remains stable and is protected from varying environmental conditions.

### Drug candidates for Zydis formulation

Numerous criteria are evaluated when considering a drug for Zydis formulation. Both water-soluble and insoluble agents can be formulated using Zydis technology, but compounds must be absorbable through the mucosa [9]. Upper dose limits are generally higher for water-insoluble drugs than for water-soluble drugs. The drug should also have an acceptable taste. Current approaches to improving the taste of a rapidly disintegrating tablet, not generally a significant consideration in the development of conventional oral tablets, include addition of sweeteners and flavors. If these additives do not mask a bitter taste, drug particles may also be coated [101]. A drug that meets these criteria and is hindered by one or more of the common drawbacks of conventional oral formulation that limit its clinical use is the best candidate for the Zydis formulation.

Figure 1. Electron micrograph (×50) of a Zydis orally disintegrating tablet demonstrating its porous architecture.



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**Actions & advantages of the Zydis formulation**

When Zydis tablets are placed in the mouth, the porous structure disintegrates and instantaneously releases the drug to dissolve or disperse in the saliva. When the patient swallows this saliva, the drug reaches the stomach and may be absorbed via the gastrointestinal tract. However, for some drugs, a significant portion is absorbed from the mouth, pharynx, and esophagus as the saliva passes down into the stomach, where the remaining portion is absorbed [9].

Advantages of oral mucosal absorption include rapid absorption and onset of action, avoidance of presystemic metabolism to attain higher drug levels than with drugs delivered via standard routes; decreased plasma concentrations of unwanted metabolites that may result from first-pass metabolism and thus improved tolerability; low risk for interaction with food and no dosing restrictions related to meals; simple administration particularly for patients experiencing difficulty swallowing pills; and the potential for improved compliance [9].

**Medications currently using Zydis technology**

Zydis technology is currently used to deliver a wide range of medications for many indications. These medications include ondansetron, a serotonin receptor antagonist used as prophylaxis against chemotherapy-induced nausea and vomiting [27]; olanzapine, an atypical antipsychotic used for the treatment of schizophrenia and schizoaffective disorder [28]; clonazepam, a benzodiazepine used for a variety of indications [29]; loratadine, a non-sedating histamine Type 1 receptor antagonist used in the treatment of allergic rhinitis [101]; piroxicam, a nonsteroidal anti-inflammatory drug [101]; rizatriptan, a serotonin Type 1<sub>B/D</sub> receptor agonist used in the treatment of migraine [30]; and famotidine, a histamine Type 2 receptor antagonist used in the treatment of acid-related diseases [101].

**Conventional oral selegiline use in Parkinson's disease****Parkinson's disease**

PD is a progressive neurodegenerative disease with a high burden of morbidity [31]. In the United States, an estimated 1.5 million people have PD, and 70,000 new diagnoses are made each year [32]. The overall prevalence of PD rises as the population ages. PD is characterized by the progressive loss of dopamine-containing

neurons in the *substantia nigra pars compacta*, and this cell death is thought to be the key factor leading to the major clinical symptoms of this disease [33,34], which include resting tremor, rigidity, bradykinesia, and postural disturbances [34,35]. Degeneration of non-dopaminergic systems is increasingly being recognized as an early and disabling process in neurodegeneration associated with PD [36].

**Treatments for Parkinson's disease**

Levodopa, the 'gold-standard' for treatment of PD, provides marked benefit in nearly all patients [37]. However, levodopa as a life-long therapy has potentially serious limitations. Most importantly, long-term levodopa administration is associated with disabling motor fluctuations in a form of wearing off and on-off patterns [38]. Up to one half of patients experience wearing-off and one third experience dyskinesias within 2 years of starting levodopa therapy [39]. These motor fluctuations, unpredictable off periods, and dyskinesias negatively affect quality of life in patients with PD [40]. These effects also increase treatment costs, medical visits, and caregiver burden [41].

