Chapter 7

Adherence to Medical Advice: Processes and Measurement

Jacqueline Dunbar-Jacob, Martin P. Houze, Cameron Kramer, Faith Luyster, and Maura McCall

1 Introduction

Traditionally adherence has referred to the percent of a prescribed or recommended regimen that is carried out historically by patients and more recently by providers (Haynes, 1979). The definition is nonjudgmental and does not imply responsibility. The value of knowing adherence rates lies in the ability to assess the effectiveness of treatment, whether it be in the evaluation of new treatments or in the development of effective treatment for the individual.

A review of the research over the past 35 years suggests that adherence has been viewed in a global manner, with an emphasis on the identification of patient characteristics which may influence treatment behavior. Data have historically shown that adherence rates across regimen hover around 50% for both patients and providers (Baumhakel et al, 2009; Claxton et al, 2001; Dunbar-Jacob et al, 2000; Thier et al, 2008). Prediction has been difficult as the same characteristics examined in different studies show varying degrees of influence on the level of adherence, and many studies have focused on a limited number of characteristics (Baiardini et al, 2009; Stilley et al, 2004). Further confusing the picture is the fact that different studies both measure and define adherence in different ways. Thus, the behavioral processes underlying adherence and related measurement strategies become important considerations for the furtherance of an understanding of adherence and ultimately the prevention and remediation of poor adherence.

Any examination of adherence needs to consider the multiple steps from prescription to action and to consider these steps in refining the definition of adherence. First, of course, is the clarity and completeness of the prescription and related instruction. Second is the capability of the patient to carry out the instruction. Third is the availability of the resources needed to carry out the instruction. Fourth is the motivation to adhere to the prescription in part or in whole. And lastly is the system to support continued adherence, e.g., cues, self-monitoring, feedback, etc. Most commonly adherence studies have focused upon motivational factors with little attention to these other key elements.

Any examination of adherence also needs to consider the patient's decision making (Bieber et al, 2006; Loh et al, 2007). First the patient must decide whether to accept the recommended treatment. If treatment is accepted, then the patient must decide whether to initiate the treatment. If the patient decides to initiate the treatment, then she/he must determine whether the value of the treatment offsets any negative consequences to following it. If the patient decides to pursue the treatment, then the decision is whether to make it an integral part of daily habits. And finally the patient must decide whether to persist when problems occur.

J. Dunbar-Jacob (✉)
University of Pittsburgh, 350 Victoria Building, 3500 Victoria St, Pittsburgh, PA 15261, USA
e-mail: dunbar@pitt.edu

A. Steptoe (ed.), *Handbook of Behavioral Medicine*, DOI 10.1007/978-0-387-09488-5_7,

A further consideration is whether the patient knows the state of their adherence. Considerable research suggests there is a poor relationship between patient self-report of adherence and adherence assessed through more direct mechanisms (Dunbar-Jacob et al, 2000; Wagner and Rabkin, 2000). While a portion of this may reflect a reluctance to report poor adherence to the provider (Sankar et al, 2007), it is likely that memory is a major factor in this discrepancy. To accurately report adherence, the patient must be able to recall and summarize their behavior over a period of time between provider visits, often as long as 6 months to a year. For the patient who has persisted with the regimen at some level over time, the regimen becomes habitual but not necessarily accurate. Such habitual behaviors become less salient and become part of a more general memory, making discrete events more difficult to recall (Barnhofer et al, 2005; McPherson, 2001; Warnecke et al, 1997). Cramer and colleagues (1990) showed that adherence improved 5 days prior to (88%) and after (86%) contact with the provider, in comparison to 1-month postvisit (67%). Hence it is reasonable to assume that many patients are recalling most recent behavior and not summarizing across time. Thus, measures may have different accuracy depending upon the variability of behavior and the length of time the patient is assessed.

Also of importance in the processes surrounding adherence is the quality of the communication that occurs within relationships (van Dulmen et al, 2008). Communication between the patient and the providers, communication between providers, communication within the interdisciplinary treatment team, and communication between inpatient and outpatient teams are all important to subsequent patient adherence. Problems in communication may further erode trust in the advice offered by the providers (Kerse et al, 2004; Thom et al, 2001). An assessment of conflicting recommendations or instruction may be important to the determination of whether adherence behavior represents poor adherence or selection among conflicting or suspect advice. This also appears in the adherence of providers to guideline recommendations when multiple guidelines from different agencies are not consistent (Lewiecki, 2005).

2 Classification of Adherence

The multiple steps that the client or patient takes and the process through which the regimen is recommended leads to multiple points at which the patient may encounter errors or need to make decisions. At each of these points adherence may become a problem. Each point may suggest a different definition or method of assessment.

2.1 Acceptance of the Regimen

The first step is the period in which the regimen is initially presented, and the patient makes a decision about whether to follow it. One area of consideration is readiness to change. Studies examining readiness to adopt a regimen have varying results in predicting subsequent adherence (Aloia et al, 2005). Many factors may go into a patient's willingness to accept a regimen, such as the patient's preferences for type of treatment, the trust that the patient has in the provider, the level of burden imposed, the patient's beliefs about the illness or the treatment, the satisfaction with care, the consistency of the advice with previous advice or knowledge, and a host of other factors. It is at this step that negotiating a mutually satisfactory treatment may influence whether the patient adheres to the recommendation or not.

2.2 Adoption of the Regimen

Patients may agree to the regimen, or at least not object to it, but fail to initiate treatment. For example, between 66 and 84% of new antihypertensive prescription medicines were filled by persons with hypertension and who had at

least two clinical encounters (Shah et al, 2009). In the same practice, 85% of new diabetes prescriptions were filled (Shah et al, 2008). For patients recently discharged from hospital after a myocardial infarction, 77% of discharge prescriptions were filled within 7 days (Jackevicius et al, 2006). In this situation, closed health-care systems may detect failure to fill through close monitoring of pharmacy fills. But for the open systems where patients may utilize any number of pharmacies, failure to adopt the regimen is unlikely to be detected until the next health-care visit, perhaps as long as 6–12 months after the prescription is written. It is unknown how many persons take the first step in behavioral interventions. Many factors may influence the patient's adoption of treatment including those noted above combined with a reluctance to question or challenge the provider. Other factors may include barriers to obtaining the prescription such as cost, accessibility, and availability.

