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Research Paper

Levodopa Slows Progression of Parkinson's Disease. External Validation by Clinical Trial Simulation

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Purpose. To externally validate the model predictions of a DATATOP cohort analysis through application of clinical trial simulation with the study design of the ELLDOPA trial.
Methods. The stochastic pharmacokinetic-pharmacodynamic and disease progress model was developed from the large DATATOP cohort of patients followed for 8 years. ELLDOPA was designed to detect a difference between placebo and levodopa treated arms in the total Unified Parkinson's Disease Rating Scale (UPDRS) taken at baseline and following 2 weeks levodopa washout after 40 weeks of treatment. The total UPDRS response was simulated with different assumptions on levodopa effect (symptomatic with/without disease modifying capability) and washout speed of symptomatic effect.
Results. The observed results of ELLDOPA were similar to the model predictions assuming levodopa slows disease progression and has a slow washout of symptomatic effect.
Conclusions. This simulation work confirmed the conclusion of the DATATOP analysis finding that levodopa slows disease progression. The simulation results also showed that a dose-related increased rate of progression in Parkinson's disease, obscured by symptomatic benefit, is very unlikely. Finally, the simulation results also shown that 2 weeks washout period was not adequate to completely eliminate the symptomatic benefits of levodopa.

KEY WORDS: clinical trial simulation; DATATOP; disease progress model; ELLDOPA; Parkinson's disease; protective treatment.

INTRODUCTION

The progression of motor signs of Parkinson's disease is caused by the ongoing degeneration of dopaminergic neurons in the nigral-striatal pathway. A functionally protective treatment would slow down, halt, or even reverse ("restorative") disease progression (1). If protective treatment is stopped the disease state will be different from that expected if no treatment

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ABBREVIATIONS: α, rate of natural disease progression; BEML, symptotic maximum value of Emax; C_1, levodopa concentration in the central compartment; C_2, levodopa concentration in the peripheral compartment; C5L, levodopa concentration at which 50% of Emax is produced; Ce, levodopa concentration in the effect compartment; Ce_{Slow}, levodopa concentration in the slow washout compartment; CL, total body clearance; CL_{ic}, intercompartmental clearance; $Dprog_{PCB}$, natural disease progression in placebo arm; ED50, levodopa concentration (relative to a 300 mg/d dose rate) at which 50% of Emax is produced; Emax, maximum lowering of total UPDRS that levodopa can produce; Emax0, emax at time 0; E_O, effect of levodopa as an offset to the disease progress model; E_S, effect of levodopa on the slope of the disease progress model; FWO, fast washout of levodopa symptomatic benefits process; KA, first-order absorption rate constant; KLD_P, protective effect parameter for the rate of disease progression in relation to levodopa concentration; KLD_T, toxic effect parameter for the rate of disease progression in relation to levodopa concentration; Pmiss, probability of missing a scheduled dose having taken a dose; PPV, population parameter variability; $Prot\_Symp\_SWO_{DOSE}$, simulated total UPDRS in a specific dose arm assuming levodopa has both functional protective and symptomatic benefits and with a slow washout process for the symptomatic benefit after levodopa withdrawal; $Prot_{DFP}$, size of protective effect (%) computed using the difference from placebo approach; Ptake, probability of taking a scheduled dose having missed a dose; S0, disease status at the start of the study; SWO, slow washout of levodopa symptomatic benefits process; $Symp\_SWO_{DOSE}$, simulated total UPDRS in a specific dose arm assuming levodopa only has symptomatic benefit and with a slow washout process; $Symp_{DFP}$, size of symptomatic effect (%) computed using the difference from placebo approach; TEML, half-life of change in Emax; TEQL, equilibration half-life of the equilibration effect compartment; TEQWO, half-life of washout of levodopa symptomatic benefits; Tlastdose, time of last levodopa dose; Tlastobs, time of last observation; UPDRS, unified Parkinson's Disease Rating Scale; V_1, volume of distribution of the central compartment; V_2, volume of distribution of the peripheral compartment; WT, body weight.

had been given. On the other hand, symptomatic treatment would only reduce symptom severity during treatment. When a symptomatic treatment is stopped the disease state will return to the expected state as if no treatment had been given (2). The symptomatic benefits of levodopa have been well recognized since Cotzias *et al.* (3) showed that orally administered levodopa relieved clinical symptoms of Parkinson's disease. Levodopa remains the most effective drug therapy in managing Parkinson's disease. However, the effect of levodopa on natural disease progression remains unclear. Some studies suggest that levodopa protects the surviving dopaminergic cells (4–8) while others propose that levodopa accelerates dopaminergic cell death (9–12). We have developed a stochastic model for anti-parkinsonian drug response and progression in Parkinson's disease (13) to try to identify symptomatic, protective and toxic effects of various long-term anti-parkinsonian therapies. The model was built based on the total Unified Parkinson's Disease Rating Scale (UPDRS) scores collected in 800 parkinsonian patients enrolled in the DATATOP (Deprenyl and Tocopherol Anti-oxidative Therapy On Parkinsonism) (15) and followed for 8 years. For the placebo-levodopa subset data, the model predicts that 300 mg/d levodopa slows the rate of disease progression by 3.4 u/year (13).

A clinical trial, ELLDOPA (Earlier *vs* Later L-DOPA), has been carried out by the Parkinson Study Group with the primary objective of determining if levodopa treatment changes the progression of early Parkinson's disease (14). ELLDOPA provided an opportunity to test our model and examine the interpretation of the results. The results of the ELLDOPA trial and of this simulation were first announced in November 2002 (16,17) and ELLDOPA was published 2 years later (18). The ELLDOPA investigators did not feel they could conclude that levodopa had a functional protective effect because of confounding with remaining symptomatic effects which had not washed out.

The ELLDOPA trial analysis and interpretation, comparing pre-levodopa treatment scores with the scores 2 weeks after withdrawal of 9 months of levodopa therapy, is dependent upon the complete washout of levodopa symptomatic effects. We therefore simulated both fast and slow washout in the model. It is impossible to separate the symptomatic and disease modifying effects of levodopa without making some assumptions about the time course of washout of symptomatic effects. Guimaraes *et al.* (19) have shown that because of the confounding effect of symptomatic benefits on disease progression, assumptions about the shape of a disease progress model in Parkinson's disease could result in a substantial change in study design, for example, sample-size calculations.

The overall objective of this report was to externally validate the model predictions of the DATATOP cohort analysis (13). Clinical trial simulation of the study design of the ELLDOPA trial was used under different assumptions of type of treatment effects (protective or toxic) and the time course of symptomatic washout of levodopa effects.

METHODS

Design of ELLDOPA Trial

The experimental design, recruitment of subjects, data acquisition and statistical method has been reported in detail elsewhere (14). Briefly, ELLDOPA is a double blind, randomized, parallel, placebo controlled and multicenter (35 centers) clinical trial. Three hundred and sixty early stage Parkinsonian patients who were not receiving anti-parkinsonian medication and who were not in need of symptomatic therapy were randomized into one of the four arms (placebo, low, medium and high dose). The daily oral carbidopa/levodopa dose was titrated from 12.5/50 mg up to 37.5/150 mg (low dose), 75/300 mg (medium dose) and 150/600 mg (high dose). The ELLDOPA study was designed to detect a 4-unit difference in total UPDRS between the placebo and the high dose arms with a power of 80% (14).

