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Measurement of Psychiatric Treatment Adherence

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Abstract

Objective—Nonadherence to medications for mental disorders substantially limits treatment effectiveness and results in higher rates of relapse, hospitalization, and disability. Accurate measurement of medication adherence is important not only in adherence research, but also in clinical trials in which medications are being evaluated, and in clinical practice where failure to detect nonadherence results in premature medication changes, unnecessary polypharmacy, and greater likelihoods of functional deteriorations and hospitalizations. This is a review of psychiatric treatment adherence methods and measures arising from a meeting on "Methodological Challenges in Psychiatric Treatment Adherence Research" held on September 27-28, 2007 in Bethesda, MD and organized by the National Institute of Mental Health (NIMH).

Methods—This paper reviews the range of modalities currently available for assessing adherence behavior including pill counts, pharmacy records, technology-assisted monitoring, biological assays, and a range of self-report and interviewer-rated scales. Measures of adherence attitudes are also reviewed.

Results—Each of the adherence measures described are imperfect estimates of actual medication ingestion but each provides informative estimates of adherence or the attitudinal factors associated with adherence. Measure selection depends on a range of factors including the patient sample, the context in which the measure is being used, and the clinical outcomes expected from various levels of nonadherence. The use of multiple measures of adherence is encouraged to balance the limitations of individual measures.

Conclusion—While adherence assessment has become increasingly sophisticated in recent years there remains a need for refinement and expansion on currently available methods and measures.

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Keywords

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Introduction

The World Health Organization (WHO) defines adherence as “the extent to which a person’s behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care professional” [1]. Nonadherence is a serious problem in psychiatric treatment and compromises effectiveness [2-6]. In schizophrenia, full or partial nonadherence can exceed 60% [7-9] and is associated with relapse, hospitalization, and elevated health care costs [7, 10, 11]. In bipolar disorder, nonadherence ranges from 20 to 60% [2, 12,13], and is associated with poorer outcomes, elevated rates of relapse, hospitalization, suicidal behavior, and greater costs of care [13-15]. Thirty percent of patients stop taking antidepressants after one month and 45-60% after 3 months. Inadequate adherence to antidepressants may lead to increased recurrence, severity, and disability, poorer responsivity to future treatment, and greater healthcare cost [16-22].

Reflecting an increasing awareness of the importance of treatment adherence on psychiatric populations, the National Institute of Mental Health (NIMH) assembled a group of experts in the area of mental health treatment research for a meeting on “Methodological Challenges in Psychiatric Treatment Adherence Research” held on September 27-28, 2007 in Bethesda, MD. During this meeting, the experts discussed and consolidated their experience based upon the extant literature and their own research on mental health treatment adherence research methods and articulated a series of recommendations for future directions. This review is a product of the 2007 NIMH meeting. While other forms of adherence such as attending office visits are also important aspects of treatment for mental disorders, this review of psychiatric treatment adherence measures focuses on medication adherence.

The Challenge of Adherence Measurement

Adherence is an observable behavior--we could continually observe an individual and record time, type and number of pills taken, and compare this to a prescribed regimen. Rules for determining mismatch between actual and prescribed use (e.g. what constitutes nonadherence) would need to be determined, but continually observing actual medication ingestion is the true gold standard of adherence measurement. Unfortunately, 24-hour observation of adherence behaviors is impractical. Such obtrusive monitoring would also prompt better adherence than would occur in unobserved contexts. Also, measuring adherence behavior does not reveal the reason(s) for nonadherence. Nonetheless, accurate assessment of adherence behavior is the foundation in which research on this topic becomes possible.

Thus necessarily, the measures of medication- taking behavior that are currently used in research and clinical practice are inexact estimates of actual medication ingestion. Even technology-assisted methods such as Medication Event Monitoring (MEMS) caps and smart pill boxes that are often presented as a “gold standard” only monitor opening and closing of medication bottles, not actual drug ingestion.

Measures of medication adherence fall into two basic categories: 1) Objective indicators of medication- taking such as pharmacy records, pills counts, electronic monitoring, and blood plasma levels, and 2) subjective measures of medication use via patient-report or interviewer ratings. In addition to measures of adherence behaviors, there are also measures of

adherence attitudes. These typically assess proximal factors associated with nonadherence including illness insight and treatment attitudes.

Objective Adherence Measures

Objective adherence assessments are widely utilized, quantifiable measures of treatment adherence. One or more of these methods, sometimes in conjunction with standardized attitudinal and self-report scales, may be utilized in clinical studies that have a primary or secondary focus on adherence assessment.

a. Pill Counts

Pill counts are a “low tech” method to measure adherence that may be applied to any patient or population, and which do not require expensive equipment or highly trained personnel. Pill counts determine how many pills are missing from a container and this number is compared to the number of pills that should have been taken within a specified time period, resulting in an estimated percentage of adherence. Multiple variables need to be considered in this deceptively simple approach. If patients are required to bring in their pill bottles for counting, missing data will result, particularly from the least adherent patients. Some patients may dump pills to appear adherent. A reliable and valid method for conducting pill counts is to count pills in the individual’s home, at unannounced and randomly scheduled visits [9]. An understanding of the home environment can enhance overall adherence assessment. Reactivity to such an assessment can be decreased by longer follow-up periods.

