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DRUG TREATMENT EFFECTS ON DISEASE PROGRESSION

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■ **Abstract** Degenerative diseases are characterized by a worsening of disease status over time. The rate of deterioration is determined by the natural rate of progression of the disease and by the effect of drug treatments. A goal of drug treatment is to slow disease progression. Drug treatments can be categorized as symptomatic or protective. Symptomatic treatments do not affect the rate of disease progression whereas protective treatments have the ability to slow disease progression down. Many current methods for describing disease progression have two common drawbacks: a linear relationship between time and disease status is assumed, and within- and between-subject variability is ignored. Disease progress models combined with pharmacokinetic-pharmacodynamic models and hierarchical random effects statistical models provide insights into understanding the time course and management of degenerative disease.

DEFINITION OF DISEASE PROGRESSION

Clinical pharmacology can be defined in terms of disease progression and drug action. Disease progression can be defined in terms of changes in disease status as a function of time. Drug action reflects the effect of a drug on disease status. For example, in degenerative disorders such as Parkinson's disease, natural disease progression is caused by a continuous degeneration of neurons, which is reflected in such disease status measures as the Unified Parkinson's Disease Rating Scale (UPDRS). In other diseases, such as diabetic neuropathy and nephropathy, natural disease progression is caused by a loss of nerve or kidney function, and status can be defined by nerve conduction velocity or creatinine clearance.

Regarding drug effects on disease, there are two main possibilities. Drugs may provide symptomatic benefit without influencing the underlying progression of the disease, or they may influence the underlying time course of progression. The goal of drug treatments in degenerative disorders is not only to relieve clinical symptoms, but also to slow disease progression.

The aim of this review is to describe models for disease progression in degenerative diseases and to define the methods and biomarkers that have been used for studying disease progression. We illustrate these models by distinguishing the symptomatic and protective components of drug effects in Alzheimer's disease, Parkinson's disease, osteoporosis, diabetic nephropathy, and respiratory disease.

COMPONENTS OF DISEASE PROGRESSION

Natural Disease Progression

Cell death and gradual loss of organ function are well-known natural phenomena of aging. Whether the occurrence of degenerative diseases is age related has been questioned (1–5). According to prevalence statistics, the answer is positive, as a higher incidence is found in advanced age groups (6–11). However, aging alone is not sufficient to explain the full story of the occurrence of degenerative diseases. This is, firstly, because the pattern of cell loss in normal aging has been found to be different from the pattern observed in such degenerative diseases as Parkinson's and Alzheimer's diseases (12, 13). For example, maximal losses were found in the ventral tier of the substantia nigra in Parkinson's disease rather than in the dorsal tier in normal aging (12). Secondly, the rate of cell loss has been found to be faster in diseases than in normal aging. For example, the rate of loss of pigmented neurons in the substantia nigra was 4.7% per decade in normal aging compared with a 45% loss in the first decade in parkinsonian patients (12). This implies that natural disease progression in degenerative diseases can only be studied in patients not receiving drug treatment. In other words, the use of healthy subjects as a control group may not be appropriate in studying disease progression in degenerative disorders.

Natural Disease Progress Models

Linear Model Figure 1 illustrates a linear pattern of natural disease progression.

$$S(t) = S0 + \alpha \cdot t. \qquad 1.$$

A linear natural history model describes a constant rate of deterioration of disease status. The rate of disease progression solely depends on the slope (α), whereas the baseline disease status is defined by the parameter $S0$. Many studies assume a linear rate of disease progression because of the convenience of data analysis (14–18).

Asymptotic Model The rate of change of disease status may vary with disease severity and duration of disease. In this case, disease progression is not simply explained by a linear model. For example, using the UPDRS bradykinesia score as a biomarker for disease severity, nonlinear disease progression was found in Parkinson's disease patients with prior treatment with levodopa/carbidopa and/or

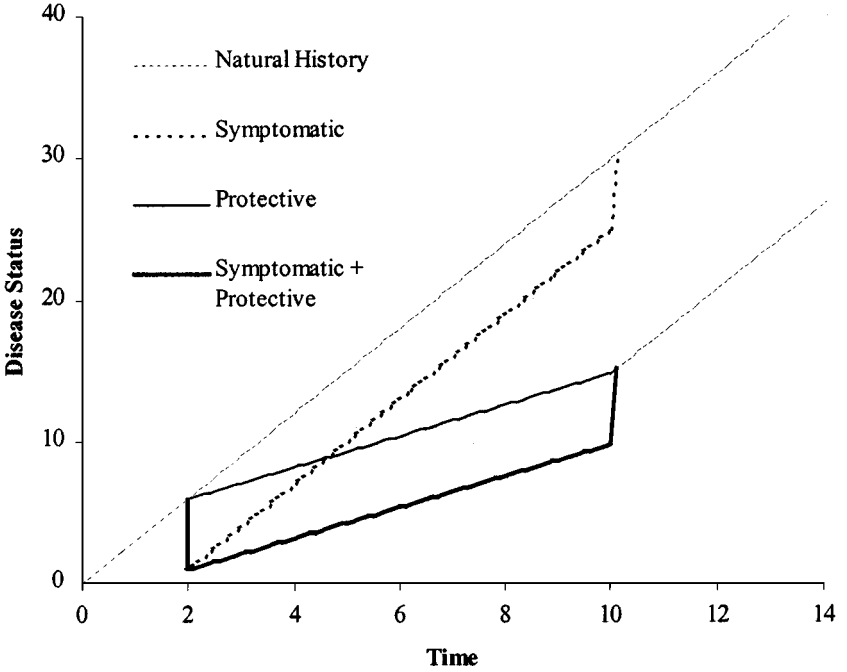

Figure 1 Linear disease progress model and drug modifications. Treatment starts at 2 and stops at 10 time units.

bromocriptine (19). Figure 2 illustrates an asymptotic pattern of natural disease progression.

$$S(t) = S0 \cdot e^{-\frac{\mathrm{Ln}(2)}{TP} \cdot t} + Sss \cdot \left(1 - e^{-\frac{\mathrm{Ln}(2)}{TP} \cdot t}\right). \qquad 2.$$

An asymptotic natural history model describes a worsening of disease status with an exponential time course approaching a steady state. The rate of disease progression depends on the progression half-life (TP) whereas the steady state depends on the maximum "burnt-out" disease status (*Sss*).

Both the linear and asymptotic models represent the possible natural history of disease progression without drug modification. However, these natural disease progress models can be modified by drug treatments, and the modification depends on the type of treatment. In general, each parameter in a disease progress model is a target for describing drug action.

Drug Modifications

Classification of Treatments

When describing the beneficial effects of drug therapy, treatments may be categorized into two classes, symptomatic and protective. Protective treatments can slow

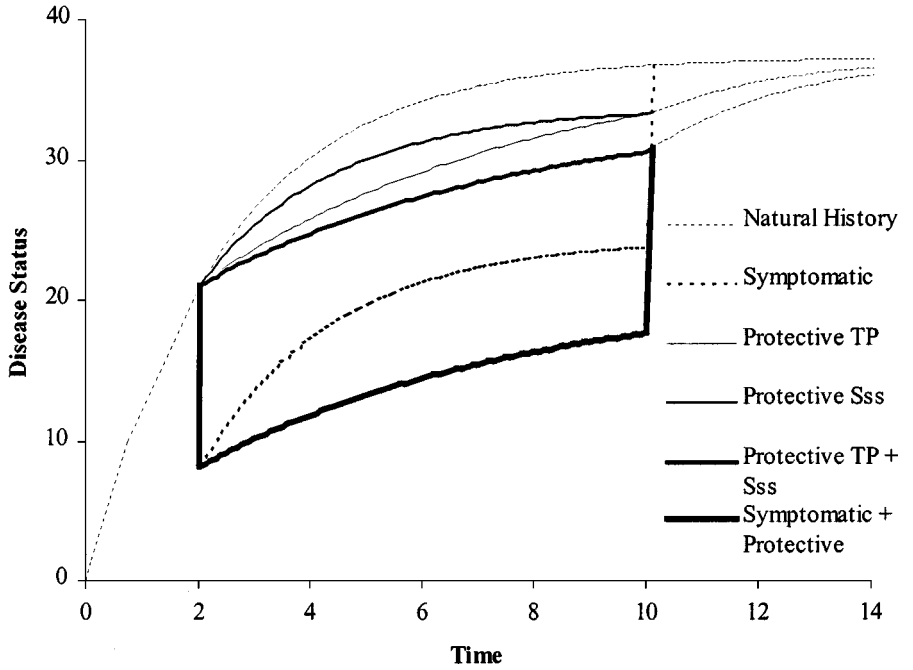

Figure 2 Asymptotic disease progress model and drug modifications. Treatment starts at 2 and stops at 10 time units. TP, progression half-life; Sss, maximum burnt-out disease status.

down, halt, or even reverse disease progress. Symptomatic treatments can only reduce symptom severity. A treatment may have both symptomatic and protective benefits, but distinguishing one from the other may be difficult, as the dominant effect is more likely to be expressed and thus mask the subdominant effect. Separation of symptomatic and protective actions may be possible if the time course of onset of these effects is sufficiently different. Symptomatic effects typically come on more rapidly whereas protective effects take a longer time before they are manifest.

