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A REVIEW OF DISEASE PROGRESSION MODELS OF PARKINSON'S DISEASE AND APPLICATIONS IN CLINICAL TRIALS

Charles S. Venuto, PharmD^{#1,2}, Nicholas B. Potter^{#1}, E. Ray Dorsey, MD, MBA^{1,2}, and Karl Kieburtz, MD, MPH^{1,2}

¹ Center for Human Experimental Therapeutics, University of Rochester, Rochester, NY, USA

² Department of Neurology, University of Rochester, Rochester NY USA

[#] These authors contributed equally to this work.

Abstract

Quantitative disease progression models for neurodegenerative disorders are gaining recognition as important tools for drug development and evaluation. In Parkinson's disease [PD], several models have described longitudinal changes in the Unified Parkinson's Disease Rating Scale [UPDRS], one of the most utilized outcome measures for PD trials assessing disease progression. We conducted a literature review to examine the methods and applications of quantitative disease progression modeling for PD using a combination of keywords including “Parkinson disease”, “progression”, and “model”. For this review, we focused on models of PD progression quantifying changes in the total UPDRS scores against time. Four different models reporting equations and parameters have been published using linear and nonlinear functions. The reasons for constructing disease progression models of PD thus far have been to quantify disease trajectories of PD patients in active and inactive treatment arms of clinical trials, to quantify and discern symptomatic and disease-modifying treatment effects, and to demonstrate how model-based methods may be used to design clinical trials. The historical lack of efficiency of PD clinical trials begs for model-based

Corresponding Author and Reprint Requests: Charles S. Venuto, PharmD, University of Rochester Medical Center, CHET/CTCC, 265 Crittenden Blvd., CU 420694, Rochester, NY 14642-0694 USA, 585-276-5622 phone, Charles.Venuto@chet.rochester.edu.

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simulations in planning for studies that result in more informative conclusions, particularly around disease modification.

Keywords

Parkinson's disease; disease progression; pharmacometrics; disease model; UPDRS

Introduction

Characterizing the long-term progression of Parkinson's disease [PD] and the rate of that clinical progression are among the highest clinical research priorities according to the National Institute of Neurologic Disorders and Stroke Parkinson's Disease 2014 Research Recommendations (1). These needs can be directly addressed through quantitative disease progression models, which are mathematical representations of the time course of change in disease status. Longitudinal data from clinical trials and observational studies are used to build these models in order to better understand and predict disease trajectories, both in the absence and presence of pharmacologic treatment(s) (2). Additionally, disease progression models can be used to correlate clinical states with structural or chemical biomarkers that also change with disease; and, facilitate in the identification of risk factors, demographics, and other covariates that affect baseline disease status and the rate of disease progression (3-5).

For chronic progressive diseases like PD, a more precise understanding of the changes in disease course as it relates to treatment effects and patient-level factors would help in the design and efficiency of clinical trials. In particular, trials designed to detect disease modifying effects could be made more informative through the application of clinical trial simulations, which require a quantitative understanding of disease progression. Through these simulations, different hypotheses can be tested to predict a range of possible outcomes (6-8). For example, an Alzheimer's disease (AD) model is available for running simulations that predict sample sizes and power based on alternative trial designs, treatment effects, and patient populations (8). Although disease progression models of PD have been published, their developments lag in comparison to other disease areas with respect to consensus and utility (e.g. Alzheimer's disease, HIV, Hepatitis C) (9-15).

Here, we review the literature on quantitative PD progression models. We focus on describing changes in scores on the total Unified Parkinson's Disease Rating Scale [UPDRS] because it is the most popular outcome in clinical trials for PD. Also, the UPDRS is a sensitive indicator of motor progression and has been shown to have sufficiently high interrater reliability, at least in controlled clinical trial settings where the majority of modeling data come from (16, 17). Therefore, it is important to review attempts to model the progression of total UPDRS by highlighting the major strengths and potential shortcomings of each. Although modeling alternative outcome measures are also discussed, it is not the focus of this review. We conclude with a discussion about improvements and potential new directions.

