Adherence to Medications: Insights Arising from Studies on the Unreliable Link Between Prescribed and Actual Drug Dosing Histories

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Abstract

Satisfactory adherence to aptly prescribed medications is essential for good outcomes of patient care and reliable evaluation of competing modes of drug treatment. The measure of satisfactory adherence is a dosing history that includes timely initiation of dosing plus punctual and persistent execution of the dosing regimen throughout the specified duration of treatment. Standardized terminology for initiation, execution, and persistence of drug dosing is essential for clarity of communication and scientific progress. Electronic methods for compiling drug dosing histories are now the recognized standard for quantifying adherence, the parameters of which support model-based, continuous projections of drug actions and concentrations in plasma that are confirmable by intermittent, direct measurements at single time points. The frequency of inadequate adherence is usually underestimated by pre-electronic methods and thus is clinically unrecognized as a frequent cause of failed treatment or underestimated effectiveness. Intermittent lapses in dosing are potential sources of toxicity through hazardous rebound effects or recurrent first-dose effects.

INTRODUCTION

PK: pharmacokinetic(s)

The topics of this review arise from the prevalence of clinically undetected partial adherence or nonadherence to prescribed medications. Such aspects of partial adherence are common but frequently unrecognized sources of diverse problems in ambulatory medical care. They include (*a*) failed treatment (1–9); (*b*) inappropriate dose escalation (6, 9); (*c*) emergence of drug-resistant, infectious microorganisms such as tuberculosis (3) and human immunodeficiency virus (HIV) (10); (*d*) hazardous rebound or recurrent first-dose effects (11–13); and (*e*) misdiagnosis, when drug response is a diagnostic criterion (14). Partial adherence or nonadherence can also be a confounding factor in the interpretation of clinical trial results, with consequences that include underestimated efficacy of new drugs (15–18), to the point of trial failure (19, 20); underestimated incidence of adverse effects (21); distorted pharmacoeconomic analyses (21, 22); and/or overestimated dosing requirements for marketed pharmaceuticals (23, 24).

Definitive recognition of partial adherence or nonadherence to prescribed medications is based on discrepancies between the patient's dosing history and the prescribed dosing regimen. The advent of automatic, electronic compilation of drug dosing histories of ambulatory patients has provided a basis for accurately identifying with high temporal resolution various types of partial adherence and nonadherence to prescribed medications in clinical trials and practice. Electronic monitoring methods were first used in 1977 (25). Prior to this, methods of assessing adherence—counts of returned, untaken doses; questionnaires; histories; diaries; assays of drug concentration in plasma (26); and audits of prescription refills—gave only fragmentary glimpses of an ambulatory patient's dosing history, typically indicating that doses must have been omitted but at indeterminable times (27–29).

Most forms of ambulatory pharmacotherapy are prescribed to achieve continuous therapeutic action for a defined period of time for acute conditions or indefinitely for some conditions. Yet pharmacological effects are subject to (*a*) intermittent interruption during periods of dose omission or (*b*) complete cessation, usually within hours or days after dosing ceases. Interpretation and understanding of such temporal patterns of interrupted drug actions are informed by richly sampled dosing history data. Recent advances in measurement and analysis make it possible to gather and analyze essentially complete dosing histories of ambulatory patients, and, through established pharmacometric methods, to project the associated time-courses of drug concentrations in body fluids and drug actions (30, 31). In this article, we focus on several foreseeable but as-yet partially achieved prospects: After being electronically captured in real time, drug dosing history data are validated as necessary, stored, and communicated when needed across distances or recalled as needed for timely management of adherence to improve decision making during drug development, regulatory review, and health-economic review.

Patient adherence is the crucial link between a prescribed effective medication and successful management of disease. The therapeutic importance of patient adherence is captured in an epigram of former U.S. Surgeon General C. Everett Koop: "Drugs don't work in patients who don't take them." One could add this corollary: Drugs work erratically in patients who take them erratically.

In modeling the sources of variance in drug response, Harter & Peck (32) estimated that variable adherence vies with pharmacokinetics (PK) as the leading source of variance in drug response in ambulatory care settings. Since then, a great deal of evidence that supports this assertion has accumulated. In contrast, unexplained variation in a patient's response to a prescribed drug has many possible sources and consequences. When, for example, a patient has an unexpectedly small response to a medication, some providers seek reasons, but the most common outcome is an escalation in the frequency of dosing or in the dosage of the prescription (14). Accurate dosing histories make possible a positive diagnosis of partial adherence or nonadherence to the prescribed dosing regimen and may resolve ambiguities about drug action, inaction, or harmful action.

Until recently, however, providers usually have had to rely on the patient for information about his/her use of the medication, even though such information is subject to problems of recall and various barriers to candor (33). Patients have multiple reasons for withholding accurate dosing history information; analysis of such reasons is a major topic in its own right but beyond the scope of this review, which focuses on the consequences of deviations from the prescribed regimens. The advent of electronic monitoring for gathering dosing history data of ambulatory patients has put the dosing history and its analysis on an objective, accurate basis, free of the subjectivity and major uncertainties that afflicted research on adherence in previous years. Many prescribers, however, still mistakenly believe that they can judge a patient's exposure to prescribed medications on clinical grounds, despite many studies showing that physicians usually overestimate the adherence of their patients to prescribed medications (34). Computerized pharmacy records of prescription refills are useful for epidemiological screening purposes but cannot project the PK and pharmacodynamic (PD) consequences of incomplete adherence because of their very low rate of data acquisition, which results from the frequency (two to six times per year) that most prescriptions are refilled. Moreover, these records provide no information on dosing patterns during the long intervals between successive refills.

PD: pharmacodynamic(s)

Thus far, most of the experience with electronically monitored drug dosing histories has been acquired in relatively small clinical studies, many of which sought to compare results of electronic and other methods of measuring ambulatory patients' exposure to prescribed medications. Such results are published in >570 peer-reviewed clinical research publications, listed on the iAdherence Web site at **http://www.iadherence.org**. The principal focus of that compilation has been on methodological comparisons and has not directed attention to important, recurring clinical problems that lead to questions such as, How often does clinically unrecognized nonadherence masquerade as drug resistance? How often does partial execution of dosing regimens mislead drug research strategies because of unrecognized type II errors in trial results? How often and by how much are therapeutic and pharmacoeconomic benefits compromised by underdosing? To what extent is it possible to achieve satisfactory adherence via management methods? What is the definitive method for determining satisfactory adherence? Answers to these and other compelling questions in clinical care and pharmaceutical research and development await further research with objective, precise assessment of patient adherence to prescribed medications, in both trials and practice.

TAXONOMY OF DOSING ERRORS IN AMBULATORY PHARMACOTHERAPY

A flourishing and burgeoning literature has developed in the four decades since serious adherence research began (a Medline search of the term "patient compliance" in March 2011 turned up 41,763 papers). This literature coexists, however, with conceptual confusion about the terms used to describe deviations from prescribed dosing regimens. Different terms, such as **compliance**, **adherence**, **persistence**, and **concordance**, have been used to define the act of seeking medical attention, acquiring prescriptions, and taking medicines appropriately. Although often used interchangeably, these terms imply different views about the relationship between patients and caregivers. The result is a lack of uniformity in terminology used to describe deviations from prescribed therapies; thus, there is a need for a sound taxonomy that supports quantifiable parameters rooted in both behavioral and pharmacological science.

This need has been addressed by a European Union (EU) project named ABC (Ascertaining Barriers for Compliance) that began in January 2009 as an international collaboration of researchers studying adherence. The objective of the ABC Project, which is sponsored by the

PDT: prescribed doses taken

Seventh Framework Program of the EU, is to produce evidence-based recommendations for quantifying and improving patient adherence in order to provide safer, more effective, and more cost-effective use of prescribed medications (**http://www.ABCproject.eu/**). The partners in this project have identified the different conceptual approaches to adherence research and have derived, through multidisciplinary consensus, a new taxonomy and associated terminology that have been extensively evaluated (B. Vrijens, personal communication).

Adherence to medications has been identified as the most relevant and explicit terminology to define the process by which patients take their medications as prescribed (B. Vrijens, S. De Geest, D. Hughes, P. Kardas, J. Demonceau, et al., unpublished data). Adherence has three components: initiation, execution, and discontinuation. The process starts with initiation of the treatment (35), which occurs when the patient takes the first dose of a prescribed medication. The process ends (discontinuation) when the patient stops taking the prescribed medication. The intervening part of the process is the execution phase of the dosing regimen, defined as the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until discontinuation. The time from a prescribed medicine's initiation to its discontinuation is known as persistence.

The term patient compliance, although essentially synonymous with medication adherence, has a widely perceived, somewhat negative connotation that limits the term's utility as the main descriptor of deviations between prescribed and actual exposure of ambulatory patients to medications. Another limiting factor is the varied use of the term compliance in other biomedical fields (e.g., compliance with drug regulations, compliance with good clinical practice, compliance with good manufacturing practice, and mechanical compliance of cardiac chambers, arteries, veins, lungs, and the chest wall).