The categorization of symptomatic and protective is primarily applicable to the beneficial effects of drug treatments. If a drug has an adverse effect, this may be reflected as an offset in the disease status marker or a change in the rate of progression, as with a beneficial effect. If a drug effect modifies the rate of disease progression adversely, it might be described as accelerating disease progression (the opposite of a protective mechanism).

When drug effects are described in terms of their effects on the parameters of a disease progression model, it provides a clear and unambiguous definition to support the claim of different types of drug effect. A change in a disease progress parameter that does not change the rate of progression is a symptomatic effect. An improvement in the rate of progression is a protective effect.

Mechanisms of Action

Selegiline and Tocopherol In Parkinson's disease, two treatments, selegiline and tocopherol, have been suggested as having primarily protective benefits. Selegiline is a monoamine oxidase inhibitor. Its effect is partly due to inhibition of monoamine oxidase B, with the assumption that this leads to decreased formation of free radicals, such as the hydroxyl radical. Tocopherol is an antioxidant vitamin. Its protective effect is based on the idea of trapping free radicals and thus reducing the degradation of neurons. However, no study has provided definitive support for the protective effects of either selegiline or tocopherol (15, 20–22).

Angiotensin-Converting Enzyme Angiotensin-converting enzyme (ACE) inhibitors have also been shown to have protective effects by slowing the decline of renal function in diabetic nephropathy (17, 23–25). The mechanism of renal protective effect of ACE inhibitors is still not clear. It has been thought that the protective effect of ACE inhibitors is due to the result of antagonizing the effects of a potent vasoconstrictor, angiotensin II, by inhibiting its formation from angiotensin I (23, 26). The disturbance of the renin-angiotensin system by ACE inhibitors results in retaining the balance between the vasoconstrictive and salt- and fluid-retentive properties of angiotensin II. The possible mechanism of renal protective effects of ACE inhibitors has been reviewed elsewhere (27).

Time Course of Drug Effects on Disease Progression

Symptomatic Effects In Figures 1 and 2, the "symptomatic" effects in both linear and asymptotic disease progress models demonstrate an improvement of disease status while treatment is given. Because there is no change in the underlying process, the drug benefit simply delays the time until the disease reaches the state observed at the start of treatment, e.g. the benefit of tacrine in Alzheimer's disease is a delay of about 6 months (28). When treatment is stopped, the beneficial symptomatic effect disappears and the same deterioration pattern as the natural disease progression is followed. The disease progress model parameters, such as the slope (α) of the linear model, the disease progression half-life (TP), and the maximum burnt-out disease status (Sss) in the asymptotic model, remain unchanged. Irrespective of the function used to describe the time course of the disease, symptomatic treatment can be modeled as if it was a function of the baseline disease state parameter, $S0$.

Protective Effects Protective drug effects describe modifications of the time course of natural disease progression. With the linear model, the protective effect is reflected in a change of the slope of the natural disease progress model. With the asymptotic model, there are three possible variants. The progression state model represents treatments that have an effect on TP. This is reflected in a change of the curvature of the natural disease progress model. The asymptotic state model represents treatments that have an ability to alter Sss.

Treatments that have protective effects on both mechanisms are illustrated in Figure 2.

METHODS FOR MEASURING DISEASE STATUS

Continuous Scale Markers

A necessary requirement for studying disease progression is a biomarker (clinical or biochemical) that can relate clinical observations to disease status. Preferably, such a biomarker is easily measured on a repeated basis and is expressed on a continuous scale: for example, creatinine clearance as an index of renal function, velocity of nerve conduction as a marker for diabetic neuropathy, bone mineral density as an index for osteoporosis, and FEV1 (force expiratory volume in 1 s) as a marker for obstructive lung disease.

Categorical Rating Scales

A number of categorical rating scales have been used to describe disease status in such neurodegenerative diseases as Parkinson's and Alzheimer's diseases. Each of these rating scales has different components (cognitive, mental, motor, and activity of daily living) to assess the functional condition of patients. The most widely used scales are the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr scale (H&Y) in Parkinson's disease and Mini Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale (ADAS) in Alzheimer's disease. Table 1 lists some of the available rating scales for measuring disease severity in neurodegenerative diseases.

Because each of the rating scales is constructed differently, the range of scores is different from one to another. This makes it difficult to compare the results of one rating scale with another. In this case, changes expressed in percentage of baseline rather than in absolute scores may be used to compare different rating scales.

Positron Emission Tomography and Single Photon Emission Tomography

Positron emission tomography (PET) and single photon emission tomography (SPECT) are quantitative techniques employed to localize and measure physiologic and biochemical processes in the brain. By following the same pharmacological pathway as intrinsic neurotransmitters, radioactive markers can be used to examine the native neural system in different regions of the brain. With different tracers, PET can differentiate between diseased and normal brain, as well as between diseases with similar clinical symptoms (29–31). In Alzheimer's disease, a 12%–24% reduction of regional cerebral glucose metabolism (compared with healthy control subjects) has been found (32, 33). SPECT is commonly used for estimating blood flow and receptor binding, as its marker does not depend on

TABLE 1 Common rating scales for assessing disease severity in neurodegenerative disease

Scale	Abbreviation	Component	Range
Parkinson's disease			
Columbia University Rating Scale	CURS	—	0–128
Cornell Weighted Scale	—	—	0–220
Modified Columbia Scale[a]	MCS	—	0–100
Hoehn & Yahr	H&Y	—	I–V
Hamilton Scale for Depression	HSD	—	0–53
New York University Parkinson's Disease Scale	NYUPDS	—	0–20
Northwestern University Disability Scale	NUDS	—	0–100
Schwab & England Activities of Daily Living Scale[b]	S&E ADL	—	0–100
University of California Los Angeles Scale	UCLA	—	0–220
Unified Parkinson's Disease Rating Scale	UPDRS	Total	0–188
		ADL	0–52
		Mental	0–16
		Bradykinesia	0–24
		Motor	0–108
Webster Rating Scale	WRS	—	0–30
Alzheimer's disease			
Alzheimer's Disease Assessment Scale	ADAS	Total	0–120
		Noncognitive	0–50
	ADASC	Cognitive	0–70
Blessed Dementia Scale	BDS	Total	0–27
		ADL	0–16
		Cognitive	0–17
Blessed Information Memory Concentration	BIMC	—	0–33
Behavior Rating Scale for Dementia	BRSD	Total	0–164
Clinical Dementia Rating (in six categories)	CDR	—	0–3
Clinician's Interview-Based Impression of Change	CIBIC	—	1–7
Sum of Boxes (Global CDR)	CDR-SB	—	0–18
Dementia Rating Scale[c]	DRS	—	0–144
Extended Scale for Dementia	ESD	—	0–250
Global Deterioration Scale	GDS	—	0–7
Mini Mental State Examination[c]	MMSE	—	0–30
Progressive Deterioration Scale	PDS	—	0–100
Severe Impairment Battery[c]	SIB	—	0–100

[a]Modification of Columbia University Rating Scale.

[b]The scale is in percentage, with no disability 100%.

[c]Higher scores indicate less impairment.

dopamine turnover. A 30%–56% reduction in striatal uptake of tracer (V_3'') was reported in Parkinson's disease (34–36). It should be noted that different tracers might generate different uptake rates because of differences in distribution and elimination processes (36).

Recently, PET has been used as a tool for detection of preclinical Parkinson's disease (37, 38) and determination of rate of disease progression (39–41). The uptake rate constant (K_i) can be taken as a distribution rate constant that describes the rate of tracer storage in neurons. Because radioactive tracer is being taken up by the surviving neurons in the brain, K_i can be used as a marker for the number of functioning neurons. It has been shown that K_i correlates well to the number of surviving nigral pigmented neurons in Parkinson's disease (42). Moreover, it has also been shown that K_i correlates well with clinical markers such as the UPDRS (41) and the H&Y scale (43). Consequently, K_i could be used as a marker for assessing disease progression in neurodegenerative disorders. A correlation between V_3'' and UPDRS has also been shown (34). Both PET and SPECT have a high reproducibility (44, 45). With the application of PET, disease progression and the effect of drugs can be measured by determining the change of K_i over time (46, 47).