Literature Search

A search of relevant terms on PubMed was conducted using a combination of keywords (Parkinson disease; progression; and model), and references of publications of interest. The search included articles published from January 1, 1987 through February 1st, 2016, and produced 459 articles. Articles were reviewed by authors, CV and NP. The primary focus of this review was restricted to those articles which used equations developed from longitudinal data to report parameter values representative of rates of change of PD status (e.g. change in disease status units/change in time). Of the 459 articles, 16 appeared to meet those criteria. After further evaluation, four publications became the primary focus of this review because they reported total UPDRS as the primary modeling outcome, an equation for the model, and model parameter values. Based on previous models developed for clinical trial simulations in other disease areas, inclusion of each these were considered key criteria for advancing PD clinical trial simulations (8-15). Significant papers about advances in modeling for other illnesses were found in a less formal manner and are used for comparison and inspiration throughout.

Modeling the Course of UPDRS Scores

Guimaraes et al. Model

Guimaraes and colleagues modeled UPDRS progression in clinical trial participants requiring symptomatic treatment (18). The goal was to model the magnitude of symptomatic treatment effects and the speed at which maximum effects were achieved with respect to longitudinal UPDRS score changes. Data came from two randomized, double-blind, controlled trials: one investigating pramipexole or levodopa/carbidopa as initial treatment for early PD patients for a study duration of 23.5 months, however, only the levodopa/carbidopa arm data were made available for modeling ($n=150$) (19); and, a trial of ropinirole ($n=168$) or bromocriptine ($n=167$) treatment for early PD patients for treatment up to 36 months (20). The former trial was conducted through the Parkinson Study Group (PSG) in North America, while the latter was conducted in Europe, Israel, and South Africa. All UPDRS scores were measured in the “on” state. Evaluations occurred approximately every 3 months for the levodopa/carbidopa data, and at months 1, 3, 6, 12 and every 6 months thereafter for the ropinirole and bromocriptine data.

To model the progression of disease and the effects of initiating symptomatic therapy on UPDRS scores, Guimaraes used the difference of two functions: an increasing linear function to describe the course of disease progression and a monomolecular growth function to describe the bounded benefit of symptomatic treatment (Table 1). This model is appealing because the parameters of the function are relatively easy to interpret. The parameters reflect the first UPDRS score at time of initiation of observation which coincided with initiation of symptomatic therapy, S_0 ; the constant rate of change in UPDRS over time, α ; the maximum clinical benefit, (i.e. UPDRS score decrease) that an individual experiences with symptomatic treatment, S_{sym} ; and the rate constant related to the time at which maximum symptomatic benefit is achieved, r . (Table 2 contains a summary of all notation.) Separate parameter values for the trials were estimated, such that progression rates and short-term treatment effects could be quantified for each treatment arm (Table 1).

There were some limitations to the data and approaches used for modeling PD progression. The data sources included only those patients in the early-to-middle stages of disease requiring symptomatic treatment (approximate disease durations of 2 years on average for enrolled participants). Therefore, earlier pre-treatment and later post-treatment evolutions of disease status cannot be described by this model. For instance, a more rapid progression of motor dysfunction may be present in the earlier stages of disease which might not have been captured with these data (21). Abbreviated study periods were also likely not long enough to track a complete evolution of UPDRS changes in response to treatments over time. Once dopaminergic therapy is initiated, there follows an average 40% decrease in total UPDRS. The UPDRS then stabilizes over the next 1 to 2 years and gradually returns to pretreatment levels by about year 5 (22). Thus, brief periods of observation of a slowly evolving disease may explain why a linear model adequately described the progression of UPDRS scores, as other nonlinear functional forms (quadratic and exponential models) did not improve the fit of models to the data. Therefore, both earlier and later phases of disease would need to be explicitly modeled and different functional forms tested, for a more complete description of disease progression and treatment response.

Additionally, approximately one-third ($n=110$) of trial participants randomized to ropinirole or bromocriptine were being treated with selegiline at baseline but its treatment effects were not explicitly quantified or accounted for in the model. Selegiline treatment may slow the progression of symptoms and introduce nonlinearity to the disease course, thus its impact on progression of symptoms remains controversial (23-25). The dosages of levodopa/carbidopa, bromocriptine, and ropinirole were also not accounted for in the models even though different doses and combinations of medicines were used throughout (19, 20). A more robust model might have been possible if the effects of all active pharmacologic agents and doses were explicitly modeled.