2.3 Initiation of the Regimen

Even though the patient acquires the treatment or its resources, the regimen may not be initiated at all or may be discontinued after a brief exposure. Indeed the first 6 months on treatment show a significant withdrawal from treatment (Perreault et al, 2005; Donnelly et al, 2008; Chapman et al, 2005). Data show as many as 50% or more of patients may terminate treatment by this point (Chapman et al, 2005; Rutledge et al, 1999; Newman et al, 2004). The factors which predict early termination of treatment are not clear. Hypotheses are directed toward the impact of side effects, financial concerns, or difficulty in carrying out the regimen.

2.4 Treatment Continuation

For those patients who continue treatment beyond the 6-month period, several adherence patterns emerge. This may constitute as many as 50% of this group. The series of figures below displays the variable patterns of adherence found in patients on medication for chronic disease who were monitored with the AARDEX Medication Event Monitoring System. Each of these patients had been on treatment for 1 year or longer before monitoring was initiated. For a portion of persons, adherence remains high and stable, though not necessarily perfect, over time (see Fig. 7.1).

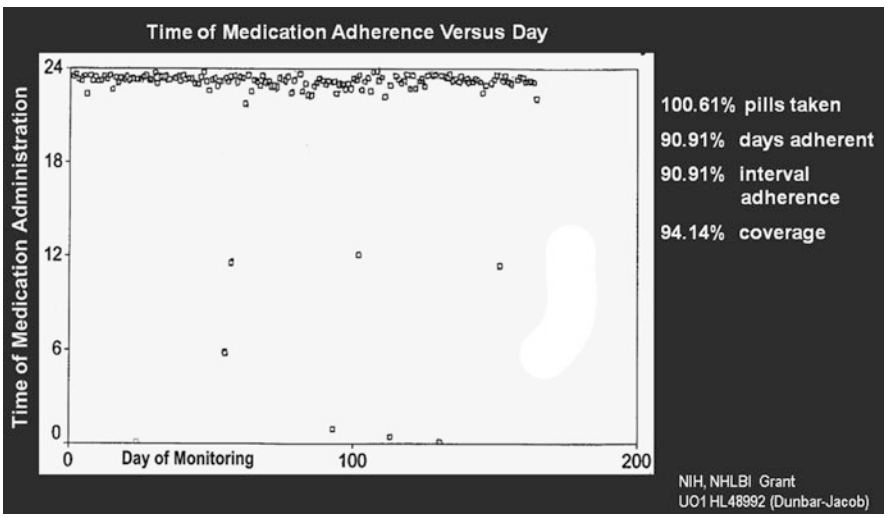

Fig. 7.1 Good adherer to once-a-day regimen

Other patients may demonstrate a persistently low adherence or a decline over time, as can be seen in Fig. 7.2.

The majority of the patients in this group, however, demonstrate variable levels of adherence over time showing a combination of missed doses (or episodes), double doses, and mistimed doses. These variable patterns are difficult to detect with the majority of measures of adherence. See Fig. 7.3 for a visual view of a variable pattern of adherence for a twice-a-day medication.

Thus, adherence can be classified at several points, depending upon the outcome of interest, acceptance of the regimen (yes/no), initiation of the regimen (yes/no), and continuation or persistence with the regimen at varying levels of adherence.

