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Modeling and Simulation of Adherence: Approaches and Applications in Therapeutics

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ABSTRACT

Partial adherence with a prescribed or randomly assigned dose gives rise to unintended variability in actual drug exposure in clinical practice and during clinical trials. There are tremendous costs associated with incomplete and/or improper drug intake—to both individual patients and society as a whole. Methodology for quantifying the relation between adherence, exposure and drug response is an area of active research. Modeling and statistical approaches have been useful in evaluating the impact of adherence on therapeutics and in addressing the challenges of confounding and measurement error which arise in this context. This paper reviews quantitative approaches to using adherence information in improving therapeutics. It draws heavily on applications in the area of HIV pharmacology.

KEYWORDS: adherence, modeling, simulation, PK/PD, NONMEM

INTRODUCTION

Adherence is a blanket term for various measures of dosing history, including aspects of persistence, or the time elapsed between a drug prescription and treatment discontinuation, and compliance, or the extent of agreement between a patient's actual record of drug intake and the prescribed regimen.[1] Neglecting to take medication as prescribed is a major cause of variability in drug exposure and has been associated with the failure of many treatments.[2-7] Particularly insidious are the public health risks of nonadherence. A well-known example is the development of drug-resistant strains due to incomplete dosing with antibiotics and antiretroviral agents. Another example is the evidence that forgetting to take several doses of an immunosuppressive results in the rejection of a transplanted organ. One group reported that nonadherence accounts for 13% of graft loss[8] and increases to 27.6% of graft loss 2 to 3 years after transplantation.[9] Adherence[6,10] is not a new problem in therapeutics. Centuries ago, physicians may have asked patients about their adherence or inferred it from their response to treatment. Records documenting physician concern about patient adherence date to the time of Hippocrates.[2-4,11]

The reliability on subjective measures of drug adherence has historically precluded its quantitative assessment. Attempts at improving the accuracy of adherence monitoring have been encouraging,[12] although a "gold standard" has yet to be established. The impact of adherence on drug exposure and, consequently, drug actions in therapeutics has been demonstrated. Likewise, clinical trial outcomes are similarly related, making adherence an important design feature and consideration during drug development.

Modeling and simulation-based approaches can be used in the exploration of these associations and certainly in the planning of trials for which drug adherence may be problematic. It is here that we encounter the work of Dr. Lewis Sheiner and others who have pioneered this approach. One of Dr. Sheiner's most valuable contributions to clinical pharmacology and medicine in general was his ability to conceptualize complex associations, formally state the relevant assumptions, and distill the essential components into a framework from which their impact could be quantified. Figure 1 is a schematic produced by Dr. Sheiner from a presentation entitled, "Causal Evidence of Effectiveness to Support a Single Clinical Trial Approval," given by Drs. Carl Peck, Donald Rubin, and Lewis Sheiner in 2002. The intention of the slide was to demonstrate the correct temporal sequence yield of causal certainty. It provided a framework by which learning versus confirming trial designs could be considered, and it led into a discussion of when and under what conditions model-based analyses were acceptable for regulatory decisions. It, likewise,

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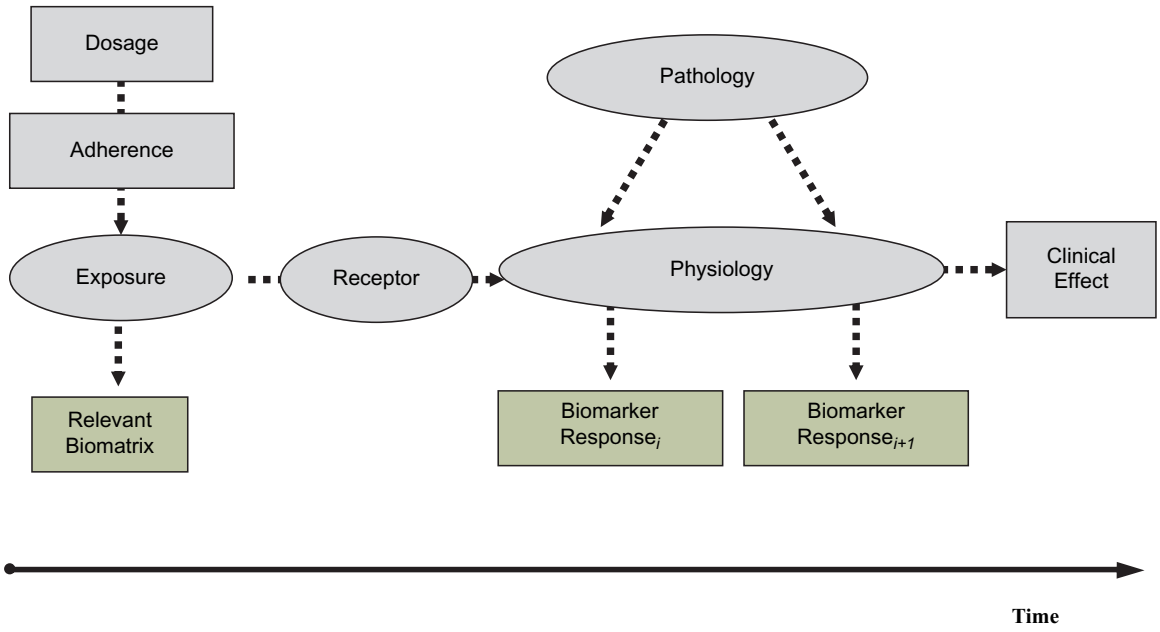

Figure 1. The temporal sequence of causal certainty illustrating the influence of adherence on drug exposure and, likewise, clinical effect.

explicitly acknowledged the upstream impact of drug adherence on clinical outcomes and the necessity of its accurate quantification. Given its upstream impact on drug exposure and the sequential associations with drug response and clinical effect, it is obvious that the ability to model and, likewise, predict the impact of adherence on clinical outcomes is a desirable goal, especially in the planning of multimillion-dollar trials.

Drugs often underperform in the context of routine clinical evaluation relative to the observed efficacy in controlled clinical trials.[13] One explanation for such observation is the influence of nonadherence on drug exposure. The goal of this article is to provide the reader with information on quantitative approaches to using information on patient drug-taking behavior to improve therapeutics. It is an area of research that Lewis tackled late in his career. As such, his approaches reflect the synthesis of a lifetime of work on sparse data analysis, confounding, missing data, measurement error, multivariate data, exposure-response, and mechanistic modeling. It also involved a highly collaborative effort of many different groups of people, most notably via the AIDS Clinical Trials Group. At the heart of each approach is a consideration of the efficiency of the usage of available data and the constraints posed by the type of data gathered.

Adherence is an unusual variable. The estimand (the actual entity one would ideally like to know) of adherence—the time each pill is swallowed—is not readily measured with current tools, and there is no single agreed-on tool for measuring it, like drug concentration. Adherence can be both a cause and effect of drug response, so the landscape for initiating modeling of adherence is complicated by the interdependencies of exposure, adherence, and outcomes. This is shown in the following relationships: (1) exposure = *fn*(regimen, drug characteristics, subject, disease, and adherence); (2) adherence = *fn*(subject, drug characteristics, drug response, and environment); and (3) outcome = *fn*(exposure, adherence, disease, subject, and drug response), where subject refers to subject characteristics (ie, demographics, health status, etc). Drug characteristics refer to pharmacokinetic (PK), formulation factors (ie, dosing frequency, clearance, taste, etc), and route of administration. Disease refers to condition-modifying effects. Drug response refers to activity measures (efficacy, toxicity, etc). Subject refers to an individual's predisposition to nonadherence. Regimen refers to dose, schedule, and timing.