The planned duration of the study was 40 weeks of levodopa treatment or placebo followed by a 2-week levodopa withdrawal period. The withdrawal period included a 3-day step down reduction of levodopa dose followed by 11 days off treatment. Subjects were not blinded to treatment withdrawal. Medications were given three times daily. All medications were taken after meals to minimize the occurrence of nausea or vomiting. Total UPDRS (range 0–188) was used to assess disease state. The higher the score, the more severe the disease.

ELLDOPA had a single study design with two outcome measures. The primary outcome measure used total UPDRS observations taken by the same blinded primary rater at 0 (before treatment) and 42 weeks (after withdrawal). The secondary outcome measure had a total of 12 observations, before treatment (screening, 0–4 weeks prior to the study), on treatment pre-dose (0, 3, 9, 24, and 40 weeks), post-dose (3, 9, 24 and 40 weeks) and after withdrawal (41 and 42 weeks) taken by the site treating investigators who did not have any interaction with the primary raters. The pre-dose observations were taken prior to the first dose of the day, while the post-dose observations were taken 1 h after the first dose of the day. Table I summarizes the design of the ELLDOPA trial.

The ELLDOPA trial design assumed that all the symptomatic benefit of levodopa would be washed out by 14 days after withdrawal of levodopa treatment. This assumption was required in order to test hypotheses about the existence of a protective or a toxic effect of levodopa on disease progression.

Input–output Models

Pharmacokinetic Model

A 2-compartment first-order absorption pharmacokinetic model was used to predict concentrations of levodopa after each dose. The central compartment concentration prediction (C_1) was used to drive the effect of levodopa on the rate of disease progression (protective or toxic).

The pharmacokinetic parameters and their between subject variability (BSV), within trial variability (WTV) and between trial variability (BTV) were obtained from a 4-year study of levodopa pharmacokinetics in 20 prior untreated subjects with Parkinson's disease (20) (Table II). All components of population parameter variability (PPV) were included in simulation as BTV and WTV together determine the between occasion variability, i.e., consider each individual visit as an occasion. Intra-subject variability (20%) was not included because it was assumed that inclusion of all

Table I. Study Design of ELLDOPA Trial

Study Property	Description
Design	Double blind, parallel, randomized, placebo-controlled, multicenter (35 centers)
Subjects	360 subjects with early, mild Parkinsonism, who have not previously received levodopa, randomly assigned to one of four arms (90 in each arm)
Arms, Carbidopa/Levodopa dose (mg/d)	Placebo, 0 Low, 37.5/150 Medium, 75/300 High, 150/600 Dose titrate from 12.5/50
Treatment duration	40 weeks
Washout period	A step down 3 day washout followed by 11 days off treatment
Observations	Total of two observations by primary rater Before treatment (0 week) and after withdrawal (42 week) Total of 12 observations by site treating investigator Before treatment (screening[a]) and after withdrawal (41 and 42 weeks) Pre-dose[b] 0, 3, 9, 24 and 40 weeks Post-dose[c] 3, 9, 24 and 40 weeks
Assumption	Rate of total UPDRS increase = 9.5 units over the 42 weeks 10% dropout rate and >95% compliance
Aim	Detect a four unit difference in total UPDRS between placebo and high dose arms

[a] Simulated trial design assumed 2 weeks before treatment for screening visit
[b] Observations taken prior to the first dose of the day
[c] Observations taken at 1 h after the first dose of the day

components of PPV provided adequate variation for different individuals at different time points.

Plasma levodopa concentration peaks about 1 h after a dose (21–25) therefore a value of 10.5 day^{-1} was assumed for the first-order absorption rate constant. Weight is a factor in explaining the differences in the levodopa pharmacokinetic parameters between subjects (20). An allometric model was applied to standardize the pharmacokinetic parameters with an assumption of a standard body weight (WT) of 70 kg (26) (Eq. 1).

$$CL(L/h/70kg) = CL \bullet \left(\frac{WT}{70kg}\right)^{3/4}$$
$$V_1(L/70kg) = V_1 \bullet \frac{WT}{70kg} \quad (1)$$

Disease Progress Model

The disease progress model for simulation of the ELLDOPA study was based on a model for the time course of total UPDRS collected in 800 early stage, previously untreated Parkinsonian patients enrolled in the DATATOP study (14) and followed for 8 years. The model is composed of two parts, natural disease progression and drug modifications of disease severity (13). Natural disease progression refers to a continuous worsening of disease status whereas drug treatments modify natural disease progression by altering its time course. The time course can be changed by a combination of symptomatic and protective drug effects. Symptomatic effects produce an offset to the natural history during treatment but have no continuing effect after washout. Protective effects change the rate or magnitude of progression with persistent benefits after treatment washout. We interpret beneficial changes in the rate of progression as evidence for functional protection while adverse effects on the rate of progression are considered evidence of toxicity. Figure 1 shows a graphical representation of these different effects and for simplicity the onset and offset of levodopa effects were assumed to be instantaneous.

With an assumption of a constant rate of worsening of disease status, (13) disease progression is simply described by a linear function (Eq. 2). S0 is the baseline disease status and α is the rate of natural disease progression.

$$S(t) = S0 + \alpha \bullet t \quad (2)$$

Pharmacodynamic Model

Symptomatic Effect for Levodopa. An Emax pharmacodynamic model (27) (Eq. 3) was used to describe the symptomatic effect of levodopa. E_O is the drug effect as an offset to the disease progress model.

$$E_o(t) = \frac{E\max \bullet Ce(t)}{ED50 + Ce(t)} \quad (3)$$

Ce is the effect compartment concentration of levodopa describing the slow onset of levodopa effect. An effect compartment describes the equilibration delay between plasma concentration and the drug effect using the equilibration half-life of the effect compartment, *TEQL* (27). *E*max is defined as the maximum symptomatic change of total UPDRS that can be produced by levodopa. ED50 is the value of *Ce*, relative to a 300 mg/d dose rate (median levodopa dose rate in the DATATOP study), producing 50% of *E*max. Based on the DATATOP cohort analysis (13) and the results from an analysis of levodopa induced changes in tapping rate over 4 years (28), the time course of Emax of levodopa was described by an exponential increase approaching an asymptote, *BEML*, with a half-life of *TEML* (Eq. 4). Emax0 denotes the maximum effect of levodopa at time 0. However in the current study design, no treatment effect would be seen at time 0 because measurement was taken prior to dosing and levodopa concentration was 0.

$$E\max(t) = E\max 0 + BEML \bullet \left(1 - e^{\frac{-Ln(2)}{TEML} \bullet t}\right) \quad (4)$$