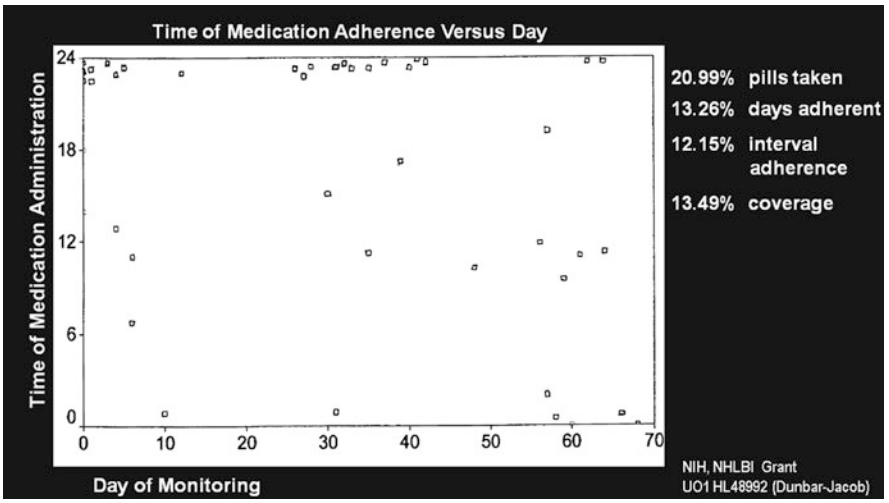

Fig. 7.2 Poor adherer to once-a-day regimen

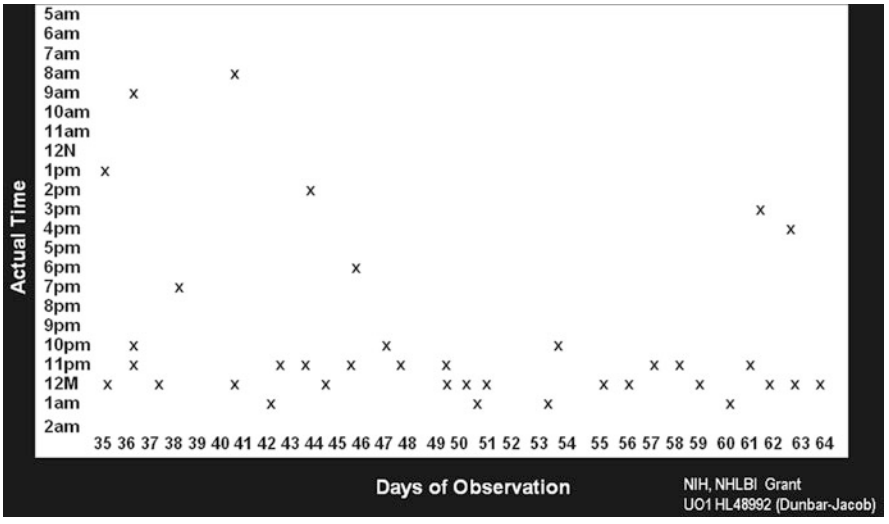

Fig. 7.3 Variable adherence to twice-a-day regimen

3 Defining Adherence

Before measuring adherence it is important to clearly define and specify just what adherence is and the step in the process that is of interest. Ideally, adherence would be defined as the proportion of the prescription or regimen required to create the desired clinical outcome. Haynes (1979) did so in the first adherence improvement randomized controlled trial (RCT) conducted. He examined adherence to antihypertensives and identified the average adherence (by home pill count) to obtain a diastolic blood pressure level of less than 90 mmHg (Haynes et al, 1976). Adherence was determined to be pill counts greater than 80%. Similarly, in the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) research subjects were prescribed six packets of cholestyramine per day designed to achieve a 20% reduction in low-density lipoprotein cholesterol (LDL). At the end of the trial, it was found that 70% adherence led to ≥20% reduction in LDL (Schaefer et al, 1994). Blagden and Chipperfield (2007) examined LDL cholesterol level changes with atorvastatin vs. atorvastatin plus ezetimibe. With 70% or greater adherence in their sample, monitored via pill counts, the LDL levels decreased by 36.5 and 50.5%, respectively. In contrast such levels of adherence are not effective in reducing viral load in HIV patients. Recommendations for effective treatment of HIV are to achieve adherence levels close to 100% (www.apha.org/ppp/hiv). Unfortunately, data are not readily available on other drugs to establish an optimal adherence level. Even less is known about optimal adherence for nonpharmacological interventions. For patients on multiple treatments, the common pattern for those with chronic disease, the picture of optimal adherence is even more confusing.

Further confounding the picture is the problem of medication which may have positive effects on one clinical parameter but negative effects on another. For example, Ames (1986) studied and reviewed studies of diuretics used in the treatment of hypertension to reduce high blood pressure levels and found that the hypertensive treatment may create a rise in various serum cholesterol measures by 4–56%; however, Ott and colleagues (2003) conducted an RCT in elderly that did not find such differences (Ott et al, 2003). Similarly, anti-hyperglycemic agents may lower blood glucose levels and glycated hemoglobin (HbA1c), but may lead to an increase in serum cholesterol (Gershberg et al, 1968). Thus, attempts to establish an optimal adherence to a cholesterol lowering regimen may potentially be confounded by adherence to the concurrent hypertension or diabetes regimen.

The answer to this dilemma has been to adopt a behavioral definition regarding the proportion of the regimen taken as the standard, typically about 80%. Alternatives to this have been to use unique definitions or qualitative definitions (good vs. poor with no numeric referent) or to fail to provide any definition at all. These variations in defining adherence impair the ability to perform adequate meta-analyses or systematic reviews of the magnitude of the problem or to evaluate the effectiveness of adherence interventions. At a minimum the provision of numeric definitions of adherence or cut points for classification is more informative. While it may not be clinically useful to set one behavioral standard across regimens or conditions, it is useful for comparison and summarization of adherence across populations.

4 Measurement of Adherence

4.1 Numeric Assessment of Adherence

The definition of adherence initially posed by Haynes and colleagues (1979), the percent or portion of the regimen carried out, suggests a numeric definition of adherence and the ability to count doses prescribed and taken. Four methods of assessment permit this, each with advantages and disadvantages. These include electronic monitoring, pill count, daily diary, and patient recall.

4.1.1 Electronic Monitoring

Electronic event monitoring (EEM) has been used increasingly over the past two decades for adherence to medication and to exercise regimens. In these cases the monitor itself is connected with the regimen and accepts passive participation on the part of the patient. The most commonly used EEM for medication consists of a microprocessor inserted in a medication bottle cap, which is activated by opening or closing of the cap (AARDEX MEMS). The date and time of opening (and subsequently closing) the cap are recorded on the microprocessor. Thus, it is possible to monitor the number of doses accessed, as well as the timing of doses. The interval between doses may be important for drug efficacy. Errors in timing (or intervals between doses) have been found to be the error of greatest magnitude in medication adherence (Claxton, 2001). Data may be monitored for short or long intervals.

Electronic technologies are also used in the assessment of adherence to lifestyle interventions, exercise, dietary behavior, and treatment of sleep apnea. Pedometers, accelerometers, and heart rate monitors allow freedom for the person exercising and are often used in research to measure physical activity (see Chapter 3). Studies have shown the reliability of these devices and often describe them as relatively inexpensive and simple to operate (Baker and Mautrie, 2005; Evangelista et al, 2005; Wilbur et al, 2001). Pedometers sense body motion and count footsteps. They are usually considered accurate if worn correctly and stride distance is predetermined. Pedometer readouts should be checked against known measurements like distance and time. Accelerometers are motion sensors that can detect changes in acceleration. Heart rate monitors usually strap a monitoring box with electrode on the chest and transmit the data to a watch-like receiver on the wrist that records heart rate over time. Dietary behavior also can be monitored through electronic diaries. Although current technologies such as personal digital assistants (PDAs) can provide dietary data in real time, all methods for collecting dietary data have inherent problems for monitoring adherence to diet recommendations (Glanz and Murphy, 2007). Similarly, in the management of sleep disorders, continuous positive airway pressure (CPAP) devices utilize smart cards, modem, or web-based methodology to convey data regarding the nightly duration of therapy at effective pressure and patterns of use. CPAP adherence typically is defined as $\geq$4 h of use for 70% of days. However, a standard definition of CPAP adherence has not been established.