**Management of 'off' episodes**

Among other strategies, adjunctive treatment with an MAO-B inhibitor, such as selegiline [14] or rasagiline [42,43], can reduce the frequency of off episodes. The clinical benefit of the MAO-B inhibitors is thought to arise from their ability to decrease the enzymatic breakdown of dopamine [26,44]. Selegiline is an orally bioavailable MAO-B inhibitor that has demonstrated modest efficacy for the treatment of motor fluctuations in levodopa-treated patients with PD [15]. However, extensive hepatic first-pass metabolism of oral selegiline results in low bioavailability of the parent compound and production of amphetamine metabolites; *l*-methamphetamine and *l*-amphetamine make up more than three quarters of the recovered metabolite volume of an oral dose of conventional selegiline (Table 1) [23,24]. Conventional oral selegiline tablets have also been demonstrated to have clinically significant interactions with antidepressants (serotonin syndrome) [45] and the opioid analgesic pethidine (meperidine) [46].

The Zydis technology has been applied to selegiline to address the limitations of the conventional oral tablet in the management of off episodes in patients with PD [26]. The remainder of the current discussion reviews pharmacokinetic, pharmacodynamic, and clinical results for this new selegiline formulation.

**Selegiline orally disintegrating tablets**

*Pharmacokinetics & metabolism*

Clarke and colleagues reported the pharmacokinetic and pharmacodynamic profiles of selegiline ODT based on seven randomized comparative studies involving 156 healthy volunteers in the USA and Europe [47]. The findings indicated that approximately one third of an oral dose of selegiline ODT 10 mg was absorbed pregastrically (predominantly buccally) within 1 min of administration. Conventional oral selegiline demonstrated more variable absorption and there was no evidence that absorption varied significantly between patients in the nonswallowed selegiline ODT group. When selegiline ODT was given across a dose range of 1.25–10 mg, plasma concentrations of the drug and its metabolites increased in a dose-dependent manner as reflected by both maximum plasma concentration ( $C_{max}$ ) and AUC (Table 1) [47].

The bioavailability of selegiline ODT 10 mg was approximately 8 times higher than that of conventional selegiline tablets 10 mg. However, consistent with the identical administered dose in both groups, plasma concentrations of selegiline metabolites, *N*-desmethylselegiline, *L*-methamphetamine, and *L*-amphetamine, were similar (Table 1) [47]. This suggested that selegiline ODT administered in a markedly reduced dose could result in equivalent plasma concentrations of selegiline when compared with 10 mg of the conventional oral formulation, but with a large reduction in the plasma concentrations of selegiline metabolites. Another comparative study described by Clarke and colleagues confirmed this hypothesis by demonstrating that selegiline ODT 1.25 mg

achieved a  $C_{max}$  similar to that of the much higher 10 mg dose of conventional selegiline tablets while resulting in more than a 90% reduction in the  $C_{max}$  of the principal metabolites [47].

*Pharmacodynamics*

Pharmacodynamic evaluations have demonstrated rapid inhibition of MAO-B after administration of lower doses of selegiline ODT than of conventional oral selegiline. Investigators assessed inhibition of MAO-B and MAO-A activity by measuring levels of  $\beta$ -phenylethylamine (PEA) and 5-hydroxyindoleacetic acid, respectively, and showed that selegiline ODT given across a range of 1.25–10 mg produced a rapid dose-related inhibition of MAO-B from 0 to 24 h [47]. Mean daily PEA excretion was similar after treatment with selegiline ODT 1.25 mg and conventional selegiline 10 mg [47], but selegiline ODT 1.25 mg resulted in markedly reduced concentrations of the principal amphetamine metabolites of the parent drug [47]. Importantly, this demonstrates that the inhibition of MAO-B results from the action of selegiline itself and not from its metabolites.

An early study in healthy volunteers compared potentiation of the tyramine pressor effect after treatment with selegiline ODT with that observed after treatment with conventional selegiline tablets [48]. In this open-label, parallel-group comparison, 24 adults were randomized to receive selegiline ODT 1.25 mg or conventional selegiline tablets 10 mg for 14 to 16 days. Escalating doses of oral tyramine were administered to determine the dose (threshold dose) that caused at least a 30 mmHg increase in systolic

**Table 1. Pharmacokinetic parameters for selegiline ODT and conventional selegiline.**

	Selegiline		<i>N</i> -desmethyl selegiline		<i>L</i> -amphetamine		<i>L</i> -methamphetamine	
	$AUC_{0-\infty}$ (ng•h/ml)	$C_{max}$ (ng/ml)	$AUC_{0-\infty}$ (ng•h/ml)	$C_{max}$ (ng/ml)	$AUC_{0-\infty}$ (ng•h/ml)	$C_{max}$ (ng/ml)	$AUC_{0-\infty}$ (ng•h/ml)	$C_{max}$ (ng/ml)
Selegiline ODT (1.25 mg)	1.31	2.36	2.40	1.19	8.90	0.34	20.00	0.93
Selegiline ODT (2.5 mg)	2.29	3.38	7.60	2.94	22.40	0.78	51.70	2.03
Selegiline ODT (5 mg)	4.88	6.43	14.50	5.58	43.10	1.26	103.20	4.69
Conventional selegiline (10 mg)	1.42	1.50	47.80	18.37	113.60	3.60	288.40	12.92

ODT: Orally disintegrating tablet.