Pill count data can be compromised when participants combine the contents of multiple bottles, throw away empty bottles, or obtain pill samples. To minimize these problems, research participants should be trained on the home-based pill count procedure, and random home visits should occur at short intervals (counting pills every 3-4 weeks). To reduce the burden of random home-based pill counts, Kalichman and colleagues [23] developed a phone-based pill count procedure shown to correlate with the home-based count for HIV adherence. This approach may be appropriate for psychotropic adherence assessment, but testing in psychiatric samples is needed. In psychiatric populations, home-based pill counts have been found to be moderately to strongly correlate with other measures of adherence [4]. Pill count measures however, have not always been found to be related to clinical course. For example, Velligan et al found little relationship between pill count adherence (or adherence based on electronic monitoring) and psychosis symptoms in a 12 week study of stable outpatients [24].

b. Technology-Assisted Monitoring

There are several types of electronic devices that capture when pill containers are opened and closed to estimate the specific timing of doses, identify patterns of medication use and calculate adherence rates. Devices used in adherence studies include the Medication Event Monitoring or MEMS® caps, Med-eMonitor®, eCaps®, and most recently, Medsignals®. MEMS and eCaps contain an electronic chip in the bottle cap that records the time and date each time the bottle is opened. Older systems required that the cap be retrieved during an office or home visit, leading to substantial missing data, but newer systems transmit data via phone line. In addition, manual data cleaning is required to eliminate openings that appear unrelated to taking medication (e.g. multiple openings over a brief period or openings to fill the container). If the caps are left off the bottle, data are lost. Helpful features in electronic systems include with ability to work with blister packs and regular prescription bottles, and the ability to scan data into a computer.

Devices such as the Med-eMonitor and Medsignals are capable of storing and simultaneously monitoring multiple medications. The devices record when a drawer is

opened. After an opening, Med-eMonitor prompts the participant to indicate if the opening was for dose-taking. Medsignals is weight sensitive to automatically detect how many tablets were removed and when. If a drawer is left open, both machines alert the patient to close the drawer. Both download data to a remote secure server and both use programmable prompts. Medsignals is smaller and more portable than the Med-eMonitor, but must be filled more often. Benefits of the Med-eMonitor and Medsignals over MEMS and eCaps include notification of openings which result in taking medications, ability to track multiple medications with one device, prompts to close drawers that are left open, and the fact that data are automatically downloaded.

Although electronic monitoring is often thought of as the “gold standard” for adherence measurement in non-psychiatric populations and has clear benefit, these devices also have drawbacks. The expense of obtaining these devices and training in the use of the software may be prohibitive. The MEMS caps and the Med-eMonitor are bulky. Individuals may prefer to remove multiple pills from the devices at one time to take at work or to place in pill boxes, leading to an underestimate of adherence behavior. The investigator must consider preprogrammed day/date cut offs (e.g. once per night dosing at 12:01 am one day and 11:59 pm the next day would be represented as 0 doses in day one and 2 doses in day 2) and multiple openings that are not dose-related (e.g. checking to see how many pills are left). An additional issue with the MEMS devices is that many individuals with psychiatric diagnoses are taking more than one medication. An investigator may choose a primary medication for monitoring or may provide caps for more than one medication. However, this latter choice can add expense and effort to the trial. Finally, dates in which the patient has been hospitalized should typically be excluded. Data cleaning procedures should be included in any report using electronic monitors.

Despite the disadvantages and difficulties, electronic monitoring has been widely used with many different populations to obtain extensive data on adherence behavior, including in populations with mental disorders [25-29]. Unfortunately, some studies collapse the richness of data available from electronic monitors into percent of doses or days adherent per week or month which could adequately be captured by less expensive methodologies. Statistical procedures are available to analyze dosing patterns, and these analyses should be considered to fully utilize the data available from electronic monitors, especially when patterns of use (e.g. intermittent missed doses) are hypothesized to have clinical outcome implications [30].

Nakonezny and colleagues [31] found that data from electronic monitors had good internal consistency and test-retest reliability. Internal consistency of EM adherence was assessed using Cronbach's coefficient alpha (the mean intercorrelation of all possible split-halves of the six adherence periods). In addition, findings indicated that lower adherence was related to higher levels of symptomatology for patients with psychotic disorders. Percentage adherence from electronic monitoring has been found to correlate to percentage adherence calculated from pill count data [4], but in that study neither measure correlated with symptoms across a 12- week period. In addition, MEMS adherence has been found to correlate with adherence from specified self-report procedures that sensitize patients to the possibility of missed doses prior to their estimating percentage adherence [32].

c. Pharmacy Refill Records

Electronic pharmacy records are an objective, unobtrusive method to determine level of adherence, and may be particularly useful when larger groups or populations are studied. Numerous measures have been derived from pharmacy data including medication possession ratios (MPRs), gaps in medication use, medication consistency and persistence. Medication possession ratios are calculated by dividing the number of days’ supply of medication the patient received during a specified time period by the number of days’

supply they needed to receive if they were taking their outpatient medication continuously. The mean gap ratio identifies the number of days in a specified time period that an individual has been without medication. Other measures may consider the duration of continuous use between a first and last prescription of a particular medication, or time until a gap in use.

Increasing availability of electronic pharmacy records make medication fill data easier to obtain, but electronic records should not be assumed to be accurate or complete. For example, clinicians may change patients' dose during a clinical conversation but not change the prescribed dose until some time later; refill dates may also be inaccurate. In longitudinal studies, decisions must be made about which refills will count for which time period. Relying on programming alone to deal with setting time frames and identifying eligible cases can lead to interpretation errors.

Advantages of pharmacy records are that there is no missing data due to patient nonadherence to the adherence assessment procedure, and no assessment reactivity compared to more intrusive and burdensome monitoring procedures such as pill counts and electronic monitoring. Pharmacy records can provide data for large numbers of individuals over long periods of time. Drawbacks include the need to make decision rules that may vary by study for specific cases such as when medications are switched or tapered. The validity of pharmacy refill data may be compromised when individuals receive sample medications, when individuals transfer in and out of a system, or if individuals other than the patient refill the medications.