Likewise, models developed to explore adherence must address these relationships. Many possibilities exist for the expression of such relationships. As with all modeling exercises, model selection depends on the objectives of the analysis. In this endeavor, we define key assumptions and metrics for evaluation and explore the diversity of models that have been used to establish correlations between adherence and outcomes and also those in which adherence has been a factor in the examination of exposure-response. Issues of confounding and the intention-to-treat (ITT) analysis are discussed, as well as attempts to generalize patient characteristics to patterns of nonadherence. Evidence for the pharmacoeconomic impact of nonadherence on health economics is presented. We examine clinical applications across therapeutic areas but have made a more thorough

assessment in the area of antiretroviral therapy, an area of interest and great passion to Dr. Sheiner.

Adherence Modeling Approaches

Models for adherence may be useful in predicting how drugs will behave in circumstances for which they have not been tested but, based on what we know about patient drug-taking behavior, may be used. The choice (or choices) of measurement tools will dictate possible models. Considerations in model building include quantifying metrics to describe (or parameterize) adherence, appropriate partitioning of adherence measurement error (random versus nonrandom), and the incorporation of adherence into model-based expressions (eg, confounding). Adherence modeling is heavily reliant on an accurate assessment of data "missingness" and randomness. The next sections address the premodeling stages of adherence assessment, as well as the means by which models evolve.

Methods of Adherence Measurement

Adherence measurement falls into two broad categories, direct and indirect measures. Biological assays and clinician observations of the patient medication ingestion[14] may be considered direct measures of adherence. Self-report, pill counts, and electronic monitors may be labeled as indirect measures.[15] Clinicians most commonly elicit patient self-reports of adherence[16,17] but may perform pill counts,[18] check plasma levels,[19-22] or record medication bottle opening and closing with an electronically monitored cap,[7,12] as well. Microelectronic devices can record the time and date of openings and closures of a drug container used by an ambulatory patient over the course of years. It has been shown that adherence seems higher when measured by self-report and pills counts than when measured by an electronically monitored cap in the same individual (Medication Event Monitoring System [MEMS]; Aprex Corp, Union City, CA).[12] It is believed that self-reporting overestimates adherence,[23-25] whereas microelectronic devices may underestimate drug adherence. It is believed that microelectronic devices are more likely to underestimate compliance than overestimate compliance given that patients, for reasons of convenience, may remove all of the doses for an entire day at one time, rather than at separate times for bid (twice a day) and tid (three times a day) regimens, than they are to consistently open and close a medication container on time but throw out pills. No method is currently considered the "gold standard."

Sources of Error in Adherence Measurement

The accuracy and precision of patient adherence measurement plays a critical role in the estimated exposure-response relation. Likewise, the accommodation of error about these measurements becomes part of the "art" of modeling. Because no adherence measuring tool records the time each tablet is swallowed, all of the measurements are prone to random and nonrandom sources of error. Table 1 summarizes the sources and types of error for each adherence measurement.

Methods for Reducing Error in Adherence Measurement

It is known that random error in an independent variable attenuates the estimated causal relationship with its dependent variable.[26] That is, even simple random error in adherence measurement yields downwardly biased estimates of the exposure-response relationship.[27] Nonrandom error in the independent variable may bias the estimated drug effect relationship upward or downward. The statistical literature has a long history of addressing measurement error.[26] The correction for measurement error can be viewed as a special class of data-analytic approaches within the general missing data framework.[27,28]

Experimental protocols can be altered to reduce error in adherence measurement. To decrease nonrandom error in self-reported adherence, investigators may carefully choose nonjudgmental language to elicit adherence information.[29,30] Electronic diaries that time stamp entries may diminish both random and nonrandom error by reducing the reliance on patient memory and making it more difficult for patients to intentionally misrepresent their intake.[31] Random error in pill counts is likely negligible if investigators perform multiple counts. Unannounced pill counts—having the study investigator unexpectedly visit the subject at his place of residence to count pills—may reduce nonrandom error in pill counts, because it offers the patient less of an impetus to dump pills.[32] Long half-life markers can be monitored to ascertain drug intake over a longer period of time than drug concentration monitoring may allow, thus, it can serve as a check for "white coat" adherence–improved drug taking just before the visit with a clinician.[33] Electronic measures may be corrected using self-reported adherence information.[32] Although electronic diaries, unannounced pill counts, long half-life marker compounds, and electronically monitored caps with supplemental self-report information may provide the most accurate measure of drug intake, they are not the most common methods used in practice. Considerations of cost and convenience strongly influence the selection of adherence monitoring tools. Because adherence assessment is subject to considerable error, some recommend the use of 2 or more instruments (eg, questionnaire and MEMS).[34] Approaches for reducing the error in adherence measurement are summarized in Table 1.

Table 1. Sources of error in adherence measurement and considerations for error expressions used in adherence models (28)

Tool	Assumptions	Data Collected	Benefits	Problems	Source(s) of Error		Model Considerations
					Random	Non Random	
Questionnaire	• Patient remembers what pills he forgot to take • Patient truthfully reports drug intake	• Patient report: number of pills missed over duration of time (generally categorical)	• Perceived as economical • Information on # pills taken • Information on reason for non-adherence	• Potential for biased data • Investigator variability • Need to validate • Nonstandard	• Forgetting	• Intentional misrepresentation	• Generally categorical data • Upward bias • Over any duration of time
Diary	• Patient remembers what pills he forgot to take • Patient truthfully reports drug intake	• # pills missed per day	• Perceived as economical • Information on # and day pills missed • Information on reason for non-adherence	• Potential for biased data • Need to validate • Nonstandard	• Forgetting	• Intentional misrepresentation	• Upward bias • Over any duration of time
Electronic Cap	• Nominal dose removed at time of cap opening • Ingestion of nominal dose at time of cap opening	• Time of container opening/closing	• Difficult to consistently bias the measure • Standard tool • Rich time series data	• Perceived as costly • Cannot gather data on number of pills taken • Cannot discern if drug ingested at time of removal	• Forgetting to take removed pill	• Intentional pattern of dose removal without ingestion or removal of different number of pills than nominal dose (eg, all the day's doses for a bid or tid regimen are removed in the morning)	• Downward bias[32,97,98] • Rich time series data • Over any period of time
Pill Count	• # pills taken during a time interval	• # pills distributed at study onset; # pills remaining after time interval; time interval	• Perceived as economical • Information on number of pills taken • Standard tool	• Easy to produce biased information	• Investigator miscount	• "White coat adherence"[33]	• Univariate descriptor of drug intake • Reflects time between visits to clinician

(*Continued*)

Table 1. (*Continued*)

Tool	Assumptions	Data Collected	Benefits	Problems	Source(s) of Error		Model Considerations
					Random	Non Random	
PK Sample	• Steady state concentration obtained • Time of last dose accurate	• Concentration of drug or marker compound	• Verifies drug ingestion over several half lives • Standard tool	• Costly • Painful • Time of dose uncertain	• Assay noise • Sample handling	• "White coat adherence"[33]	• Allows concentration-response modeling • Over last several half lives
Physician Assessment	• Physician assessment of adherence	• Adherent versus nonadherent	• Convenient	• Biased		• Bias[79] • Nonstandard	• Generally binary metric
Directly Observed Therapy	• Patient swallows drug • Drug not taken at another time	• Time and amount of dose ingested	• Time of dose known	• Inefficient		• Not swallowing	• Time and amount of dose ingested