Adapted with kind permission from J. Neural Transm. [48].

blood pressure from baseline. The first tyramine challenge was performed using a tyramine dose of 100 mg. The tyramine dose was increased by 100 mg increments (to a maximum of 700 mg) until a pressor response was achieved. A second 2-day test was carried out after 14 days of treatment with either selegiline ODT or conventional selegiline. The challenge doses for the first day of the second test were 25, 50, and 100 mg. On the second day of the test, the initial tyramine dose was 200 mg and it was increased by 100 mg increments until a pressor response was achieved. Blood pressure was measured at 5-min intervals after the tyramine challenge [48].

Administration of tyramine 400 mg both before and after 14 days of treatment with selegiline ODT resulted in no change in sensitivity to tyramine. However, the tyramine pressor response was elicited by a significantly lower dose (400 vs 200 mg;  $p < 0.0001$ ) after a 14-day regimen of 10 mg conventional selegiline tablets [48].

#### Efficacy

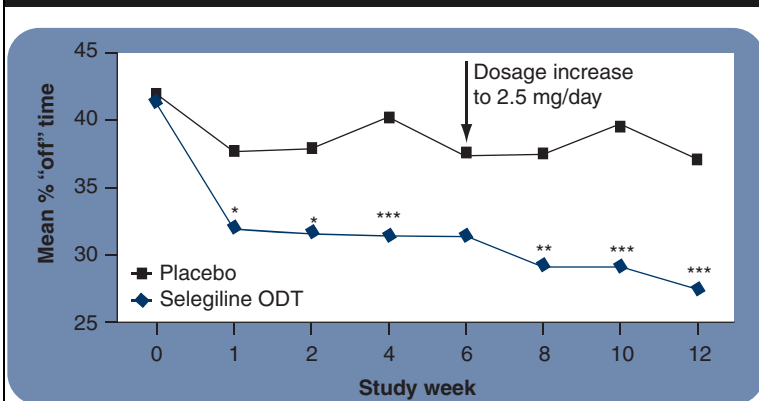
Selegiline ODT 1.25 or 10 mg was compared with conventional selegiline tablets 10 mg in a clinical trial conducted in 197 patients with stable PD who were previously treated with conventional selegiline as an adjunct to levodopa/dopamine agonist therapy [48]. Patients in the USA and the UK were randomized to continue receiving conventional selegiline tablets 10 mg ( $n = 68$ ) or to switch to selegiline ODT 1.25 mg ( $n = 64$ ) or 10 mg ( $n = 62$ ) for 12 weeks. The selegiline ODT 1.25 mg group showed a more robust improvement in the Unified Parkinson's Disease Rating Scale (UPDRS)

after 12 weeks ( $p = 0.01$  vs baseline) than the conventional selegiline group. Furthermore, a higher proportion of patients treated for up to 3 months indicated a preference for selegiline ODT (1.25 mg: 90%; 10 mg: 86%) over conventional selegiline tablets. Among all patients treated with selegiline ODT, more than 90% found selegiline ODT easy to take, with 61% rating it as extremely easy to take [48].

In another trial conducted in the United States, selegiline ODT was evaluated in a 12-week, randomized, double-blind, placebo-controlled, multicenter trial that included 140 patients with PD who were experiencing motor fluctuations during treatment with levodopa [26]. Patients were randomized in a 2:1 ratio to receive selegiline ODT 1.25 mg/day or placebo. At week 6, the selegiline ODT dose was increased to 2.5 mg/day and maintained for the rest of the study. The primary efficacy variable was the reduction in percentage of daily off time over the 12 weeks reported in patient dairies. Efficacy variables also included effects of treatment on both total daily on time as well as dyskinesia-free on time, a potentially important efficacy variable since it may be closely associated with improvements in quality of life for patients with PD [26,40]. Signs and symptoms of PD were assessed using the UPDRS subscales for motor function and activities of daily living, the Clinical Global Impression-Improvement (CGI-I) scale, and the Patient's Global Impression (PGI) scale [26].