We illustrate the components of adherence to medications in **Figure 1** and adherence in a cohort of patients in **Figure 2**. Each of the four patients in **Figure 2** has taken 90% of his/her prescribed once-daily dose over a period of 1 year. Each individual's dosing history can be visualized through a chronology plot that displays the time of each dose on a scatter plot of 24-h clock time of the opening of the bottle containing the drug (ordinate) and calendar date (abscissa). The electronically compiled drug dosing history data reveal major differences in the dynamics over time of the three components of adherence to medications, although the aggregate percentage of prescribed doses taken (PDT) is essentially the same in each case.

Figure 1 summarizes the components of medication adherence in a cohort of 16,907 participants derived from 95 clinical studies ranging from 30 to 1,400 days. The persistence line represents the decline over time from the start of treatment in the proportion of trial participants still engaged with the dosing regimen. By the end of 1 year, almost 40% of the participants who started treatment in these clinical trials had stopped taking the medication(s), despite the protocol-specified regimen of continuously maintained dosing. The initial abrupt small drop in the persistence curve represents the proportion of participants who never initiated the dosing regimen. These occurrences of noninitiation represent 4% of this study population, although noninitiation is higher in other settings (35). After the initial sharp but small drop of noninitiation, the persistence curve decreases gradually but progressively over time. For example, at day 100, 20% of the participants had stopped the medication(s)—that is, only 80% persisted with treatment. Also on day 100, among the participants still engaged with the dosing regimen, 12% did not take their medication (nonexecution). The percentage of the trial participants constituting the inception cohort who took their dose on day 100 is thus 70% (88% $\times$ 80%), which is a measure of the overall shortfall in drug intake.

Short persistence accounts for the largest numerical fall in adherence to medications. Suboptimal execution represents a smaller numerical fall but is often recurrent and, as illustrated in **Figure 2**, can take many different forms that can jeopardize treatment effectiveness, ultimately

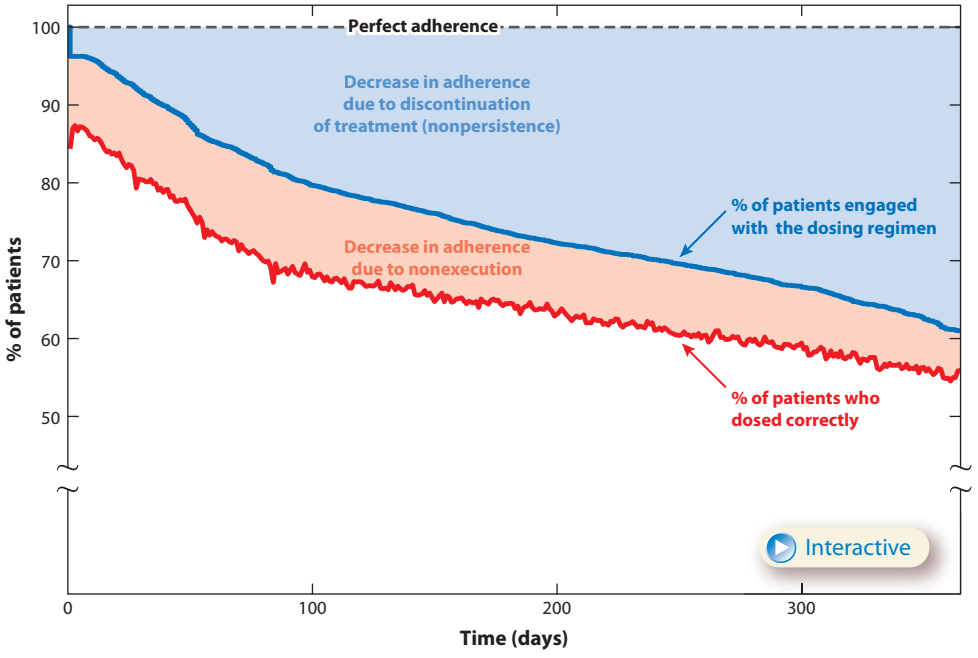

Figure 1

Kaplan-Meier plots of the time-course of adherence parameters of 16,907 patients prescribed oral medications for one of a variety of medical conditions in 95 studies, during the first year of electronic compilation of the patients' dosing histories. The horizontal dashed line at the top illustrates how perfect adherence of all patients would be depicted. The blue line shows the percentage of patients still engaged with their dosing regimen as time passed after the start of treatment. The abrupt drop in the blue line at zero time reflects noninitiation of treatment by approximately 4% of the patients. Thereafter, the decline of the blue line indicates patients' permanent discontinuation of their engagement with the dosing regimen, which occurred at a somewhat higher rate during the first 100 days than later. The red line shows the percentage of patients who dosed correctly on each day after the start of the observation period. Thus, the red line wobbles slightly from day to day. The pink area between the blue and red lines indicates the shortfall in drug exposure arising from missed doses. The light blue area between the horizontal dashed line and the blue line indicates the shortfall in drug exposure arising from noninitiation by approximately 4% of patients and subsequently from short persistence with the prescribed dosing regimen by approximately 35% of patients. Data from the iAdherence database. (An interactive version of this figure is available online; access the PowerPoint version of the figure from the journal's home page at **http://pharmtox.annualreviews.org/**.)

leading to treatment discontinuation. **Figure 3*a*** illustrates the large variability in persistence when stratified by medical conditions, and **Figure 3*b*** illustrates the strong association between execution and persistence by showing the persistence curves stratified by execution levels. These results thus indicate that a large proportion of patients with a variety of clinically important conditions are not receiving optimal treatment within the first few months after initiating drug therapy.

MAGNITUDE AND IMPORTANCE OF THE PROBLEM IN DRUG DEVELOPMENT AND TYPICAL USE

Many researchers and health care providers assume that nearly perfect adherence prevails in randomized, controlled clinical trials, but reliable data clearly show otherwise. Thus, trials whose

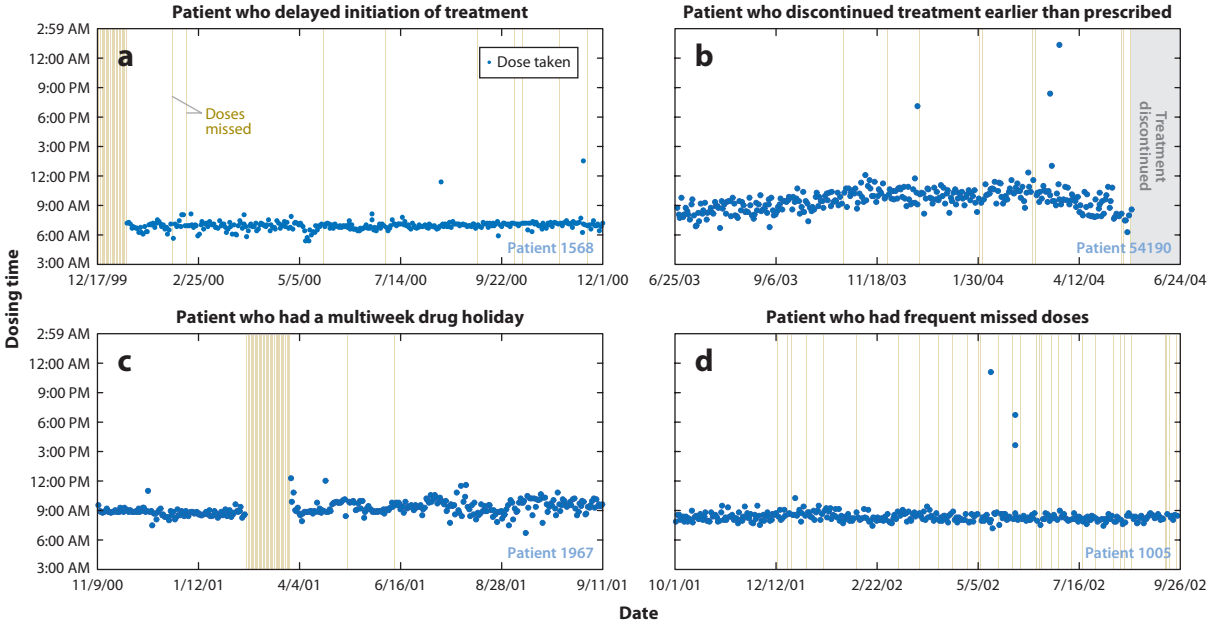

Figure 2

Dosing chronology plots of four patients. Calendar date (mm/dd/yy) is shown on the horizontal axis, and 24-h clock time is shown on the vertical axis. Each blue dot indicates the electronically recorded time and date of dosing. The vertical tan lines depict missed doses. Extended periods without dosing (drug holidays) are shown by vertical tan bars, the width of which reflects the number of days without dosing. During the depicted periods of study, each patient took 90–91% of prescribed doses, with the indicated wide variations in the temporal patterns of dose omissions. Data from the iAdherence database.

results are used to make crucial decisions during clinical drug development are affected by variable, mostly unrecognized deviations from the prescribed dosing regimen: (*a*) delayed onset; (*b*) underdosing, with or without intermittent complete lapses; and (*c*) early, complete cessation. Importantly, these errors jeopardize Phase 2 trials designed to address critical issues of efficacy or proof of concept and also jeopardize the selection of optimal dosing regimens for Phase 3 registration (confirmatory) trials and beyond.