A significant obstacle in detecting meaningful clinical slowing of disease progression is the confounding effect of symptomatic benefits of PD treatments in the interpretation of trial results. By modeling the rate at which maximum symptomatic therapy is achieved and fully apparent, trials can be designed around these estimates and enroll treated patients after symptomatic effects are washed-in and motor decline is at a steady worsening. The Long-term Study-1 [LS-1] conducted by the NINDS Exploratory Trials in Parkinson's Disease [NET-PD] employed this approach, citing the Guimaraes model estimate of 6 months to attain maximum symptomatic effect. Thus, measurement of the first disease status outcomes was delayed until 3-6 months after participants initiated dopaminergic therapy (26).

Holford et al. Model

Holford et al. tested linear and nonlinear models to fit UPDRS scores from PD patients originally enrolled in the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism [DATATOP] clinical trial (27). The DATATOP trial was conducted in North America by the PSG and is one of the largest and longest prospective studies of therapeutic interventions for PD (24). The original cohort enrolled 800 de novo patients who had average baseline disease duration of 2.1 years (23, 28). Additional extension studies of the DATATOP cohort resulted in nearly 8 years of follow-up, with an average length of 5 years (29-32). There were various

pharmacologic treatment combinations possible over the course of study, including randomized deprenyl, tocopherol, or placebo, and as-needed levodopa/carbidopa, bromocriptine, and pergolide. Total UPDRS scores were measured in the “off” state at baseline, months 1 and 3, and then at approximately 3-month intervals. The goal of modeling these data was to explicitly quantify the short-term and long-term treatment effects of each medication on the underlying changes in disease status.

Hierarchical nonlinear mixed effects models were used to test functions for describing UPDRS changes by estimating disease progression parameters and their variability. A simple linear model defined by a baseline disease status parameter and slope parameter was initially tested and used as comparison against asymptotic exponential, logistic, and two segment linear models. An individual's antiparkinsonism drug regimen, including dose and duration of therapy, were also used to model UPDRS progression. Thus, pharmacodynamic models relating dose and symptomatic effects were incorporated. The functions used to describe these relationships depended on the drug; for levodopa, a classic sigmoid $E_{\max}$ model (i.e. Hill equation) related dose to treatment effects, while a linear model with a constant slope was used to describe the effects of bromocriptine, pergolide, deprenyl, and tocopherol. Exponential functions based on daily dosages of drugs were also entered into the disease progression model to test for disease modifying effects on UPDRS progression. In contrast to the Guimaraes model, combinations of treatments were also tested.

It was empirically determined that asymptotic, rather than linear models, were more appropriate in describing the longitudinal UPDRS score changes over an extended period of time while accounting for pharmacologic effects of PD medications. In particular, the logistic function provided the best overall fit to the data as determined by minimizing the value of the objective function and the ability of the model to describe the time course of UPDRS changes for each individual. Holford et al. refer to their equation as a Gompertz equation which differs in terms of mathematical nomenclature, but is highly related to their model of the logistic differential equation.

The logistic curve is sigmoidal and among the most popular equations for describing bounded growth (33). It is characterized by a slow rate of growth or progression in the early and late stages with a maximal slope attained in between. This flexibility permitted the logistic function to fit UPDRS scores reasonably well in the presence of different treatment regimens during the first year of study. When running simulations with the model, UPDRS scores were sometimes over-estimated beyond a year compared to the observed scores. It was hypothesized that this divergence may have been due to more severely ill participants dropping out of the study over time, thus resulting in overall lower observed versus model-predicted UPDRS scores. Dropout effects can be included and would need to be added to produce a more robust model for predictive purposes (34-36).