Significant reductions in daily off time occurred at 4–6 weeks in the selegiline ODT 1.25-mg group ( $p = 0.003$  vs placebo) and at 10–12 weeks in the 2.5-mg group ( $p < 0.001$  vs placebo) [26]. Percent reduction in total daily 'off' time was 9.9% ( $\pm 13.3\%$ ) at weeks 4–6 and 13.2% ( $\pm 15.1\%$ ) at weeks 10–12, compared with 3.2% ( $\pm 10.7$ ) and 3.8% ( $\pm 10.3$ ) for placebo, respectively (Figure 2). At weeks 10–12, the mean total daily 'off' time was reduced from baseline by 2.2 h in selegiline ODT-treated patients and by 0.6 h in controls ( $p < 0.001$ ). Secondary efficacy variables also demonstrated significant benefit of selegiline ODT versus placebo. At week 12, the average number of dyskinesia-free on hours increased from baseline by 1.8 for selegiline ODT-treated patients and by 0.4 h for controls, and time on with dyskinesia was not significantly elevated with selegiline ODT versus placebo. There was no change in mean percentage of asleep time throughout the study. CGI-I and PGI scores improved significantly in patients treated with selegiline ODT versus controls ( $p = 0.026$  and  $p < 0.05$ , respectively) [26].

**Figure 2. Percentage of daily 'off' time by study week (initial dose of selegiline ODT was 1.25 mg/day).**



ODT: Orally disintegrating tablet

\* $p \leq 0.05$ ; \*\* $p \leq 0.01$ ; \*\*\* $p \leq 0.001$ .

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### Highlights

- Zydys® technology is used to create a rapidly disintegrating dosage form of numerous medications in a freeze-dried tablet.
- Long-term administration of levodopa, the gold standard in the treatment of PD, is associated with disabling motor fluctuations in a form of 'wearing off' and 'on-off' patterns.
- Clinical utility of conventional oral selegiline to treat motor fluctuations is limited by first-pass metabolism resulting in low bioavailability of the parent compound and production of amphetamine metabolites.
- Selegiline orally disintegrating tablets (ODT) utilize the Zydys formulation and an improved pharmacokinetic and pharmacodynamic profile that includes avoidance of presystemic metabolism to provide higher and more reliably achieved drug levels and lower levels of amphetamine metabolites than standard formulations.
- A clinical trial was conducted in the USA and the UK in 197 patients with stable PD who were previously treated with conventional oral selegiline as an adjunct to levodopa/dopamine agonist therapy. Patients who were switched to selegiline ODT 1.25 mg once daily showed more robust improvements in the United Parkinson's Disease Rating Scale after 12 weeks compared with those continuing conventional oral selegiline ( $p = 0.01$ ).
- Selegiline ODT was evaluated in two 12-week, randomized, double-blind, placebo-controlled, multicenter US trials in patients with PD who were experiencing motor fluctuations during levodopa therapy. Patients received selegiline ODT 1.25 mg/day for the first 6 weeks followed by 2.5 mg/day for the final 6 weeks. Results from one of these studies showed that patients receiving selegiline ODT achieved a mean reduction of total daily off time of 2.2 h compared with a reduction of 0.6 h in the placebo group ( $p < 0.001$ ).
- Selegiline ODT has been shown to be safe and well tolerated in clinical trials.

Selegiline was also evaluated in a third trial identical in design to that described immediately above. This study enrolled 180 patients, of whom 100 were randomized to selegiline ODT and 50 to placebo. In this trial, treatment with selegiline ODT reduced daily off time at weeks 10–12 by 11.6 versus 9.8% for placebo ( $p = 0.467$ ). The major difference in the results for the two trials was the very large placebo response in this study. The reason for this response is not clear. Combined results for the two trials demonstrated that selegiline ODT significantly decreased percentage off time at weeks 10–12 (12.4 vs 6.9%,  $p = 0.003$ ), indicating maintained efficacy for this primary end point across the larger pooled population. Complete results of this trial and a pooled analysis are currently being prepared for publication.