In the DATATOP analysis (13), the effects of levodopa were assumed to be related to *Ce*. No concentration measurements were made and *Ce* was therefore predicted by assuming plasma concentration was proportional to the daily levodopa dose. In the ELLDOPA trial simulation, *Ce* was predicted from the levodopa concentration and TEQL (Eq. 5). C_1 is the levodopa concentration predicted in the

Table II. Parameter Estimates for Simulation

Model	Parameter	Mean	PPV (%)		
			BSV (%)	WTV (%)	BTV (%)
Pharmacokinetic[a]	V_1 (L/70kg)	11.4	12	16	40
	CL (L/h/70kg)	30.9	13	13	17
	V_2 (L/70kg)	27.3	15	8	21
	CL_{ic} (L/h/70kg)	34.6	28	18	34
Natural Disease Progression[b]	S0 (u)[c]	21.4		50	
	α (u/y)	12		63	
Symptomatic Drug Effect[b]	BEML (u)	−20		75	
	ED50 (u/0.3g/d)[d]	0.0376		63	
	TEQL (days)	642		149	
	TEML (days)	215		91	
Protective Drug Effect[b]	KLD_P (1/y/0.3g/d)[d]	−0.894		78	
Residuals Error[b]	(u)	5.79		–	
Concentration (Ce) Washout Process[e]	TEQWO (h)	2.54		26	
Direct Effect Washout Process[f]	TEQWO (h)	5.65		69	

[a] Values obtained from population pharmacokinetic analysis of levodopa.(20) Population parameter variability (PPV) is partitioned into between subject variability (BSV), within trial variability (WTV) and between trial variability (BTV).
[b] Values obtained from DATATOP cohort analysis.(13)
[c] Correlation of S0 and α = 0.355
[d] Normalized by median daily levodopa dose in DATATOP cohort analysis.
[e] Values were from the effect compartment analysis of observations from Hauser and Holford study (29)
[f] Values obtained from Hauser and Holford.(29)

central compartment of a two-compartment pharmacokinetic model.

$$\frac{dC_e}{dt} = \frac{Ln(2)}{TEQL} \bullet (C_1 - C_e) \quad (5)$$

Process for Washout of Symptomatic Effect. Once levodopa therapy has stopped, the symptomatic effect disappears (Fig. 1). Hauser and Holford (29) have developed a model to describe the time course of loss of levodopa benefits in 20 early Parkinsonian patients using total UPDRS. Each of the subjects showed a clear decrease of clinical benefits over 2 weeks following discontinuation of anti-parkinsonian medications. It was assumed that the benefit of levodopa would decline and reach an asymptote reflecting the complete washout of levodopa effect according to an exponential model. The half-life of washout of levodopa symptomatic benefit was estimated to be 5.65 days. This clinically observed slow washout is in contrast to the ELLDOPA design assumption of a fast washout involving complete loss of symptomatic effect after 2 weeks (Fig. 2).

Two processes of washout of symptomatic effect were examined: effect site concentration (*Ce*) washout; and direct effect washout. The details of the direct effect washout process can be found in Appendix.

Effect Site Concentration Washout Process. Washout of symptomatic effects after withdrawal of levodopa was modeled as a fast (instantaneous) or a slow process. The symptomatic effect for the fast washout process (FWO) was assumed to be zero after the last levodopa dose (day 3 of washout, Tlastdose). This represents instantaneous disappearance of symptomatic effects. After the last levodopa dose, the concentration for the slow washout process was simulated using a slow washout half-life (TEQWO). TEQWO was computed by fitting the total UPDRS observations from the study of Hauser and Holford (29) with an effect compartment model. The disappearance of effect site concentration (*Ce*) after withdrawal of levodopa was modeled by an exponential decay with a half-life of TEQWO from an estimated baseline (Ce_0) (Eq. 6).

$$C_e(t) = C_{e0} \bullet e^{\frac{-LN(2)}{TEQWO} \bullet (t - Tlastdose)} \quad (6)$$

*E*max was computed using Eq. (4) with BEML and TEML fixed to the parameter estimates obtained from the DATATOP cohort analysis (13) and a time of 14 months (duration of levodopa treatment in the Hauser and Holford study (29)). EC50 and covariance between parameters were also fixed to the values predicted from the DATATOP cohort analysis (13). For patients taking only levodopa, the estimated TEQWO was 2.54 days ± 26% (45% of the Hauser and Holford estimated washout half life (5.65 days ± 69%)).

The concentration in the slow washout compartment (Ce_{Slow}) was predicted by continuing the solution of Eq. (5) but with *TEQL* replaced by *TEQWO*. The symptomatic effect arising from the slow washout process (SWO) was determined by the Emax model (Eq. 3) using Ce_{Slow}.

Functional Protective and Toxic Effects of Levodopa. The effect of levodopa on the rate of disease progression was modeled by Eq. (7). *KLD* is a parameter describing the effect of levodopa on the rate of disease progression in relation to predicted plasma levodopa concentration (C_1). E_s is the drug effect on the slope of the disease progress model.

$$E_s(t) = e^{KLD \bullet C_1(t)} \quad (7)$$

The protective effect of levodopa was modeled by the parameter KLD_P. The value of KLD_P was obtained from the DATATOP cohort analysis (13) (Table II).