With electronic monitoring, adherence itself is calculated by the number of presumptive events divided by the number of dosing events prescribed within the monitored time interval. The determination of what constitutes "good" adherence is left to the investigator or clinician. When gaps appear in dosing or a cessation of recorded events occurs, a concurrent interview is necessary to determine whether the patient utilized the monitor or whether the patient was hospitalized or otherwise had a change in either prescription or circumstances. The ultimate calculation of adherence permits the determination of the percent of doses or events, the percent of days on which the patient was adherent, as well as the percent of doses occurring within the scheduled interval. For exercise, intensity and duration can also be observed, and duration of CPAP use monitored. Additionally, information on "drug holidays," periods of time off, as well as patterns of adherence may be viewed. There is evidence that these monitors can stimulate behavior change itself (Baker and Mautrie, 2005; Deschamps et al, 2006).

There is evidence that the use of pedometers alone can increase reported motivation to exercise as well as increase self-reported physical activity, and actual physical activity as recorded by the pedometer, at least for the short term (Baker and Mutrie, 2005). In this particular study of intervention groups using the transtheoretical model to increase step count, significant reported increases in motivation and activity were only seen in the group using the pedometer.

4.1.2 Pill Counts

Pill counts, one of the common measures of adherence in pharmacological clinical studies, also permit a numeric estimate of adherence. Adherence is calculated as the number of pills taken divided by the number prescribed over the interval of interest, typically between periods of dispensing. It is important to note that the pill count does not identify patterns of adherence nor interdose intervals. Patients who miss a dose of medication and then compensate by taking an extra dose the next day, a pattern found with electronic monitoring, is not identifiable; nor is it possible to discriminate early cessation of treatment from low but relatively stable dosing, both resulting in low adherence estimates.

The pill count has been found to have a low but statistically significant correlation with EEM measures. For example, Hamilton (2003) reported correlation rates of 0.29–0.39, $p \leq 01$, for hypertensive patients. For AIDS patients, Bangsberg et al (2001) noted a correlation of 0.7, $p < 0.001$, between unadjusted EEM and pill counts. Pill counts typically estimate a higher adherence than EEM (Bangsberg et al, 2001; Hamilton, 2003). Therefore the choice of methods of adherence depends upon what the clinician or investigator is interested in detecting. If one is interested in early changes in patterns of adherence, poor timing of medication, or information for the development of early intervention strategies, the EEM will most likely be useful. If an overall interest in adherence is of interest, then the pill count may give a reasonable estimate.

4.1.3 Pharmacy Refills

In a closed health system, where the provider of care and the dispensing pharmacy are fixed within the system, pharmacy refills may be used to estimate adherence. As with pill counts, the daily patterns of medication taking are not available. However a percent adherence can be calculated by examining the amount of medication dispensed divided by the number of tablets that should have been taken between refills. As long as the patient remains in the system it is possible to detect withdrawal from treatment.

Multiple methods of extracting data and estimating adherence are used, based on pharmacy fill rates and result in several measures. Hess and colleagues (2006) identified 11 measures in examination of pharmacy administration databases. These included "Continuous Measure of Medication Acquisition (CMA); Continuous Multiple Interval Measure of Oversupply (CMOS); Medication Possession Ratio (MPR); Medication Refill Adherence (MRA); Continuous Measure of Medication Gaps (CMG); Continuous, Single Interval Measure of Medication Aquisition (CSA); Proportion of Days Covered (PDC); Refill Compliance Rate (RCR); Medication Possession Ratio, modified (MPRm); Dates Between Fills Adherence Rate (DBR); and Compliance Rate (CR)" (Hess et al, 2006, p.280). Calculating rates of adherence to medication adherence by each mechanism for participants in a weight loss trial showed adherence rates ranging from 63 to 109.7%, depending on method of calculation. Thus, it is important to consider the procedure for calculating adherence over time from databases.

4.1.4 Daily Diaries

Daily diaries form a third method of evaluating event data. Diaries have been used for patient reporting of treatment-related behavior for several decades. Patients or research participants are instructed to record events near to the time of occurrence to minimize forgetting. Further detail around the events may be recorded either qualitatively or as a component of the structured diary. Thus, information can be learned about the circumstances that surround errors in regimen management or successful performance. Diaries have been particularly useful in monitoring food intake and exercise. However, there have been some examples of use in medication management.

Unfortunately, studies of the accuracy of self-report indicate that the data may be problematic. In a sample of women with sedentary lifestyles participating in a home-based walking program, self-report logs indicated that the women reported performing 64% of the prescribed walking exercises while the heart rate monitor data revealed that the women on average met 60% of the goal. This indicates a greater than 90% agreement (Wilbur et al, 2001). In a study comparing an instrumental paper and electronic diaries, however, 90% of events were reported on time but electronic assessment indicated that actual adherence was just 11%; in 32% of days with events entered, the diary had not been opened. Thus, false reporting was high (Stone et al, 2003). This also happens in the case of dietary diary entries. Patients may neglect to complete the diary as instructed and will consequently complete it prior to the clinic visit. The diary is dependent further upon the individual's recall of the foods and beverages consumed and, in some instances, the amount consumed and the nutritional and caloric content. Furthermore, the act of recording food consumption may influence the person's eating behavior resulting in an inaccurate representation of patient's dietary intake. Additionally, patients may censor the report of food consumption in order to be in accordance with known dietary recommendations.