In practical terms, PET and SPECT are time-consuming and expensive screening methods. Because of these reasons, the change of K_i or V_3'' is often computed based on two observations. The assumption of a linear rate of loss of neurons is one of the limitations of using changes in K_i as a measure of disease progression. This limitation may be overcome by taking more observations over a longer interval.

METHODS FOR DESCRIBING DISEASE PROGRESSION

There have been many reports of the longitudinal change of disease status in degenerative diseases. However, few have attempted to explicitly quantify the rate of disease progression. Generally, there are several methods of dealing with longitudinal data.

ANOVA/ANCOVA

Frequently, the treatment effect on an outcome measure is determined by simple statistics (parametric or nonparametric) or through the application of analysis of variance (ANOVA) or analysis of covariance (ANCOVA). The purpose of ANOVA is to test for significant differences between the means of the control and treatment groups. The rate of disease progression in either the control or the treatment group is not taken into account by this method.

Survival Analysis

Survival analysis is the use of endpoints, for example death or the need for additional treatment, as an objective to measure the fraction of patients reaching the endpoint over time. Kaplan-Meier analysis is a common approach to interpreting the outcome using survival analysis.

Change from Baseline

Change from baseline analysis uses two observations to determine the rate of disease progression. The baseline and the final observations are used, and the rate of progression is determined from the change in the two outcome measures divided by the length difference in the two time points. This is also known as two-point analysis.

Linear and Nonlinear Modeling

Modeling is the use of mathematical functions to describe quantitative relationships, e.g. time and disease status, through linear or nonlinear regression. The power of modeling is that it not only describes the data, it also predicts and explains the time course and drug effect beyond the study period. Pharmacokinetic-pharmacodynamic models relate plasma drug concentrations to clinical responses (48). Parameter estimations can be performed under individual- or population-based approaches. NONMEM (nonlinear mixed effect model) is a program that allows model building and parameter estimation using a population approach (49). A key feature of population analysis is the ability to account for and describe within- and between-subject variability. Another advantage of modeling is the ability to take into consideration the effects of covariates when estimating parameters.

The rate of disease progression depends on the disease status scale used to calculate it. Table 2 lists the natural rate of Alzheimer's disease progression with different scales and analyses (14, 28, 50–65). In one study, Stern et al (57) has shown that the rate of disease progression varied from 3.9 to 5.2 points/year in patients with Alzheimer's disease with Blessed test of information, memory, and concentration (BIMC) as a marker for assessing disease severity.

Studies of short duration that assume a linear model may overestimate the rate of disease progression if the progression model is actually asymptotic. A high patient drop-out rate is also responsible for the imprecision in estimating the rate of change. None of the studies has taken into account the influence of covariates, such as age and duration of symptoms, in determining the rate of disease progression. More important, these methods lack the ability to determine the within- and between-subject variability.

RATE OF DISEASE PROGRESSION

Changes in Pharmacokinetics and Pharmacodynamics in Parkinson's Disease

Several studies have compared the pharmacokinetics and pharmacodynamics of patients with different stages of Parkinson's disease (66–69). These studies aimed to find out how the time course of levodopa effects might be modified as Parkinson's disease progresses (Table 3). Contin et al (70–72) have performed several longitudinal studies to investigate the change of pharmacokinetics and pharmacodynamics

TABLE 2 Rate of disease progress in Alzheimer's disease with different analysis methods and biomarkers[a]

				Rate of progression	
Reference	**Method**	**Scale**	**Baseline (points)**	**(points/year)**	**(%/year)**
50	Two point	MMSE	17.20	2.20	12.79
51	Two point	MMSE	16.47	4.18	25.39
52	Two point	MMSE	17.40	2.81	16.15
53	Two point	MMSE	10.00	3.50	35.00
54	Two point	MMSE	18.70	3.90	20.86
55	Two point	MMSE	11.10	4.30	38.74
56[b]	Linear	MMSE	17.90	0.62	3.46
57[c]	MIM	BIMC	—	4.10	—
58	Two point	BIMC	13.17	4.40	33.41
59	Two point	BIMC	17.40	4.50	25.86
52	Two point	BIMC	16.60	3.24	19.52
57	Two point	BIMC	—	3.90	—
60	Two point	BIMC	17.10	2.60	15.20
61	Linear	BIMC	—	4.10	—
57	Linear	BIMC	—	4.00	—
51	Two point	ADAS	22.40	8.28	36.96
62[b]	Two point	ADASC	29.60	2.77	9.36
56[b]	Linear	ADASC	28.50	5.88	20.63
28	Linear	ADASC	28.70	6.17	21.50
63	Linear	ADASC	28.40	5.00	17.61
64	Linear	ADASC	—	6.29	—
63	Linear	CIBIC	4.00	0.61	15.25
64	Linear	CIBIC	—	0.69	—
65	MIM	PSMS	12.76	2.44	19.12
65	MIM	IADLS	22.32	2.06	9.23
60	Two point	BDS	17.50	3.50	20.00
14[c]	Two point	BDS	20.70	7.56	36.52
55	Two point	SIB	79.10	17.10	21.62
52	Two point	DRS	98.30	11.38	11.58
56	Linear	PDS	46.70	13.00	27.84

[a]MIM, multiple interval method. For other abbreviations, see Table 1.

[b]Rate of progression converted from points/week.

[c]Rate of progression converted from points/month.

TABLE 3 Pharmacodynamic comparisons in patients with different disease stage of Parkinson's disease[a]

Reference	Parameter	Levodopa naive	Stable	Fluctuating	Fluctuating + Peak dose dyskinesia
66[b]	E0 (taps/min)		107 ± 8	93 ± 7	
	Max change from E0 (taps/min)		29 ± 3	49 ± 8	
67	E0 (taps/min)	116 ± 9	144 ± 25	106 ± 23	
	E_{max} (taps/min)	44 ± 34	56 ± 28	98 ± 17	
	EC_{50} (ng/ml)[c]	2504 ± 1459	2288 ± 1499	2110 ± 1420	
	Hill (U)	6.3 ± 8.0	1.4 ± 0.8	1.3 ± 0.8	
68	E_{max} + E0		166 ± 44	153 ± 44	
	E_{max} (taps/min)		40.5 ± 18.3	51.5 ± 25	
	EC_{50} (ng/ml)[d]		240 ± 130	640 ± 260	
	Hill (U)		2.8 ± 1.5	16.3 ± 12.7	
	*T*eq (h)[e]		2.72 ± 1.17	0.48 ± 0.35	
69	E0 (CURS)	24 ± 10	30 ± 12	41 ± 21	35 ± 12
	E_{max} (CURS)	10 ± 31	2 ± 5	24 ± 13	18 ± 7
	EC_{50} (ng/ml)	389 ± 138	346 ± 203	543 ± 245	711 ± 215
	Hill (U)	3	4	5	6
	*T*eq (h)	0.81 ± 0.49	1.28 ± 0.50	0.39 ± 0.20	0.28 ± 0.22

[a]For abbreviations, see Table 1.

[b]Only simple statistical comparisons were made. No pharmacokinetic-pharmacodynamic modeling has been performed.

[c]50% effective concentration (EC_{50}) converted from nanomoles per milliliter.

[d]EC_{50} converted from micrograms per milliliter.

[e]Equilibration half-life (*T*eq) converted from minutes.

over time (Table 4). According to these findings, changes in pharmacodynamic parameters appeared after 3–4 years of levodopa treatments.

Nutt & Holford (73) used a pharmacokinetic-pharmacodynamic approach to explain the transition from the stable to the fluctuating response state in Parkinson's disease. They argued that a change in sensitivity (50% effective concentration) could not account for differences in the time course of the acute response to levodopa as the disease progressed. A shortening of the delay between changes in plasma concentration and subsequent changes in response, describable by differences in the equilibration half-life (*T*eq), was most likely the reason for the altered response in the fluctuating state.

Natural Rate of Disease Progression

Parkinson's Disease

The first study looking at disease progression in patients with Parkinson's disease was conducted in 1967 (74). In this study, the rate of progression was investigated

TABLE 4 Changes in pharmacodynamic parameters over time in Parkinson's disease[a]

Reference	Parameter	Baseline	Final	% Change[b]	Study duration
70	EC_{50} (ng/ml)	370 ± 50	580 ± 80	41 ± 5	4 years
	Hill (U)	8.0 ± 1.3	21.0 ± 5.0	163[c]	
	*T*eq (min)	109 ± 19	36 ± 8	-55 ± 8	
71	EC_{50} (ng/ml)	420 ± 260	690 ± 200	64[c]	3 years
	*T*eq (min)	62 ± 57	21 ± 13	-66[c]	
72	E0 (taps/min)	127 ± 35	122 ± 26	-4[c]	4 years
	Max change from E0 (taps/min)	43 ± 19	53 ± 24	23[c]	

[a]All 50% effective concentrations (EC_{50}) were converted from micrograms per milliliter.