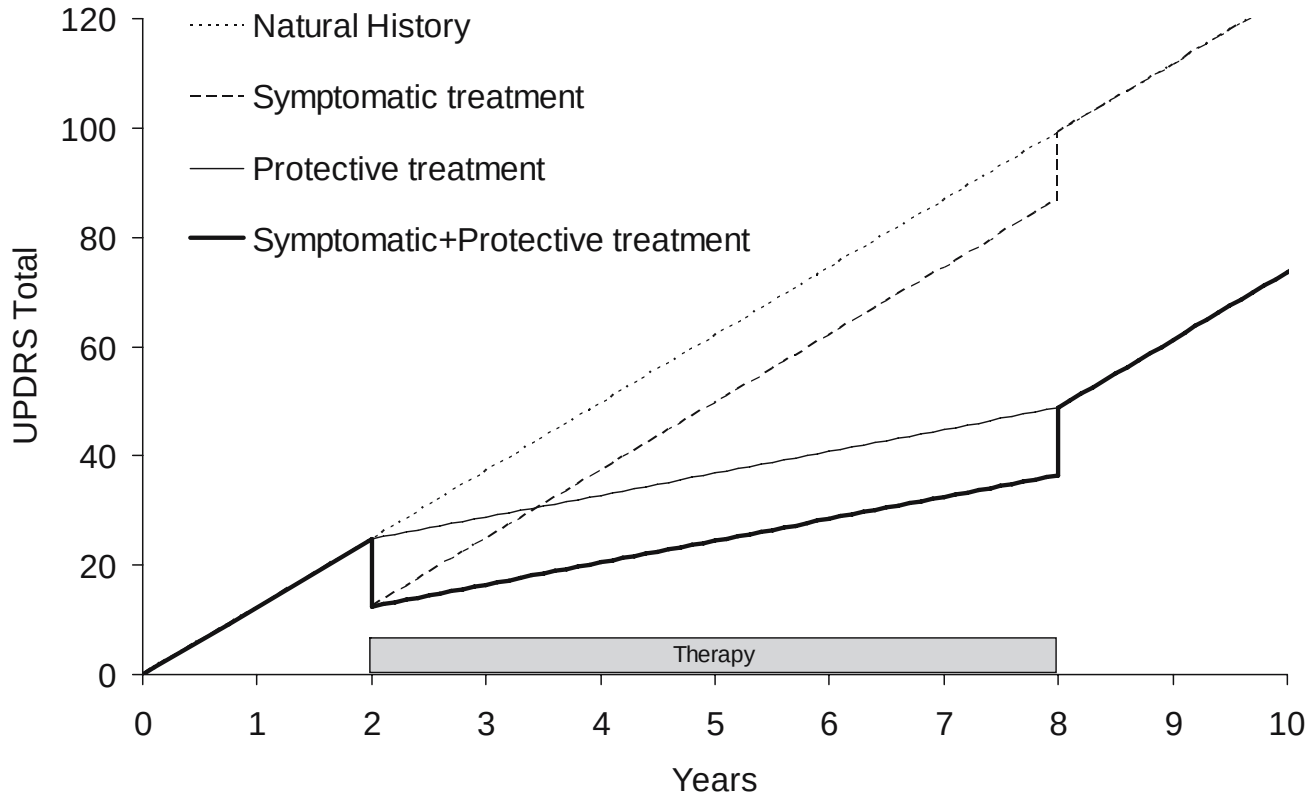
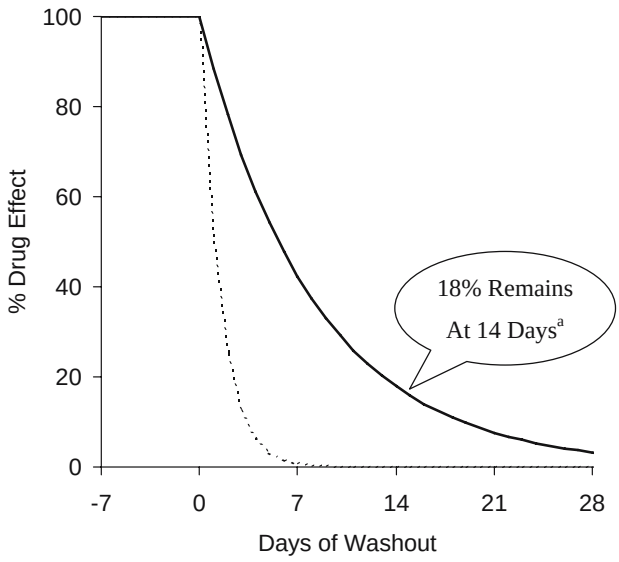


Fig. 1. Linear disease progress model. Entry to DATATOP is predicted at 2 years after onset of disease. Levodopa is stopped at 8 years to illustrate loss of symptomatic and/or protective effect on disease progression. For simplicity the onset and offset of levodopa effects were assumed to be instantaneous.

A toxic effect parameter (KLD_T) was used for an adverse effect of treatment. KLD_T was assumed to produce a 2 unit worsening in total UPDRS over 9.5 months on a daily levodopa dose of 300 mg (0.4723 1/y/mg/L). This is equivalent to a 20% worsening of the rate of progression in the medium dose arm.

Size of Treatment Effect. With an assumption of a slow washout process of levodopa symptomatic effect, the size of treatment effect after 2 weeks levodopa withdrawal was expressed in two ways: change from baseline and difference from placebo approaches. No baseline adjustment in the simulated total UPDRS was needed in both approaches. For the change from baseline approach, baseline effect was cancelled out when computing the size of symptomatic effect (Eq. 8). For the difference from placebo approach, size of treatment effect was computed using values simulated under different assumptions of drug actions within an individual, again baseline effect was cancelled out.

Change from Baseline Approach. The change from baseline approach expressed the size of symptomatic effect at the end of the 2 weeks withdrawal period (*Tlastobs*) in relation to the size of symptomatic effect at the time of the last levodopa dose (*Tlastdose*) given on the third day of the withdrawal period (Eq. 8). This approach describes the rate of washout of symptomatic effect given the non-linear pharmacokinetic and pharmacodynamic relationship, i.e., *E*max model. The size of protective effect remains



[a] From Hauser and Holford (29).

Fig. 2. Simulated time course of slow washout of levodopa symptomatic effect completed by 2 weeks washout period as assumed in the ELLDOPA trial design (*dotted*) and with a washout half-life of 5.65 days (*thick solid*). *Thin solid line* represents before treatment withdrawal.

unchanged as the model assumed only the symptomatic effect could be washed out.

$$Symp_{CFB}(\%) = \frac{E_O(Tlastobs)}{E_O(Tlastdose)} \bullet 100\% \quad (8)$$

Difference from Placebo Approach. The difference from placebo approach expressed the size of symptomatic ($Symp_{\mathrm{DFP}}$) and protective ($Prot_{\mathrm{DFP}}$) effects at the end of the 2 weeks withdrawal period for each of the dose arms in relation to the natural disease progression in the placebo arm, $Dprog_{PCB}$ (Eq. 9). $Symp\_SWO_{\mathrm{DOSE}}$ is the total UPDRS in a specific dose arm simulated by a model assumed that levodopa only has symptomatic benefit and with a slow washout process. $Prot\_Symp\_SWO_{DOSE}$ is the total UPDRS in a specific dose arm simulated by a model assumed that levodopa has both functional protective and symptomatic benefits and with a slow washout process for the symptomatic benefit after levodopa withdrawal. The size of protective and symptomatic effects is expressed as a percentage of the total treatment effect at the time of the last observation.

$$\mathrm{Symp}_{DFP}(\%) = \frac{D\mathrm{prog}_{PCB} - \mathrm{Symp\_SWO}_{DOSE}}{\mathrm{Dprog}_{PCB} - \mathrm{Prot\_Symp\_SWO}_{DOSE}} \bullet 100\% \quad (9)$$

$$\mathrm{Prot}_{DFP}(\%) = 100\% - \mathrm{Symp}_{DFP}(\%)$$

The difference from placebo approach describes the difference in total UPDRS of the treatment arms from placebo that is due to the remaining drug effects that have not been washed out. This approach differs from the change from baseline approach as it allows the prediction of the true protective effect that existed at the time of the last observation without the assumption of a continuing protective effect which is assumed not to wash out in the change from baseline approach.

Clinical Pharmacology Model. The overall model for disease progression and levodopa symptomatic effects and effects on the rate of disease progression is shown in Eq. (10).