An increasing body of evidence indicates that variable degrees of underdosing are prevalent in drug trials involving ambulatory patients. Extensive data that support this conclusion can be found in the largest open-source database of drug dosing histories, the Pharmionic Knowledge Centre (PKC®) Database on the iAdherence Web site (**http://www.iadherence.org**). (Pharmionics is the discipline concerned with the study of how patients actually take prescribed medicines.) This database includes 95 clinical studies that range in duration from 15 to 1,400 days, including almost 19,000 subjects/patients whose regimens called for dosing daily (11,643 patients), twice daily (3,731 patients), thrice daily (1,308 patients), and four times daily (225 patients). It also contains results for 28 therapeutic areas, including diseases in which poor outcomes are associated with failures to initiate, execute, or continue dosing of prescribed drugs that are thought to have critical importance in the care of the trial subjects. Such diseases and clinical conditions include, for example, patients with organ transplants (36–39), with HIV infection (5, 10, 40, 41), requiring breast cancer prophylaxis (42, 43), and being treated for heart failure (44–49). Numerous other references describe problems of nonadherence in clinical trials during drug development (e.g., 15, 17, 19).

Pharmionics: the discipline concerned with the study of how patients actually take prescribed medicines

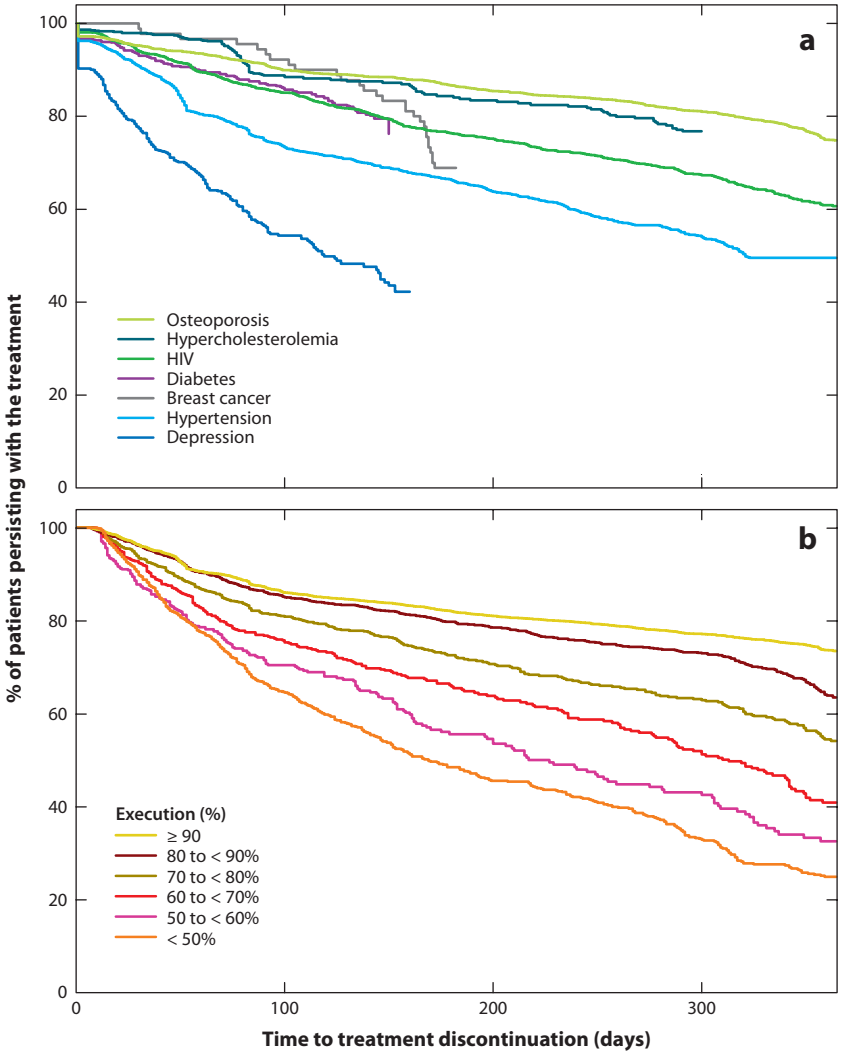

Figure 3

Noninitiation and short persistence in seven disease conditions, based on Kaplan-Meier persistence curves across (*a*) therapeutic areas, and (*b*) percentages of prescribed drug taken (execution). (*a*) Note the between-disease differences in the percentage of patients who did initiate the prescribed treatment. (*b*) Relationships between the quality of regimen execution, in percentage of prescribed doses taken, and persistence. Data from the iAdherence database.

An excellent summary of early research based on electronic medication-event monitoring is in the book edited by Cramer & Spilker, *Patient Compliance in Medical Practice and Clinical Trials* (50). Two of the pioneers of electronic monitoring, Gordon & Kass (51, p. 172), pointed out that "the [electronic] monitor provides far more detailed information about medication compliance than the patient can possibly be expected to provide," noting recurring patterns of mistimed dosing likely to impair effectiveness or induce toxicity.

Several problems may result from noninitiation, poor execution, and/or early discontinuation in premarketing trials, which alone or in combination may dilute estimates of the efficacy of a

drug under investigation. These can include a Type II error and termination of the development of a promising agent or class of agents. Moreover, a Type II error has the potential to misdirect medicinal chemical strategies away from alternative leads that may offer more "forgiveness" to missed doses. Thus, the analysis of a failed trial should include an assessment of the roles played by each of the main sources of variance in drug response and their origins. The same logic applies to a failed treatment in medical practice. Part of the value of dosing histories in clinical trials lies in their ability to provide insights into the causes of failure, in keeping with the learn/confirm paradigm in drug development (52).

Detailed drug dosing histories can also be used to project continuous estimates of drug concentrations in plasma (30, 31). The basic effect of these maneuvers is to quantify the two biggest sources of unallocated variance, adherence and PK, and to help explain clinical events. Such data also have the potential to provide quantitative estimates that can answer the question "How much adherence is enough?" to define, for example, a degree of drug exposure that maximizes the likelihood of achieving virological control in the management of HIV infections (5, 7, 41, 53).

Avoidance of Type II errors in Phase 2 trials can be facilitated by careful attention to the recognized sources of variance in drug response, as outlined in the Harter-Peck model (32), and the risk of a Type II error can be quantitatively assessed by modeling and simulation studies based on crucial measurements. It is therefore surprising that Phase 2 trials, especially those of drugs assessed in ambulatory patients, do not routinely collect data for drug dosing history. Dosing histories provide a data-rich, low-cost set of measurements that can expose otherwise undetected gaps in adherence, which can be a primary reason for a failed trial. When combined with measurements of drugs in plasma, dosing histories allow accurate, subject-specific projections of the entire time-course of drug concentrations in plasma (30, 31). From the dosing history, one can identify discrepancies between projected and actual dosing-dependent concentrations of the test drug in plasma—another data-rich, low-cost set of measurements that can be combined with biomarker data and serial measurements of drug action to define the dose dependence and concentration dependence of a drug's actions. The added dimension provided by drug dosing history data can enrich PK/PD models and thus be useful in establishing robust, recommended dosing regimens in Phase 3 studies and beyond. Adherence problems, particularly when unrecognized or undocumented in Phases 2 or 3 trials, can result in an underestimate of the effectiveness of a drug as typically administered (54). This problem is illustrated in **Figure 4**.

During the premarketing phases of drug development, the goal is to estimate not only the efficacy and toxicity but also the forgiveness of the drug being tested. Forgiveness has both PK and PD components (55, 56), the latter becoming apparent when the therapeutic actions of a drug continue in the face of variously long gaps in the dosing history, occurring during happenstance variations of drug intake or purposely imposed gaps in dosing (57–59). Understanding the time- and exposure-dependent drug actions under various conditions of disease severity and against the backdrop of the drug's basic dose-response and concentration-response relationships can be the foundation not only for robust efficacy, and proof thereof, but also for the selection of an optimal dosing regimen that maximally uses forgiveness and minimizes the likelihood of a postmarketing/postpricing reduction in the label-recommended dosing regimen (23, 24, 56, 60).

These considerations assume increased importance with the growing emphasis on comparative effectiveness research. Patient adherence and the product's forgiveness are two principal factors in determining, for a given degree of product efficacy, the comparative effectiveness of different products in the real world, in which partial adherence is likely to be an important contributor to deteriorated effectiveness.

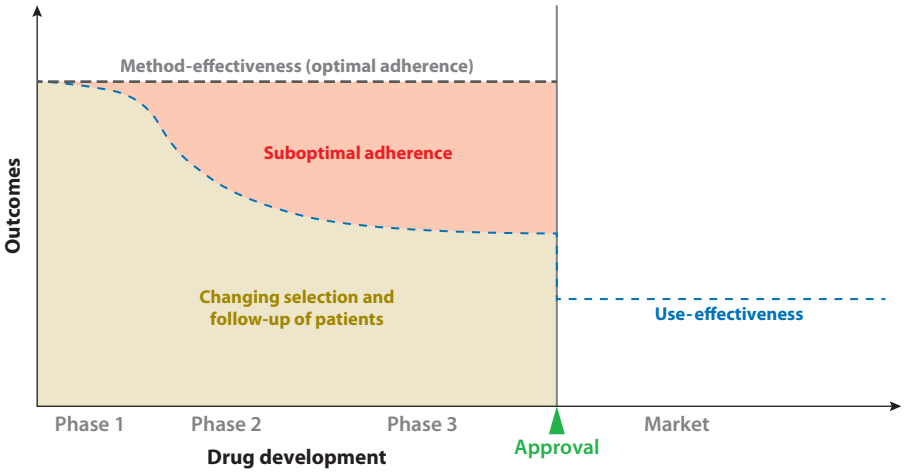

Figure 4

Idealized schematic projection of changes in adherence and changes in treatment outcomes during successive phases of clinical drug development. The gap between use-effectiveness and method-effectiveness increases as adherence declines during progressively less strict management of patients' medication and progressively more varied severity of disease and comorbidities of treated patients. In a perfect world, use-effectiveness and method-effectiveness would be equal.