Adherence measures based on pharmacy data have shown to have strong relationships with patient outcomes. A study of more than 67,000 veterans, [33] found that rates of hospital admission were lowest for those whose medication possession rates were closest to 1.0. Rates of admission increased as possession rates decreased. Gilmer et al. [7] found that rates of psychiatric hospitalization were lower for those who were adherent (14%) than for those who were nonadherent (35%), partially adherent (24%), or had excess refill rates (25%). Based on California Medicaid, data from 4.325 outpatients with schizophrenia, [11] found that risk of hospitalization increased with increasing durations of medication gaps, with the odds ratio increasing from 1.98 with a gap of 1–10 days to 2.81 with a gap of 11–30 days to 3.96 with a gap of more than 30 days. Finally, studies in schizophrenia have shown that interventions to improve adherence effect both pill count adherence and adherence estimated from pharmacy records [9], although larger effects were found for pill counting measures.

d. Biologic Measures

Measurements of a drug or its metabolite in serum, urine, saliva, and hair are possible for some medications. These measures are objective, and vary with respect to utility, degree of intrusiveness, cost and availability. For a limited number of compounds, such as lithium or valproate, serum levels, may be readily utilized to evaluate adherence. However, individual medication differences in metabolism and half-life make biologic markers for most psychotropic medications (ie, antipsychotics and newer antidepressants) only useful for determining whether a particular medication has been taken or not taken, rather than how much of the medication has been taken. Reidel and colleagues [34] found a positive, but relatively weak linear relationship between plasma levels of risperidone active moiety and symptomatic improvement in a 6 week trial. Since the majority of individuals with adherence problems are partially adherent, biologic markers of a medication may not fully characterize this group of individuals [4].

Because of the problems with mapping medication levels to adherence, some adherence studies have used biologic tracers added to the medication [35]. These tracers are selected

based on their safety, detectability in biological samples, consistency of levels within and across patients for a given medication dose, and for being essentially inert with respect to therapeutic effects or interactions with other drugs. Producing a tracer that possesses all of these attributes is difficult and expensive, resulting in this method seldom being used. Mathematical modeling of simulated tracers with varying half-lives suggests that tracers may be accurate only within 4 to 8 doses per month under the best of conditions [35]. Further research is needed on developing inexpensive tracers that are sensitive to small changes in adherence.

Self and Interviewer Rating Measures of Adherence

Adherence Attitude Assessments—Ignoring the distinction between adherence *attitudes* and adherence *behaviors* has made it difficult to understand and interpret many of the adherence studies published to date, yet also represents an opportunity to improve adherence research methodology. One fundamental reason to assess attitudes is that one's behavior is not always the same as one's attitude toward the behavior. Table 1 illustrates possible combinations of attitude and behavior. If not accounted for in research designs, the two misaligned cells (“likes but does not take” and “does not like but takes”) can present serious problems with interpreting the results of adherence studies. It must be noted that this concept differs from the standard definition of adherence as a mismatch between what is prescribed and what is taken.

In it simplest form, adherence attitude can be defined as an explicit statement made by the patient pertaining to their overall like or dislike of taking medication. Adherence attitudes are multidimensional. At any given moment, the person may have attitudes that would be favorable to taking medication, and simultaneously have attitudes that are unfavorable. These contradictory attitudes can and do coexist simultaneously [36, 37]. Not surprisingly, the greater the ambivalence, the harder it is to correlate attitude and subsequent behavior. There are several threats to the validity of self-reported adherence attitudes. These include psychiatric symptoms such as paranoia or thought disorder as well as social desirability and stigma. Methods have been developed to address these barriers, such as simplifying the interview, assessing patients when stable or minimally symptomatic, not disclosing undesirable material to the treating clinician, and avoiding administering potentially stigmatizing assessments (e.g. a symptom rating scale) when conducting the adherence assessment.

Adherence Attitude Rating Scales

Adherence attitude scales cover three general domains: 1) subjective response to medication [38-40, 8) insight and awareness measures [41-43], and 3) comprehensive measures of adherence influences [44, 45]. The scales vary in their correlation with actual treatment adherence behavior. Selected self and interviewer adherence attitudes scales are briefly described below, and outlined in Table 2.

Selected Self and Interviewer Rating Scales for Adherence Attitudes

a. **Rating of Medication Influences (ROMI)** [45] measures adherence attitudes in psychiatric patients, particularly those with schizophrenia, and has a 20- year literature base showing relationships of the ROMI to adherence behaviors, medication levels, and treatment outcomes. The ROMI was developed based on the Health Belief Model, literature review, expert opinion, and patient feedback, and is one of the few measures that made use of preliminary testing with patients to refine items. The ROMI is divided into two subscales that separate reasons for adherence (Reasons for Compliance) from reasons for nonadherence (Reasons for Noncompliance), and assess a broad range of factors influencing a patient's personal decisions on adherence. The 20 interviewer -rated items have good

interrater agreement (kappa > .60) with kappa coefficients ranging from .75 to 1.0 for Reasons for Compliance items, and .63 to 1.0 for Reasons for Noncompliance items. Factor analyses revealed a three factor structure within the Reasons for Compliance scale, and a five factor structure for the Reasons for Noncompliance scale. These two sub-scales correlate moderately with the Drug Attitudes Inventory (.56 for Reasons for Compliance and −.47 for Reasons for Noncompliance.

b. Drug Attitude Inventory (DAI) [46, 47] is a 30-item, self- report scale that evaluates subjective effect of antipsychotic drugs among patients with schizophrenia. The DAI also evaluates insight into illness, and has been utilized in various psychiatric populations. The original pool of items was primarily derived from clinical practice. One hundered items were originally selected by the ability of each item to distinguish between patients who took their medication vs. those who did not. Subjective responses are scored on a euphic-dysphoric continuum with scores ranging from maximum dysphoria (−44) to maximum euphoria (+44). The reliability of the 30-item version of the scale is reported to be 0.93 as determined by the developers using the Kuder-Richardson formula. The scale also shows high discriminative validity. The scale developers [47] interpreted a positive score as ‘adherent” while a negative score was interpreted as “nonadherent” .