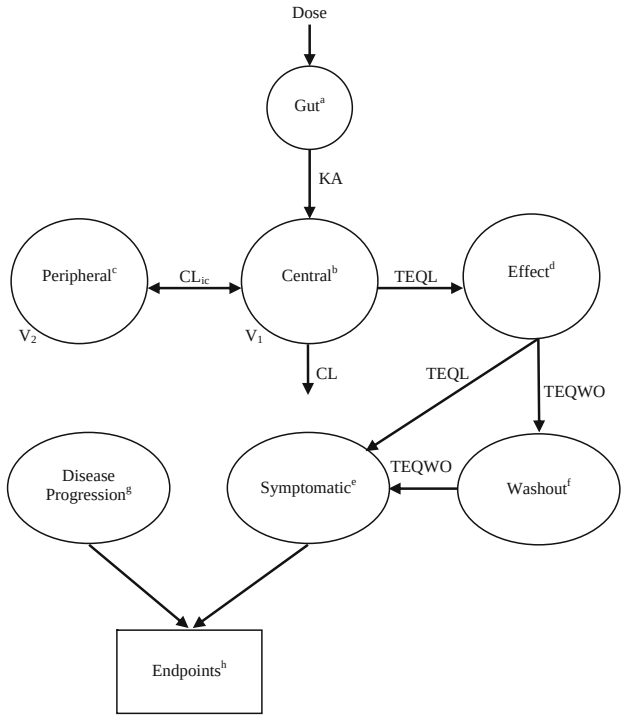
$$S(t) = S0 + E_o(t) + (E_s(t) \bullet \alpha) \bullet t \quad (10)$$

Figure 3 illustrates the interaction of the individual components of the input–output models for describing the dynamical system of the ELLDOPA trial.

Random Effects Model

Between Subject Variability. Between subject variability (ηBSV) was assumed to be random variable with mean zero and standard deviation of BSV. For parameters which must have the same sign for all individuals, ηBSV was assumed to arise from a lognormal distribution (Eq. 11). $S0_{\mathrm{ijk}}$ is the predicted individual $S0$ for the ith subject at the jth time point of the kth trial and $S0_{\mathrm{POP}}$ is the population value for S0. i takes in the value of 1–360 representing 360 subjects in a particular trial and k takes in the value of 1–100 representing 100 replicates.

$$S0_{ijk} = S0_{POP} \bullet e^{\eta BSV_{S0_{ijk}}} \quad (11)$$



[a] $\frac{dC_{Gut}}{dt} = -C_{Gut} \bullet KA$

[b] $\frac{dC_1}{dt} = \frac{C_{Gut} \bullet KA + C_2 \bullet CL_{ic} - C_1 \bullet (CL + CL_{ic})}{V_1}$

[c] $\frac{dC_2}{dt} = \frac{(C_1 - C_2) \bullet CL_{ic}}{V_2}$

[d] Refer to Equation 5

[e] $E_O(t) = \frac{E\max \bullet C_e(t)}{C5L + C_e(t)}$, Also refer to Equation 4

[f] Refer to Equation 6 and Equation 14

[g] $\frac{dDP}{dt} = \alpha \bullet E_s(t)$, Also refer to Equation 7

[h] Refer to Equation 10

Fig. 3. Input–output models.

On the other hand, for parameters which allow different sign for individuals, ηBSV was assumed to arise from a normal distribution and proportional to the size of the parameter (Eq. 12).

$$\alpha_{ijk} = \alpha_{POP} \bullet \left(1 + \eta BSV_{\alpha_{ijk}}\right) \quad (12)$$

A variance-covariance matrix was used to specify covariance between the parameters within a multivariate distribution block. The values of the variance-covariance matrix for the pharmacokinetic parameters (V_1, CL, V_2 and CL_{ic}) were obtained from the population pharmacokinetic analysis (20). The values of the variance-covariance matrix for disease progression parameters (S0 and α), and the symptomatic effect parameters (BEML, C5L and TEML) were obtained from the DATATOP cohort analysis (13).

Residual Error. Residual error of the total UPDRS was described using an additive error model (Eq. 13). A normal distribution was assumed with mean zero and standard deviation of ERR_{SD}.

$$Y = S(t) + \varepsilon ERR_{SD} \quad (13)$$

Simulation Parameters

Parameter estimates from the DATATOP cohort analysis (13) were used as the true parameter values for simulation (Table II). In the DATATOP analysis, daily levodopa dose divided by the median dose 300 mg/d was used to normalize levodopa pharmacodynamic parameters. The relationship between daily dose and equivalent plasma concentration was calculated with a population CL of 741.6 L/d (20). The predicted average steady state concentration was then used to correct the DATATOP dose normalized parameters to the concentration based equivalent.

Covariate Distribution Model. A normal distribution with mean 78.65 kg and standard deviation 12.42 kg were used to simulate patient weights. These values were obtained from 20 previously untreated patients with Parkinson's disease followed up to 4 years (30).

Simulation. The Pharsight Trial Simulator 2.1.2 (31) was used for data simulation on a Dual AMP Athlon 2000+ PC under Windows 2000. Differential equations were solved using a fifth order Runge-Kutta-Fehlberg algorithm.

The ELLDOPA study design, the population pharmacokinetic model and the DATATOP cohort analysis model were used as inputs for simulation. A 2 week lead-in phase was included to represent the screening visit where no medications were given. The study timeline for simulation was 44 weeks (2 weeks lead-in phase, 40 weeks treatment and 2 weeks washout). Subjects were assumed to be enrolled in a single center.

The ELLDOPA study design was simulated with combinations of different assumptions on the drug action model and the speed of the washout process. No missing observations were generated in the simulation step. A scenario is defined as a simulated trial with specified assumptions on the study design and drug model. Three main scenarios were simulated with different assumptions on the drug action model.

Scenario I. The first assumption about the drug action model was that levodopa only has symptomatic benefits and does not have an effect on the rate of disease progression. Therefore, the term $E_s(t)$ in Eq. (10) was equal to 1 at all times. This was done by fixing KLD in Eq. (7) to 0.

Scenario II. The second assumption was that levodopa has symptomatic benefits as well as a functional protective effect. This assumption was based on the findings of the DATATOP cohort analysis (13). In this case, KLD in Eq. (7) was in fact KLD_P and its parameter estimate was obtained from the DATATOP cohort analysis (13) (Table II).

Scenario III. The third assumption was that levodopa has symptomatic benefits and a functional toxic effect. In this case, KLD in Eq. (7) was changed to KLD_T and its value was computed by assuming an equivalent to a 20% worsening of the rate of progression in the medium dose arm (see Functional Protective and Toxic Effect of Levodopa section).

Model Validation. The simulation model was qualified by comparing the Trial Simulator total UPDRS with values simulated using NONMEM (32) without random sources of variability.

Bootstrapping For Confidence Interval

Bootstrapping approaches were used to assess the imprecision of the estimated size of treatment effects of levodopa. As 100 replications were simulated for each scenario, 100 parameters (decision or statistic) resulted. A bootstrap sample was generated by repeated random sampling, with replacement from the set of 100 interested parameters. The 95% confidence interval was computed from 1,000 bootstrap samples for each of the scenarios.