4.1.5 Daily Recall

Recalls over a specific number of days may also be used to estimate percent adherence. If the patient can recall and is willing to report accurately, event data and timing can be assessed. Chesney and colleagues (2000) reported utility in 3 day recalls in identifying HIV patients with raised viral load. Studies have shown that physical activity recall questionnaires can provide a relatively accurate account of physical activity when compared with accelerometers with as much as 90% agreement. However, correlations between the subjective self-report data and the electronic data vary between gender, intensity of the activity, and weight status of the individual (Timperio et al, 2003). Lu and colleagues (2008) reported that 1-month estimates were better than 3- or 7-day recalls when compared with EEM data. However, our own research has suggested that patients with rheumatoid arthritis may have difficulty in remembering the detail of medication taking beyond 3 days. In a 7-day recall of medication taking it was common for patients to begin to report "the same" beyond the third day (unpublished data). Lee et al, (2007) further reported that 24-h recalls were unrelated to pill counts and insensitive to temporal change. Thus, brief recalls may or may not correlate with concurrent clinical data. The question arises as to how much data can be reliably collected to build a picture of adherence over time.

5 Global Assessment of Adherence

Many adherence studies have used assessment strategies which lack a numeric estimate of the portion of the regimen carried out. Examples include a variety of self-report questionnaires, interviews, and clinician estimates. An examination of one measure may present the issues that arise when self-reported questionnaire assessment is used. The most commonly used generic adherence questionnaire is the Morisky Medication Adherence Questionnaire (MMAQ), a four-item (or eight-item version) self-report inventory used to screen for poor adherence (Morisky et al, 1986). An adherence percent is not obtained. The questionnaire yields a score of 0–4, with 0 reflecting good adherence. Studies reflect varying levels of sensitivity and usefulness. For example, Ruslami and colleagues (2008) reported that a combination of the self-report and clinical estimate detected all cases of nonadherence reported by the Medication Event Monitoring System. Yet Shalansky et al, (2004) noted a considerable difference in the detection of nonadherence between the MEMS (13%) and the MMAQ (3%). It has been noted that questionnaire data for adherence may not correlate with clinical

data (Södergård et al, 2006) and that its utility may vary across settings (van de Steeg et al, 2009). As with patient recalls, the data rely upon the accuracy of the patient's memory. And, as noted, the questionnaire does not yield information on the level of adherence over time nor the pattern of adherence.

To be meaningful in assessing adherence the scoring and establishment of cut points would need to be considered carefully in conjunction with either more direct measures of adherence or established clinical cut points. It is also likely that the global measures will be most useful for recent periods when memory is most accurate. Analysis would only permit an estimation of the proportion of persons who recall and report problems related to adherence. It is unlikely to be useful in the assessment of adherence interventions as the sensitivity to change is unknown and unlikely to be sufficient to detect the modest changes seen in intervention studies (Arbuthnott and Sharpe, 2009; Conn et al, 2009; Kripalani et al, 2007).

6 Issues in Analysis of Adherence Data

Analysis is influenced by the method of measurement chosen within a study. For the use of electronic monitoring, where the most detailed information is collected, several issues arise. First is the length of time that data are collected and summarized. Current technology permits the capture of data for 1 day up to 1–2 years. Thus it is important to examine the length of time that data need to be collated to reach a stable estimate of adherence (Houze, Sereika, Dunbar-Jacob, unpublished). Deschamps and colleagues (2006) suggest that in HIV and in kidney transplant patients, an intervention effect of electronic monitoring can be found which decreased and stabilized over 35–50 days. Data can then be summarized over the relevant time period.

The next issue with electronic monitoring is the determination of what view of adherence is important. For example, a simple count of adherence events can be determined, much like a pill count. This will provide a percent of actual events compared with the percent of prescribed events. The outcome can be influenced by over-adherent events, yielding rates greater than 100% or masking the extent of poor adherence. Summarizing across patients can inflate the level of group adherence if there are over-adherers within the group.

An alternative view is the proportion of days in which the events were accurate. This overcomes the problem of adherence above 100%. Individuals who miss a dose in the evening and make it up the next day will appear as adherent when the count of doses is performed but will have 2 days of poor adherence when the proportion of days adherent is calculated.

A third view is considering doses taken at the advised time, within a range. Adherence is likely to be lowest with this estimate. In cases where the timing of medication is important this assessment provides very useful data.

Thus, estimations of individual adherence and of group adherence need to consider the view of adherence that is important. Similar considerations can be given to daily diary adherence, although there is less likely to be reliable data gathered. These are the only two methods of assessment which require a decision of this nature before adherence can be estimated and ultimately analyzed.

Regardless of assessment method, the data for adherence over a group tend to be J-shaped (Dunbar-Jacob et al, 1998, see Fig. 7.4). Multiple strategies to transform the data have failed. Therefore non-parametric analyses are most useful. Newer strategies for analyzing J-shaped data are being examined and may yield more sensitive and accurate analytic strategies (Rohay, 2009).

Unfortunately, often the level of detail just noted is missing from studies of adherence. Further parametric analyses are often presented, typically in the absence of information about the nature of the distribution of the data. Attention to the nature of measurement, the definitions, and view of adherence, as well as the use of appropriate analytic strategies are important