This logistic model was a new way to characterize PD progression. The U.S. Food and Drug Administration (FDA) has since endorsed a logistic model for a clinical rating scale of cognition [ADAS-cog] for Alzheimer's disease patients (8). The model parameters are different than those of a linear model and may be unfamiliar to some. The parameters describing the logistic model are the progression time constant, T_{prog} ; the steady-state

disease status, S_{ss} ; as well as baseline disease status, S_0 (Table 2). The T_{prog} parameter affects the maximum slope and can be used to derive the time half-way between the baseline and maximum disease status, S_{ss} .

A change in T_{prog} or S_{ss} upon the initiation of treatment should indicate modifying effects, meaning that the progression of disability is slowed in patients with Parkinson's (Figure 1). Although this could be caused by neuroprotection, it is misleading to say that one can use a model representing a clinical outcome to test for changes in neurodegeneration. The converse, however, seems plausible though unproven: if a drug is neuroprotective or causes some other beneficial change in pathology, then the effect on the model will be a change over time of the parameters S_{ss} and T_{prog} . The disconnection between clinical progression and underlying pathology is apparent in the results from Holford's model. Levodopa, deprenyl, bromocriptine, and pergolide were all found to have significant effects on T_{prog} , suggesting functional protective effects of UPDRS progression yet unknown effects on underlying disease processes. For example, studies examining the effects of levodopa on PD pathology remain inconclusive in terms of protective effects on dopamine neurons (37).

Bhattaram et al. and Lee & Gobburu Models

There have been several publications from individuals at the Division of Pharmacometrics at the FDA advocating the use of disease modeling and simulation for drug development and regulatory decisions in PD (38, 39). Bhattaram and colleagues developed models of PD progression using placebo data from four unspecified clinical trials with durations of 3 to 18 months (38). Participants from these studies did not require symptomatic treatment and were early in the course of disease. The main objective of modeling disease progression was to use the parameter estimates for clinical trial simulations to construct a method of testing for disease modification in a delayed start clinical trial design.

Similar to Guimaraes et al. (18) and Holford et al. (27), nonlinear mixed effects models were fit to derive disease progression parameters. It was assumed that covariates did not influence rate of disease progression. Bhattaram et al. persistently advocate for the assumption of linearity for natural progression, up to five years. Thus, other models were not tested, which does raise some concern about the validity of the assumption. Linearity, even with super-added curves, might not be the best approach because of how varied PD progression can be over time (28, 40-44). A monomolecular growth model for placebo effect was used, which was the function Guimaraes et al. chose for maximum symptomatic effects of active agents (Table 1). The rate constant influencing the time to reach maximum placebo effect, r , was unreliably estimated indicating that the model would not perform well for describing and simulating placebo effects. Choosing a monotonic function is interesting and disputed, because it relies on the placebo effect approaching a maximum and constant benefit as time increases. Further discussion about handling the placebo effect can be found in the "What can models do for PD, right now?" section.

Using the estimated disease progression parameters and assumed drug effects, simulations of clinical trials were performed. The simulated trial design was a 72-week delayed-start study with placebo and active control phases lasting 36 weeks each. Dropout effects were included to account for missing data from participants needing symptomatic treatment based on

UPDRS score changes and randomly due to adverse events. Mixed effect model repeated measure analysis was used to analyze the longitudinal changes of UPDRS scores after 9 to 12 weeks randomization. These post-randomization times corresponded to hypothetical (rather than modeled) peak effects of placebo or symptomatic treatment thus permitting a comparison of UPDRS slopes. The simulations were able to demonstrate that their model-based analysis had sufficient power to detect potential disease-modifying effects through total UPDRS changes and slope comparisons.

Lee and Gobburu modeled UPDRS as change from baseline at each visit, rather than raw scores, using linear and monomolecular functions analogous to the Guimaraes et al. and Bhattaram et al. models (Table 1) (39). The focus of their paper was to use Bayesian inference to quantify disease progression parameters; that is, use prior estimates of UPDRS changes from one clinical trial to quantify UPDRS changes from another trial in order to limit the uncertainty in parameter estimates. The data sources used were a dose-ranging, double-blind, 40-week trial of levodopa/carbidopa in early de novo PD patients (n=361), which served as historical data for estimates of prior distributions of the parameters (45); and, a fixed-dose, double-blind, 26-week study of rasagiline in early de novo patients (n=404), which served as the observed data to update the posterior parameter estimates (46). Placebo and symptomatic effects of dopaminergic therapies were modeled separately but different dosages were not accounted for. Also, an unexplained assumption in the model was that the rate constants to attain maximum placebo effects and symptomatic effects of treatment were equal.