RESULTS

Treatment Effect of Levodopa

In general, the size of predicted differences of change in total UPDRS increased as levodopa dose increased for the (fast and slow) Ce washout processes (Table III). The only exception was when levodopa has symptomatic benefits with a slow washout process and a functional toxic effect, that an opposite trend was shown. The opposite trend was caused by the adverse effects of levodopa which were against the symptomatic effects. It should also be noted that an improvement in total UPDRS was shown in the low and medium dose arms in the slow washout process under the levodopa toxic effect assumption. This was caused by the overwhelming symptomatic benefits that masked the toxic effect of levodopa. With a fast washout process, the size of adverse effect increased as levodopa dose increased. The 95% confidence interval (CI) obtained from bootstrapping was similar to the one computed using the standard error of the bootstrapped mean (with an assumption of normal distribution).

Size of Treatment Effect

Change from Baseline Approach

With the assumption of a slow washout of symptomatic benefits, the Ce washout process with a washout half-life of 2.54 days showed an increased size of symptomatic effect after 2 weeks of levodopa withdrawal as levodopa dose increased (Table IV). The size of symptomatic effect ranged from 21% in the low dose arm to 37% in the high dose arm. In short, over 20% symptomatic effects relative to the size of symptomatic effects at the time of the last levodopa dose remained after 2 weeks of withdrawal with the assumption of a slow washout of symptomatic benefits.

Difference from Placebo Approach

With the assumption that levodopa has both symptomatic and functional protective benefits, the Ce washout process expected a relatively constant fraction of symptomatic (57–59%) and protective (39–41%) drug effects after 2 weeks levodopa withdrawal (Table IV). In short, up to 41%

Table III. Predicted Differences of Change from Baseline in Total UPDRS at 42 Weeks

Drug Action	Washout	Effect Site Concentration Washout Process								
		Low			Medium			High		
		Mean[a]	95% CI[b]		Mean	95% CI		Mean	95% CI	
Symptomatic + Protective	Fast	2.0	1.7	2.2	3.0	2.8	3.3	4.2	3.9	4.4
	Slow	3.8	3.5	4.1	5.9	5.7	6.2	8.4	8.1	8.7
Symptomatic	Fast	−0.1[c]	−0.4	0.2	0.2	−0.1	0.5	0.2	0.04	0.5
	Slow	1.9	1.6	2.2	2.7	2.4	3.0	4.1	3.8	4.4
Symptomatic + Toxic	Fast	−1.2	−15	−1.0	−2.4	−2.7	−2.2	−5.8	−6.1	−5.5
	Slow	1.0	0.7	1.2	0.4	0.1	0.7	−1.4	−1.7	−1.1

[a] Mean = mean of 1,000 bootstrapped samples.
[b] 95% CI = 95% confidence interval of 1,000 bootstrapped samples
[c] Negative values represent an increase in total UPDRS in comparison with the placebo arm
Values are subtracted from the mean of the placebo arm for each replication (mean 9.85 units, 95% CI 9.69–10.0 units).

of the predicted difference in total UPDRS between the levodopa and placebo treated groups after 2 weeks levodopa withdrawal was accounted by the protective effect.

DISCUSSION

Clinical Pharmacology Model

Time Course of Symptomatic Response

The time needed to wash out the symptomatic component of levodopa effects on total UPDRS is critical to the interpretation of the results of the ELLDOPA study. There are reasons to question the completeness of washout of symptomatic effects by two weeks as done in the ELLDOPA trial. The full therapeutic benefits of levodopa have a slow onset of action. Using the total UPDRS to assess disease severity, a long onset time with a half-life of 642 days was estimated in the DATATOP cohort analysis (13). It is usually assumed that the time course of onset is mirrored in the time course of offset of response. However, Hauser and Holford (29) reported that the loss of clinical benefit following withdrawal of levodopa has an estimated half-life of 5.65 days. There may be several phases to the loss of effect just as different phases have been recognized for the delay in onset. In addition to the quantitative description of washout of response a panel of movement disorder experts was asked to decide if full washout had occurred by 15 days after stopping treatment. By examining the plots of total UPDRS scores *versus* days after withdrawal they found only 23% of patients appeared to have fully washed out. These observations imply that a 2 week washout would not be long enough to separate levodopa effects on rate of disease progression from its symptomatic benefits.

Our model predicts that 21–37% (Ce washout process) of symptomatic effect remained at 2 weeks after low and high dose levodopa withdrawal (Table IV). The predicted size of symptomatic effect with the Ce washout process is higher but comparable with the time course simulated using the estimated washout half-life of 5.65 days from Hauser and Holford, (29) i.e. 18% remained after 14 days of washout (Fig. 2).

Size of Treatment Effect

In order to illustrate the size of treatment effects remained after 2 weeks of levodopa withdrawal, the time course of drug effect was simulated using the dosing schedule of the high dose arm of the ELLDOPA design with the clinical pharmacology model and a direct effect washout process but without stochastic variability. The size of treatment effects is computed using the difference from

Table IV. Size of Treatment Effects After 2 Weeks Levodopa Withdrawal Under An Assumption of Slow Washout of Symptomatic Benefits

Washout Process	Size of Effect (%)	Change from Baseline									Difference from Placebo[c]								
		Low			Medium			High			Low			Medium			High		
		Mean[a]	95% CI[b]		Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI	
Effect Site Concentration	Symptomatic	21.1	21.0	21.3	27.4	27.3	27.6	37.3	37.0	37.6	59.2	54.0	66.6	57.2	52.1	66.1	57.1	53.9	61.5
	Protective	–	–	–	–	–	–	–	–	–	39.4	32.0	44.7	40.8	31.7	45.9	40.7	36.2	43.8

[a] Mean = mean of 1,000 bootstrapped samples.
[b] 95% CI = 95% confidence interval of 1,000 bootstrapped samples
[c] Components of symptomatic and protective do not add up to 100% because of random effects in simulation parameter estimates.
Change from baseline represents the fraction of drug effect after 2 weeks levodopa withdrawal relative to the drug effect at the time of last levodopa dose. Difference from placebo represents the difference in predicted total UPDRS between dose arms and placebo arm expressed as a fraction of the total drug effect after 2 weeks levodopa withdrawal.

placebo approach. Figure 4 shows that about 50% of the total drug effect after 2 weeks levodopa withdrawal is attributable to the protective effect assuming that levodopa has protective and symptomatic benefits and with a slow washout process. This means that a 2 week washout period would not be long enough to completely eliminate the symptomatic benefits of levodopa treatment.

In our simulation models, only symptomatic effect is allowed to be washed out. The implementation of the direct effect washout process in our analysis is different from that used by Hauser and Holford (29) because they could not distinguish between washout of symptomatic and protective components. However, using a simulation model we could use a direct effect slow washout process and apply it to the symptomatic component alone. The protective effect of levodopa on the rate of progression is assumed to be lost immediately after drug withdrawal but the benefits of slowed progression from previous treatment persist. While it is reasonable to propose that the protective effect on rate of progression might be washed out slowly it would be very hard in practice to distinguish immediate from slow protective effect washout. The difference is shown in Fig. 4 by comparing the slow symptomatic washout time courses with and without protective effect and immediate compared with slow protective washout. We predict that 50 ± 14% (direct effect washout process) of the observed difference between the high dose levodopa group and placebo is attributable to slowing of disease progression (Table IV). It should be noted that because of stochastic influences on the simulation parameters, the sum of the protective and symptomatic effects does not necessarily sum to 100%.