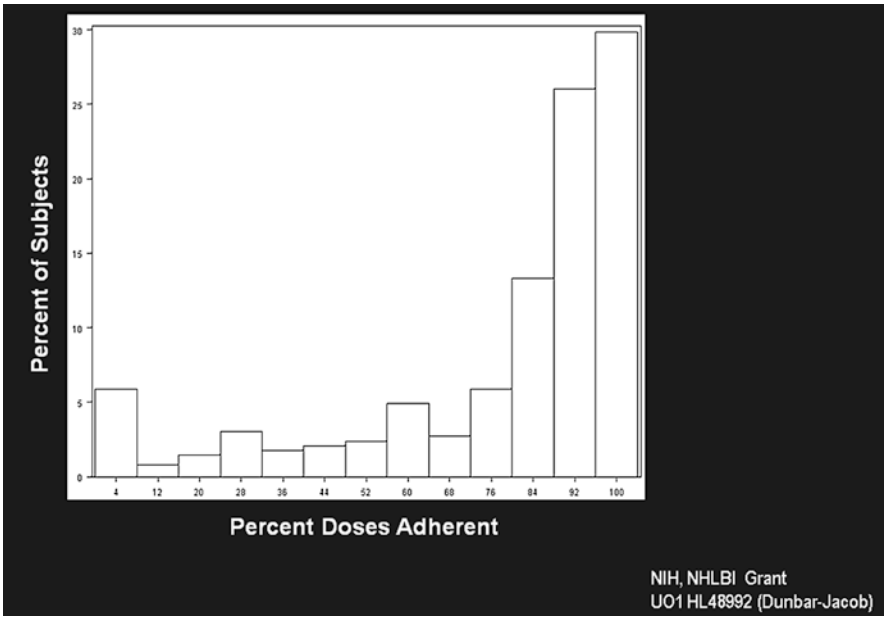

Fig. 7.4 Distribution of days adherent by EEM

to moving the field forward. Similarly meta-analyses need to consider not only intervention strategies, but also definitions and assessment strategies as well. Thus, the full picture of adherence, phase of adopting/managing the regimen, a prior definition of adherence, measurement method, and appropriate analytic strategy are crucial as we continue to develop an understanding of patient adherence.

7 Implications for Understanding Adherence

Numerous studies have been undertaken in an effort to understand who is likely to have adherence difficulties. The results of these studies have shown inconsistent relationships between predictors and adherence (Dunbar-Jacob et al, 2009). Few predictors have been found to be very robust within studies. It is not unreasonable to find inconsistency in the prediction of adherence when we note the variability in the phase of adhering to a treatment and the inconsistency in classification of a person's adherence given the varying methods of defining and assessing adherence. More careful description of the population and its stage of treatment (agreement with treatment, initiation of treatment, adjustment to new treatment, continuation of treatment) as well as clearer descriptions of the definition and assessment methodology will be required before we can begin to understand the predictors of adherence.

Similarly, numerous studies have examined strategies to improve adherence. A meta-analysis by Peterson et al (2003) showed that interventions increased adherence by 4–11%, a very small amount. Kripalani and colleagues (2007) reported that just 54% of studies reviewed reported improvements in adherence while just 30% showed clinical improvements, not always related to adherence. Looking within hypertension care, Schroeder et al (2004) found that 78% of adherence studies which simplified the regimen, 44% of those using complex interventions, and 42% of those using motivational strategies reported improvements in adherence. Adherence improvements ranged from 5 to 41%. However, the heterogeneity in measurement of adherence and methods of study prevented conduct

of a pooled analysis. Thus, our knowledge of both intervention strategies and of predictors of adherence is hampered by the variability with which adherence is treated in studies.

8 Summary and Recommendations

As we examine the processes and measurement of patient adherence, we find considerable heterogeneity between studies in terms of definitions, measurement, analytic strategies, and the patient's phase of adopting and maintaining a new treatment regimen. This has resulted in difficulty in evaluating strategies for improving adherence as well as in identifying factors robustly and consistently associated with adherence. The processes required at the different phases of regimen behaviors are likely to be associated with different predictor variables and likely to be responsive to different strategies. However, future research is needed to evaluate more precisely the factors that impact the patient's behaviors during the various processes of accepting, initiating, implementing, and sustaining adherence to a new treatment. Similarly future research needs to examine intervention strategies designed for each phase. Both measurement and analysis strategies can influence the outcomes of studies. Measurement strategies should be chosen with care, selected with attention to the sensitivity to adherence itself and sensitivity to change. Similarly, analysis strategies need to be appropriate for the measurement strategy and the nature of the adherence distribution. While much has been learned about adherence over recent decades, our future understanding can be deepened with greater attention to processes and measures of adherence.

References

APHA (2004). Adherence to HIV treatment regimens: recommendations for best practices. www.apha.org/ppp/hiv June 2004. Accessed January 6, 2010.

Aloia, M. S., Arnedt, J. T., Stpenowsky, C., Hecht, J., and Borelli, B. (2005). Predicting treatment adherence in obstructive sleep apnea using principles of behavior change. *J Clin Sleep Med, 1*, 354–356.

Ames, R. P. (1986). The effects of antihypertensive drugs on serum lipids, I. diuretics. *Drugs, 32*, 260–278.

Arbuthnott, A., and Sharpe, D. (2009). The effect of physician-patient collaboration on patient adherence in non-psychiatric medicine. *Pat Educ Couns*, *77*, 60–67.

Baiardini, I., Braido, F., Bonini, M., Compalati, E. and Canonica, G. W. (2009). Why do doctors and patients not follow guidelines? *Curr Opin Allergy CI, 9*, 228–233.

Baker, G., and Mutrie, N. (2005). Are pedometers useful motivational tools for increasing walking in sedentary adults? Paper presented at Walk21-VI, 6th international conference on walking in the 21st century, Zurich, Switzerland.

Bangsberg, D. R., Hecht, F. M., Charlebois, E. D., Chesney, M., and Moss, A. (2001). Comparing objective measures of adherence to HIV antiretroviral therapy: electronic medication monitors and unannounced pill counts. *AIDS Behav, 5*, 275–281.

Barnhofer, T., Kuehn, E., and de Jong-Meyer, R. (2005). Specificity of autobiographical memory and basal cortisol levels in patients with major depression. *Psychoneuroendrocrinology, 30*, 403–411.

Baumhakel, M., Muller, U., and Bohm, M. (2009). Influence of gender of physicians and patients on guideline-recommended treatment of chronic heart failure in a cross-sectional study. *Eur J Heart Fail, 11*, 299–303.