[b]Percentage of change was computed by the following equation: (final-baseline)/baseline.

[c]100% change.

by looking at the time required for deterioration of one stage of H&Y scale. Marttila & Rinne (75) also performed a similar study with 442 levodopa naïve parkinsonian patients. Figure 3 shows the plots of H&Y stage against time. The natural rate of disease progression can also be estimated by looking at placebo groups in studies investigating the effects of drug treatments. With the assumption of linear deterioration, the rate of disease progression in Parkinson's disease was found to be 13.11–14.02 points/year (UPDRS total) and 3.62–13.4 points/year (UPDRS motor) (Table 5) (15, 20, 76–78).

Disease Progression Using PET The application of PET to describe the rate of disease progression has been performed for Parkinson's disease. The published rates of change in K_i range from 0.4% to 7% of the mean baseline K_i in healthy control subjects. Table 6 summarizes the rate of K_i progression in Parkinson's disease (39–41, 79, 80). All studies showed that parkinsonian patients have a smaller K_i value than do healthy control subjects. For example, putamen (K_i) was found to be 0.0054 min^{-1} and 0.0101 min^{-1} in parkinsonian patients and healthy control subjects, respectively (79). The rate of change is expressed as percentage of normal mean per year. This is the mean annual deterioration in K_i in the patients expressed as a percentage of the mean K_i in the control group at baseline scan. The annual rate of progress varied with the method of analysis. The large range of annual rate of progression between studies indicates the difficulties in applying PET techniques.

Besides PET, computed tomographic scans and magnetic resonance imaging (MRI) scan have also been employed to monitor disease progression in Alzheimer's disease. In comparison with normal aging controls, a decrease in brain volume was found in Alzheimer's disease (81, 82). Based upon this phenomenon, it has been proposed that rates of change in brain volume could be a marker of disease progression in Alzheimer's disease. Not surprisingly, the annual rate of change

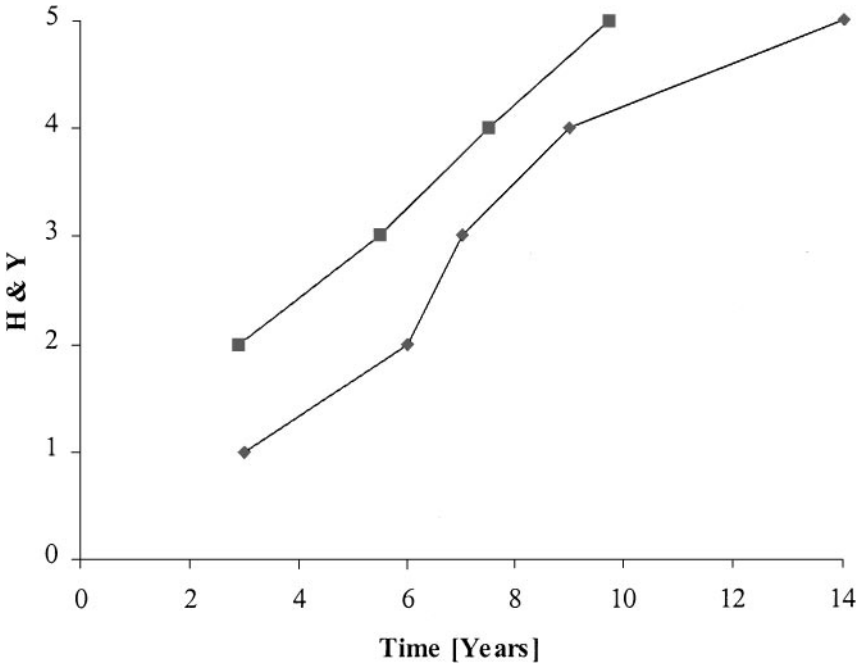

Figure 3 Observed rate of disease progression measured by the time required for deterioration of one stage of Hoehn & Yahr (H&Y) scale: closed diamond (74); closed square (75).

varied with the structural measures (Table 7) (83–91). In general, with MRI scan, a larger decrease in brain volume was shown in Alzheimer's disease patients in comparison with the control group. For example, the annual decrease in total brain volume was 2.37%–2.78% in Alzheimer's disease in comparison with 0.24%–0.41% in the normal group.

Alzheimer's Disease

In Alzheimer's disease, several studies have explored the natural disease progression by using a multiple-interval method (repeatedly computing change over a specified time interval, i.e. every 6 months), two-point analysis, or linear regression (Table 2). The rate of progression has a large range because of the use of different rating scales and analysis methods (2.77–6.29 ADASC, 2.2–4.3 MMSE, 2.6–4.5 BIMC points/year). The absolute scores are not comparable because of different rating scales used; thus, a plot of percentage of change from baseline is shown in Figure 4 (28, 51, 52, 56, 92, 93). The heavy lines show the rate of disease progression predicted by using the progression rates reported by Holford & Peace (28), Knopman & Gracon (56), and Yesavage et al (51). The Figure illustrates the variability in rate of disease progress with different rating scales.

TABLE 5 Natural and treatment-altered rate of disease progress in Parkinson's disease with different rating scales as clinical markers[a]

Ref.	Treatment	Scale	Baseline (points)	Rate of progression (Points/year)	Rate of progression (%/Year)
76	—	UPDRS	25.4 ± 11.6	13.11 ± 14.30	51.61
	Selegiline	UPDRS	25.3 ± 12.0	5.50 ± 11.27	21.74
20	—	UPDRS	25.4 ± 11.6	14.02 ± 12.32	55.20
	Selegiline	UPDRS	25.3 ± 12.0	7.00 ± 10.76	27.67
	Tocopherol	UPDRS	25.4 ± 11.6	15.16 ± 16.12	59.69
	Selegiline + tocopherol	UPDRS	25.3 ± 12.0	7.28 ± 11.11	28.77
77	Levodopa	UPDRS	20.6 ± 10.9	3.8 ± 8.5	18.45
	Levodopa[b]	UPDRS	23.6 ± 11.1	1.2 ± 7.7	5.08
15	—	UPDRSm	21.41 ± 2.18	13.40 ± 1.82	62.59
	Selegiline	UPDRSm	21.93 ± 1.47	6.75 ± 1.05	30.78
76	—	UPDRSm	16.8 ± 8.8	.58 ± 9.88	51.07
	Selegiline	UPDRSm	16.8 ± 8.8	4.02 ± 8.29	23.93
20	—	UPDRSm	16.8 ± 8.8	3.62 ± 3.74	21.55
	Selegiline	UPDRSm	16.8 ± 8.8	2.66 ± 3.22	15.83
	Tocopherol	UPDRSm	16.8 ± 8.8	3.92 ± 4.47	23.33
	Selegiline + tocopherol	UPDRSm	16.8 ± 8.8	2.51 ± 3.86	14.94
78	Selegiline + Sinemet	UPDRSm	14.6 ± 1.5	−1.4 ± 1.0	−9.59
	Sinemet	UPDRSm	12.8 ± 1.0	3.3 ± 1.0	25.78
	Selegiline + bromocriptine	UPDRSm	14.2 ± 1.0	2.4 ± 1.1	16.90
	Bromocriptine	UPDRSm	11.4 ± 1.3	5.0 ± 1.1	43.86
77	Levodopa	UPDRSm	14.2 ± 8.6	2.6 ± 6.8	18.31
	Levodopa[b]	UPDRSm	16.7 ± 8.8	0.7 ± 6.1	4.19
15	—	H&Y	1.46 ± 0.13	0.73 ± 0.15	50.00
	Selegiline	H&Y	1.59 ± 0.10	0.26 ± 0.10	16.35
76	—	H&Y	1.7 ± 0.5	0.38 ± 0.69	22.35
	Selegiline	H&Y	1.6 ± 0.5	0.19 ± 0.60	11.88
15	—	UPDRS ADL	8.00 ± 0.90	4.45 ± 1.01	55.63
	Selegiline	UPDRS ADL	7.74 ± 0.52	2.69 ± 0.58	34.75
76	—	UPDRS ADL	7.47 ± 3.6	3.97 ± 4.97	53.15
	Selegiline	UPDRS ADL	7.38 ± 3.8	1.58 ± 4.08	21.41
20	—	UPDRS ADL	7.47 ± 3.6	2.10 ± 2.28	28.11
	Selegiline	UPDRS ADL	7.38 ± 3.8	1.04 ± 1.95	14.09
	Tocopherol	UPDRS ADL	7.47 ± 3.6	1.62 ± 2.02	21.69

TABLE 5 (*Continued*)

Ref.	Treatment	Scale	Baseline (points)	Rate of progression (Points/year)	Rate of progression (%/Year)
	Selegiline + tocopherol	UPDRS ADL	7.38 ± 3.8	1.13 ± 2.16	15.31
78	Selegiline + sinemet	UPDRS ADL	9.6 ± 1.0	-0.3 ± 1.0	-3.13
	Sinemet	UPDRS ADL	9.9 ± 0.6	1.5 ± 0.6	15.15
	Selegiline + bromocriptine	UPDRS ADL	10.7 ± 0.8	-0.1 ± 0.9	-0.93
	Bromocriptine	UPDRS ADL	8.7 ± 0.6		

[a]UPDRSm, UPDRS motor. For other abbreviations, see Table 1.