Protective or Toxic Effects on Disease Progression?

Assuming levodopa had a dose-responsive toxic effect as well as a beneficial symptomatic effect, an improvement in total UPDRS was predicted for the low and medium dose arms at 42 weeks by the symptomatic and toxic model with slow washout process (Table III) one might falsely conclude that levodopa has a protective rather than toxic effect.

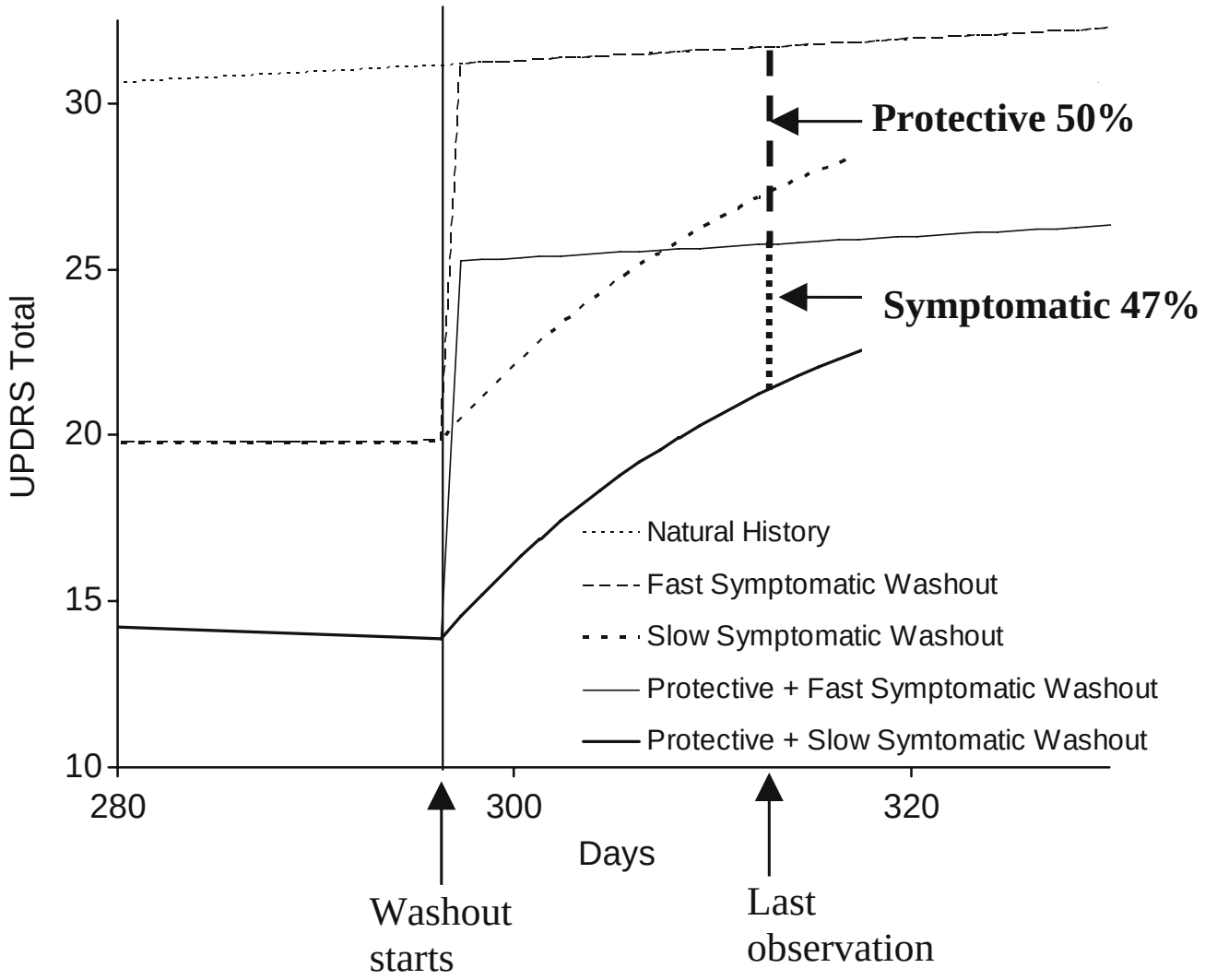


Fig. 4. Simulation of symptomatic and protective effects after levodopa withdrawal using the dosing schedule of the high dose arm of the ELLDOPA design without stochastic variability. The difference from placebo method was used to describe the size of the effects.

Table V. Observed and Predicted Total UPDRS Change from Baseline For Placebo Treatment at 42 Weeks and Difference from Placebo For Levodopa Treatment Arms

Effect of levodopa on disease progression	Scenario	Placebo[a]	Low[b]	Medium[b]	High[b]
	Observed ELLDOPA[c]	7.8 ± 1.1	5.9 ± 0.7	5.9 ± 0.8	9.2 ± 0.9
Protective	Predicted Effect Site Concentration Washout[d]	9.9 ± 1.0	3.8 ± 1.4	5.9 ± 1.3	8.4 ± 1.3
Toxic	Predicted Effect Site Concentration Washout[d]	10.0 ± 1.0	1.0 ± 1.3	0.4 ± 1.5	−1.4 ± 1.5[e]

[a] Difference between 0 and 42 weeks
[b] Difference from placebo
[c] Mean ± SE calculated from treatment mean difference from placebo and placebo SD and number of patients in active dose arms
[d] Bootstrap mean ± SD of 100 simulated trial replications. The SD is equivalent to the SE for placebo change from baseline
[e] Negative value represents an increase in total UPDRS
Predictions assume levodopa has symptomatic and disease modifying effects with slow symptomatic washout.

However at the highest dose the underlying toxic effect was revealed by worsening of total UPDRS at 42 weeks.

Implications for Interpretation of ELLDOPA Results

Table V shows the observed and predicted total UPDRS difference from placebo for the low, medium and high dose arms. Predictions from the protective effect model with a slow direct effect washout model closely matched the observed differences. There was no clinical evidence for a toxic effect of levodopa in the ELLDOPA results. The simulation model showed that a toxic effect could have been hidden by the slow washout process of the symptomatic benefit but in this case the difference from placebo should be smaller as the levodopa dose increased. In contrast, the observed changes in ELLDOPA at different doses show a greater difference with increasing dose and therefore provide further support against masking of a dose related toxic effect by slow symptomatic washout.

The observed difference from placebo could arise from an initial washout of symptomatic effect (as observed in ELLDOPA) with a subsequent washout (not observed because of the short period of withdrawal) of all effects without any protective effect. However, there is no direct evidence to support the hypothesis that all levodopa effects will eventually be washed out. In contrast the close quantitative prediction of the observed effects based on the DATATOP cohort (13) and the study by Hauser *et al* (33) provide strong support for the observed ELLDOPA results being due to a combination of continuing protective effect and partial washout of symptomatic effect.