Metrics to Describe Adherence

After the collection of adherence data, the choices for the expression or transformation of this data[35] dictate the relevant modeling strategies. Percent adherence, defined in Table 2, is most commonly used and most often defined as the fraction of prescribed doses taken during some interval of intake observation. That interval may be the entire duration of dosing or, perhaps, just a few days before a visit with the clinician. The duration of time that can be described is dictated by the technique used to measure adherence.[27,28]

An observed drug level reflects subject adherence over several previous half-lives, whereas pill counts reflect adherence over the entire period of time between counts. Self-reported adherence can reflect intake over the entire study duration if the patient uses a diary to record adherence daily. Because of the limitations imposed by memory, when questionnaires are used, subjects are usually asked to recall their intake just a few days before visiting the clinician. Electronic caps monitor adherence continuously, so there is no technically imposed limit on the duration of time over which percent adherence can be measured. In addition to percent adherence, other common adherence metrics have been used and are reported in Table 2, such as persistence and drug holidays. For univariate analysis, local-time and global-time average adherence fractions can be calculated and used as adherence measures. The global-time average is the time-weighted average of all of the adherence fractions available for an individual. The local-time average is the single adherence fraction computed from adherence data closest in time to a PK study (eg, within 1 week).

Calibration of Adherence Tools

Questionnaires and diaries are the most commonly used tools to assess drug intake in clinical trials and in therapeutics, likely for reasons of perceived convenience and economy. Unfortunately, these tools are associated with considerable measurement error. It has been suggested that one approach to efficiently assess adherence is to measure adherence with the most convenient, but, possibly biased, tool in all subjects in a clinical trial and to calibrate the measure to those taken using a more accurate tool in a random subset.

To calibrate, one proposal is to model the relationship between 2 available measures of adherence, treating the unavailable measure of adherence (ie, with the more accurate tool) in a subset of subjects as "missing" data, and integrating over the missing adherence data as follows:[27,28] $p(Y|D) = p(Y|D(C_Q,C_M))p(C_Q,C_M)dC_M$, where $p(Y|D)$ is the exposure-response model; $D(C_Q,C_M)$ is the exposure model; $p(C_Q,C_M)$ is the adherence calibration model; Y is

Table 2. Metrics used to describe adherence

Metric	Derivation
Percent Adherence	Ratio number of pills taken/number of pills prescribed[12]
Percent Adherent Dosing Days	Ratio number of days dose taken/number of days of dosing[35]
Therapeutic Coverage	Ratio time spent with inefficacious drug concentrations/time on therapy[10,99,100]
Frequency of Drug Holidays	Frequency of $\geq$3 days without drug intake[35,85,101]
Persistence	Time spent on therapy (time from when first dose taken to when last dose taken)[1]

the pharmacodynamic response; D is the exposure; and C_Q is the self-reported adherence ("compliance"); C_M is the monitored adherence ("compliance").

The performance of this calibration model relative to other methods for determining drug exposure was compared with respect to its ability to estimate exposure-response. The authors showed that better estimates of exposure-response could be obtained by calibrating the adherence measures than by using various other approaches to analyzing the available data to estimate drug exposure. These results were robust to variation in study design, drug effect, and the accuracy of the 2 adherence measuring tools.[27] Note that the calibration approach was explored for categorical measures of adherence given that biased measures (eg, self-reported adherence) are often measured on a discrete scale.

Methods to Model the Effect of Adherence on Exposure-Response Relationships

Models incorporating adherence data into an analysis of exposure-response enable one to quantify the expected response given the actual dosing behavior as opposed to assuming all of the subjects have the same dosing history. Using adherence information in this manner effectively treats adherence as an independent variable. Because adherence is unknown at the outset of a trial and is, technically, an outcome of the treatment, the extent to which a subject's intake causes his or her pharmacodynamic response (through drug exposure) versus the possibility that both response and adherence are driven by another confounding factor is unknown. Thus, the use of adherence in an exposure-response model requires explicit assumptions around the confounding.

Several model-based approaches have been explored in the determination of exposure-response when confounding may be present.[36-40] These approaches fall into the following 2 general categories: one that treats adherence as a stratifying variable[36] and one that models the confounding.[37-40] Sheiner and Rubin[39] made a great contribution to the formal statement of challenge of confounding of compliance with response and assumptions needed to address it. The key was to identify the appropriate control group for compliers to the test product among subjects receiving the alternative therapy. The reason is that factors driving the decision to adhere to the test drug may be different from those influencing the decision to adhere to the alternative therapy. Therefore, the proper control for the subjects who comply with the test drug is not necessarily the group of subjects who comply with the alternative therapy. The proper control for subjects who comply with the test agent, instead, is the group of subjects receiving the alternative treatment who also would have complied with the test agent if had been offered to them. Having the same distribution of adherence in the investigational and alternative treatment groups does not preclude the need to address this issue. The clearest separation of these terms is made only by measuring adherence with both treatment options in the same individual.

Efron and Feldman[38] developed a causal estimator of the effect of exposure to the lipid-lowering drug cholestyramine on coronary heart disease using data collected during the Lipid Research Clinics Coronary Primary Prevention Trial. The Lipid Research Clinics Coronary Primary Prevention Trial data set received much attention, because it suggested that there is confounding between adherence and response; a trend between adherence and response was observed in both the treatment and placebo groups. Furthermore, the subjects were observed to have lower adherence with the drug than with the placebo, complicating the task of finding the proper control for subjects assigned to the dose in the placebo group.[38] The authors note that the steep adherence-response relationship observed in subjects assigned to the drug and the shallow adherence-response relationship observed in subjects assigned to the placebo is evidence of a dose-response relationship. Their strategy was to recover the dose-response relationship from the adherence-response relationship by estimating the difference in response for those assigned to the drug and those assigned to the placebo at matched levels of adherence. The authors formally assume the following: (1) there is no difference in response

between 0% compliers to drug and 0% compliers to treatment, and (2) adherence is an inherent attribute of the patient ("perfect blind assumption"), which allows them to write a model relating an individual's adherence with drug to the individual's adherence with placebo. The results may be sensitive to these assumptions—it has been demonstrated that incorrectly assuming that compliers to the placebo are the proper control group for compliers with the drug leads to a bias in estimates of the drug effect.[41] Robins[36] addresses the problems of confounding by assuming that adherence is nonrandom and can be predicted by time-dependent prognostic factors (covariates).

Methods for Dealing With Confounding-Instrumental Variables

Sheiner and Rubin[39] addressed the issue of confounding by modeling the relation via an instrumental variables approach. The instrumental variables approach requires identifying a variable ("causal instrument") W such that W influences Y (eg, response) only via its influence on X (eg, exposure). That is, W is "conditionally independent" of Y given X. Sheiner and Rubin[39] use dose as the instrument, and their analysis rests on 2 assumptions. First, the decision to comply or not comply occurs early in the trial, which provides a basis for believing the second, and key, assumption that outcomes in drug noncompliers are the same as they would have been had the noncompliers been assigned to the control treatment. Under this scenario, in theory, only the marginal distributions of adherence to the placebo and adherence to the drug are required to yield an unbiased estimate of the causal relationship between exposure and response. However, as the authors point out, this approach requires additional investigation to extend to applications beyond the analysis of their application to simple vaccine trials. Note that vaccine trial designs were used as an example for which the following key assumptions are valid: (1) no drug is available to those who are not assigned to receive it, (2) subjects have all-or-none adherence, and (3) the control group is guaranteed to receive the "standard of care."