[b]Group pretreated with selegiline as monotherapy for approximately a year and stopped for 8 weeks before levodopa started.

It should be noted that a linear deterioration is assumed in all cases. Certainly, a linear disease progression model has its limitations because disease status cannot deteriorate indefinitely. There must be a point where the disease cannot further deteriorate or the marker is insensitive to measure such a change in disease status. Brooks et al (94) have proposed a trilinear model to describe the time course of Alzheimer's disease. The trilinear model introduced a lag time or a latent phase before the start of the period of constant rate of deterioration, which was followed by a resistant phase where there is no further worsening of disease status. The trilinear model has more flexibility in the two extremes than the simple linear model. However, within the period of decline, both linear and trilinear models appeared to be the same. The trilinear model resembles the asymptotic model described earlier, but it has six parameters instead of three.

Physiological Function and Aging

Some studies have used regression to explore the relationships between aging and physiological functions. It has been found that bone mineral density and FEV1 vary with age and gender; weight and height are also essential determinants of these physiological terms (95–102). Figures 5 and 6 show the changes in bone mineral density and FEV1 with age. Table 8 lists some of the regression models for describing the relationship between FEV1 and age with covariates such as sex, body mass, and height (97–99, 103–108). It is interesting that the models and parameters vary with different age groups studied. In order to focus on the effect of age on FEV1, other covariates were assumed to be constant in Figure 6. The difference between genders depends on the type of model being used. Although a nonlinear relationship is seen in Figure 6, for simplicity, a linear relationship is often assumed for ages above 25 years.

TABLE 6 Disease progression in Parkinson's disease using uptake rate constant (K_i) using PET[a]

Ref.	No. of subjects		Age (years)		Analysis method	Rate of change (% normal mean/year)	Study duration
	Control	Patient	Control	Patient			
79	8	32	72 ± 9	58 ± 13	Putamen (K_i) Caudate (K_i) Total striatum (K_i) Putamen (ratio) Caudate (ratio)	4.7 2.8 3.9 2.1 0.4	18 months
41	10	17	66 ± 16	56.3 ± 15.1	Putamen (K_i) Total striatum (K_i) Putamen (ratio) Striatum (ratio)	7 4.0[b] 3.2 1.8	18 months
40	10	16	54 ± 16	51 ± 14	Striatal:cortex (ratio)	1.7[b]	7.4 years
80	9	5	67 ± 8	55 ± 14	Putamen (K_i) Caudate (K_i)	18 ± 16[b] 6 ± 14[b]	52 months
39	7	9	54.8 ± 17.7	58.1 ± 10.7	Striatal:cortex (ratio)	1.6[b]	40 months

[a]PET, positron emission tomography; K_i, uptake rate constant. Annual rate of the change in K_i is the deterioration rate expressed as a percentage of the normal mean per year.

[b]Rate of change in K_i expressed as a percentage of the baseline of the patient group rather than the normal mean per year.

TABLE 7 Rate of change in brain volume in Alzheimer's disease determined by CT and MRI scans with different structural measures[a]

	No. of Subjects		Age (years)		Scan interval (days)			Rate of change (% vol/year)[b]	
Ref.	Control	Patient	Control	Patient	Control	Patient	Structural measure	Control	Patient
CT scan									
83[c]	12	18	65.1 ± 4.3	66.8 ± 2.9	1197 ± 108	480 ± 98	Lateral ventricles	−1.18	24.71
84	—	63	—	79.3 ± 6.2	—	365	Ventricular/ brain ratio	—	9.3
85	17	20	62 ± 8	66 ± 9	858	402	Lateral ventricles	2.4	14.2
86	47	61	68.4	73.1	584	664	Minimum thickness of medial temporal lobe	−1.5	−11.6
87	35	41	67.4 ± 7.4	70.7 ± 7.6	949	767	CSF volume in ventricular system	1.33	7.51
MRI scan									
88	18	12	86.8 ± 1.9	90.4 ± 5.2	1290	1409	Hippocampus	−2.09	−2.33
							Parahippocampus	−2.16	−2.92
							Temporal lobe	0	−1.27
89	9	9	54.4 ± 6.6	54.3 ± 8.2	399 ± 37	401 ± 170	Total brain	−0.24 ± 0.32	−2.78 ± 0.92
90	24	24	81.04 ± 3.78	80.42 ± 4.02	715	690	Hippocampus	−1.55 ± 1.38	−3.98 ± 1.92
							Temporal horn	6.15 ± 7.69	14.16 ± 8.47
91	18	18	65.0 ± 10.5	65.0 ± 6.4	326 ± 90	336 ± 62	Total brain	−0.41 ± 0.47	−2.37 ± 1.11

[a]CT, computed tomography; MRI, magnetic resonance imaging.

[b]Rate calculated by yearly change in volume divided by initial brain volume and expressed in percentage.

[c]Values are mean ± standard error.

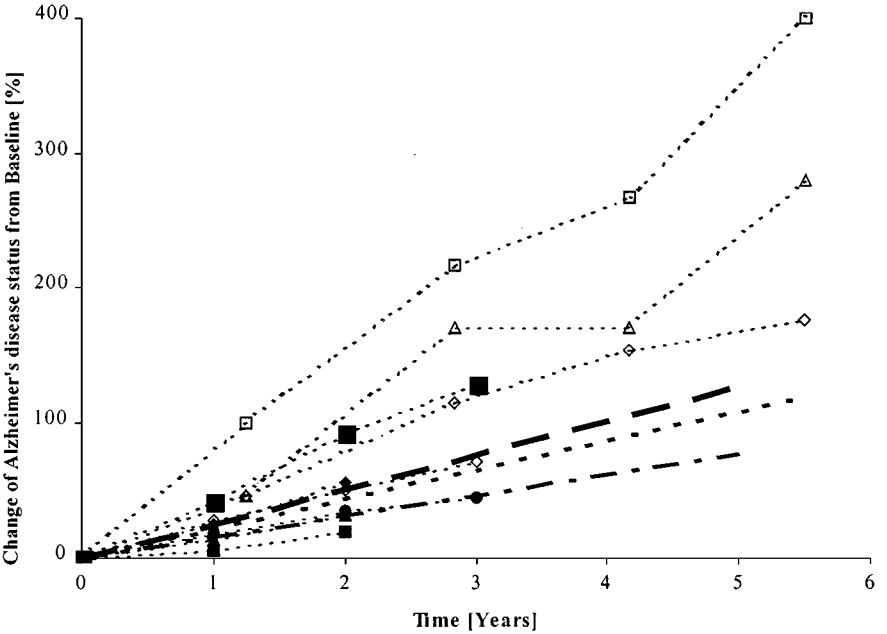

Figure 4 Natural disease progression in Alzheimer's disease measured by different rating scales. From Salmon et al (52): closed diamond, Blessed test of information, memory, and concentration; closed triangle, Mini Mental State Examination (MMSE); small closed square, Dementia Rating Scale (DRS). From Glasko et al (92): closed circle, MMSE; large closed square, Blessed Dementia Scale–Activities of Daily Living Scale; open diamond, Clinical Dementia Rating (CDR). From Berg et al (93): open circle, CDR; open triangle, Blessed Dementia Scale (DS); open square, Blessed Dementia Scale—Cognitive (DSC). Heavy dotted line predicted Alzheimer's Disease Assessment Scale—Cognitive (ADASC) (28), heavy dotted-dashed line predicted ADASC (56), heavy dashed line predicted MMSE (51).