Simply observing the change from baseline is not adequate for distinguishing between symptomatic and protective effects in degenerative diseases (1) unless the washout period is sufficient to completely eliminate any symptomatic effect. We predict the time necessary for complete withdrawal of effects to be in excess of 25 days with a washout half-life of 5.65 days. Therefore the ELLDOPA study is incapable of identifying the effect of levodopa on natural disease progression from symptomatic benefits using the change from baseline method of analysis.

Our simulation successfully predicted the magnitude of change in placebo and treated groups (Tables V and VIII) and gives us some confidence that we can also predict that between 40 to 50% of the total UPDRS difference from placebo is due solely to protective effects (Tables IV and VII and Fig. 4).

In summary, the current analysis provided an external validation of the predictions of the DATATOP cohort analysis. Our analysis of the ELLDOPA trial results confirm the prediction from our model based on the DATATOP that levodopa has functional protective effects and finds no

Table VI. Predicted Differences of Change from Baseline in Total UPDRS at 42 Weeks

Drug Action	Washout	Direct Effect Washout Process								
		Low			Medium			High		
		Mean[a]	95% CI[b]		Mean	95% CI		Mean	95% CI	
Symptomatic + Protective	Fast	1.9	1.6	2.1	3.2	3.0	3.5	4.1	3.9	4.4
	Slow	4.1	3.8	4.3	5.5	5.3	5.8	6.8	6.5	7.1
Symptomatic	Fast	−0.1[c]	−0.3	0.1	0.02	−0.2	0.3	−0.1	−0.3	0.2
	Slow	2.2	2.0	2.5	2.6	2.4	2.9	2.8	2.5	3.0
Symptomatic + Toxic	Fast	−0.8	−1.1	−0.6	−1.9	−2.2	−1.6	−4.3	−4.6	−4.1
	Slow	1.5	1.1	1.7	0.9	0.6	1.2	−1.5	−1.8	−1.2

[a] Mean = mean of 1,000 bootstrapped samples.
[b] 95% CI = 95% confidence interval of 1,000 bootstrapped samples
[c] Negative values represent an increase in total UPDRS in comparison with the placebo arm
Values are subtracted from the mean of the placebo arm for each replication (mean 9.85 units, 95% CI 9.69–10.0 units).

Table VII. Size of Treatment Effects After 2 Weeks Levodopa Withdrawal Under an Assumption of Slow Washout of Symptomatic Benefits

Washout Process	Size of Effect (%)	Change from Baseline									Difference from Placebo[c]								
		Low			Medium			High			Low			Medium			High		
		Mean[a]	95% CI[b]		Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI	
Direct Effect	Symptomatic	27.1	26.7	27.4	27.0	26.7	27.4	26.8	26.5	27.1	56.3	54.3	59.3	51.6	49.6	54.0	47.4	44.8	50.2
	Protective	–	–	–	–	–	–	–	–	–	41.9	38.9	43.9	46.6	44.1	48.6	50.2	47.4	52.9

[a] Mean = mean of 1,000 bootstrapped samples.
[b] 95% CI = 95% confidence interval of 1,000 bootstrapped samples
[c] Components of symptomatic and protective do not add up to 100% because of random effects in simulation parameter estimates.
Change from baseline represents the fraction of drug effect after 2 weeks levodopa withdrawal relative to the drug effect at the time of last levodopa dose. Difference from placebo represents the difference in predicted total UPDRS between dose arms and placebo arm expressed as a fraction of the total drug effect after 2 weeks levodopa withdrawal.

evidence for a toxic effect on disease progression. The observed dose response relationship is exactly opposite to what would be predicted if levodopa accelerated the rate of progression. These findings indicate that there is no reason to delay levodopa because of possible toxic effects and that there may be benefits to beginning symptomatic therapy earlier rather than later. Symptomatic therapy could include dopamine agonists as well as levodopa and deprenyl as suggested by our results of modeling the DATATOP cohort.

APPENDIX

This section described an alternative washout process for the symptomatic effect that we have examined.

Direct Effect Washout Process

We considered a washout process based directly on the time course of effect without the use of linking concentration-effect model. This process is the same as that used by Hauser and Holford (29). The symptomatic effect for the fast washout process (FWO) was assumed to be zero after the last levodopa dose. For the slow washout of symptomatic effect after the last levodopa dose, the time course was predicted by Eq. 14. The symptomatic effect at the time of the last levodopa dose (Tlastdose) was used as the initial value for this process (E_O(Tlastdose)). The change of total UPDRS during the 3 day levodopa dose step down washout period was predicted from the reduced dose and subsequent decrease in Ce and thus $E_O(t)$. The change in total UPDRS over these 3 days is expected to be small because of the long value of TEQL.

$$\text{IF}(t > \text{Tlastdose})\ \text{THEN}$$
$$E_O(t) = E_O(\text{Tlastdose}) \bullet e^{\left(\frac{-Ln(2)}{TEQWO}\bullet(t-Tlastdose)\right)}\text{ENDIF} \quad (14)$$

The concentration (Ce) washout process is different from the direct effect washout process because the symptomatic effect is computed using the drug concentration at the effect site via a pharmacodynamic model whereas the direct effect washout process models the time course of effect without consideration of the effect site concentration. The direct effect washout process was based upon the method of Hauser and Holford (29) where the drug effect was simply observed after levodopa withdrawal.

In general, the predicted treatment effect size of the direct effect washout process was comparable with the Ce washout process in the low and medium dose arms. A smaller predicted change from baseline in total UPDRS at 42 weeks was seen with the direct effect washout process (Tables III and VI). The Ce washout process gave a closer prediction of the change from baseline at 42 weeks for the high dose arm to the observed change (Table V) than the direct effect washout process (Table VIII). The predicted size of symp-

Table VIII. Observed and Predicted Total UPDRS Change from Baseline For Placebo Treatment at 42 Weeks and Difference from Placebo or Levodopa Treatment Arms

Effect of levodopa on disease progression	Scenario	Placebo[a]	Low[b]	Medium[b]	High[b]
	Observed ELLDOPA[c]	7.8 ± 1.1	5.9 ± 0.7	5.9 ± 0.8	9.2 ± 0.9
Protective	Predicted Direct Effect Washout[d]	9.8 ± 0.9	4.1 ± 1.3	5.5 ± 1.3	6.8 ± 1.5
Toxic	Predicted Direct Effect Washout[d]	10.0 ± 1.0	1.5 ± 1.6	0.9 ± 1.5	−1.5 ± 1.5[e]

[a] Difference between 0 and 42 weeks
[b] Difference from placebo
[c] Mean ± SE calculated from treatment mean difference from placebo and placebo SD and number of patients in active dose arms
[d] Bootstrap mean ± SD of 100 simulated trial replications. The SD is equivalent to the SE for placebo change from baseline
[e] Negative value represents an increase in total UPDRS
Predictions assume levodopa has symptomatic and disease modifying effects with slow symptomatic washout.

tomatic effect was also smaller for the direct effect washout process (Tables IV and VII).

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