Methods to Model Unknown Dosing History

For concentration-time data collected in clinical trials to be useful for explanatory exposure-response analyses, the following 2 assumptions about the data must hold: (1) the time of the concentration observations are known, and (2) the patient's recent past dosing history (times and amounts) is known. If either (or both) of these assumptions do not hold, and data analysis proceeds as if it did, biased estimates may result. The first assumption usually holds, because study personnel observe and record the PK sampling times. The second assumption is a problem when, as is often the case of outpatient studies, one must rely on patient recall for past dosing history. Lu et al[24] proposed a method to avoid the assumption that the patient's recent past dosing history (times and amounts) is known and ascertained only from patient recall in an explanatory population PK and pharmacodynamic analysis. This is accomplished by identifying for deletion those PK observation occasions likely exhibiting unreliable preceding dose histories. A Bayes objective function (posterior density) maximized in its parameters for each individual is used in this procedure. The likelihood factor of this function is a mixture pharmacostatistical model expressing the likelihood of observed concentration(s) under the following 3 mutually exclusive events: (1) the prescribed dose preceding the occasion was not taken at all (NT), (2) the prescribed dose was taken at the specific time (T), or (3) the prescribed dose was taken but at an unspecified time (U). This method assumes that the times of the concentration observations are known, the population PK is known (at least approximately), the PK samples (at least 1 or 2 per occasion) are available, the doses taken are of the stated magnitude, and the drug has a short half-life.

When only 1 of the first 2 cases holds, the probability density for an observation y_i is then:

$$p(y_i) = p(NT)p(y_i \mid NT) + p(T)p(y_i \mid T) \qquad (1)$$

where p(T) is the probability that the individual takes the dose on the generic occasion, and p(NT) is the probability that he does not. Each of the cases T and NT can be additionally considered as 1 of 2 subcases depending on whether the observation is reported to be below the quantification limit or a particular value equal to or greater than the quantification limit.

In the case that the third possible (U) case, an additional contribution to the likelihood equation for the U case is:

$$p(U)p(y_i|U = p(U)\int_0^{t\infty} p(y_i|s_i + \tau)p(\tau|U)d\tau \qquad (2)$$

where $s_i = t_i - t_1$ (where t_1 is the time of the first PK observation on the occasion). To combine all of the cases and generalize to the case that not one but n observations are taken on a generic occasion, let $y = (y_1, y_2, \ldots, y_n)$ be the set of PK observation taken on the occasion. They have:

$$p(y) = p(NT)\prod_{i=1}^{n} p(y_i|NT) + p(T)\prod_{i=1}^{n} p(y_i\lambda|T) + t_{\infty}^{-1}p(U)\prod_{i=1}^{n}\int_0^{t\infty} p(y_i|s_i + \tau)d\tau \qquad (3)$$

subject to p(T) + p(NT) + p(U) = 1 (see Ref. 24 for more details). Simulations using this technique revealed that especially when >1 PK sample is available, the methodology chooses a set of PK observations that should perform better in subsequent exploratory PK (or pharmacodynamic) analyses than other simpler methods.

Jonsson et al[42] developed an approach for identifying the most plausible dosing history for each individual in a data set when >1 dosing history is available. They developed a population model that weighs the information in subjects for whom adherence measures agree by both tools to select the best dosing history in subjects for which there is disagreement in drug intake information.[42]

Applications of Adherence Modeling

This section reviews applications of adherence modeling and provides examples in which accounting for adherence has promoted more safe and efficacious use of medications. Although clinical applications across therapeutic areas are provided, a more thorough assessment in the area of antiretroviral therapy has been made, an area of interest and great passion to Dr. Sheiner.

Application to Statin Agents

Adherence to statin therapy appears to be high (ie, MEMS adherence rate of 95%) in Chinese patients[43] but is unsatisfactory in routine clinical settings in Western countries. The ratio of observed-to-expected (based on controlled clinical studies) reduction in low-density lipoprotein cholesterol concentration with statins is approximately 0.8.[44] Typical 1-year persistence rates range from 40%[45] to 90%.[46] Reported 5-year persistence rates are in the order of 45%.[47] Hughes and Walley[48] describe a pharmacodynamic model that simulates the effect of partial adherence with statin therapy on low-density lipoprotein concentrations to predict the use-effectiveness of drugs expected in routine practice. The authors conclude that model-based simulations provide insights on how forgiving drugs can be in the face of missing doses and can be used to explore alternative dosing regimens, such as alternate-day or once-weekly dosing. Modeling of adherence has enabled the clinical assessment of this problem both in qualitative and quantitative terms.

Application to Oral Contraception

Drug developers were mindful of the impact of adherence on efficacy when developing dosing recommendations for low-dose estrogen oral contraceptives in the 1970s. To assess the impact of drug-taking behavior on response, a novel clinical trial was designed—placebo pills were substituted for active tablets to define the interval between a last-taken pill before the ovulation-inducing surge of pituitary gonadotropins appeared. Five placebo-substitution studies were published during the 1980s, and the results were translated in the early 1990s into labeling in the United States and the United Kingdom. The resulting label informs patients about the limits of dose timing consistent with full-contraceptive protection, what to do when those limits are exceeded, and how best to phase back into correct dosing.[49,50] This approach allows estimation of the causal relation between drug intake pattern and response without the risk of confounding—a potential method to consider if one needs to confirm any findings of retrospective analyses of adherence data. Its widespread application, however, is limited by ethical and practical concerns.

Application to Antihypertensive Agents

Sudden discontinuation and restarting of antihypertensive dosing regimens can be dangerous.[51] Clinical studies have shown that the omission of doses of a short-acting calcium channel blocker, a β-blocker, or nonintrinsic sympathomimetic activity blockers may lead to rebound hypertension and cardiovascular events.[52,53] Doxazosin, a peripheral vasodilator, has also been associated with poor outcomes if doses are skipped for several days.[51] Nonadherence with antihypertensive medication remains an obstacle to the management of hypertension. Specific study designs for comparing the effects of missing daily doses of antihypertensive drugs have been evaluated.[52,54,55] A double-blind randomized comparison of 2 angiotensin-converting enzyme inhibitors has been used in a clinical study in which blood pressure was monitored over a steady-state dosage interval and the subsequent 24 hour period, the latter being designed to mimic a missed dose of drug.[54] By using a double-blind randomized design, Leenen et al[55] have evaluated the blood pressure-lowering effect of amlodipine versus diltiazem both on active maintenance treatment and after active treatment was interrupted for 2 days by placebo. Logistic regression modeling has been used to relate adherence to demographic factors in a retrospective cohort of elderly outpatients newly starting antihypertensive therapy.[56] A Bayesian approach to analyzing general structural equation models with dichotomous variables has been applied to a study of hypertensive patient nonadherence to a drug.[57] The authors have used an algorithm based on the Gibbs sampler to draw the parameter values and the hypothetical missing values from the joint posterior distribution. Their method allows for the analyses of dichotomous data by avoiding the assumption of the normal distribution of the data, which is violated when analyzing dichotomous data. This, likewise, permits a more-accurate, less-biased estimate of nonadherence.