PHARMACOKINETIC AND PHARMACODYNAMIC CORRELATES OF VARIABLE ADHERENCE

A diversity of temporal patterns of drug dosing is revealed by electronic monitoring because of its ability to resolve the times of occurrence of the medication events from which dosing times, and thus drug exposure, are projected. The ensuing variety of temporal patterns of drug exposure creates, in turn, a variety of temporal patterns of: (*a*) concentrations of a drug in plasma (PK) and (*b*) actions of the drug (PD).

Pharmacokinetic Correlates

The vast majority of prescriptions call for regular ingestion of one or more dosage forms at a stated interval or frequency. Whether specified by dosing interval or frequency, the usual prescription anticipates metronome-like repetition of ingestion of the specified doses. **Figure 5** shows the plasma concentration profile of a drug taken at regular intervals as prescribed, in this case daily. The superimposed line shows the plasma concentration profile in a patient with the same PK parameters who varies the time interval between doses (e.g., misses some doses or takes extra doses). A delay in the ingestion of the next-scheduled dose is the most commonly recurring deviation from the prescribed regimen.

If the next dose is delayed, the concentration of drug in plasma continues to decline until a dose is taken, at which time the concentration rises to a peak that is lower than what would have occurred had the dose been taken at the prescribed time. If the next dose is taken at a time sooner than prescribed, the concentration of drug in plasma rises to a higher-than-usual peak because the rise starts from a higher-than-usual concentration. An exceptionally long or short interval between doses may require a sequence of several correctly timed doses until the cyclic pattern of peak and trough concentrations of drug in plasma returns to values that are essentially the same from one cycle to the next.

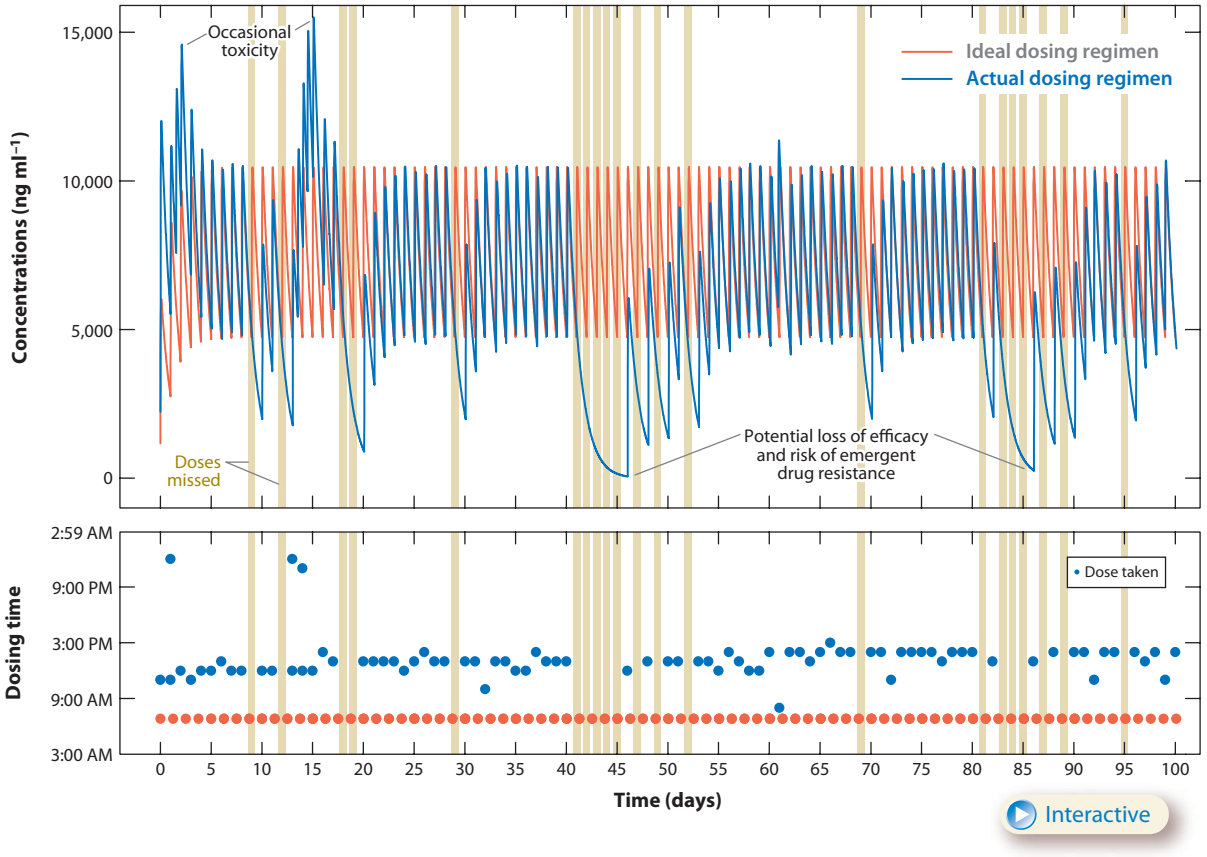

Figure 5

Dosing chronology (*lower plot*) and model-based projections (*upper plot*) of the concentration in plasma of an antiretroviral protease inhibitor under two dosing conditions. The red dots in the lower plot indicate a hypothetical prescribed drug dosing regimen that is perfectly executed: There are no missed doses and no variations in daily dosing times. The associated fluctuating red line in the upper plot shows the projected time-course of drug concentration in plasma associated with perfect execution of the once-daily dosing regimen. In contrast, the blue dots in the lower plot indicate electronically captured dosing times of an HIV-infected patient's execution of his prescribed, once-daily regimen of an antiretroviral protease inhibitor. Omitted doses are indicated by the vertical tan bars, each of which indicates a single omitted dose. The blue line in the upper plot shows the model-projected continuous time-course of the concentration of the electronically monitored antiretroviral protease inhibitor (31). Lapses in dosing lead to lower-than-usual projected concentrations of drug, and extra doses lead to higher-than-usual projected concentrations of drug. Data from the iAdherence database. (An interactive version of this figure is available online; access the PowerPoint version of the figure from the journal's home page at **http://pharmtox.annualreviews.org/**.)

Projecting Drug Concentrations in Plasma

PK models are capable of projecting the time-course of drug concentration in plasma from accurate dosing history data. Strong experimental evidence supports the validity of that method. Such evidence was first reported by Rubio et al. (30) in 1992 in a study of the drug diltiazem, in which the patients' sequential openings of the electronically monitored drug package were time stamped, thus creating the dosing history. Those data, along with blood sampled at carefully recorded times and the plasma concentration of diltiazem measured in those samples, were used as input to a

model of diltiazem's PK and to project the entire time-course of diltiazem's concentration in plasma during the experiment.

A decade and a half later, Vrijens et al. (31) carried out a similar analysis on 35 HIV+ patients participating in a 1-year PK study on ritonavir-boosted lopinavir. Six blood samples were drawn from each of the 35 subjects at intervals throughout the 1-year study, for the measurement of the plasma concentration of lopinavir. In parallel, each patient's twice-daily dose of the ritonavir-lopinavir combination was dispensed from a MEMS^{TM} monitor, with each patient's dosing history fully compiled throughout the 1-year study. Analysis of the residual errors between the projected and measured concentrations in plasma showed that only 3 of the 216 samples were outside the statistical range of concentrations identical to the projected concentrations of lopinavir at the times of blood sampling. The residuals were distributed symmetrically around zero and had uniform variance. These results constitute a robust validation of electronic medication-event monitoring as a method for compiling drug dosing history data in ambulatory patients.

The methods used here illustrate the use of electronic monitoring data to generate complete time-histories of drug concentration in plasma over extended periods of time, thus putting the evaluation of drug concentrations on a continuous basis. Such continuous monitoring contrasts with traditional single-time-point analysis, an approach that contributes to the random basis that can characterize therapeutic drug monitoring and that, in addition, is subject to the bias of white-coat adherence (26, 61, 62). Further validation studies will be necessary, but the availability of reliable, continuously projected concentrations of drug in plasma should bring new insights into the interpretation of drug concentration data in many clinical situations, without the costs and inconvenience of multiple venipunctures and the use of assays conducted at single time points.

Pharmacodynamic Aspects of Variable Adherence to Prescribed Drug Dosing Regimens

The output of the PK model for a drug is the time-varying concentration of drug in blood or plasma. That PK output is, in turn, the input to the drug's PD model, and the output of the PD model is the time-course of the drug's ensuing actions.