Effect of Drug Treatment on Disease Progression

Alzheimer's Disease

An attempt to compare the treatment effects of different drug treatments and different markers has been made in Alzheimer's disease (Figure 7) (28, 109–112). This was done by obtaining the absolute values of disease status at different time points and expressing the changes as a percentage of the baseline value. Similar comparisons have been made in Parkinson's disease, diabetic nephropathy, respiratory disease, and osteoporosis.

It should be noted that the study duration was fewer than 2 years in most of the studies; thus, the pattern of drug modification of natural disease progression is applicable only for a relatively short period. The dotted and dashed lines represent predictions of natural disease progression and the symptomatic treatment effect of tacrine using information by Holford & Peace (28). Additionally, it has been shown

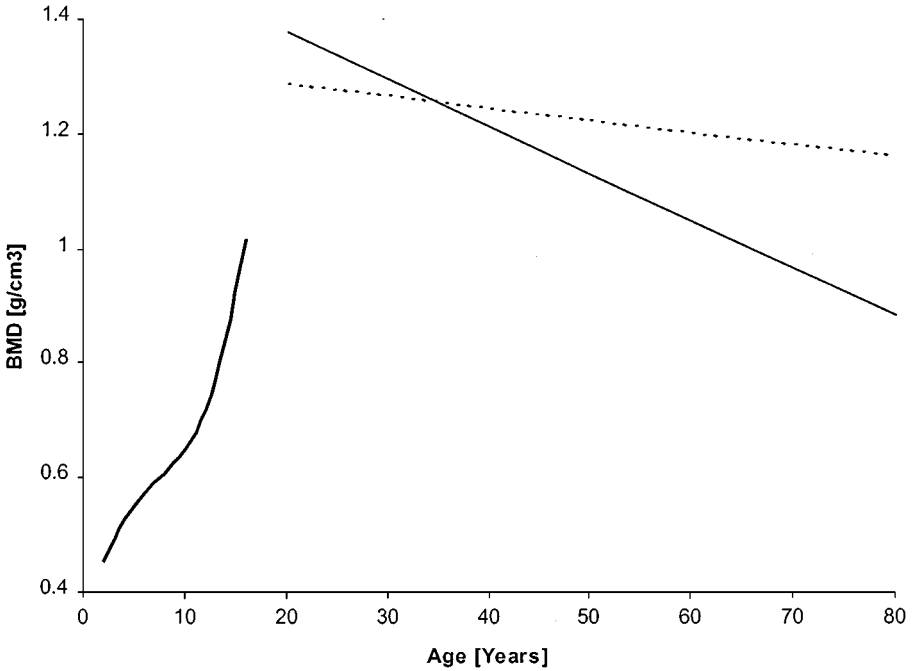

Figure 5 Predicted change of bone mineral density (BMD) in lumbar spine with age in healthy children (heavy line) (96), males (dotted line), and females (solid line) (95).

that the effect of rivastigmine is about 10 times greater than tacrine using ADASC and Clinician's Interview-Based Impression of Change (CIBIC) as clinical markers (Table 1) (64).

Parkinsons' Disease

Lee et al (19) described disease progression in Parkinson's disease by using a naïve pooled data approach from 238 parkinsonian patients with prior treatment of levodopa/carbidopa and/or bromocriptine. The naïve pooled data method treats data gathered from all individuals as if it came from a single subject, thus ignoring between-subject correlation of response. With the application of multiple linear and nonlinear regressions, three functions (quadratic, exponential, and linear) have been used to describe the relationship between bradykinesia score (derived from UPDRS) and age or duration of disease. Bradykinesia score has been shown to be one of the best clinical measures in relating disease severity to Parkinson's disease (113). With further exploration of these functions, Schulzer et al (114) developed a theoretical model that describes an age-related cell loss and describes how events, such as disease-caused neuronal death, modify the rate of cell loss. The model consists of a linear function to describe

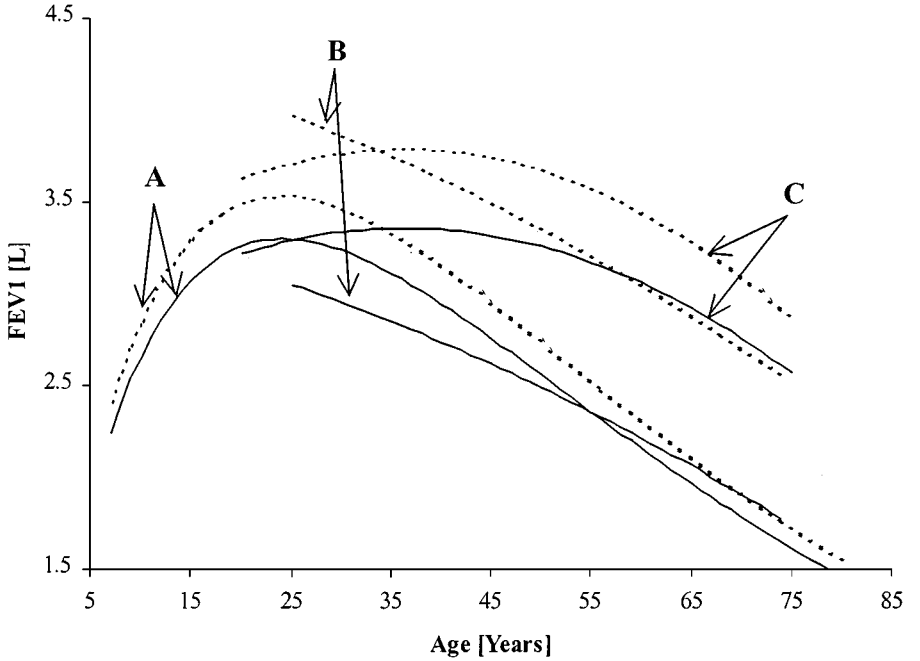

Figure 6 Predicted change of FEV1 (forced expiratory volume in 1 s) with age in healthy males (dotted line) and females (solid line). (*A*) Age range 6–81 years (103); (*B*) 25–74 years (97); (*C*) 20–75 years (98).

the loss of nigral dopaminergic neurons with a slope defining the rate of age-related loss and a quadratic function to describe the disease-related rate of cell loss.

In Figure 8, the effect of selegiline is compared with levodopa using different rating scales (115). The dotted line represents a predicted disease progress model on bradykinesia score (derived from UPDRS) in Parkinson's disease (19). As the patients in the study of Lee et al had prior treatment of levodopa/carbidopa and/or bromocriptine, Figure 8 actually illustrates the difference in protective and symptomatic effects. Because of the short study duration, it is hard to tell whether selegiline alters the rate of disease progression. However, it is clear that the effect of selegiline is small in comparison to disease progression. Table 5 shows the rate of disease progression in Parkinson's disease and how drug treatments altert it. It should be noted that a linear progression was assumed in all cases. According to the findings, selegiline seems to slow the rate of progress with UPDRS total (selegiline vs placebo, 5.5–7.0 vs 13.11–14.02 points/year) and UPDRS motor (2.66–6.75 vs 3.62–13.4 points/year) as clinical markers. Tocopherol does not seem to alter the rate of disease progression (tocopherol vs placebo, 15.16 vs 14.02 UPDRS, 3.92 vs 3.62 UPDRS motor points/year).

TABLE 8 Models for predicting FEV1 (liters) in normal subjects[a]

Ref.	Model	Age range (years)
103[b]	$\ln FEV1 = 0.7298 \ln A + 0.5278 \ln M + 0.0041H - 0.0036M - 0.0303A - 3.0119$	6–81
104[c]	$FEV1 = 6.844 + 0.040A - 0.281H + 0.003H^2$	5–25
97[d]	$FEV1 = H^3(1.541 - 0.209SEX - 0.00406A - 0.0000614A^2)$	25–74
99	$FEV1\ (males) = 2.081 + 0.5846H^3 - 0.01599AH$ $FEV1\ (females) = 1.597 + 0.5552H^3 - 0.01574AH$	18–78
98	$FEV1\ (males) = 758.5 + 634.9H^3 - 0.128H3(A - 36.3)^2$ $FEV1\ (females) = 798.2 + 517.6H^3 - 0.136H3(A - 36.7)^2$	20–75
105[c]	$FEV1\ (males) = 0.092H - 0.032A - 1.260$ $FEV1\ (females) = 0.089H - 0.025 - 1.932$	20–84
106[c]	$FEV1\ (females) = 67.6H - 23.0A - 918$	18–71
107[b]	$FEV1\ (males) = 0.036H - 0.027A - 1.65$ $FEV1\ (females) = 0.025H - 0.022A - 0.62$	25–74
108[b]	$FEV1\ (males) = 0.037H - 0.028A - 1.59$	18–66

[a]FEV1, force expiratory volume in 1 s; A, age (years); M, body mass (kilograms); H, height (meters).