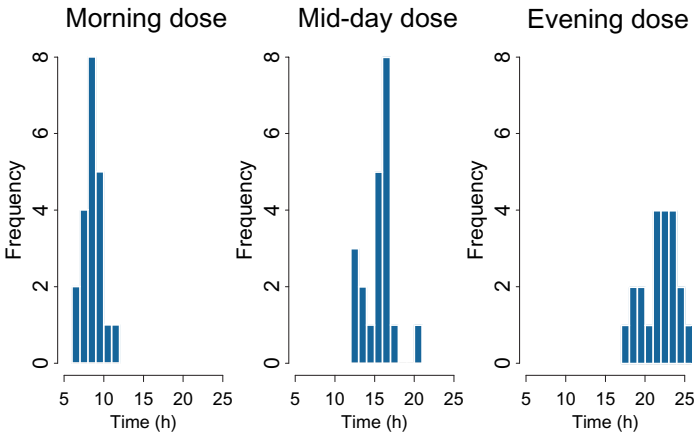

Figure 2. Histogram of times of day that patients habitually take their thrice-daily zidovudine doses.

Application to Antiretroviral Agents

Suboptimal adherence has been postulated to be one of the main factors associated with the emergence of resistant HIV.[58-60] Bangsberg et al[61] reported that only 23% of drug resistance mutations occur in individuals in the top quintile of adherence (92% to 100%), but >50% of all drug resistance occurs in the 40% most adherent patients (79% to 100%). Pfister et al[62] integrated adherence fractions from MEMS and an adherence questionnaire in a physiologic "well-stirred" model to quantify the effect of adherence scores on drug exposure of efavirenz. Clearance (CL) is calculated as $Q\ \mathrm{CL}_{int}/(Q + \mathrm{CL}_{int})$, in which Q is hepatic plasma flow and CL_{int} is intrinsic (hepatic) clearance. F is net bioavailability, which is equal to $F_{gut} \times F_{hep}$, where F_{hep}, which is equal to $Q/(Q + \mathrm{CL}_{int})$, is the fraction of drug surviving a first passage through the liver, and F_{gut} is the fraction of drug surviving the first passage across the gut wall. This model allows researchers to incorporate adherence as a covariate effect on biovailability F_{gut} and to explore drug-drug interactions on biovailability F_{gut} and/or F_{hep}.[62] This model agrees with the observation that patient adherence is the ultimate barrier to drug delivery, because it sets the upper limit on drug exposure.[63]

Kastrissios et al[64] have reported descriptive analyses of compliance in the field of HIV. Girard et al[65,66] showed that the error between the actual dose times associated with each nominal time is multivariate normally distributed and that the subject-specific probability of taking zero, 1, or >1 dose associated with a given nominal dose time depends on the value of certain covariates and on the number of doses associated with the immediate previous time but is independent of any other previous or future dosing events. Girard et al[66] used a hierarchical Markov model to describe adherence patterns of patients with a thrice-daily zidovudine treatment. The adherence behavior of these patients is illustrated in Figures 2 and 3. Girard transformed sequences of dose times into "data" vectors (see Figure 4 for details) and modeled the observed dose times for a specific patient in terms of the following 3 components: (1) the nominal times that the patient takes his medication, (2) the number of doses he takes at each of these times denoted n, and (3) the differences between actual dose-taking times and the nominal times with which they are associated, denoted Δ. Their analysis strategy was, for computational convenience, to estimate the individual-specific nominal times in a first stage, to create observed data Δ and n, and to define a population model for these data using the following decomposition:

$$p(\mathrm{n}, \Delta) = p(\mathrm{n})p(\Delta|\mathrm{n}) \qquad (4)$$

and fit this model to the data via a maximum likelihood approach.[66] This model has several interesting features. First, the Markov model captures the stochastic nature of dose taking. Second, the analysis reveals a covariate of compliance: the drug is taken most accurately in the mornings and on weekdays.

Longitudinal (Markov) models have also been proposed to estimate the effect of patient adherence on the rate at which patients progress through the HIV infection. Vrijens[67] has proposed recently a clinically meaningfully categorized measure of viral load and provides a Markov model for analyzing the repeated ordinal responses. The Markov model is an empirical model in which the present response at any time point (t+δ) is made conditional on that in the previous time period (t) such that: $p(Y_{t+\delta}|Y_t) = f(\theta)$. Vrijens[67] related "timing error," the third moment of the distribution of interdose intervals, to RNA levels and reported that timing error adds explanatory power to a simple adherence fraction. Using a Markov model, Labbé et al[68] have investigated the effect of adherence to prescribed antiviral drugs on viral response of the bimonthly viral RNA increment/decrement. Bimonthly viral RNA values within each patient are categorized into 1 of 3 classes: low ($\log_{10}$ RNA $\leq$2.5), medium (2.5 $<$ $\log_{10}$ RNA $\leq$4), and high ($\log_{10}$ RNA >4). The response (Y) for each interobservation interval is the change in RNA category (Δ) over the interval (decreases/remains the same/increases). The covariates (X) include prestudy exposure to the nonnucleotide reverse-transcription inhibitor (N; a baseline variable), duration of AIDS Clinical Trial Group protocol 398 therapy (T; early/late), and drug adherence (ADH) during the interval, as measured by questionnaire (AQ) and electronic adherence monitoring caps (MEMS). The following different summaries of daily MEMS-based exposure were evaluated: the moments of the distribution of interdose intervals, the fraction of interdose intervals greater than a specific value, and the fraction of days on which medication was taken. All of the independent variables were