Some aspects of modeling and simulation. The output of a PK model that uses the actual dosing history as input is the time-varying concentration of drug in blood or plasma that is, in turn, the input to a model of the drug's PD. It is advisable to select measurable entities as key variables, not derived factors such as ratios or percentages. In circumstances in which the binding of the drug to plasma proteins partitions drug (or hormone) between bound and unbound moieties, it is also advisable to utilize both concentrations.

In both pharmacology and endocrinology, the typical dose-response or concentration-response relationship is often described by an Emax model (see **Figure 6**) showing that the concentration-response relationship has a high-slope region at lower concentrations and transitions into a low-slope or virtually zero-slope region at higher concentrations. In the high-slope region, small variations in the concentration of an agent have a strong influence on the agent's actions. In contrast, variations in the concentration of the agent in the low-slope region have a relatively weak influence on the agent's action, verging on zero effect as the concentration-response relationship approaches a slope near zero. For a full discussion, see the monograph by Rowland & Tozer (63), pp. 36–43.

Attenuation of variance in the low-slope region. Variations in either concentration or dose, arising from variations in adherence, have muted or even negligible effects, as long as the system is

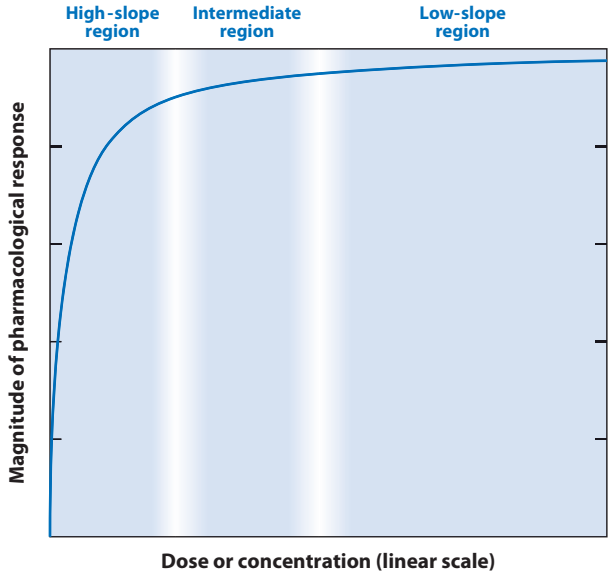

Figure 6

Idealized schematic of a relationship of drug response to changes in drug concentration plotted on a linear, arithmetic scale. The arithmetic scale reveals the large changes in slope that are hidden when dose or concentration is plotted on a logarithmic scale.

operating in the low- to zero-slope region of the concentration-response curve. Changes in drug concentration in this region allow for relative constancy of drug actions despite variability arising from PK factors or adherence-related variations in exposure to the drug. Because the latter usually involve underdosing, they tend to lower the system's operating point toward the high-slope region of the concentration-response relationship, in which small changes in drug concentration result in relatively large changes in drug action. The foregoing exemplifies one type of nonlinearity inherent in PD. Another type is the Pythagorean nonlinearity, described below.

The Pythagorean nonlinearity in the confluence of variance arising from multiple sources. The term Pythagorean arises from the principle that confluent variance, arising from multiple sources, is the square root of the sum of the squares of the variances due to each source. This nonlinearity limits what can be gained from applications of research (e.g., pharmacogenomics) that strongly impact some, but not all, sources of variance.

Harter & Peck identified four major sources of variance in drug response: drug formulation, patient adherence, PK, and PD (32). Their work provoked debate about the relative magnitudes of variance assigned to these four sources and diverted attention from the nonlinearity in the confluence of multisource variances. The achievement of a substantial reduction in overall variation requires a substantial reduction in each major source of variance. In the case of drug responses, there are three major sources of variance: variability in patient adherence, variability in PK, and variability in PD.

For therapeutics, striking reductions in either PK- or PD-derived sources of variance are predicted to result in disappointingly small effects on the overall variance in drug response. To illustrate, we use the original values of Harter & Peck (**Figure 7**), who chose coefficients of variation (CV) to express variance and assigned the following CVs to each of the four sources: drug formulation, 20%; patient adherence, 50%; PK, 50%; and PD, 30%.

CV: coefficients of variation

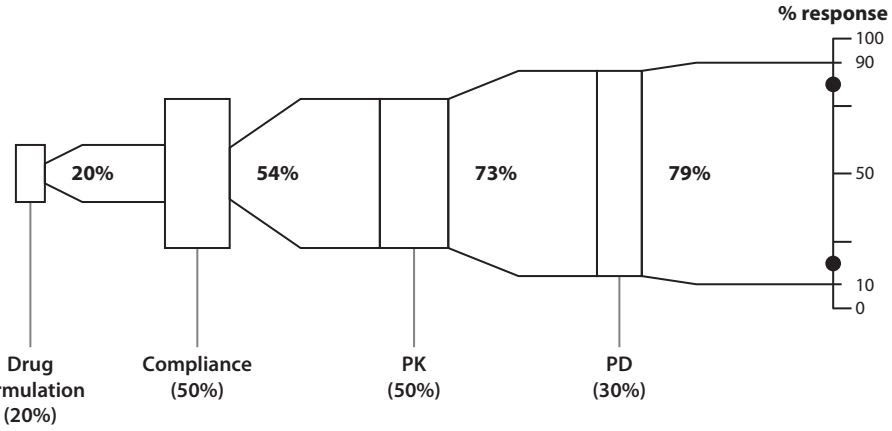

Figure 7

Sources of variability in drug response, as plotted by Harter & Peck (32), to show the nonlinear confluence of variance from its main sources. Abbreviations: PD, pharmacodynamics; PK, pharmacokinetics. Reproduced from Reference 32 with permission.

Thus, the sum of the squares is $400 + 2{,}500 + 2{,}500 + 900 = 6{,}300$, the square root of which is 79.4%—a high-end estimate of variation in drug response, based on the choice of the highly variable drug theophylline as a focus for analysis. With a standard deviation of drug response of ~80% of the mean, the predictability of the response to a given dose of the drug is very low. This leads to the question, How could the variability in response to such a drug be reduced, apart from switching to a less variable drug? If one looks toward applying pharmacogenomics to the variance arising from PK and PD and makes the optimistic assumption that nine-tenths of the CVs attributable to PK and PD can be reduced by using pharmacogenetic information, the resulting square root of the sum of the squares is 54.2%—a modest 32% reduction in overall variance. If we were also able to reduce variance in formulation from 20% to 2%, the overall variance drops only from 54.2% to 51.1%. This illustration demonstrates that a major reduction in overall variance can be obtained only if major reductions are achieved in each of the high sources of variance, which, importantly, include a major reduction in variations due to partial or nonadherence. There are few data on the magnitude of the reduction in the variance that can be achieved through the use of patient-specific pharmacogenetic data. A paper often cited is Klein et al. (65), which reports that only a modest reduction in the variation in warfarin dosage was found when a genetic test was used to predict dose requirements. In our example here, we show that even an "optimistic" reduction (90%) in the variability resulting from genetic differences leads to only a small improvement in overall variability in response.

Asymmetries in "on" and "off" responses to drug treatment. In general, much more attention is paid to the events associated with starting drug treatment than to those associated with stopping drug treatment. Yet the time-courses for the onset and offset of drug responses are often quite different. Following the cessation of dosing, the time-course of drug concentrations (i.e., PK) is usually completely predictable. In contrast, the time-course of drug actions (i.e., PD) following the cessation of dosing is often unpredictable and may differ substantially from the time-course of drug actions at the onset of dosing. These asymmetries can arise from many possible reasons, such as differences in the on/off rates of drug-receptor interactions (e.g. with omeprazole),

altered expression or sensitivity of receptors (β-blockers, clonidine), and induction or inhibition of cytochrome P450 enzymes (many drugs).

Adherence research has revealed a previously unsuspected high frequency of interruptions in dosing, which create repeated instances of sequences of onset and offset of drug action in individual patients (see **Figure 2**). Vrijens et al. (64) studied the dosing patterns of 4,783 patients treated with once-daily antihypertensive drugs of recent vintage that have few or no side effects. They found that only 5% of the patients went through their first year of treatment with no interruptions in dosing, i.e., one onset of dosing per patient per year in that small subgroup of patients. The authors also found that approximately 50% of patients completely stopped treatment during the first year, usually after several weeks of multiple dosing interruptions of varying lengths. Furthermore, they found that in the ~50% of patients who continued dosing throughout the year, most had recurring temporary holiday-type interruptions (i.e., onsets and offsets) in dosing. A full understanding of the PD of each of the 20+ agents involved in this study would have to include careful characterization of responses to the start of dosing, to the cessation of dosing after variously long intervals of more or less constant exposure to the agent, and to the resumption of dosing after variously long intervals without exposure to the agent (see **Supplemental sidebar**, A Minimal Cassette of Temporal Patterns of Drug Administration; follow the **Supplemental Materials link** from the Annual Reviews home page at **http://www.annualreviews.org**).