There is a 10-item version of the scale that is commonly utilized and was derived from stepwise discriminate analysis of responses of 150 patients with schizophrenia to the DAI-30 [47]. Items are rated by participants as either true or false with correct items scoring +1 and incorrect items scoring −1. Overall, the DAI appears to be a easily administered and reasonable tool to measure subjective response to psychotropic treatment, particularly antipsychotic drugs [48]. The correlation of the DAI with current or future adherence behavior is less clear.

c. Medication Adherence Rating Scale (MARS; [49, 50] is a 10-item, self-report scale derived from the Drug Attitudes Questionnaire (DAI) and the Medication Adherence Questionnaire (MAQ). The MARS was developed for use in populations with schizophrenia and psychoses. Internal consistency is only marginally adequate (alpha = .75) due in part to a three-factor structure, one factor measuring adherence behaviors and the other two measuring adherence attitudes (attitude toward taking medication and negative side effects and attitudes to psychotropic medications). Initial validity data is mixed. The MARS did not correlate with carer-rated adherence, but in small sub-sample taking lithium, the MARS was moderated correlated (.61) with lithium levels [49]. In a subsequent validation trial [50], internal consistency was less than found in the initial study (.60 vs. .75), but the three-factor structure was confirmed in a larger sample. However, Cronbach's alpha for the factor scales were marginal (.67 for factor 1, .44 for factor 2, and .53 for factor 3) and none of the factor scales correlated with keyworker ratings of adherence. Test-retest correlations of .52 at 12 months with an intervening treatment indicate adequate stability, but may also indicate inadequate sensitivity to change. The absence of relationship to clinician and significant other ratings of adherence are not a concern given the lack of validity of such ratings, but the global score appears less meaningful than the factor scale scores that separate adherence behavior from attitudes. The MARS factor 1 score has been demonstrated to correspond with the Morisky adherence scale [51], and it has been suggested that the factor 1 total score may be a preferable measure of adherence behavior than the total MARS score [50].

d. Brief Evaluation of Medication Influences and Beliefs (BEMIB): [52] is an 8-item scale measuring costs and benefits of medication use based on Health Belief Model. The BEMIB was developed to identify non-adherence in patients with schizophrenia and related psychotic disorders. Participants rate each of 8 items on a 5-point Likert-type scale. The BEMIB has modest internal consistency of .63, but a three-factor structure indicates

multidimensionality of the scale. In a small sample (N =13), test-retest reliability at one week was .86. The measure shows reasonable relationships with pharmacy record data (sensitivity of 83% and specificity of 71% based on 10% gap ratio of days meds available/ days in interval). The BEMIB has been shown to correlate significantly with the DAI. Although the DAI measure is theoretically based and shows good concordance with pharmacy records, other psychometric data are limited.

e. ASK-20 Adherence barrier survey [53, 54] is a recently developed measure of barriers to adherence designed for broad patient populations and tested in depression, asthma, and diabetes samples. The ASK-20 consists of 20 clinical actionable items that represent multiple factors known to affect treatment adherence. Based on a review of potential adherence barriers, candidate items were developed and refined via patient focus groups. Based on web-based survey responses from over 600 individuals with reported depression, asthma, or diabetes, a 12-factor structure was identified, and 20 items were retained based on factor loadings, content coverage, and floor-ceiling coverage, and lack of redundancy. Despite the 12 factor model, a Cronbach's alpha of .85 was obtained. The ASK-20 score was associated moderately with a number of self-reported medication adherence questions, but no other validity assessments or test-retest were performed. While early data is promising, more psychometric data is needed to confirm the exploratory validity of the ASK-20 in psychiatric populations.

Self and Interviewer Reports of Adherence Behavior

Self-report is the most often used measure of adherence behavior, [20] but is also often criticized as the least valid [55]. This is due in part to factors such as social desirability, memory biases, and poor insight that limit the accuracy of patient reports, but also to the use of ad-hoc items and scales of unknown psychometric properties. Although reports of nonadherence are often accurate, reports of adherence are often inaccurate and influenced by social desirability and memory biases that overestimate adherence [56]. There are two types of self reports that appear to measure different behavioral constructs [57]. The first type of self-reports takes the form of retrospective recall of actual medication-taking events (for example, “How many times did you take your pills over the past 3 days?”) while the second is a more general adherence rating (“I took my medications as prescribed.” With response assessed as strongly disagree to strongly agree). Selected adherence behavior rating scales are described briefly below and in Table 2.

a. Brief Adherence Rating Scale (BARS) [32] measures adherence behaviors. This 4-item, clinician-administered patient-report scale is adapted from a lengthier adherence questionnaire used in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study [58]. In a sample of 61 patients with schizophrenia, Cronbach's alpha for the BARS was .92, high for a 4 item scale. Across the six monthly assessment periods, test-retest reliabilities ranged from .46 to .86. Spearman correlations between MEMS and the BARS for each month of the 6 month trial were moderate (.42 to .59), and using a cutoff of 70% adherence, the BARS showed good sensitivity (73%) and specificity (71%) compared to the MEMS classification of 70% adherence. Although more validity data is needed, the initial data from the BARS is promising as a self-report-to-clinician measure of adherence behavior. Relative to electronic monitoring, the BARS appears to provide valid, reliable, sensitive, and specific estimates of antipsychotic medication adherence of outpatients with schizophrenia and schizoaffective disorder [32].