Bieber, C., Muller, K. G., Blumenstiel, K., Schneider, A., Richter, A., et al (2006). Long-term effects of a shared decision-making intervention on physician-patient interaction and outcome in fibromyalgia: a qualitative and quantitative 1 year follow-up of a randomized controlled trial. *Patient Educ Couns, 63*(3), 357–366.

Blagden, M. D., and Chipperfield, R. (2007). Efficacy and safety of ezetimibe co-administered with atorvastatin in untreated patients with primary hypercholesterolaemia and coronary heart disease. *Curr Med Res Opin, 23*, 767–775.

Chapman, R. H., Benner, J. S., Petrilla, A. A., Tierce, J. C., Collins, S. R. et al (2005). Predictors of adherence with antihypertensive and lipid-lowering therapy. *Arch Intern Med, 165*, 1147–1152.

Chesney, M. A., Ickovics, J. R., Chambers, D. B., Gifford, A. L., Neidig, J. et al (2000). Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: The AACTG Adherence Instruments. *AIDS Care, 12*, 255–266.

Claxton, A. J., Cramer, J. and Pierce, C. (2001). A systematic review of the associations between dose regimens and medication compliance. *Clin Ther, 23*, 1296–1310.

Conn, V. S., Hafdahl, A. R., Cooper, P. S., Ruppar, T. M., Mehr, D. R. et al (2009). Interventions to improve medication adherence among older adults: meta-analysis of adherence outcomes among randomized controlled trials. *Gerontologist, 49*, 447–462.

Cramer, J. A., Scheyer, R. D., and Mattson, R. H. (1990). Compliance declines between clinic visits. *Arch Intern Med 150*, 1509–1510.

Deschamps, A. E., van Wijngaerden, E., Denhaerynck, K., De Geest S., and Vandamme, A. M. (2006). Use of electronic monitoring induces a 40-day intervention effect in HIV patients. *J Acq Immun Def Synd, 43*, 247–248.

Donnelly, L. A., Doney, A. S. F., Morris, A. D., Palmer, C. N. A., and Donnan, P. T. (2008). Long-term adherence to statin treatment in diabetes. *Diabetes Med, 25*, 850–855.

Dunbar-Jacob, J., Erlen, J. A., Schlenk, E. A., Ryan, C. M., Sereika, S. M. et al (2000). Adherence in chronic disease. *Annu Rev Nurs Res, 18*, 48–90.

Dunbar-Jacob, J. Gemmell, l. A., and Schlenk, E. A., (2009). Predictors of patient adherence: patient characteristics. In J. K. Ockene & K. A. Riekert (Eds.). *The Handbook of Health Behavior Change, 3rd Ed* (pp. 397–410). New York: Springer.

Dunbar-Jacob, J., Sereika, S., Rohay, J., and Burke, L. (1998). Electronic methods in assessing adherence to medical regimens. In D. Krantz & A. Baum (Eds.). *Technology and Methods in Behavioral Medicine* (pp. 95–113). Mahwah, NJ, Lawrence Erlbaum Associates.

Evangelista, L. S., Dracup, K., Erickson, V., McCarthy, W. J., Hamilton, M. A. et al (2005). Validity of pedometers for measuring exercise adherence in heart failure patients. *J Cardiac Fail, 11*, 366–371.

Gershberg, H., Javier, Z., Hulse, M. and Hecht, A. (1968). Influence of hypoglycemic agents on blood lipids and body weight in ketoacidosis-resistant diabetics. *Ann New York Acad Sci, 148*, 914–924.

Glanz, K. and Murphy, S. (2007). Dietary assessment and monitoring in real time. In A. Stone, S. Shiffman, A. Atienza, & L. Nebeling (Eds.), *The Science of Real Time Data Capture: Self-Reports in Health Research* (pp. 151–168). New York: Oxford University

Hamilton, G. (2003). Measuring adherence in a hypertension clinical trial. *Eur J Cardiovasc Nurs, 2*, 219–228.

Haynes, R. B. (1979). Introduction. In R. B. Haynes, D. W. Taylor, & D. L. Sackett (Eds.), *Compliance in Health Care* (pp. i–xv). Baltimore: Johns Hopkins University Press.

Haynes, R. B., Sackett, D. L., Gibson, E. S., Taylor, D. W., Hackett, B. C. et al (1976). Improvement of medication compliance in uncontrolled hypertension. *Lancet, 1*, 1265–1268.

Hess, L. M., Raebel, M. A., Conner, D. A., and Malone, D. C. (2006). Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother, 40*, 1280–1288.

Houze, M., Sereika, S., and Dunbar-Jacob, J. (2009). Medication adherence: time to stability. Unpublished manuscript.

Rohay, J. (2009). Statistical assessment of medication adherence data: a technique to analyze the J-shaped curve. Doctoral Thesis, University of Pittsburgh.

Jackevicius, C. A., Paterson, J. M., and Naglie, G. (2006). Concordance between discharge prescriptions and insurance claims in post-myocardial infarction patients. *Pharmacoepidem Dr S,16,* 207–215.

Kerse, N., Buetow, S., Mainous, A. G., Young, G., Coster, G. et al (2004). Physician-patient relationship and medication compliance: a primary care investigation. *Ann Fam Med, 2*, 455–461.

Kripalani, S., Yao, X., and Haynes, R. B. (2007). Interventions to enhance medication adherence in chronic medical conditions: a systematic review. *Arch Intern Med, 167*, 540–549.

Lee, J. K., Grace, K. A., Foster, T. G., Crawley, M. J., Erowele, G. I. (2007). How should we measure medication adherence in clinical trials and practice? *Ther Clin Risk Manag*, *3*, 685–690.

Lewiecki, E. M. (2005). Review of guidelines for bone mineral density testing and treatment of osteoporosis *Curr Osteo Rep, 3,* 75–83.

Loh, A., Simon, D., Wills, C. E., Kriston, L., Niebling, W. et al (2007). The effects of a shared decision-making intervention in primary care of depression: a cluster-randomized control trial. *Pat Educ Couns, 67*, 324–332.