Supplemental Material

These observations of multiple episodes of starting and stopping dosing serve as a reminder that first-dose effects may occur frequently. In addition, such effects especially apply to asymptomatic diseases, such as hypertension and other cardiovascular diseases. These settings sometimes involve the administration of drugs that have hazardous rebound effects upon sudden cessation of dosing [e.g., non–intrinsic sympathomimetic activity (non-ISA) and ISA β adrenergic receptor antagonists (12) and central α receptor agonists (66)] or that have hazardous first-dose effects upon abrupt onset of full-strength dosing (e.g., some α_1-adrenergic receptor blockers, such as doxazosin and prazosin) (67).

Anti-arrhythmic agents represent a therapeutic category of drugs with especially great problems associated with on-off-on dosing. A number of these agents are prone to hazardous pro-arrhythmic first-dose effects. To avoid these potentially hazardous, even fatal, pro-arrhythmic effects at the start of treatment with these agents, clinicians titrate patients carefully with a multiday sequence of small stepwise increases in dose until the desired therapeutic dose level is reached. The risk of first-dose effects raises the possibility that such drugs might produce fatal arrhythmias when patients resume full-strength dosing after multiday lapses in dosing. The ubiquity of multiday, or holiday, lapses in dosing in every other field of ambulatory therapeutics studied thus far suggests that multiday lapses in dosing occur with anti-arrhythmic drugs. Whether the holiday patterns of interrupted dosing contribute substantially to the mortality of ambulatory patients who are prescribed anti-arrhythmic drugs awaits proper measurements.

Role of intermittent dosing in the emergence of drug resistance. Broad consensus holds that intermittent, suboptimal dosing of anti-infective agents is a leading cause of the emergence of drug-resistant microorganisms (68, 69). The argument is as follows: Lapsed dosing initiates a decline in plasma concentrations of the anti-infective agent. If the lapse is long enough, the concentrations of drug in plasma and infected tissues become sufficiently low to allow the infecting agent to resume replication, which is accompanied by mutations, some of which may be resistant to the prescribed anti-infective agent. Researchers have postulated an intermediate concentration of the anti-infective agent that is low enough to allow resumption of replication but high enough to exert selection pressure on drug-sensitive microorganisms—not those with a mutation-acquired resistance to the anti-infective agent, however, allowing the latter to prevail (7, 70, 71). This

phenomenon is widely believed by investigators to occur for bacteria, viruses, various parasites, and insects. It is not clear if such adaptation also contributes to drug resistance in oncology.

An intriguing question is the impact of on-off-on patterns of dosing, which are common in disease settings such as hypertension, lipid management, and osteoporosis, and therapies directed at specific metabolic targets such as the BCR-ABL1 tyrosine kinase of chronic myelogenous leukemia that is inhibited by imatinib. If that inhibition alternates between on and off, owing to erratic adherence to imatinib, does it allow imatinib resistance to gain predominance and thus allow the leukemic cells to escape from the therapeutic benefits of the drug (9)? See the further discussion below.

A note on forgiveness. The term forgiveness was coined as a way to define the impact of lapses in dosing of various lengths. The original definition of forgiveness is "the post-dose duration of therapeutically effective drug action, minus the recommended interval between doses" (55, p. 458; 72, p. 215). Thus, an agent such as amlodipine (used in the treatment of hypertension), which has a postdose duration of therapeutically effective action of approximately 72 h and a once-daily dosing regimen, has a forgiveness of 72 h – 24 h = 48 h (73). One can estimate that the omission of two successive once-daily doses of amlodipine could be incurred with minimal loss of therapeutic action, assuming resumption of dosing by ~48 h after the scheduled time of the first missed dose. A more realistic view recognizes that transitions between therapeutically effective and ineffective actions are not switch-like but instead are gradual. The paper by Lowy et al. (74) explicitly represents a gradual transition between on and off after a last-taken dose.

A further step toward more realistic application of the forgiveness principle is to recognize that forgiveness carries an implicit promise about how long one expects therapeutic effects to prevail in the face of sequentially omitted doses. In keeping with that view, it has been suggested (55, 72) that the optimal definition of postdose duration of effective therapeutic action should be based not on population averages but on a definable point among outliers who have the shortest durations of effective therapeutic action. If that definition is used, the vast majority of treated patients would be expected to realize at least the forgiveness provided by that minimum period of postdose duration of drug action.

Using the minimal cassette to characterize pharmacodynamics. As illustrated in **Figure 2**, the dosing histories of many ambulatory patients reveal that long-term drug treatment of chronic diseases frequently involves recurrent lapses in dosing for various periods of time, followed by usually abrupt resumption of dosing. Then, after varyingly long periods of resumed dosing, cessation of dosing may recur. These on-off-on cycles of drug exposure occur despite prescribers' intention to have continuity of drug action. The result is that many patients are exposed to multiple episodes of starting and stopping of drug actions. If these episodes occur with a drug that can produce hazardous rebound effects after abrupt cessation of dosing, these effects are likely to happen multiple times. Similarly, drugs that are subject to hazardous first-dose effects may produce multiple episodes of first-dose effects when dosing restarts after variously long lapses.

Consequently, it is crucial to understand the times when these abrupt changes in drug exposure occur, their clinical correlates, and the extent to which recurrent rebound or first-dose effects depend on the length of the time intervals between abrupt changes in drug exposure: either on to off or off to on. Controlled experiments to answer these questions are likely to be difficult and may be unethical to perform, but the minimal cassette of test patterns offers a framework for experimental design (see **Supplemental sidebar**). An alternative approach, which is often more practical once the drug is marketed, is observational; it is based on richly sampled drug dosing histories obtained during typical use and on a search for clinical correlates of spontaneously occurring, abrupt changes

Supplemental Material

in drug exposure. In particular, studying the on/off effects is most important and can be done using the observational approach or using a planned placebo substitution for active study, as has been done for antihypertensives (59, 74, 75), antidepressants (58), and oral contraceptives (76).

IMPORTANCE OF RICHLY SAMPLED, TIMELY DOSING HISTORY DATA

Clinical events that follow in the wake of changes in patients' exposure to a drug can be regarded as natural experiments in dose ranging. In the case of actions thought to be induced or modulated by a drug, one needs reliable data on when changes occur in the level of drug exposure and when the clinical events in question occur. The temporal sequence of events is crucial evidence for or against the inference of a causal relationship. The plausibility of a presumed cause is dependent on its having preceded, not followed, the event that it is postulated to cause. Causality is not proven just because the presumed cause precedes the putative effect, but at least the hypothesis has passed the test of temporal sequence, and needs to be challenged in other ways to build or refute the case for a causal relationship. Biological plausibility is another factor to be considered in testing the hypothesis.

To judge temporal sequences of exposure of patients to prescribed medicines, one must acquire pertinent data at a sufficiently high sampling rate to give an adequately sharp definition of the times of occurrence of the changes in (*a*) drug exposure and (*b*) clinical events or markers that those changes are postulated to induce. The field of adherence research, however, is fraught with ambiguity and confusion on these points. This confusion arises from pre-electronic methods that estimate exposure of patients to prescribed drugs and that are based on values aggregated during many days, weeks, or even months—typically the intervals between clinic visits, refills of prescriptions, occasional lab tests, and so forth, which usually occur only a few times per year.

The reliable ascertainment of times of key clinical events can itself be a challenge, e.g., the times of occurrence of the seizures that are described by Cramer et al. (77, 78). Observer bias is a consideration that should prompt researchers to reach a conclusion about the times of occurrences of key clinical events before knowing the details of the patients' dosing histories, as did Cramer and colleagues (J.A. Cramer, personal communication to J.U.). Electronic capture and time stamping of key clinical events, e.g., cardiac arrhythmias via pacemakers or defibrillators, can provide richly sampled, unequivocally timed data on changes in cardiac rhythm, for example.

CLINICAL IMPLICATIONS OF DOSING/TIMING ERRORS OR OMISSIONS

One of the many clinical implications in patients who are mistiming doses or discontinuing therapy is that they are often termed nonresponders. Two studies using electronic monitoring of dosing histories illustrate this point, one by Burnier et al. (6) and one by Marin et al. (9). Burnier et al. (6) assessed patients presumed to have drug-resistant hypertension. The authors found that approximately half of drug-resistant hypertensives turned out to be nonadherers. Recent guidelines from the American Heart Association regarding the management of patients with "treatment-resistant hypertension" state that the first step is to rule out pseudoresistance, of which patient nonadherence to medications is a main cause (79). As Burnier et al. noted, "without any objective measurement of drug compliance, physicians have become used to opting almost always . . . for enhancing doses or prescribing new drug combinations . . . However, there is usually no rational basis for this decision" (6, p. 339).