b. Morisky Adherence Scale [51] is a 4-item self-reported measure of treatment adherence behavior that was originally developed involving populations with hypertension. However, the Morisky scale has subsequently been utilized to evaluate treatment adherence in various disease states including mental disorders such as depression, bipolar disorder and

schizophrenia [59-61]. The 4 items on the Morisky scale are answered yes (score = 0) or no (score=1). Possible scores range from 0-4 with higher scores indicating non-adherence. The sensitivity of the Morisky scale in medical populations is 0.81 and the specificity is 0.44. Reliability (Cronbach's alpha value) 0.61. A significant limitation of the Morisky scale is the fact that there is no specified time frame in which respondents refer to with respect to self-reported history making adherence assessments over time difficult.

c. Tablets Routine Questionnaire (TRQ) [62, 63] was developed to evaluate treatment adherence in populations with bipolar disorder and shows a high correlation with lithium levels [62, 63]. The TRQ identifies partial and full adherence, identified as failure to take 30% or more of prescribed medication. The TRQ determines proportion of prescribed medication taken and is not dependent upon timing of medication provided that medication is consumed within the required day/24 hour period. The TRQ consists of 2 general questions regarding any difficulties taking or coping with medications followed by 4 questions regarding approximate number of missed doses in the past week and past month. This rating has demonstrated statistically significant association with past non-adherence, repeated past non-adherence, any non-adherence in the past month, and non-adherence in the past week (X^2=7.2, df=6, p=.03). Compared with non-adherence in the past two years, missing 30% or more of prescribed mood stabilizers in the past week has a specificity of 100% and a sensitivity of 65%. Compared with non-adherence in the past week, it has specificity of 87% and a sensitivity of 84% [62]. While useful to generally determine individuals who have clinically significant non-adherence, the TRQ does not provide a specific measure of missed doses.

Clinician Assessment of Treatment Adherence—A number of studies have shown that clinician judgment is not a useful screen for nonadherent patients [4, 28, 64, 65] although there are methodological limitations in published studies and additional research is needed in this area. Byerly and colleagues [32] showed that while MEMS caps reported 48% of schizophrenia patients being classified as nonadherent (< 70% days adherent), clinician ratings failed to classify even one patient as nonadherent. Clinician ratings generally rely on patient reports of adherence [5], and judgments independent of patient reports tend to have poor interrater reliability [45].

Issues to Consider in Selecting Adherence Measures

Relationship of Adherence to Outcome—Haynes and Sackett [66] advocated that medication adherence interventions target both adherence behavior and a well-established clinical outcome (e.g. symptom reduction). However, data linking medication adherence to clinical outcomes are mixed. In some conditions, poor adherence has been linked to poorer outcomes [67] while others have not found this relationship [4]. Despite the difficulties in linking adherence to outcomes, the relationship of adherence and outcomes is an important consideration in selecting adherence measures. For medications in which only a few skipped doses or missed doses could have negative clinical impacts, electronic monitoring, frequent pill counts, and/or retrospective recall every few days may be necessary to detect clinically important intermittent nonadherence. In contrast, medications with long half-lives whose effects are retained for weeks following discontinuation may need less fine-grained adherence measures. If adherence attitudes are being considered as contributors to adherence and especially if adherence-enhancing interventions targeting these attitudes are being evaluated, self and interviewer rating scales measuring adherence attitudes are warranted.

Context of Adherence Measurement—There are costs and benefits for all adherence measures. In studies specifically focusing on adherence as the primary outcome and on the effects of more intensive adherence-enhancing interventions on relatively small samples, the

costs of intrusive and expensive measures (e.g. electronic monitoring) are often outweighed by the precision required for such studies. For outcomes trials in which adherence is a secondary endpoint or mediator variable or studies in which adherence is a primary measures but sample sizes are very large, less intensive measures such as pharmacy records may be adequate. Assessment of adherence in large survey and epidemiologic studies will often differ from adherence assessment in randomized clinical trials. For each research or clinical context, the cost of the measure should be balanced against the needed precision of the adherence estimate.

Multiple medications—When study participants take multiple medications the average adherence for each drug class is often calculated as the variable of interest. Assessing the adherence for each medication separately may reveal differential adherence patterns and inform a decision about the appropriateness of combining adherence rates for two medications. Along with theoretical concerns regarding whether to assess adherence to single or multiple psychiatric medications, or with both psychiatric and non-psychiatric medications, cost issues are also likely to arise.

Combining Adherence Measures—Since all adherence measures have strengths and weaknesses, it is generally recommended that investigations combine two or more complementary measures of adherence. Selection and justification of assessment method should depend on type of adherence of interest (pattern of use vs. discontinuation), target of any adherence-enhancing intervention, the nature of research and the illness or treatment being investigated.

Multiple adherence measures also require an a priori analysis plan for combining these measures. One common method for combining adherence behavior measures is to develop a hierarchical plan for determining nonadherence, essentially using one measure as a validation or confirmation of adherence or nonadherence determined by the other measure. Another strategy for combining adherence measures uses a statistical procedure such as structural equation modeling to estimate the latent trait of adherence from the various adherence measures obtained in the study. Using multiple adherence measures combined in rational ways mitigates the disadvantages of any one measure and may provide a reasonably accurate estimate of actual adherence.

Conclusions

A range of measures of adherence attitudes and behaviors are available to researchers and clinicians studying populations with mental disorders. It must be remembered however, that all of these measures of adherence with medication treatments are inexact measures of drug ingestion and suffer from limitations. In addition to techniques that directly or indirectly measure adherence behaviors, a number of self-report and interviewer ratings of adherence attitudes with good psychometric properties are available. Measure selection should be based on the similarities of the samples in which these measures have been studied to the sample of interest, the resources available to the investigators, and the goals of the study. Smaller and/or prospective studies with adequate resources may implement such methods as use of electronic devices to measure adherence, while pill –counts and/or self-report (such as the TRQ or the Morisky Adherence Scale) where technology-assisted methods are not practical or affordable. Studies in populations with mood disorders might assess adherence via serum levels if treatments include lithium, divalproex, carbamazepine or some antidepressant agents. Larger-scale studies with centralized pharmacy records (for example VA or HMO databases) are ideal settings for use of pharmacy refill records to evaluate adherence.