Lu, M., Safren, S. A., Skolnik, P. R., Rogers, W. H., Coady, W. et al (2008). Optimal recall period and response task for self-reported HIV medication adherence. *AIDS Behav*, *12*, 86–94.

McPherson, F. (2001). Autobiographical memory. http://www.memory-key.com/EverydayMemory/autobiographical.htm.

Morisky, D. E., Green, L. W., and Levine, D. M. (1986). Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care, 24,* 67–74.

Newman, S., Steed, L., and Mulligan, K. (2004). Self-management interventions for chronic illness. *Lancet, 364*, 1523–1537.

Ott, S. M., LaCroix, A. Z., Ichikawa, L. E., Scholes, D., and Barlow, W. E. (2003). Effect of low-dose thiazide diuretics on plasma lipids: results from a double-blind, randomized clinical trial in older men and women. *J Am Ger Soc, 5*, 340–347.

Perreault, S., Lamarre, D., Blais, L., Dragomir, A., Berbiche, D. et al (2005). Persistence with treatment in newly treated middle-aged patients with essential hypertension. *Ann Pharmacother, 39*, 1401–1408.

Peterson, A. M., Takiya, L., and Finley, R. (2003). Meta-analysis of trials of interventions to improve medication adherence. *Am J Health-Syst Pharm, 60*, 657–665.

Ruslami, R., Crevel, R. v., de, B. E. v., Alisjahbana, B., and Aarnouste, R. E. (2008). A step-wise approach

to find a valid and feasible method to detect non-adherence to tuberculosis drugs. *SE Asian J Trop Med, 39*, 1083–1087.

Rutledge, J. C., Hyson, D. A., Garduno, D., Cort, D. A. et al (1999). Lifestyle modification program in management of patients with coronary artery disease: the clinical experience in a tertiary care hospital. *J Cardiopul Rehab Prev, 19*, 226–234.

Sankar, A. P., Nevendal, D. C., Neufeld, S., and Luborsky, M. R. (2007). What is a missed dose? Implications for construct validity and patient adherence. *AIDS Care, 19*, 775–780.

Schaefer, E. J., Lamon-Fava, S., Jenner, J. L., McNamara, J. R., Ordovas, J. M. et al (1994). Lipoprotein(a) levels and risk of coronary heart disease in men: The Lipid Research Clinics Coronary Primary Prevention Trial. *JAMA, 271*, 999–1003.

Schroeder, K., Fahey, T., and Ebrahim, S. (2004). How can we improve adherence to blood pressure-lowering medication in ambulatory care? *Arch Intern Med, 164*, 722–732.

Shah, N. R., Hirsch, A. G., Zacker, C., Taylor, S., Wood, G. C. et al (2008). Factors associated with first-filled adherence rates for diabetic medications: a cohort study. *J Gen Intern Med, 24*, 233.237.

Shah, N. R., Hirsch, A. G., Zacker, C., Wood, G. C., Schoenthaler, A. et al (2009). Predictors of first-fill adherence for patients with hypertension. *Am J Hypertension, 22*, 392–396.

Shalansky, S. J., Levy, A. R., and Ignaszewski, A. P. (2004). Self-reported Morisky score for identifying nonadherence with cardiovascular medications. *Ann Pharmacother, 38*, 1363–1368.

Södergård, B., Halvarsson, M., Brannstrom, J., Sonnerborg, A., and Tully, M. P. (2006). A comparison between AACTG adherence questionnaire and the 9-item Morisky medication adherence scale in HIV-patients. *Int Cong Drug Therapy HIV, 8*: Abstract No. P174.

Stilley, C. S., Sereika, S., Muldoon, M. F., Ryan, C. M., and Dunbar-Jacob, J. (2004). Psychological and cognitive function: predictors of adherence with cholesterol lowering treatment. *Ann Behav Med, 27*, 117–124.

Stone, A. A., Shiffman, S., Schwartz, J. E., Broderick, J. E., and Hufford, M. R. (2003). Compliance with paper and electronic diaries. *Comp Clin Trials 24*, 182–199.

Thier, S. L., Yu-Eisenberg, K. S., Leas, B. F., Cantrell, R., DeBussey, S., Goldfarb, N. I., and Nash, D. B. (2008). In chronic disease, nationwide data show poor adherence by patients to medication and by physicians to guidelines. *Managed Care, 17*, 48–52, 55–47.

Thom, D. H., and the Stanford Trust Study Physicians. (2001). Physician behaviors that predict patient trust. *J Fam Pract, 50*, 323–328.

Timperio, A., Salmon, J., and Crawford D. (2003). Validity and reliability of a physical activity recall instrument among overweight and non-overweight men and women. *J Sci Med Sport, 6*, 477–491.

Van Dulmen, S., Sluijs, E., van.Dijk, L., de.Ridder, D., Heerdink, R. et al (2008). Furthering patient adherence: a position paper of the international expert forum on patient adherence based on an internet forum discussion. *BMC Health Serv Res, 8*, 1–8.

Van de Steeg, N., Sielk, Pentzek, M., Bakx, C., and Altiner, A. (2009). Drug-adherence questionnaires not valid for patients taking blood-pressure-lowering drugs in a primary health care setting. *J Eval Clin Practice, 15*, 468–472.

Wagner, G., and Rabkin, J. G. (2000). Measuring medication adherence: are missing doses reported more accurately than perfect adherence?. *AIDS Care, 12*, 405–408.

Warnecke, R. B., Sudman, S., Johnson, T. P., O-Rourke, D., Davis, A. M. et al (1997). Cognitive aspects of recalling and reporting health-related events: Papanicolaou smears, clinical breast examinations, and mammograms. *Am J Epidemiol, 148,* 11, 982–992.

Wilbur, J., Chandler, P., and Miller, A. M. (2001). Measuring adherence to a women's walking program. *West J Nurs Res, 23*, 8–24.