[b]Height is in centimeters.

[c]Height is in inches.

[d]SEX: 0, males; 1, females.

A hazard function has been used to study disease progression and the effect of selegiline in Parkinson's disease (116). The hazard function defines the probability of patients reaching an end point at a given point in time. We might expect the hazard of patients requiring levodopa to increase with time in patients not receiving drug treatment, whereas drug therapy may decrease the hazard. In this study, selegiline decreased the hazard in the first 300 days compared with the placebo group. After day 300, the hazard of the placebo group unexpectedly decreased and approached the hazard for the selegiline group, at approximately 530 days. Based upon this finding, the authors suggested that the effect of selegiline is symptomatic rather than protective, but no clear explanation has been proposed for the pattern of hazard in the placebo group.

Respiratory Disease

Corticosteroids Inhaled corticosteroids such as budesonide and beclomethasone are used in the management of chronic obstructive pulmonary disease. Table 9 shows the rate of disease progression in respiratory disease and the effect of inhaled corticosteroids (117–119). All studies of the rate of disease progression used a linear model and showed that corticosteroid treatments produced a slower decline in FEV1 in respiratory diseases (range 30–46 ml/year; control range 50–64 ml/year)

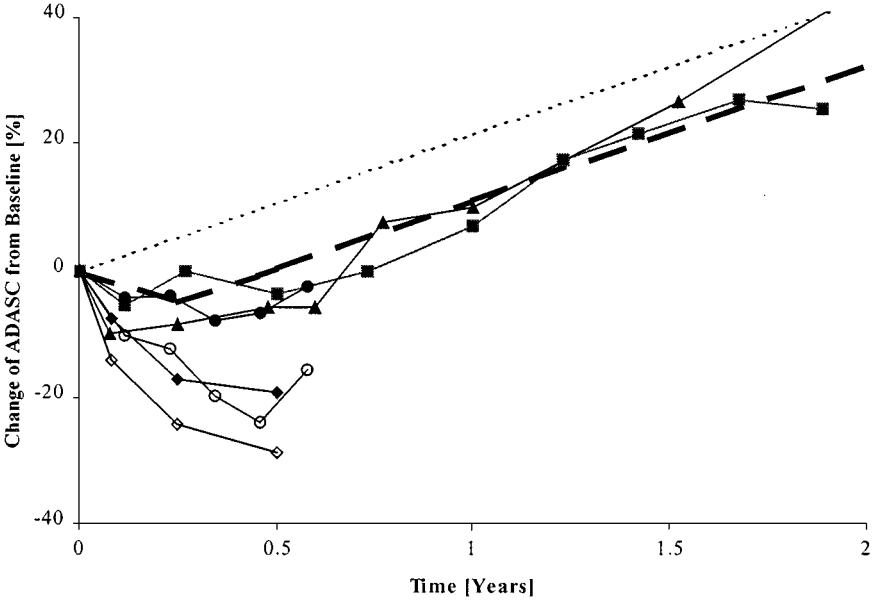

Figure 7 Observed effects of treatments in Alzheimer's disease using Alzheimer's Disease Assessment Scale—Cognitive (ADASC) as a marker. Solid lines indicate treatment groups. Closed diamonds, idebenone (90 mg/day) (109); open diamonds, idebenone (270 mg/day) (109); closed squares, donepezil (110); closed triangles, eptastigmine (111); closed circles, tacrine (112); open circles, tacrine + oestrogen (112). Dotted line indicates predicted natural disease progression (28). Dashed line is predicted response to treatment with tacrine (28).

(117–119). Nevertheless, these studies claimed that the difference in rate of decline in FEV1 was not significantly different between the treatment and the control groups.

Bronchodilator The effects of a smoking intervention and the use of an anticholinergic bronchodilator (ipratropium bromide) in patients with chronic obstructive pulmonary disease has been studied (120). A 27.6 ml increase in FEV1 was shown in the group receiving ipratropium bromide compared with the placebo group (ipratropium bromide, 38.8 ml; placebo, 11.2 ml). The effect of ipratropium bromide is symptomatic, as the rate of decline in FEV1 was similar between the two groups (ipratropium bromide, 52.7 ml/year; placebo, 52.3 ml/year).

Smoking Effect When comparing the rate of decline in FEV1 between the smoking intervention group (without bronchodilator) and the no-intervention group, a similar rate of decline in FEV1 was seen (no intervention, 56.2 ml/year; smoking intervention, 52.3 ml/year). However, the effect of smoking intervention differed when comparing the rate of decline between sustained quitters and continuing

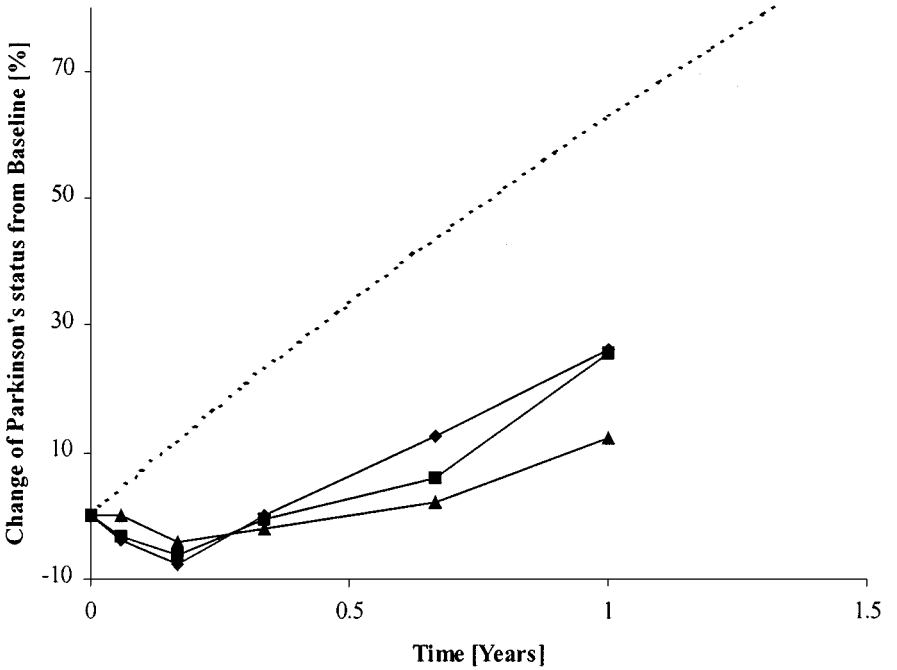

Figure 8 Effect of selegiline on natural disease progression in Parkinson's disease. Dotted line predicts the exponential change in bradykinesia score (derived from Unified Parkinson's Disease Rating Scale) in patients with prior treatment of levodopa/carbidopa and/or bromocriptine (19). Solid lines indicate selegiline-only treatment groups status at time zero. Closed diamonds, Webster Rating Scale (115); closed triangles, Northwestern University Disability Scale (115); closed squares, Columbia University Rating Scale (115).

smokers (continuing smokers, 63 ml/year; sustained quitters, 34 ml/year) over the 5-year study period. The slowing down in the decline of FEV1 suggested that smoking cessation has a protective effect similar to a protective drug treatment effect or, conversely, that smoking accelerates the natural progression.

Diabetic Nephropathy

All studies of the rate of disease progression in diabetic nephropathy have assumed a linear model. Table 10 shows the rate of disease progression in diabetic nephropathy and the treatment effect of ACE inhibitors (17, 23–25, 121–123). ACE inhibitors slow the decline of glomerular filtration rate in diabetic nephropathy (range 0.98–9.2 ml/min/year) compared with the placebo control group (range 4.55–13.4 ml/min/year). Laffel et al (25) reported an increase of 0.9 ml/min/year in glomerular filtration rate after 2 years of treatment with captopril. The ability to alter the rate of disease progression suggests that ACE inhibitors have a protective drug effect rather than a symptomatic drug effect.

TABLE 9 Rate of disease progress in respiratory disease and effect of drug treatment using FEV1 as a biomarker[a]

Ref.	Treatment	Baseline FEV1 (liters)	Rate of progression (Liters/year)	Rate of progression (%/Year)	Duration (years)
117	—	2.39	−0.0496	−2.08	3
	Budesonide	2.36	−0.046	−1.95	3
118	—	2.29	−0.064	−2.79	3
	Beclomethasone	2.38	−0.033	−1.39	3
119	—	1.9	−0.060	−3.16	2
	Budesonide	2.16	−0.030	−1.39	2
	Budesonide + prednisolone	1.86	−0.040	−2.15	2

[a]FEV1, force expiratory volume in 1 s.