One of the goals of adherence research is identification of modifiable factors for adherence improvement. For this reason, inclusion of adherence attitude measures such as the ROMI, DAI, BEMIB or ASK-20 are helpful, as they may assist in informing interventions that can then be implemented in selected psychiatric populations. Multiple and complementary adherence measures are recommended.

Finally, additional research is needed to refine and expand the assessment methods and measures for treatment adherence in populations with mental disorders. Specific gaps in the adherence literature include lack of consensus on the most appropriate methods of adherence assessment in populations with specific mental disorders and specific treatment settings, need for refining a broadly accepted definition of non or partial adherence, and need for further exploration of relationships between adherence and clinical outcomes, as well as methods to appropriately combine multiple adherence assessment measures and approaches. Given the scope and negative consequences of nonadherence in psychiatric clinical populations, efforts to address these gaps in knowledge have important implications for the treatment of individuals with mental illnesses.

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References

1. World Health Organization. Adherence to Long Term Therapy: Evidence for Action. 2003. http://www.who.int/chronic_conditions/adherencereport/en/ accessed Jan 8 2009
2. Perlick DA, Rosenheck RA, Kacynski R, et al. Medication non-adherence in bipolar disorder: A patient-centered review of research findings. Clinical Approaches in Bipolar Disorders. 2004; 3:54–56.
3. Marder SR. Overview of partial compliance. J Clin Psychiatry. 2003; 64(Suppl 16):3–9. [PubMed: 14680412]
4. Velligan DI, Lam YWF, Glahn DC, Barrett JA, Maples NJ, Ereshefsky L, Miller AL. Defining and assessing adherence to oral antipsychotics: A review of the literature. Schizophrenia Bulletin. 2006; 32:724–742. [PubMed: 16707778]
5. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med; 2005; 353:487–97.
6. Pomykacz G, Mao M, Wiss RD, Teter CJ. A review of breif medication-adherence insturments used in patients with schizophrenia and bipolar disorder. Harv Rev Psychaitry. 2007; 15(5):259–63.
7. Gilmer TP, Dolder CR, Lacro JP, Folsom DP, Lindamer L, Garcia P, Jeste DV. Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. American Journal of Psychiatry. 2004; 161:692–699. [PubMed: 15056516]
8. Valenstein M, Ganoczy D, McCarthy JF, Kim HM, Lee TA, Blow FC. Antipsychotic adherence over time among patients receiving treatment for schizophrenia: A retrospective review. Journal of Clinical Psychiatry. 2006; 67:1542–1550. [PubMed: 17107245]
9. Velligan DI, Diamond PM, Mintz J, Maples N, Li X, Zeber J, Ereshefsky L, Lam YW, Castillo D, Miller AL. The use of individually tailored environmental supports to improve medication adherence and outcomes in schizophrenia. Schizophr Bull. 2008; 34:483–93. [PubMed: 17932089]
10. Fenton WS, Blyler CR, Heinssen RK. Determinants of medication compliance in schizophrenia: Empirical and clinical findings. Schizophrenia Bulletin. 1997; 23:637–651. [PubMed: 9366000]
11. Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. Psychiatric Services. 2004; 55:886–891. [PubMed: 15292538]
12. Lingam R, Scott J. Treatment non-adherence in affective disorders. Acta Psychiatrica Scandinavica. 2002; 105:164–172. [PubMed: 11939969]