With Bayesian modeling, assumptions have to be made regarding the degree to which one “borrows” information from the previous data source to make inferences from. Therefore, subjectivity is introduced which is often a criticism to this approach (47). In this paper, the influence of the degree of borrowing information was tested by varying a scalar parameter to different fixed values. Markov Chain Monte Carlo simulations estimated the model parameters and it was observed that their precision improved with the use of prior information.

The idea of applying Bayesian statistical methods to quantifying disease progression and drug effects is attractive for making model-based inferences and decisions when data might be limited. It is also a strong way to utilize prior information. For the Lee and Gobburu model, employing Bayesian inference provided a novel way to characterize disease progression and compare the efficacy of the two drugs. Both modeling exercises from the FDA employees exhibit the potential utility of modeling total UPDRS scores for planning clinical trials. Furthermore, these should indicate the receptiveness of such model-based methods for PD at the FDA, if validated.

Modeling the Course of Alternative PD Outcomes

Modeling PD progression has not been limited to total UPDRS scores but examples of other outcome measures are less consistently available in the literature. Progression of the motor score of the UDPRS (part III) was modeled recently using data from over 2000 PD patients followed for nearly a decade (48). A linear mixed effects model was used to characterize

longitudinal changes in motor progression and adjusted for age at diagnosis, gender, subtype (akinetic rigid vs. tremor dominant), cognitive impairment, and baseline motor scores, but concomitant symptomatic treatments were not accounted for. Motor progression was found to vary substantially at different points in time, ranging from 0.67 to 3.96 units/year change from baseline. The overall evolution of motor scores followed a non-linear pattern. These general findings are similar to the total UPDRS changes modeled by Holford et al. by providing further evidence that progression is non-linear over longer durations of follow-up (27).

Progression of the non-motor symptoms of PD like neuropsychiatric symptoms, sleep disorders, cognitive dysfunction, autonomic and sensory symptoms, and others are also important to quantitatively understand. For example, several papers have focused on modeling cognitive decline in PD patients using mini-mental state examination (MMSE) scores (49, 50). Aarsland and colleagues used two linear functions that met at an inflection point reflecting a change from a stable period to a more dramatic change in rate of cognitive decline (2.8 points/year) (49). The inflection point did not occur until approximately 13 years into disease. In contrast, Vu et al. used a single linear model to describe 8 years of longitudinal MMSE scores with minimal rate of decline (~ 0.006 units/year) (50). The differences between these models indicate that long follow-up times are needed in order to observe significant declines in MMSE scores, and the appropriate functions used are dependent on these durations of time.

Modeling a biological measurement has also been done with assessments of presynaptic dopaminergic integrity using positron emission tomography (PET) measurements (51). Supposing these measurements are appropriate as biomarkers, the analysis done by Kuramoto et al. was able to suggest that pathophysiological changes might occur up to 17 years prior to symptomatic onset in some patients. Initial regression models at least four years prior to Kuramoto's paper lend support to the claim that the measurements could serve as a biomarker (21). Furthermore, those without PD showed linear progression while those with PD exhibited exponential progression on PET imaging measurements. Similar pathologic patterns of nonlinear progression were found in other PET imaging analyses of PD patients (52, 53). Collectively, these types of studies provide a more mechanistic understanding to the nature of neurodegeneration in PD unlike clinical scale assessments.

An ongoing development in Parkinson's research is the investigation of potential biomarkers. The FDA issued a letter of support to the Coalition Against Major Diseases to further investigate molecular neuroimaging of the dopamine transporter [DAT] (54). As DAT is studied, the necessary data to create a model of this potential biomarker will be generated. If the modeling approach is utilized by those studying potential biomarkers, it is possible to have a reasonable model ready as soon as the biomarker itself is available. Thus, modeling potential biomarkers is an approach that could be strongest as they are under investigation in order to quantitate and compare their temporal evolution with traditional clinical measures of disease severity.