It is important to note that patients in large-scale studies of selegiline ODT had an average age of approximately 65 years and mean PD duration of 6–7 years. At baseline, patients in the two trials had an average 'off' period of approximately 7 h/day. All of these results indicate relatively advanced disease [26,49]. Additional information would be useful to assess the efficacy of selegiline ODT in patients with less severe PD.

### Safety

Selegiline ODT has been shown to be safe and well-tolerated in clinical trials. Waters and colleagues demonstrated that selegiline ODT had a systemic adverse event profile similar to that of placebo when added to ongoing levodopa/dopamine agonist therapy [26]. Overall, 32% of the selegiline ODT-treated patients experienced at least one drug-related event compared with 21% of the placebo-treated patients. Adverse events encountered during treatment with selegiline ODT were consistent with known effects of levodopa therapy. The most frequently observed adverse events judged by the investigators to be drug-related were dizziness, dyskinesias, hallucinations, headache, and dyspepsia. Most of these events were reported during the first 6 weeks of treatment with the 1.25 mg dose. There have been no reported effects of selegiline ODT on clinical laboratory values [48] or electrocardiograms [26].

In their report of three clinical studies, Clarke and colleagues reported minor oral irritation for some patients receiving selegiline ODT 1.25, 5, or 10 mg [48]. This adverse event was more common among patients receiving selegiline ODT 10 mg than among those receiving 1.25 mg. Most occurrences with either selegiline ODT dose were transient and resolved spontaneously during the first 2 weeks of therapy [48].

### Expert commentary

Oral administration of medications is convenient, but can be associated with numerous limitations. Zydys is an innovative, well-established fast-dissolve drug delivery system with numerous advantages over traditional oral formulations. Zydys technology has been used to improve the pharmacokinetic and pharmacodynamic profiles of many commonly used medications and to enhance the convenience and compliance of the drug regimens.

A Zydys formulation of selegiline has significantly improved the drug's pharmacokinetic and pharmacodynamic profile in the treatment of PD. Selegiline ODT given once daily avoids presystemic metabolism to provide higher and more reliably achieved drug levels and lower levels of amphetamine metabolites than standard formulations. Selegiline ODT provides good tolerability with minimal risk for clinically relevant MAO-A inhibition or tyramine pressor responses. Addition of selegiline ODT to levodopa therapy in PD patients experiencing wearing off episodes significantly reduced 'off' time,

increased 'on' time, and improved motor function. Overall, clinical trials have demonstrated selegiline ODT to be efficacious and safe with good tolerability. The product is currently awaiting approval by the FDA for use as adjunctive therapy with levodopa in patients with PD. In February 2006, the US FDA approved transdermal selegiline (Emsam<sup>®</sup>) at 6, 9, or 12 mg of selegiline per 24 h, as the first drug patch for depression.

### Outlook

No current therapeutic regimen halts the neurodegenerative progression associated with PD. Although patients with advanced PD are commonly treated with levodopa, many experience debilitating motor fluctuations. Several approaches have been used to treat 'off' and 'on-off' episodes. The results reviewed in this paper indicate that treatment with selegiline ODT safely decreases 'off' time in patients with

relatively severe PD by about 2 h/day. This reduction is comparable to those observed with other medications that may be used to treat 'off' episodes in patients receiving levodopa, including rasagiline [43], the catechol-*O*-methyltransferase inhibitor entacapone [50,51], and the dopamine receptor agonist pramipexole [52].

During the next several years, we expect to see expanded treatment options for PD. Research is being conducted on such varied approaches as neuroprotective disease-modifying agents, neurotrophic molecules, and nerve growth factors. Stem cell research, direct molecular implantation, and genetic manipulation may also hold promise for the future.

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**Affiliations**

*Anthony Clarke, PhD*  
*Amarin Neuroscience Ltd,*  
*Laurellbill Business Park, Stirling,*  
*FK7 9JQ, UK*  
*Tel.: +44 1786 476 000*  
*Anthony.clarke@amarincorp.com*

*Joseph Jankovic, MD,*  
*Professor of Neurology, Director,*  
*Parkinson's disease Center and*  
*Movement Disorders Clinic,*  
*Baylor College of Medicine,*  
*Department of Neurology,*  
*The Smith Tower, Suite 1801*  
*6550 Fannin, Houston, TX 77030, USA*  
*Tel.: +1 713 798 5998*  
*Fax: +1 713 798 6808*  
*josephj@bcm.tmc.edu*