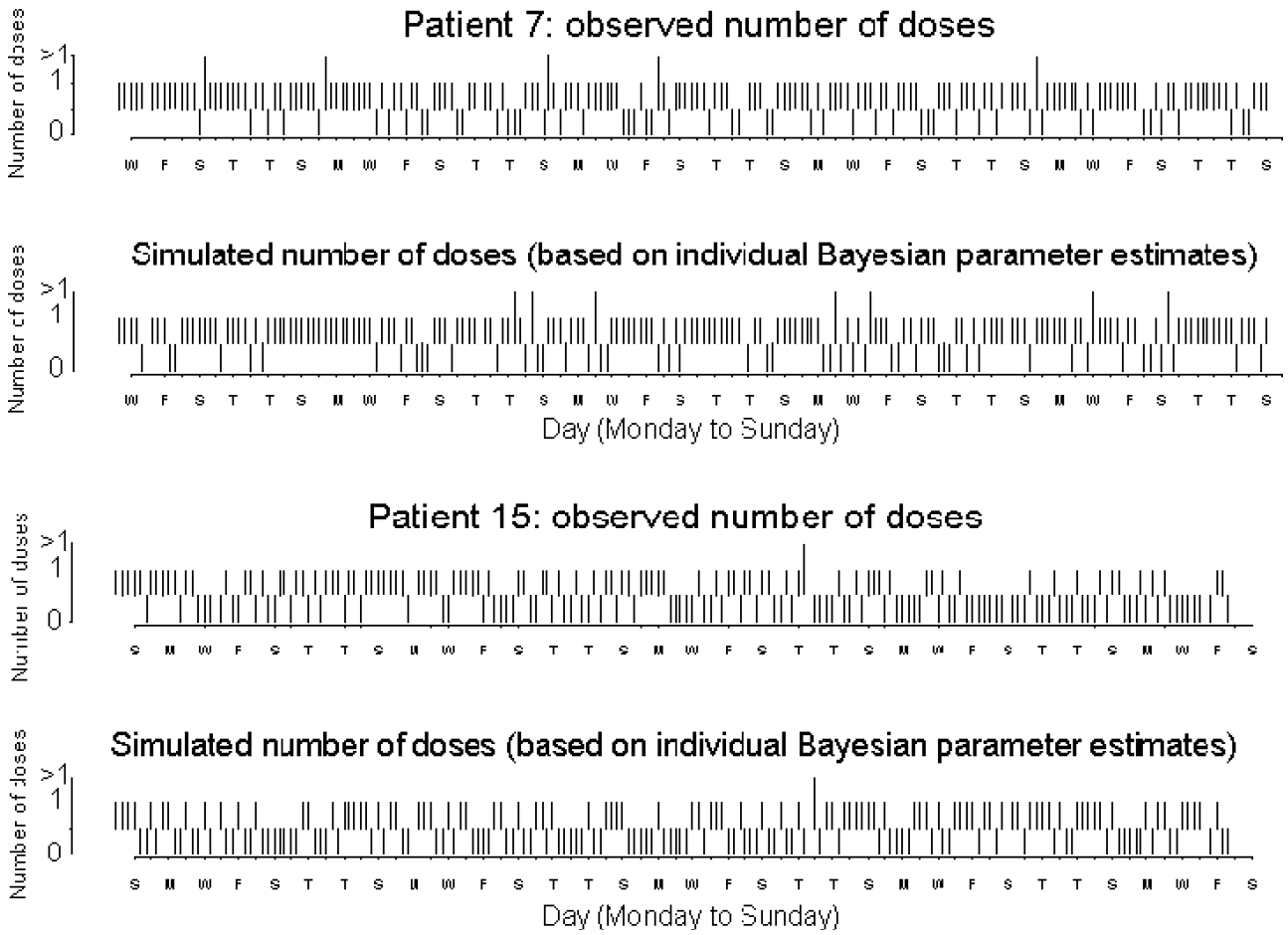

Figure 3. Number of doses taken at each nominal dosing time (n) during the first 7 weeks (approximately) of thrice-daily zidovudine treatment for 2 subjects together with the simulated number of doses for the same subject using Markov chain model (66). Days of the week are indicated along the abscissa by the first letter of their names. On the ordinate, each vertical line of unit height above the unmarked tick represents the taking of a single dose; a line of 2 units in height above the unmarked tick represents the taking of 2 doses. A line of unit height plotted between 0 and the unmarked tick represents a nominal dosing time at which no dose was taken.

dichotomized by finding the cut point yielding the highest explanatory power in the model. The Markov property is conferred by conditioning on the starting RNA value (RNA^{START}). Hence, the response can be expressed as

$$Y = \Delta | RNA^{START} \quad (5)$$

Since probabilities must sum to unity, and certain transitions are impossible, 3 responses $\times$ 3 values of RNA^{START} yield 9 possible transition probabilities which can be uniquely specified using only 4 parameters ($A_1 - A_4$), modeled as

$$\ln(A_i) = \beta_{ij} Z_{ij} + \beta_{ij} Z_{ij} T + \beta_{ij} Z_{ij} N + \beta_{ij} TN + \eta_i, \quad (6)$$

where i, j is 1, 4; Z_{ij} is $1 + \alpha_{ij}$ADH; ADH is λMEMS + $(1-\lambda)$AQ; the β, α, and λ are parameters to be estimated; and the η_i are normally distributed, random individual effects. NONMEM is used for estimation, which is stabilized by penalizing all of the fixed-effect parameters, except for the baseline effect (β_{11}), for deviation from zero, the "null" value. Multiple imputation is performed for missing MEMS and AQ. In contrast to Vrijens, Labbé et al[68] found that the simple fraction of adherent days for

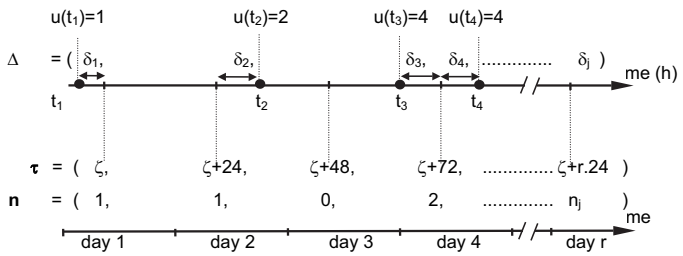

Figure 4. Schematic representation of the transformation of the sequence of dose times, t (● on the upper time line), into the data vectors, n and Δ (a vector of subvectors, δ), using τ, the sequence of nominal dose times, each at within-day time ζ. The integer *r* is the number of the treatment day on which the j^{th} nominal dose time occurs. For the simple once-per-day dosage scheme shown here, j = r. The record does not necessarily terminate at day *r*.

MEMS is as good as moments of the distribution of interdose intervals and fraction of interdose intervals greater than a specific value to explain the viral outcome. Labbé and Verotta[69] have proposed a nonlinear, mixed-effect model characterizing the long-term dynamics of viral load, including resurgence of the HIV virus, in clinical data and quantifying the effect of adherence in the dynamic of HIV1-RNA.

In clinical trials, some patients will dropout (withdraw from a study) prematurely for various reasons. Diggle and Kenwood[70] classified the dropout process (also called persistence) in the following 3 categories: completely random, random, and informative. Completely random dropout may be ignored. Random dropout may be modeled separately of the disease progress, whereas informative dropout must be modeled together with the disease. Hu and Sale[71] proposed a joint, nonlinear mixed-effect model with informative dropout. They explored the impact of the dropout model on the ability of the joint model to predict observed longitudinal data patterns by using data from clinical trials. Their informative dropout model is useful to correct certain biases in modeling longitudinal data with dropouts.

Implications of Adherence Modeling

In this section we discuss the implications of adherence modeling on pharmacotherapy, pharmacoeconomy, clinical trials, and regulatory guidelines.

Therapeutic Implications

Drugs often underperform in the context of routine clinical settings relative to the observed efficacy in controlled clinical trials.[13] The extension of modeling and simulation coupled with therapeutic drug monitoring (TDM) is expected to improve patient response in routine clinical settings, because physicians can intervene to hopefully improve adherence behavior. TDM is an approach to monitor and possibly adjust a drug dose to achieve maximal benefit and/or minimal toxicity via measuring the blood or plasma concentration of the active entity. The TDM procedure most commonly used involves the measurement of drug concentration in the blood or plasma at its lowest value, just before the next scheduled dose (the trough concentration). Many factors are responsible for the varied drug exposure in different people. These include known and unknown genetic variations, as well as differences in absorption, clearance, protein binding, food, and/or concomitant drugs. The patient characteristics and/or clinical setting in which TDM may have the most value during pharmacotherapy are suspected drug-drug or drug-food interactions; states that impair hepatic, gastrointestinal, or renal function; possible sensitivity to high doses in antiretroviral-experienced persons; suspected drug-associated toxicities; lack of response in a patient starting a first regimen; patients at extremes of body weight; women approaching menopause; people taking a once-daily boosted protease inhibitor; pregnancy; childhood; use of >2 drugs that influence cytochrome P450 activity; elderly; change in clinical or physiologic status suspected of causing abnormal drug levels; dose intensification of failing regimens; and salvage therapy.

Among the reasons for not using TDM more routinely, particularly in the United States, are questions regarding the optimal specimen type (eg, total versus free drug assay), the optimal timing for specimen collection (trough, peak, or limited sampling to predict AUC), and dose-adjustment mechanism (based on measured concentration values or outcome driven). Ironically, these are exactly the type of questions that can be explored via modeling and simulation. Model-based methods to assess the clinical utility of patient-specific PK data for antiretroviral agents have been evaluated, and the predictive performance of trough concentrations with respect to "true" drug disposition was assessed in an effort to develop strategies for monitoring drug exposure in HIV-infected patients.[72] Despite such research, most thought leaders would prefer to see a trial in which the outcomes are compared with and without TDM used. Modeling and simulation approaches facilitate both the scheme for TDM assessment and the decision analysis regarding dose adjustments if recommended. The impact of adherence as a covariate or as a response is, likewise, an important consideration in the TDM decision tree.