Marin et al. (9) conducted a study designed to determine, during a 3-month period, the dosing histories of patients with chronic myeloid leukemia who were prescribed the tyrosine kinase

inhibitor imatinib once daily. The goal was to correlate the adherence to imatinib with the molecular response to imatinib treatment. The authors used 3 months of dosing history data as a snapshot of drug exposure during a multiyear period of treatment. Analysis of the dosing history data was limited to a single value: the percentage of prescribed doses of imatinib taken during the 3-month period of observation. Thus, the study provided a one-dimensional view—an aggregate quantity of drug taken—of an inherently two-dimensional phenomenon—the times and quantities of a drug dosing history—during a narrow segment of time within a multiyear period of observation. Those limitations notwithstanding, the study by Marin et al. (9) added a great deal of new information about the dynamics of tyrosine kinase inhibition via imatinib. The authors found that in spite of a high average percentage of PDT, i.e., 98% in the 87 patients studied, the range was wide (24–104% PDT). Twelve of the 87 patients (14%) were taking <80% of prescribed doses, which implies some exceptionally long intervals between successive doses. Importantly, Marin et al. also found a high correlation between each patient's electronically measured percentage of PDT and his/her 6-year probability of a major molecular response (MMR) to treatment, defined as a 3-log reduction in transcripts of the abnormal fusion gene, *BCR-ABL1*. In the study, 94% of patients who took >90% of prescribed doses of imatinib achieved an MMR, in contrast to 28% of patients who took <90% of prescribed doses. The correlation was also high between %PDT and the achievement of a complete molecular response (CMR), defined as undetectable transcripts of the fusion gene: 44% of patients who took >90% of prescribed doses of imatinib achieved a CMR, versus 0% of those who took <90% of the prescribed doses. In a multivariate analysis, adherence was the only predictor for CMR; no molecular responses of either type—MMR or CMR—were observed in patients who took <80% of prescribed imatinib doses during the 3-month observation period.

The authors stated the following: "Ideally, a study of the influence of adherence on prognosis would be performed in newly diagnosed patients and would require prolonged follow-up to ascertain the interactions between prognostic features, adherence, and overall outcome. . . . In [not] doing so, we accepted that our study could not address the impact of adherence on early failure of imatinib. . . . [I]t is quite possible that some of the patients who did not respond to imatinib in the first 2 years failed to respond or lost an initial response primarily because the adherence was poor" (9, p. 2396).

These low adherence values also illustrate a point that many find counterintuitive and others have denied: A substantial number of patients are poorly adherent even when treated with an often effective, relatively unobtrusive, potentially curative drug for an otherwise uniformly fatal disease. Given the literature in this field and the data shown in **Figure 3**, it is remarkable that no one has identified a disease condition that combines a poor prognosis and available effective treatment and results in full adherence to prescribed drug treatment. Furthermore, these incomplete observations illustrate a possible reason that dose-escalating prescriptions are given to clinically unrecognized nonadherers: Their limited or absent responses to treatment are misinterpreted as a problem to be overcome by raising the dose of the currently prescribed drug or by adding more drugs to the patient's regimen.

A critical clinical implication for patients who are mistiming doses of medications or omitting doses altogether is the phenomenon of rebound effects, as discussed above. Rebound effects are best documented in the treatment of hypertension with β-blockers, α_2 agonists, methyldopa, and guanabenz, but they can also be seen in the use of sedative hypnotics, stimulants, and antidepressants (80–83). Severe hypertension is a well-known phenomenon that has been observed with the abrupt withdrawal of β-blockers and the central α-adrenergic agonist clonidine, resulting in dramatic elevation of blood pressure that can lead to myocardial infarction, stroke, heart failure, and even death (82, 84, 85). Patients being treated for hypertension are at risk for these withdrawal effects during lapses of adherence, depending on the dose and PK of the drug being used.

Patients being treated with β-blockers such as metoprolol or central α agonists such as clonidine can experience rebound hypertension to levels well above pretreatment blood pressure levels within 24–36 h since the last-taken dose (82). In studies using electronically compiled dosing histories of patients treated for hypertension, lapses of 1–3 days in the treatment of antihypertensive therapy are relatively common events in many patients, putting those who are being treated with agents that have rebound potential at significant risk for adverse clinical outcomes related to the dramatic elevation of blood pressure and pulse (86).

STUDYING THE CONSEQUENCES OF PARTIAL ADHERENCE

Partial adherence compromises the cost-effectiveness of currently available, approved therapies (21, 22). A guiding principle in pharmacology is that the actions of all drugs are dose dependent, implying that underdosing, the main manifestation of partial adherence, results in diminished or absent drug actions. There are, however, many challenges associated with the investigation of the relationship between variable drug exposure and clinical outcomes resulting from poor execution or early discontinuation. Although the theoretical framework is apparent, there are three practical challenges:

1. Nonadherence to medications can include late initiation or noninitiation of the prescribed treatment, suboptimal execution of the dosing regimen, early discontinuation of the treatment, or a combination of those three elements. Partial adherence to medications was difficult to diagnose and to characterize effectively until the advent of electronic monitoring.
2. Given the many temporal patterns of partial adherence to medications, its consequences can span a wide range of possibilities. Investigation of partial adherence requires precise assessment of health outcomes and detailed and reliable assessment of drug exposure.
3. Because variable drug exposure and clinical outcomes can influence each other over time (so-called adherence selectivity) (87, 88), conventional statistical methods cannot be used to estimate the causal pathway between exposure and outcomes. Novel statistical methods are required to take into account potential adherence selectivity.

The past decade has seen major advances with regard to those challenges. Dosing history data can now be automatically compiled through electronic monitoring, an approach that allows diagnosis of nonadherence as well as reliable and detailed estimation of the elements of partial adherence to medications. Advances in modeling and simulation (88, 89, 90), as well as in methods for causal inference, provide statistical tools to deal with potential adherence selectivity. However, the exact relationship between adherence to various medications and health outcomes remains substantially uncharted across the combination of ~500 approved drugs that treat ~1,000 diseases. Those relationships are likely not only to be disease-specific but also to differ on the basis of disease severity, comorbidities, and their respective severities. In the coming decade, we anticipate a veritable explosion of studies that combine measures of adherence and health outcomes that will likely substantially enhance the understanding of the relationship between exposure of patients to particular drugs and the resultant clinical outcomes.

HIV/AIDS is one therapeutic area in which the relationship between adherence and outcome has been carefully studied and widely acknowledged. Paterson et al. (5) demonstrated a strong association between partial adherence to unboosted protease inhibitors and virological failure: The proportion of patients with virological failure ranged from 22% among patients with >95% PDT to 82% among patients with <70% PDT. Yet puzzling and important questions still remain: (*a*) Why was there virological failure in 22% of patients with >95% PDT, and (*b*) why was there 18% virological success in patients with <70% PDT? To illustrate the complexity of the issue,

Figure 2 plots the dosing history data of four patients, each of whom took 90–91% of their once-daily prescribed doses. From those plots, one can see that for the same percentage of PDT, the patterns of drug dosing histories can differ greatly and likely lead to very different clinical outcomes, depending on the drug. For example, one might expect a different relationship with viral success between a boosted and an unboosted protease inhibitor, owing to differences in the forgiveness of these two regimens (7, 55).

Premarketing Approaches and Designs

It is commonly believed that during drug development, one can assume an ideal trial scenario. For example, in the early phases of clinical development (e.g., Phases 1 and 2a), during which drug administration is under professional supervision, often in a clinical study unit for Phase 1, near-perfect adherence is likely the norm. However, once drug dosing becomes the responsibility of study participants in an outpatient setting, often as early as Phase 1, imperfections in dosing can be expected to occur. In general, the personnel who direct the trials can reinforce initiation and persistence with the test drug. Moreover, strict patient selection, various incentives, and close patient monitoring and follow-up can contribute to higher rates of initiation and durations of persistence. Execution of the dosing regimen remains, however, highly dependent on the vagaries of participants' habits in daily routine: more missed doses during (*a*) weekends than weekdays, (*b*) evenings than mornings, (*c*) holiday periods, (*d*) life-disrupting events, and so forth. When irregular drug intake prevails in the learning phase of drug development, a substantial gain of precision in PK/PD parameters can be expected, owing to properly measured adherence (91). Compiling drug dosing history data during all phases of drug development can help convert the variable adherence of trial participants from a source of confusion to a source of knowledge about a test drug's dose- and time-dependent actions across a wide range of exposures. An analysis that incorporates drug exposure in all participants can thus provide a robust estimate of the correctly taken drug's efficacy, resulting in better-informed and earlier strategic decisions throughout drug discovery and development.

Postmarketing Studies

The current practice regarding postmarketing studies is often characterized by separation of the assessments performed by regulators and by payers. Estimation of method-effectiveness is the important consideration for regulatory approval, whereas estimation of use-effectiveness is the important consideration for payers. Eichler et al. (92) predict more interaction between the regulatory and the payer communities in the era of comparative effectiveness assessment and with more active-controlled, randomized trials becoming the basis for marketing approval.

This trend calls for improved and faster learning phases, followed by a confirming phase on a broader population, as would be expected after approval. To bring a drug to market in the setting of research on comparative effectiveness and cost-effectiveness, it will be crucial to understand and address the variability in drug response resulting from partial adherence. Quantifying adherence to the drug regimen in all phases of drug development, including the postapproval phase, is the foundation for gaining a precise understanding of the magnitude and the consequences of prevalent patterns of dosing. Such information sets the stage for understanding and managing the differences between method-effectiveness and use-effectiveness (54) in typical therapeutic settings.

Noninitiation of treatment and poor persistence are major challenges in postmarketing settings. Minimizing these problems calls for proper management of adherence to medications and involves the different stakeholders in the health care system. From the perspective of payers, medication purchased but not taken is a cost that does not benefit the patient. For the pharmaceutical industry,

short persistence is the single largest untapped opportunity for revenue growth. Tackling and improving initiation, execution, and persistence of drug therapy in the marketplace is thus a "win" situation for all stakeholders: health care providers, payers, the commercial developer of the drug in question, and, most importantly, patients.