13. Colom F, Vieta E, Tacchi MJ, Sánchez-Moreno J, Scott J. Identifying and improving non-adherence in bipolar disorders. Bipolar Disorders. 2005; 7:24–31. [PubMed: 16225557]
14. Svarstad BL, Shireman TI, Sweeney JK. Using drug claims data to assess the relationship of medication adherence with hospitalization and costs. Psychiatric Services. 2001; 52:805–811. [PubMed: 11376229]
15. Scott J, Pope M. Self-reported adherence to treatment with mood stabilizers, plasma levels, and psychiatric hospitalization. American Journal of Psychiatry. 2002a; 159:1927–1929. [PubMed: 12411230]
16. 1Demyttenaere K. Compliance during treatment with antidepressants. Journal of Affective Disorders. 1997; 43:27–39. [PubMed: 9127828]
17. Frank E, Kupfer D, Perel J, Cornes C. Three-year outcomes for maintenance therapies in recurrent depression. Archives of General Psychiatry. 1990; 47:1093–1099. [PubMed: 2244793]
18. Melfi CA, Chawla AJ, Croghan TW, Hanna MP, Kennedy S, Sredl K. The effects of adherence to antidepressant treatment guidelines on relapse and recurrence of depression. Arch Gen Psychiatry. 1998; 55:1128–32. [PubMed: 9862557]
19. Roy-Byrne P, Post R, Uhde T, Porcu T, Davis D. The longitudinal course of recurrent affective illness. Acta Psychiatrica Scandinavica. 1985; 71(Suppl. 317):1–34. [PubMed: 3969837]
20. Kupfer D. Long-term treatment of depression. Journal of Clinical Psychiatry. 1991; 52(Suppl. 5): 28–34. [PubMed: 1903134]
21. Thompson D, Buesching D, Gregor KJ, Oster G. Patterns of antidepressant use and their relation to costs of care. Managed Care. 1996; 2:1239–1246.
22. Thompson D, Hylan TR, McMullen W, Romeis ME, Buesching D, Oster G. Predictors of a medication-offset effect among patients receiving antidepressant therapy. American Journal of Psychiatry. 1998; 155:824–827. [PubMed: 9619157]
23. Kalichman SC, Amaral CM, Stearns H, White D, Flanagan J, Pope H, Cherry C, Cain D, Eaton L, Kalichman MO. Adherence to antiretroviral therapy assessed by unannounced pill counts conducted by telephone. Journal of General Internal Medicine. 2007; 22:1003–6. [PubMed: 17390095]
24. Velligan DI, Wang M, Diamond P, Glahn DC, Castillo D, Bendle S, Lam YWF, Ereshevsky L, Miller AL. Relationship among subjective and objective measures of adherence to oral antipsychotic medications. Psychiatric Services. 2007; 58:1187–1192. [PubMed: 17766564]
25. Remington G, Kwon J, Collins A, Laporte D, Mann S, Christensen B. The use of electronic monitoring (MEMS) to evaluate antipsychotic compliance in outpatients with schizophrenia. Schizophrenia Research. 2007; 90:229–237. [PubMed: 17208414]
26. Diaz E, Levine HB, Sullivan MC, Sernyak MJ, Hawkins KA, Cramer JA, Woods SW. Use of the Medication Event Monitoring System to estimate medication compliance in patients with schizophrenia. J Psychiatry Neurosci. 2001; 26:325–329. [PubMed: 11590972]
27. Acosta FJ, Bosch E, Sarmiento G, Juanes N, Caballero-Hidalgo A, Mayans T. Evaluation of noncompliance in schizophrenia patients using electronic monitoring (MEMS) and its relationship to sociodemographic, clinical and psychopathological variables. Schizophrenia Research. 2009; 107:2–3.
28. Byerly M, Fisher R, Whatley K, Holland R, Varghese F, Carmody T, Magouirk B, Rush AJ. A comparison of electronic monitoring vs. clinician rating of antipsychotic adherence in outpatients with schizophrenia. Psychiatry Research. 2005; 133:129–133. [PubMed: 15740989]
29. Demyttenaere K, Mesters P, Boulanger B, Dewe W, Delsemme MH, Gregoire J, Van Ganse E. Adherence to treatment regimen in depressed patients treated with amitriptyline or fluoxetine. 2001 Journal of Affective Disorders. 2001; 65:243–52. [PubMed: 11511404]
30. Aloia MS, Goodwin MS, Velicer WF, Arnedt JT, Zimmerman M, Skrekas J, Harris S, Millman RP. Time Series Analysis of treatment adherence patterns in individuals with Obstructive Sleep Apnea. Annals of Behavioral Medicine. In press.
31. Nakonezny PA, Byerly MJ, Rush AJ. Electronic monitoring of antipsychotic medication adherence in outpatients with schizophrenia or schizoaffective disorder: an empirical evaluation of its reliability and predictive validity. Psychiatry Research. 2008; 157:259–63. [PubMed: 17935793]

32. Byerly MJ, Nakonezny PA, Rush AJ. The Brief Adherence Rating Scale (BARS) validated against electronic monitoring in assessing the antipsychotic medication adherence of outpatients with schizophrenia and schizoaffective disorder. Schizophrenia Research. 2008; 100:60–69. [PubMed: 18255269]
33. Valenstein M, Copeland LA, Blow FC, et al. Pharmacy data identify poorly adherent patients with schizophrenia at increased risk for admission. Med Care. 2002; 40:630–639. [PubMed: 12187177]
34. Riedel M, Schwarz MJ, Strassnig M, Spellmann I, Müller-Arends A, Weber K, Zach J, Müller N, Möller HJ. Risperidone plasma levels, clinical response and side-effects. Eur Arch Psychiatry Clin Neurosci. 2004; 255:261–268. [PubMed: 15565299]
35. Shine D, McDonald J. Limits of confidence in tracer compounds as a means of measuring patient compliance with medication. J Clin Pharmacol. 1999; 39:1233–1241. [PubMed: 10586388]
36. Ajzen I. Nature and operation of attitudes. Annu Rev Psychol. 2001; 52:27–58. [PubMed: 11148298]
37. Conner M, Povey R, Sparks P, James R, Shepherd R. Moderating role of attitudinal ambivalence within the theory of planned behaviour. Br J Soc Psychol. 2003; 42(Pt 1):75–94. [PubMed: 12713757]
38. Emerich DF, Sanderg PR. Neuroleptic dysphoria. Biologic Psychiatry. 1991; 29:201–203.
39. Van Putten T, May PRA. Subjective response as a predictor of outcome in pharmacotherapy (The consumer has a point). Archives of General Psychiatry. 1978; 35:477–480. [PubMed: 727898]
40. Voruganti LNP, Awad AG. Neuroleptic dysphoria: towards a new synthesis. Psychopharmacology. 2004; 171:121–132. [PubMed: 14647964]
41. Cuesta MJ, Peralta V, Zarzuela A. Reappraising insight in psychosis. Multi-scale longitudinal study. British Journal of Psychiatry. 2000; 177:233–40. [PubMed: 11040884]
42. Sanz M, Constable G, Lopez-Ibor I, et al. A comparative study of insight scales and their relationship to psychopathological and clinical variables. Psychological Medicine. 1998; 28:437–46. [PubMed: 9572100]
43. Tait L, Birchwood M, Trower P. Predicting engagement with services for psychosis: insight, symptoms and recovery style. British Journal of Psychiatry. 2003; 182:123–8. [PubMed: 12562739]
44. Maeda K, Kasai K, Watanabe A, et al. Effect of subjective reasoning and neurocognition on medication adherence for persons with schizophrenia. Psychiatric Services. 2006; 57:1203–1205. [PubMed: 16870974]
45. Weiden PJ, Rapkin B, Mott T, et al. Rating of medication influences (ROMI) scale in schizophrenia. Schizophrenia Bulletin. 1994; 20:297–310. [PubMed: 7916162]
46. Hogan TP, Awad AG, Eastwood R. A self-report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. Psychol Med. 1983; 13:177–183. [PubMed: 6133297]
47. Awad G. Subjective response to neuroleptics in schizophrenia. Schizophrenia Bulletin. 1993; 19(3):609–18. [PubMed: 7901897]
48. Sajatovic, M.; Ramirez, L. Rating Scales in Mental Health. Lexi-Comp; Cleveland, OH: 2003.
49. Thompson K, Kulkarni J, Sergejew AA. Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. Schizophr Res. 2000; 42:241–7. [PubMed: 10785582]
50. Fialko L, Garety PA, Kuipers E, Dunn G, Bebbington PE, Fowler D, Freeman D. A large-scale validation study of the Medication Adherence Rating Scale (MARS). Schizophr Res. 2008; 100:53–9. [PubMed: 18083007]
51. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986; 24:67–74. [PubMed: 3945130]
52. Dolder CR, Lacro JP, Warren KA, Golshan S, Perkins DO, Jeste DV. Brief evaluation of medication influences and beliefs: development and testing of a brief scale for medication adherence. J Clin Psychopharmacol. Aug. 2004; 24(4):404–9. [PubMed: 15232332]
53. Hahn SR, Park J, Skinner EP, Yu-Isenberg KS, Weaver MB, Crawford B, Flowers PW. Development of the ASK-20 Adherence Barrier Survey. Current Medical Research and Opinion. 2008; 24:2127–2138. [PubMed: 18554431]