Pharmacoeconomic Implications

Pharmacoeconomic concerns about cost/adherence have driven a number of investigations on the impact on society in terms of quality of life and cost effectiveness. Modeling and simulation methodologies have been used to assess the economic and quality of life consequences of alternate treatment strategies. Clinical decision analysis models that account for adherence rates and associated outcomes (eg, rehospitalization) have been used to compare direct treatment costs associated with alternate strategies. Goldie et al[73] have used a mathematical model of HIV infection to simulate the effect of alternative adherence interventions and to explore their likely effects on life expectancy, quality-adjusted life expectancy, and lifetime costs. To enhance the generalizability of simulations, the following 3 target patient samples were defined: a clinical trial cohort with early disease, a trial cohort with late disease, and an urban cohort with patients similar to those in the Johns Hopkins Clinic Cohort Trial.[74] Output from simulations suggested that interventions that improve adherence to combination antiretroviral therapy, such that failure rates, are reduced

by at least 10% to 20% and will provide quality-adjusted life expectancy gains of a similar magnitude to opportunistic infection prophylaxis. For patients with early disease, the interventions that reduced virologic failure rates by 10% increased the quality-adjusted life expectancy by 3.2 months, whereas those that reduced the failure by 80% increased the quality-adjusted life expectancy by 34.8 months, as compared with standard care. In patients with advanced disease and those with lower levels of baseline adherence, even very expensive interventions, if moderately effective, would yield cost-effectiveness estimates that compare favorably with other interventions in HIV disease.

Glazer and Ereshefsky[75] have reported on outpatient neuroleptic strategies for "revolving-door" schizophrenic patients in which various antipsychotic treatment options were evaluated; traditional oral neuroleptics, depot neuroleptics, and atypical oral agents (eg, risperidone) were compared. In this setting, a decision-analysis model (based on reasonable outcome probabilities and costs) suggested that, under 5 sets of cost and outcome assumptions, switching to the depot route in a patient with a history of relapse and rehospitalization may reduce the total direct treatment costs by approximately $650 to $2,600 per year compared with an atypical agent and approximately $460 to $1,150/year compared with a traditional oral neuroleptic. A key assumption in this analysis was an adherence rate with an atypical oral drug (80%) equal to that with the depot agent and an average wholesale price of the atypical drug that was 25% lower than current wholesale price; the atypical oral drug treatment option would be approximately $700 less than treatment with a depot agent, and $1,860 less than treatment with a traditional neuroleptic. The proposed model can, of course, be used in other clinical situations, as well as with other associated outcome probabilities and costs. The application of such models in different clinical scenarios associated with different outcome probabilities and treatment costs is likely to provide a framework from which the impact adherence will be evaluated.

Implications on Clinical Trials

Wide intraindividual[76,77] and interindividual[78] variability in adherence has been observed in controlled clinical trials. Patients took an average of 76% (range, 0% to 100%)[79] of the prescribed topical pilocarpine for glaucoma, 76% (range, 30% to 100%)[12] of an oral epileptic, and 81% of a nonsteroidal anti-inflammatory drug (range, 10% to 100%).[17] Adherence in clinical trials is as much a determinant of outcome as in clinical practice.[80] If patients are less than perfectly adherent with an effective therapy, the ITT approach yields a downwardly biased estimate of the method effectiveness and can possibly impact the result of a clinical trial.[78,81] Statistically, poor adherence increases the chance that an ITT approach will fail to reject the null hypothesis when it should be rejected.

The similarity between adherence distributions for a wide variety of ambulatory patients suggests that patient adherence is more related to multivariate behavioral qualities than to pathophysiological conditions. Interventions to improve adherence involve alerting patients to take the drug at each dosing event or counseling behavioral modifications that enable patients to self-medicate.[82] Systems for alerting patients range from notification via e-mail and pagers to having support staff telephone the subject.[7] The most extreme form of intervention is directly observed therapy,[83,84] which requires subjects to visit the study site to receive treatment at every dosing event.

Historically, investigators have had a few options available (Table 3) to address the problem of nonadherence on clinical trial outcome. The conventional solution of choice was to overpower the study, which somewhat addressed the downward bias in nonadherence. This, of course, is a more expensive, less efficient, less informative approach with reduced ability to estimate the drug effect and runs the risk of underestimating the drug response. The randomized adherence trial is yet another approach, but of course it constitutes a separate investment in drug development costs and, basically, is a confirmatory step only (ie, it does not allow for real understanding of nonadherent behavior). These solutions, likewise, do not offer the ability to "learn" about nonadherence but also do not address the ability to modify study designs or to adjust response measures to account for nonadherence.

When analyzed correctly, noncompliance during clinical trials can be viewed as a "natural dosing experiment."[85] This type of analysis fits in with the "learning and confirming" approach proposed by Sheiner.[86] Exploratory modeling and simulation of data from a confirmatory trial may supplement the ITT approach and promote an efficient use of resources, which will yield information most relevant in practice. Girard[87] proposes models as tools for identifying weaknesses or limitations in a study design, which may be anticipated, avoided, or resolved to increase the robustness of the study design before implementation of the actual clinical trial. Ultimately, the quality of the clinical trial results will depend on the quality of the adherence data. Thus, one should use the best tools available to collect reliable dosing histories during clinical trials.

Regulatory Implications

Some consider drugs to be mislabeled if the ITT average values for drug efficacy are offered as the only dosing guidelines.[88] Although the US Food and Drug Administration does not require that the relationship between adher-

Table 3. Approaches to account for drug adherence (28)

Approach	Description	Benefits	Problems
Directly Observed Therapy	Patient receives medication from clinician and his dosing is observed	• Time and amount of dose accurate	• Inefficient
Increase # Subjects	Overpower study to account for nonadherence	• Improve ability to reject null hypothesis	• Inefficient • Does not allow for estimation of true exposure-response
Perform Run-in	Determine in advance of trial who will comply	• Better estimate of true exposure-response	• Adherence to placebo not necessarily same as adherence to drug • Blinding affected • Inefficient • May not generalize to actual population • Don't learn effect of compliance
Test Adherence Patterns	Randomly assign placebos in dosing cycle to evaluate effect of adherence on outcome	• Estimate true exposure-response • No confounding issue	• Ethical concerns • Practical concerns
Formulation Change	Create formulations that promote adherence	• Estimate true exposure-response	• Feasibility
Model Nonadherence	Propose model for nonadherence; use to predict true exposure to drug in exposure-response analysis	• Estimate exposure-response • Evaluate impact of adherence on outcomes	• Adherence measurement error can bias results • Confounding; but can model confounding

ence and response be provided in drug labeling,[80] information on how patients should alter dosing behavior or how adherence will affect drug response is increasingly being incorporated in written materials about drugs. Oral contraceptives and β-blockers were the first drug classes with such information available provided in labeling. The relationship between actual drug intake and response to oral contraceptives was determined via randomized prescribed nonadherence[52,54,89-93] by replacing certain tablets in the cycle to simulate skipping pills. This causal design, one solution to the issue of confounding, may not be readily adapted to other therapeutic areas for ethical reasons. Adherence modeling then offers the ability to provide more descriptive exposure-response relationships that account for nonadherence but also in the direct guidance for managing nonadherence given safety and efficacy concerns.