Designing Dosing Regimens on the Basis of Typical Dosing Histories

In the 22 years since the introductory work of Cramer et al. (2), many researchers have sought solutions to problems created by pervasive nonadherence in ambulatory pharmacotherapy. Only recently have we learned that the feedback of recent dosing history data to patients is crucial in the effort to manage their adherence to prescribed medications (93). Looking ahead, it should be possible to answer this key question: How well, through soundly measured dosing history data, can one manage long-term pharmacotherapy for chronic diseases, e.g., epilepsy, hypertension, congestive heart failure, lipid disorders, osteoporosis, posttransplant immunosuppression, antiretroviral treatment of HIV infections, and other difficult medical conditions? The aim is threefold: (*a*) to avoid unwarranted escalations in numbers and/or doses of prescribed drugs; (*b*) to achieve, through a higher degree of punctual dosing, the fewest possible episodes of inadequate responses to, or outright failures of, treatment; and (*c*) in the case of anti-infective drugs, to prevent emergence of drug resistance among infectious microorganisms. It is clear that data on patients' dosing histories can provide strong and useful insight into reasons for failed treatment and new means for improving the management of many diseases.

Interventions using objective monitoring systems, in a process known as measurement-guided medication management, compile patients' drug dosing histories, day by day, hour by hour, and are used as feedback to patients and caregivers. When combined with counseling and patient support, this approach significantly enhances medication adherence, setting the stage for improving outcomes in patients. Future research should focus on determining the most effective combinations of intervention strategies that improve medication adherence (93, 94).

Electronic compilation of dosing history data readily defines the adherence pattern of individual patients (termed IAP for individual adherence pattern). The IAP is based on identifiable characteristics in dosing by an individual: missed doses on specific days of the week, consecutively missed doses, the time of drug intake, variability in the time of drug intake, medication overuse, and so forth. Once the IAP has been established through the patient's most recent dosing history, one can decide between three possibilities:

1. The IAP passes a key "stress test" for the drug in question, meaning that the observed deviations in adherence to the prescribed medication neither compromise their efficacy nor create hazards.
2. The IAP can suggest a change in the prescribed dosing regimen. For example, the IAP of the patient shown in **Figure 8** suggests that a change from twice-a-day to once-a-day dosing would be desirable.
3. The IAP is unacceptable and requires a behavioral change by the patient.

This approach is, in effect, a new type of personalized medicine that uses a patient's most recent dosing history data to help him/her attain full benefit from the treatment in question.

OTHER APPROACHES TO IMPROVING ADHERENCE IN AMBULATORY PATIENTS

Despite advances in technology and the many interventions that have been tried to improve medication adherence in chronic illness, only a few studies have shown significant improvements in

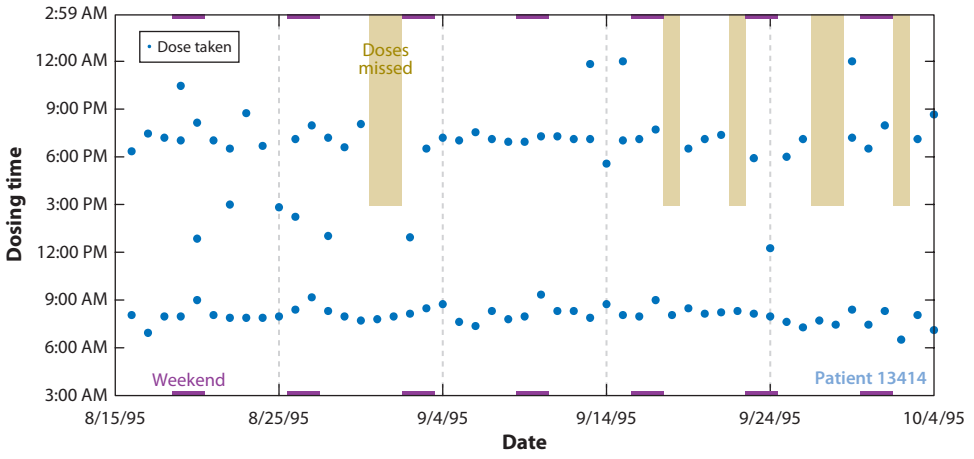

Figure 8

Chronology plot of a type 2 diabetic patient's dosing history during prescribed treatment with a twice-daily oral dosing regimen of a hypoglycemic agent. The same conventions apply as described for **Figure 2**. Data from the iAdherence database.

adherence. Complex interventions have been required for even modest improvements, and simple interventions typically have shown little or no effect, with all interventions' effects typically waning with time unless ongoing reinforcement strategies are used (44). A recent Cochrane Systematic Review assessed 83 interventions in 70 randomized clinical trials; 36 of the interventions showed some improvement in adherence, and only 25 improved at least one clinical outcome (95). The majority of interventions were complex, combining interventions in the following areas: more convenient care, information, reminders, telephone follow-up, self-monitoring, reinforcement, counseling, family therapy, psychological therapy, crisis intervention, manual care, and supportive care (95). Most of these studies of strategies to improve adherence used imprecise measures of adherence, such as patient self-reporting, which overestimates the degree of adherence (95, 96). Because imprecise measures obscure the differences among groups receiving different interventions, these studies may underestimate the effects of the interventions used.

One promising approach for improving adherence to medications and health outcomes is the use of medication therapy management services by pharmacists or other ancillary health care providers. However, effective medication therapy management interventions have required complex and multidimensional approaches that involve a combination of a patient-centered approach, education, dosing history monitoring and feedback, counseling, troubleshooting, adherence-facilitating packaging, and reminders (44, 49, 97, 98, 99).

More studies that incorporate electronic methods to measure medication adherence should be encouraged to move this field forward. Effective adherence improvement strategies have the potential to generate benefits that may rival even those from new medications, which inevitably have to be taken correctly if their full range of benefits is to be achieved.

CONCLUSIONS

The large increase over the past decade in publications on patient adherence attests to the increased recognition of its importance in new drug development and patient care. In this review, we show the need for consistent terminology, via a new taxonomy, and discuss many of the diverse consequences

of partial adherence or nonadherence, especially when clinically unrecognized. Accurate dosing histories of prescribed medications are a cornerstone of (*a*) efficient and cost-effective patient care; (*b*) learning in Phase 2 trials of new drugs and defining optimal dosing regimens after marketing; (*c*) valid comparative effectiveness research; and (*d*) quantitative analysis of the causes of failure of drug therapy in ambulatory patients.

SUMMARY POINTS

1. The ubiquity of poor execution and nonpersistence with ambulatory dosing regimens supports the need for accurate, routine compilation of drug dosing histories and assessment of their consequences during drug development and in routine clinical care.
2. The compilation of dosing histories, via electronic monitoring methods, may help reveal key clinical events that follow changes in the exposure of patients to drugs. Such sequences can be seen as natural experiments in dose ranging that may play a causal role in both the benefits and risks of use of a particular drug: e.g., effects that may be associated with (*a*) the sudden cessation of dosing or (*b*) the sudden resumption of previously interrupted dosing.
3. Long-term pharmacotherapy for chronic disease usually involves the prescription of multiple medications. There is a strong linkage between adherence to the trial placebo and adherence to nontrial medications, and this is a widely overlooked potential explanation for the so-called healthy adherer effect (19, 77, 100).

FUTURE ISSUES

1. A conceptual framework for studying the potentially hazardous first-dose and rebound effects of drugs lies in the minimal cassette described in the **Supplemental sidebar**. Such studies have the potential to identify safety problems arising from patterns of drug exposure, particularly recurrent on-off-on cycles of drug action, thus improving the content of drug labeling and facilitating the determination of optimal dosing regimens for clinical use.
2. Practical, cost-effective methods are needed to improve each component of adherence—initiation, execution, and persistence. Multiple approaches to achieve this objective are required, with careful attention to the provision of rates of data sampling that are high enough to define the salient dynamics of exposure of patients to prescribed drugs and that provide timely feedback for sound analysis and rapid interventions.
3. Statistical analysis of adherence-informed clinical data involves time-series analysis and other methods such as causal inference, which collectively change current conceptions of what constitutes conventional statistical analysis of the results of clinical trials. Thus, a need exists for the development and implementation of novel statistical methods, in addition to training opportunities in their applications to the analysis of results of adherence-informed trials.
4. There is a need to understand the similarities and dissimilarities in dosing histories of concomitantly prescribed drugs. This need is especially critical in clinical trials in which multiple nontrial medications are, for sound medical reasons, used.

DISCLOSURE STATEMENT

T.F.B. is a consultant for Proteus Biomedical, which is developing products that address complex therapeutic areas involving patient monitoring requirements, therapeutic efficacy, and poor adherence. L.O. is a consultant for Proteus Biomedical. B.V. is director general and a minority shareholder of AARDEX Group, Ltd., which is involved in developing, manufacturing, and marketing electronic medication-event monitors that measure, analyze, and facilitate adherence of patients and trial participants. J.U. is chairman, chief scientist, and a minority shareholder of AARDEX Group, Ltd.

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Errata

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