What can models do for PD, right now?

The primary usage for the models thus far is application in drug development and clinical trial design and planning. An increase in the efficiency of clinical trials is sorely needed from human and financial cost perspectives (55). In each PD model paper, the authors demonstrated how disease progression models could be incorporated into designing or analyzing clinical trials. For example, some of the authors use the models to generate data to simulate a clinical trial (38, 39). Because the models reflect data and there is some knowledge of their error, one can simulate many trials to calculate power, sample sizes, and to estimate treatment effects of pharmacologic agents on disease progression. While there is no publically available trial simulation tool as there is in Alzheimer's disease (8), the present modeling results can be of interest to those who design studies.

An entire section of the Guimaraes et al. paper discusses the implications of modeling on sample size for clinical trials. This discussion was within the context of an endpoint-based outcome following the wash-in of symptomatic therapy. However, it has recently been argued that endpoint-based clinical trial analysis may have been one important reason for the failure of previous studies that sought to assess disease modification (38). Some have pressed for quantitative modeling over the entire time course of the clinical study, with separation of three concomitant events – that is, disease progression, symptomatic effects, and disease modifying properties – to improve trial design and analysis (56). For these analyses, sample size calculations using simulations could be made with updated models.

Another implication of the models is on the understanding of pharmacodynamic wash-in and wash-out effects of treatment. In particular, how long it takes for full symptomatic effect to appear and disappear, respectively. One can use a model to compute values for both pharmacodynamic processes of particular interventions. The method of detecting divergence of slopes from the Bhattaram et al. paper using a delayed-start trial design relies on knowledge of wash-in effects. A real-world example of this was the ADAGIO study, which assumed subjects had attained maximum symptomatic effect in 12 weeks (57). Most of the models represent the symptomatic effect as a monomolecular curve, sometimes called a bounded exponential curve. This means that we can calculate the amount of time needed for pharmacodynamic wash-in to occur for any pharmacologic intervention, and design trials based on these estimates. On the other hand, understanding of the complete wash-out of symptomatic effects of levodopa was required in the ELLDOPA trial (Early vs. Later L-DOPA) which tested the disease modifying potential of levodopa (45). Simulations using Holford's model predicted wash-out time of at least 25 days was needed rather than the 14 days the trial actually used (58).

Inferences can also be made about the placebo effect in PD. Discussion about how long the placebo effect lasts remains controversial: are the effects of placebo confined to the earliest weeks of a trial, or do the effects stabilize and remain throughout? It has been reported that the placebo response remains apparent up to at least 6 months after initial follow-up with no evidence of “wearing-off” or early placebo effects (59, 60). In the models thus far, the monomolecular function is used to describe placebo and symptomatic effects (Equation 1). However, this usage relies on the assumption that the placebo effect never wears off.

Parkinson's researchers should look to the progress made in Alzheimer's disease models for an alternative approach, as the Bateman function may be more appropriate (Equation 2) (61, 62). Parameter interpretations can be found in Table 2.

$$\text{monomolecular}(t) = \beta \left(1 - e^{-r_a t}\right) \quad \text{Equation 1}$$

$$\text{bateman}(t) = \beta \left(e^{-r_e t} - e^{-r_a t}\right) \quad \text{Equation 2}$$

Notice that the two functions are identical except for one parameter. If $r_e=0$, then it is equal to the monomolecular function. When $0 < r_e < r_a$, then the placebo effect 'wears off' according to the model. The algorithms that fit the equation to the data are responsible for picking all parameters. This implies that the wearing-off or stabilizing of the placebo effect is determined from the actual data. Not only is modeling as close to measuring the placebo effect as any researcher can come, but there are minimal assumptions made about the nature of the effect. Figure 2 depicts the shape of these functions according to the actual models and to their respective outcome measures (means of the reported or accessed parameters were used to generate the figure). The parameter, r_e , is not negligible. Therefore, the placebo effect of ADAS-cog wears off according to the AD model, likely in a longer time span than is sometimes assumed. However, one model's implication on the nature of the placebo effect (e.g. magnitude and time course) in AD does not necessarily equate to the placebo effect in PD with a different outcome measure. Therefore, this observation in ADAS-cog scores should be tested with models specific to PD and the UPDRS.