54. Matza LS, Yu-Isenberg KS, Coyne KS, Park J, Wakefield J, Skinner EP, Wolever AR. Further testing of the reliability and validity of the ASK-20 adherence barrier questionnaire in a medical center outpatient population. Current Med Res Opin. 2008 [Epub ahead of print].
55. Garber MC, Nau DP, Erickson SR, Aikens JE, Lawrence JB. The concordance of self-report with other measures of medication adherence: a summary of the literature. Med Care. 2004; 42:649–52. [PubMed: 15213489]
56. Spector PE. Perceived control by employees: A meta-analysis of studies concerning autonomy and participation at work. Human Relations. 1986; 39:1005–1016.
57. Jerant A, DiMatteo R, Arnsten J, Moore-Hill M, Franks P. Self-report adherence measures in chronic illness: retest reliability and predictive validity. Med Care. 2008; 46:1134–9. [PubMed: 18953223]
58. Stroup TS, McEvoy JP, Swartz MS, et al. The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project: schizophrenia trial design and protocol development. Schizophrenia Bulletin. 2003; 29:15–31. [PubMed: 12908658]
59. Brown C, et al. Beliefs about antidepressant medications in primary care patients. Medical Care. 2005; 43:1203–1207. [PubMed: 16299431]
60. Copeland LA, et al. Treatment adherence and illness insight in veterans with bipolar disorder. The Journal of Nervous and Mental Disease. 2008:16–21. [PubMed: 18195637]
61. Gray R, et al. Adherence therapy for people with schizophrenia. British Journal of Psychaitry. 2006; 189:508–514.
62. Scott J, Pope M. Non-adherence with mood stabilizers: prevalence and predictors. J Clin Psychiatry. 2002; 63:384–390. [PubMed: 12019661]
63. Peet M, Harvey NS. Lithium maintenance: A standard education programme for patients. Br. J. Psychiatry. 1991; 158:197–200. [PubMed: 1707323]
64. Stephenson BJ, Rowe BH, Haynes RB, et al. Is this patient taking the treatment as prescribed? J. Am Med Associ. 269:2779–2781.
65. Demyttenaere K, Enzlin P, Dewe W, et al. Compliance with antidepressants in a primary care setting,1: Beyond lack of efficacy and adverse events. J. Clin Psychiatry. 2001; 62(Suppl 22):31–3.
66. Haynes, RB.; Sackett, DL., editors. Compliance with Therapeutic Regimens. Johns Hopkins University Press; Baltimore, Md.: 1976.
67. DelBello MP, Hanseman D, Adler CM, Fleck DE, Strakowski SM. Twelve-Month Outcome of Adolescents with Bipolar Disorder Following First Hospitalization for a Manic or Mixed Episode. J Psychiatry. 2007:2–590.

Table I

Potential Relationships between Adherence Attitudes and Adherence Behaviors

	Positive Attitude	**Negative Attitude**
Positive Behavior	Likes and takes medication	Doesn't like it but takes it
Negative Behavior	Likes but does not take	Doesn't like/doesn't take

Table II

Selected Measures of Psychiatric Medication Adherence Attitudes and Behaviors

Name of Scale	Number of items	Mode of administration	Time to complete (minutes)	Reliability	Validity
Rating of Medication Influences (ROMI)	20	Clinician/Trained Rater	10-15	+	+
Drug Attitude Inventory (DAI)	10 (10-item)	Self-report	5-10	+	-
Medication Adherence Rating Scale (MARS)	10	Self-report	5-10	+	-
Brief Evaluation of Medication Influences and Beliefs (BEMIB)	8	Self-report	5-10	+	+
ASK-20 Adherence Barriers Survey	20	Self-report	10-15	+	+
Brief Adherence Rating Scale (BARS)	4	Clinician/Trained Rater	5	+	+
Morisky Adherence Scale	4	Self-rated	5	+	+
Tablets Routine Questionnaire (TRQ):	10	Clinician/Trained Rater	10-15	+	-

+ = Some Information

- = Incomplete or Inconsistent Information

-- = No Data