Osteoporosis

The change in bone mineral density with different drug treatments has been described recently (124). The common drug treatments of osteoporosis can be classified into different groups: hormone replacement therapy such as estrogen; selective estrogen receptor modulators such as tamoxifen; bisphosphonates such as alendroate and pamidronate; and calcium supplementation. Figure 9 shows the effects of different drug treatments on bone mineral density in osteoporosis (125–133). A symptomatic treatment effect rather than a protective effect is seen in studies with trial durations longer than 1 year. Pors Nielsen et al (133) compared

TABLE 10 Rate of disease progress in diabetic nephropathy and the treatment effect of ACE inhibitors

Ref.	Treatment	Baseline GFR[a] (ml/min/1.73 m^2)	Rate of progression (ml/min/year)	(%/Year)	Duration (years)
23	Enalapril	46 ± 14	−2.0	−4.35	3
121	—	83	−5.7	−6.87	5
24	—	79 ± 35	−13.4	−17.00	4
	Captopril	84 ± 46	−9.2	−11.00	4
17	Captopril	98 ± 5	−4.4	−4.48	10
25	—	81 ± 3	−4.9	−6.05	2
	Captopril	79 ± 3	0.9	1.1	2
122	Lisinopril	67 ± 18[b]	−0.98	−1.5	6
123	—	110 ± 15	−4.55	−4.1	3
	Lisinopril	113 ± 16	−1.33	−1.18	3

[a]GFR, glomerular filtration rate.

[b]Values converted from milliliters per second per 1.73 m^2.

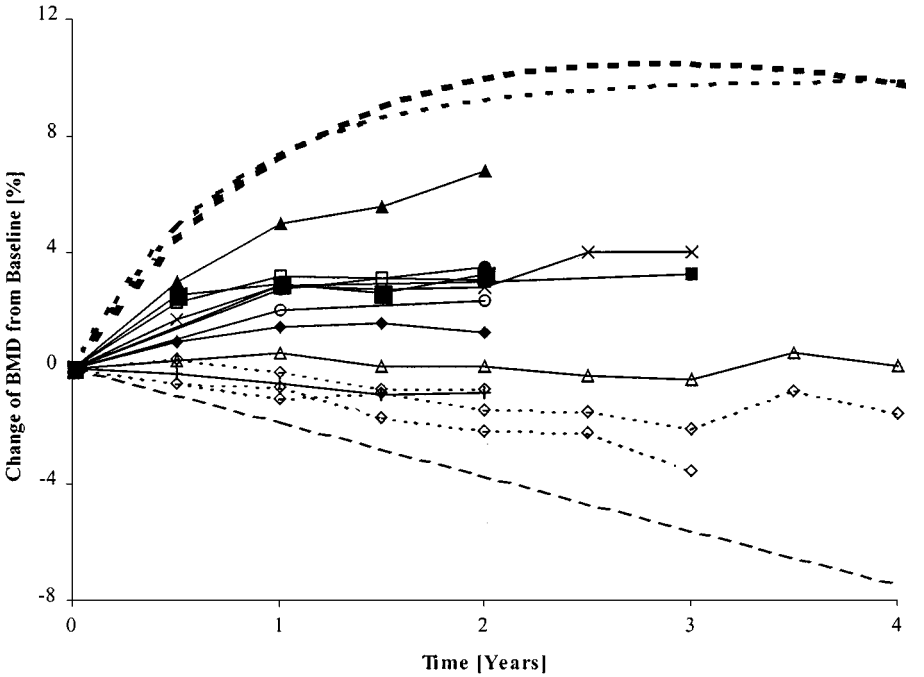

Figure 9 Effects of symptomatic treatments in osteoporosis using bone mineral density in lumbar spine as a marker. Dotted lines indicate placebo groups. Solid lines indicate treatment groups. Closed diamonds, tamoxifen (126); open squares, raloxifene (60 mg/day with calcium) (128); small closed squares, raloxifene (120 mg/day with calcium) (129); large closed squares, raloxifene (150 mg/day with calcium) (128); x, estrogen/progestin (125); open circle, alendronate (2.5 mg/day) (130); closed circle, alendronate (5 mg/day) (130); closed triangle, pamidronate (150 mg/day with calcium) (131); +, calcium (500 mg/day) (132); open triangle, calcium (1000 mg/day) (127). Heavy dashed lines, predictions of estrogen/progestin effect using exponential model with (heavier) and without (lighter) linear decline of bone mineral density (133). Light dashed line, prediction of natural disease progression by (133). BMD, bone mineral density.

an exponential model with and without a linear component to describe the change in bone mineral density seen in response to estrogen in postmenopausal women (heavy dotted lines). The linear decline in bone mineral density with no drug treatment is illustrated as a dashed line. A similar study was performed by Hart et al (134), with a follow up period of 10 years. Unfortunately, these authors only present graphs of their model without numerical parameter values.

In general, our review of a range of diseases and treatments indicates that the percentage of change from baseline and the rate of progression has a wide range due to different markers, types of treatment, and duration of study. Generally, the shorter the duration of study, the greater the rate is. This seems likely to be due to symptomatic effects rather than protective effects. The current two-point method of computing rate of progression has a critical limitation, which is the assumption

of a linear change over time. This leads to an inability to distinguish protective drug effects from symptomatic ones.

A serious limitation of most models described in the literature is the use of the naïve pooled approach, which makes it hard to assess the importance of covariates, such as the duration of drug therapy or age at onset. A population-based approach that accounts for individual trajectories is essential for understanding the differences between individual responses.

FACTORS INFLUENCING RATE OF DISEASE PROGRESSION

The variability in predicting individual time course of disease progression may be explained in part by covariates such as age of onset, duration of symptoms, gender, initial disease severity, etc. In this section, two common covariates, age of onset and gender, are discussed.

Age of Onset

Several factors have been thought to play a role in determining the rate of disease progression in Parkinson's disease. They are age, duration of drug treatment, gender, age of onset, and levodopa dosage. Among these factors, age of onset seems to be the most notable. A study done by Diamond et al (135) compared 54 parkinsonian patients grouped according to age of onset. They illustrate an increased rate of progression with increased age of onset by using the University of California Los Angeles Scale (UCLA) disability score as a clinical marker, but no specific values were presented. A faster rate of disease progression in patients with older age of onset has been confirmed by others (40, 41, 136–138). A similar finding was also seen in Alzheimer's disease (14, 60). In addition, age of onset may also have a role in determining the degree of drug improvement. In the study by Diamond et al (135), the degree of drug improvement decreased with increased age of onset. The improvement from baseline in the UCLA disability score after 6 years of levodopa treatment was 39.7, 38, and 7.1 points for groups with age of onset <50, 50–59, and >60 years, respectively.

Gender

Gender is another notable cofactor in altering the rate of disease progression in degenerative diseases. It has been suggested that women have a lower risk (0.40) than men of neurodegenerative disorders (74). This is thought to be caused by differences in hormonal state and by the menstrual cycle in premenopausal women (139). In osteoporosis, a higher risk of bone fracture is found in postmenopausal women, but this is much more clearly linked to loss of estrogen. In other studies of gender differences on disease progression rate, there have been inconsistent results (57, 60, 140–142).

CLINICAL TRIAL SIMULATION

Disease progression can only be investigated by longitudinal studies. However, longitudinal studies have practical difficulties, such as expense and high patient drop-out rates, for reasons that may be linked to the disease progression itself. Studies with high patient drop-out rates should be analyzed with different approaches when attempting to recover the lost information. Ali & Siddiqui (143) have performed a simulation study to compare different analysis methods in handling missing data results from patients dropping out.

A promising technique aimed at helping the design of such clinical trials has been proposed. This is the application of clinical trial simulation (144, 145). The aim of clinical trial simulation is to reduce the cost and shorten the drug development process by helping to design a more informative clinical trial. The power of clinical trial simulation is the ability to test a planned trial and preview the possible outcomes before actually carrying out a trial. This enables an inadequate design to be improved. A few studies have demonstrated the ability to explore designs of clinical trials through the application of clinical trial simulation (146–148).

SUMMARY

The current means of studying disease progression in degenerative diseases have several major shortcomings. The methods for describing disease progression are often simplistic and limit the information the data can provide. Failure to identify between-subject variability prevents understanding of individual time course and response to treatment. The use of hierarchical modeling can overcome these shortcomings through its ability to describe the disease time course and through estimating both within- and between-subject variability. The significance of modeling disease progression is in describing not only the time course of disease but also the effects of treatment. Incorporation of pathophysiological understanding with pharmacological concepts holds the promise for developing better drugs and describing their effects more precisely.

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