Future Directions

The use of disease progression models in the drug development process will continue to expand as additional models are developed and the benefits of such assessments become more widely recognized. As the understanding of various aspects of PD improves and new datasets become available, these models will require adjustment to reflect an increased understanding of disease. Therefore, efforts should be aimed at reevaluating PD progression models by updating and testing them with additional data that have become available since their creation. In order to do this, the entire PD clinical trial research community needs to be made more aware of these models so that they can contribute to their refinements and implementation as clinical trial planning tools.

Another data source that will soon become a viable option for modeling comes from telemedicine and remote monitoring. PD clinical trials of the future might move away from clinician-based rating scales to more objective and sensitive measures of disease by using remote sensors (e.g. smartphone applications, wearable technologies) (55). However, before implementing these technologies, it will be necessary to develop methods that can interpret these large, continuous data generated from such devices, and compare how these measures relate to the current standard markers of disease progression. Model- and algorithm-based

techniques to quantitatively evaluate and compare these expansive datasets will need to be developed in order to draw appropriate conclusions from them. Data scientific methods, like big data analytics, machine learning and ensemble methods have been particularly useful for making predictions. For example, the DREAM-Phil Bowen ALS Prediction Prize4Life challenge was a crowdsourcing competition to create algorithms that could predict future scores on a rating scale for amyotrophic lateral sclerosis (63). All of the simple regression based approaches were outperformed by random forest and Bayesian trees for predicting progression. These approaches approximated individuals' future disease severity scores rather than generating data that resemble scores from a sample of patients, which has been the statistical approach reviewed in this paper. Although these algorithms may not accomplish the goal of simulating a trial, their ability to make predictions could be used in other ways for aiding clinical trial designs, like stratification tools and enrichment strategies. Or these predictions could be applied to having a virtual control arm for some studies in which each patient in the treatment arm is compared with a sufficiently accurate prediction made from their baseline disease status, early progression pattern, and demographic information.

Not only do models have potential in aiding the design of clinical trials, they might also be useful for guiding clinicians in projecting progression and optimizing treatment strategies for individual patients. The algorithms that won the ALS Prize4Life competition consistently outperformed clinicians in prognostics. For PD, prognostic prediction is challenging and clinicians often feel they lack the necessary tools to provide their patient with accurate prognostic information. Therefore, disease progression models of PD may uncover unknown markers of progression for clinicians to incorporate into routine patient assessments or eventually have a "tool" by which key patient factors are quantified and prognosis predictions provided. None of these techniques have been developed with data for PD to date.

Conclusions from Previous Model-based Experiences

The models developed for PD have thus far been descriptive. They have focused on summarizing data primarily using regression-based techniques for use in making decisions such as those involved in planning clinical trials. The models reviewed here tested for symptomatic effects and found that nonlinearity in progression is present when these therapies are introduced. After accounting for symptomatic effects, however, linear and nonlinear functions have been used to characterize total UPDRS score changes. Because there is a limited understanding of the key molecular events causing neurodegeneration in PD, mechanistic approaches like systems biology and systems pharmacology modeling have not been employed. Nevertheless, development of empirical disease progression models of PD offer important knowledge for future therapeutic development. As emphasized by the FDA in their Critical Path Initiative, the most immediate and tangible benefits of disease modeling is likely in trial simulations, which will modernize PD clinical trials (64).

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Authors' Roles

Charles Venuto was responsible for the conception, organization, and execution of this review, as well as performing the literature search, analyzing and interpreting data, and writing the first draft.

Nicholas Potter was responsible for the organization and execution of this review, as well as performing the literature search, analyzing and interpreting data, and updating the various drafts of the paper.

Karl Kiebertz was responsible for the conception and organization of this review, as well as reviewing and critiquing the various drafts.

Ray Dorsey was responsible for the conception and organization of this review, as well as reviewing and critiquing the various drafts.

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No Treatment

Treatment Effects

S_{ss} decreases

T_{prog} increases

— $S(t)$ Effected; --- S_{ss} ; -.- $S(t)$ Unaffected

Figure 1.