DISCUSSION

Dosing guidelines are often developed via an iterative process that only begins during clinical trials. Of all of the drugs granted Food and Drug Administration approval between 1980 and 1999, 22% underwent significant postmarketing dose adjustment(s). Most often, the dose originally recommended in product labeling was too high.[94] Reducing the dose over time can have dire consequences on the pricing structure of a drug. More importantly, it jeopardizes patient health and safety. Incorrect dosing is estimated to be the fourth to sixth leading cause of death in the United States. Each year, it is estimated that >100,000 persons in the United States are killed by drugs taken as directed. This statistic excludes adverse drug reactions caused by errors in drug administration, nonadherence, overdose, drug abuse, and therapeutic failure.[95] Whereas some consider this value an overestimate,[96] other research suggests that it may be an underestimate. Approximately 125,000 deaths per year have been attributed to nonadherence with cardiovascular drugs alone.[2] Hence, the investment in modeling and simulation techniques would appear to be well supported by the potential gains in information that is applicable to drug development and therapeutics.

Table 4. Representative approaches of adherence modeling

Modeling Approaches	Objectives	Features	Application Examples
Covariate Model	*Pharmacokinetics*: to characterize adherence effect on exposure	To evaluate adherence effect on pharmacokinetic parameters	Adherence is modeled as a covariate effect on the fraction of drug surviving the first passage across the gut wall (*Fgut*)[62]
	Pharmacodynamics: to characterize adherence effect on response	To identify and quantify adherence effect on pharmacodynamics	Adherence is modeled as a covariate effect on the viral response in HIV-infected patients[69]
Markov Model	To describe adherence patterns of patients by transforming sequences of dose times into data vectors	To model observed dosing times in terms of (i) the nominal dosing times; (ii) the number of doses taken at each of these times; and (iii) the differences between actual dose-taking times and the nominal dosing times	Adherence to zidovudine, an antiretroviral drugs, is described by a Markov model[66]
	To analyze adherence data in function of times	To model adherence data without reducing adherence data to an univariate	Adherence measured by MEMS and questionnaires is incorporated in a Markov model for viral response[68]
Bayesian Model	To use prior information in adherence modeling	To analyze dichotomous data without assuming a normal distribution	Dichotomous adherence data from hypertensive patients is analyzed with Bayesian approach[57]
Logistic Model	To relate adherence to demographic characteristics, outcome or others variables	To determine the relationship between adherence and other variables	Antihypertensive treatment[56]
Causal Model	Instrumental variables	To recover the true exposure-response relationship from studies with nonadherence; only the marginal distributions of adherence to placebo and adherence to drug are required to yield an unbiased estimate of the causal relationship between exposure and response	Vaccines[39]
	Model placebo and drug adherence	Assume: (i) no difference in response between 0% compliers to drug and 0% compliers to treatment, and (ii) adherence is an inherent attribute of the patient	[38]
Measurement Error Model	To choose the most accurate dosing history	Use data from subjects for whom adherence measures agree to select the best dosing history in subjects for whom adherence measures do not agree	[42]
	To calibrate 2 measures of adherence	Efficiently calculate exposure by measuring adherence with an accurate tool in a random subset of subjects when biased adherence information is available in all subjects	[27]

Some measurements (eg, pill count) have little or no value in this endeavor, and others (eg, questionnaire responses) need to be objective, be less reliant on patient memory, and have adequate data density (number of observations) to be useful. The questionnaire coupled with MEMS appears to be the current, best combination of adherence response. The models developed to quantify the impact of drug intake behavior must address the interdependencies of exposure, adherence, and outcomes. Diverse models have been used to establish correlations between adherence and outcomes and also to explore the role of adherence as a factor in exposure-response relationships. Although there are many examples of modeling and simulation techniques in the characterization of exposure-response relationships, the field is still in development, particularly with regard to the application of modeling and simulation to predict adherence behavior. Adherence has lagged as a routine covariate in exposure-response analysis largely because of issues of measurement. The use of adherence information in this regard improved as more accurate and rich measures of adherence became available. It is expected to improve even more, given the increasing availability of rich dosing history data from long-term trials using MEMS devices.[1] It is clear from the published examples that adherence modeling has added value in both drug development science and patient care. There are still more gains to be made in drug development from the standpoint of drug candidate selection (selecting agents that have less likelihood to promote nonadherent behavior), optimizing dose and regimen selection, developing plans for advising patients on what to do if they miss pills, devising alternative dosing regimens, and designing more informative trials. The early adoption of adherence measurement and inclusion in exposure-response modeling may yield more efficient drug development and, ultimately, reduce the cost of pharmacotherapy.

With respect to patient management, modeling approaches should facilitate the identification of subject characteristics that are correlated with adherence. This is highlighted in the modeling and simulation of Girard,[66] which captures drug intake pattern. Modeling affords the ability to pool existing adherence data with the appropriate assignment of measurement errors obtaining more information from historical data by weighting the information on exposure appropriately without the exclusion of data. Modeling coupled with TDM offers yet another mechanism to manage patient outcomes. On the level of individual outcomes, if adherence were predictable, one could use it to direct interventions to improve adherence or use it as a stratifying variable in trial design.

As with all of the models, the performance of adherence models may be judged by the extent to which it fulfills the modeling requirements and study objectives. Adherence modeling efforts have generally fallen into the following 2 main categories: efforts to explain variation in drug exposure, actions, and, ultimately, outcomes; and a means to discriminate nonadherent behavior among patients. In the first setting, adherence is treated as an independent variable and enters the model as a covariate of either PK or pharmacodynamic response. The assignment of the adherence covariate can take many forms (continuous or categorical, univariate or multivariate) and be based on a variety of adherence metrics.

Table 4 summarizes the general approaches to adherence modeling. Modeling adherence, as a response in an effort to understand patterns of nonadherence, has been attempted in a variety of approaches as well. In this setting, modeling nonadherence with a Markov-based approach can address the time-dependency limitation if appropriate measures are used in the expression of adherence. Specifically, many of these approaches have not been able to identify patterns or covariates, because time-averaged measures of adherence (eg, the percentage of taken, pill counts) were used as the response. When multiple tools have been used (eg, adherence questionnaires and MEMS) or adherence over time has been appropriately accounted for, pattern recognition sensitivity has improved, and measurement errors have been more well defined. The requisite models for these approaches are, likewise, much more complex. Their incorporation into trial simulation settings and pharmacoeconomic analyses would represent the most reasonable application of these relationships.

The future application of adherence modeling should benefit from what has been learned to date. Model-based approaches to capture exposure-response relationships that account for adherence should incorporate measurement errors and time dependencies. The use of modeling and simulation approaches to recover the causal relations among adherence, exposure, and response (eg, instrumental variables) permits researchers to address the confounding relations among adherence, response, and exposure. Although we have presented models for adherence measurement error, predictors of adherence, adherence as a covariate for exposure, and response in separate sections, each of these modules can be linked together as needed to address the full complexity of issues in a particular circumstance. Certainly, more work needs to be done in this area, and the theoretical basis for the approach needs to be evaluated clinically via prospective, model-based approach beyond the simulation studies conducted to date. The investment in modeling and simulation techniques would appear to be well supported by the potential gains in information content and, ultimately, drug prescription.

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