Visualization of Parameter Changes The graphs all show years vs. UPDRS totals and depict a change of parameters, S_{ss} and T_{prog} , in Holford's Logistic Model caused by a hypothetical treatment initiated at two years.

Placebo Effect

Figure 2.

Graphs of the models for placebo effect. The red graph indicates that the placebo effect wears off over time. The labeled point indicates the average maximum placebo effect is a drop of 4.5 points on ADAS-cog and it is usually reached in 19 weeks.

Table 1

Summary of Models

In the graphs, treatment effects are in red solid and natural progression in black dashed.

Reference	Purpose	Equation $[S(t)]^*$	Years v. UPDRS	Parameter Estimates
Guimaraes <i>et al.</i> 2005	Disease-drug model for evaluating monomolecular curve as maximum symptomatic benefit. Treatment value shown.	$= (S_0 + \alpha t) - S_{sym}(1 - e^{-rt})$ $= (\text{Linear}) - (\text{Monomolecular})$		S_0 : 30.8 – 32.9 units α : 2.8 – 3.3 units/year S_{sym} : 12.0 – 15.2 units r : 4.9 – 9.4 year ⁻¹
Holford <i>et al.</i> 2006	Disease-drug model. $E(t)$ depends on pharmacological properties of treatment. Symptomatic effect depicted. Placebo values shown.	$= (S_0 + \alpha t) - E(t)$ $= (\text{Linear}) - (\text{Bounded Offset})$		S_0 : 21.4 units α : 11.9 units/years
	Similar to the linear model, but tailored toward longitudinal data. Possible disease modification depicted. Placebo values shown.	Differential Form: $= S_0 + \int_0^t \frac{ln(2)}{T_{prog}} * (S_{ss} - S) * S - E(t)$ Alternate Form **: $= \frac{S_{ss} * S_0}{S_0 + (S_{ss} - S_0) * exp\left(-ln(2) * \frac{S_{ss}}{T_{prog}} * (t)\right)}$		S_0 : 21.8 S_{ss} : 94.0 T_{prog} : 117 years
Bhattaram <i>et al.</i> 2009	Disease-drug-trial model for running simulations to assess a new analysis method in studies < 5 years. Placebo values shown.	$= (S_0 + \alpha t) - S_{sym}(1 - e^{-rt})$ $= (\text{Linear}) - (\text{Monomolecular})$		S_0 : 22.4 – 25.8 units α : 5.7 – 14.1 units/year S_{sym} : 1.24 – 1.59 units r : 3.12 – 18.2 year ⁻¹
Lee & Gobburu 2011	A Bayesian disease-drug-trial model to compare two trials. Symptomatic effects only. Kasagiline values shown.	$(t) = (\alpha t) - S_{sym}(1 - e^{-rt})$ $(t) = (\text{Linear}) - (\text{Monomolecular})$		α : 23.3 units/year S_{sym} : 2.7 units r : 75.9 – 97.2 year ⁻¹

Parameter values are provided to lend intuition for the informed reader to understand how the model behaves and are not for rigorous use. They depend heavily on the context of their source. In addition, the equations have been significantly simplified in the interest of summarizing the characteristics of the model. Consult the source for more information.

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* The function, γ , constructed by Lee and Gobburu, is of change from baseline rather than objective score.
** When there is no effect on S_{SS} , the solved form of the differentiable equation is readily available.

Table 2

Summary of Notation

Notation	Meaning
α	Slope of a linear model
β	Magnitude of placebo effect on a rating scale
	Change from baseline UPDRS score; $S(t) - S_0$
$E(t)$	Effect of a treatment that does not alter natural progression
r	Reflects rate at which maximum symptomatic benefit is approached
r_a	Reflects rate at which placebo effect increases
r_e	Reflects rate at which placebo effect decreases
S_0	Baseline UPDRS Score
S_{ss}	Upper asymptote for logistic model
S_{sym}	Asymptote for symptomatic benefit
$S(t)$	Function which predicts UPDRS; does not include random effects
T_{prog}	Reflects time course in Holford's logistic model