# Methodological Challenges in Psychiatric Treatment Adherence Research

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## Abstract

Reflecting an increasing awareness of the importance of treatment adherence on outcomes in psychiatric populations, the National Institute of Mental Health (NIMH) convened a panel of treatment adherence researchers on September 27–28, 2007 to discuss and articulate potential solutions for dealing with methodological adherence research challenges. Panel discussions and presentations were augmented with targeted review of the literature on specific topics, with a focus on adherence to medication treatments in adults with serious mental illness. The group discussed three primary methodological areas: participants, measures, and interventions. When selecting patients for adherence-enhancing interventions (AEIs), a three-tier model was proposed that draws from the universal (targeting all patients receiving medication treatment for a specific condition, regardless of current adherence), selective (targeting patients at risk for nonadherence), and indicated (targeting patients who are currently nonadherent) prevention model and emphasizes careful patient characterization in relevant domains and appropriate matching of interventions to the selected population. Proposals were also made to reduce problematic selection biases in patient recruitment and retention. The panel addressed the pros and cons of various methods that can be used to measure adherence, and concluded that it is appropriate to use multiple measures whenever possible. Finally, the panel identified a broad range of intervention approaches, and conditions under which these interventions are likely to be most effective at reducing barriers to adherence and reinforcing adherence behavior.

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## Introduction

Nonadherence compromises the effectiveness of available psychiatric treatments and interferes with recovery. In clinical practice, a working general definition of adequate adherence is the minimum level of adherence required for each person to achieve adequate treatment response and avoid relapse that is mutually agreed upon by patient and provider. In schizophrenia, rates of full or partial nonadherence can exceed 60% (1-3). In total, 74% of patients become noncompliant within two years of hospital discharge. Inadequate adherence is associated with relapse, hospitalization, and elevated healthcare costs (1, 4, 5). Rates of nonadherence in bipolar disorder range from 20 to 60% (6-8), and are generally associated with poorer outcomes, including elevated rates of relapse, hospitalization, suicidal behavior, and greater costs of care (7, 9, 10). Nonadherence in major depression is estimated at 53% (6). On average, 30% of

patients stop taking antidepressants after one month and 45 to 60% after three months of treatment. The risks of inadequate adherence to antidepressants include increased recurrence, severity and disability, poorer responsiveness to future treatment, and greater healthcare cost (11-18).

Despite the considerable negative impacts of inadequate adherence to psychiatric treatments, research on predictors and interventions for nonadherence has been slowed by a number of methodological challenges. In response to these challenges, the National Institute of Mental Health (NIMH) convened a panel of treatment adherence researchers on September 27–28, 2007 to discuss adherence research challenges and propose potential strategies to address these challenges. The program chief for the NIMH treatment adherence program (WTR) invited the panel of treatment adherence experts drawn primarily from psychiatric treatment adherence grantees or authors of recent major publications in this area, and augmented by treatment adherence researchers from other areas (e.g., cardiovascular or HIV). The meeting attendees consisted of these invited experts and National Institutes of Health (NIH) staff with interest in treatment adherence methodology. The agenda for the meeting was developed by the program chief for the NIMH treatment adherence program, with consultation from other NIMH staff, and paralleled the outline of this paper with presentations from the panel on methodological issues related to participants, measures, and adherence interventions/study design. Key points from the presentation and discussion were recorded in outline form which served as the detailed outline for this paper. Following the meeting, primary and secondary writers for each of the sections were assigned. Panel discussions were supplemented with targeted review of the literature by assigned writers. Draft sections were reviewed by all participants and merged/synthesized by the first author. The result reflects the consensus of the panel. While the meeting focus was on methodological challenges to medication adherence research, the challenges addressed have potential implications for adherence to other treatments. Adherence to psychosocial interventions is equally important and understudied, but was not addressed by this panel. The focus of this report is on adherence to medication in adults with severe and persistent mental illness: specifically, schizophrenia, bipolar disorder, and major depression. This report is organized around the three major methodological areas specified by the NIMH: participants, measures, and interventions.

Limitations include that the panel did not include all researchers studying adherence in severe mental illness. Consumers, mental health providers, and other stakeholders were not included in the meeting. The report does not include systematic review of the literature, but targeted review on specific topics. Not all topics related to adherence in severe mental illness are covered and others were mentioned only briefly (e.g., forensics and community treatment orders, the role of culture). The reader is encouraged to seek additional resources on these topics. Finally, the report is focused on the healthcare system in the United States, with its unique attributes and challenges.

## Participants

### *Defining the Population of Interest*

Clearly defining the study population of interest is essential in adherence intervention research because it allows investigators, policy makers, and clinicians to determine the degree to which adherence-enhancing interventions (AEIs) might be applicable to other populations and settings. Traditionally, adherence intervention research has specified the population of interest by diagnostic status or by the receipt of specific treatments (e.g., antipsychotics, antiretrovirals) (19), although studies of broader groups, such as patients with serious mental illnesses or mood disorders, have also been performed (20). Few studies, however, have examined adherence among patients with comorbid conditions receiving complex medication regimens, even though such patients reflect real-world populations (19, 21). The panel primarily considered adherence research methods relevant to adult individuals with more serious mental health conditions (e.g., schizophrenia, bipolar disorder, and major depression) who must continue medications longer term and who often have comorbid conditions and complex medication regimens.

There are potential research advantages of limiting study participants to those with a specific psychiatric diagnosis. These include ameliorating concerns about the generalizability of risk factors for poor adherence and responses to specific interventions that may arise in studies including individuals with a variety of diagnoses. The assessment of adherence and patient outcomes is also simplified if it is limited to the medication regimen for a single targeted disorder. However, limiting adherence interventions to patients with specific mental disorders also has drawbacks, including reduced applicability of research interventions to "real-world" patients who often have substantial comorbidity (22-25), and reduced potential to assess the impact of important variables or intervention components across major psychiatric disorders. For example, other clinical factors, such as functional status, cognitive impairments, or phase of illness (i.e., recent onset versus long-standing) may be more important than the primary diagnosis in determining the effectiveness of adherence-enhancing interventions (AEIs). For example, an individual may have few cognitive difficulties and ben-

efit most from an intervention that increases the willingness to take medication. Alternatively, an individual may have many cognitive difficulties and require high levels of assistance with remembering to take medications, indicating that tailored repetitive reminders or direct family or caregiver involvement in medication administration may be most useful.

Developing unique adherence interventions for specific disorders complicates the dissemination of AEIs, as clinicians are unlikely to adopt a unique AEI for each diagnostic group. Thus, from a dissemination and implementation perspective, developing AEIs that are applicable to large and diverse groups of patients is desirable. AEIs focusing on individuals with specific diagnoses or treatments might be reserved for patients at greatest risk for nonadherence or those who fail broader adherence-enhancing efforts.

Whether a diagnosis-focused or a broader adherence intervention is examined, researchers should describe the range of clinical presentations in their patient population, including relevant psychiatric and general medical comorbidities. Potential procedures for defining participants' diagnoses vary by type of study. Large retrospective studies may identify clinical diagnoses from chart reviews or claims records. Concordance between diagnoses in administrative databases and chart reviews varies by diagnosis and treatment setting, and (26, 27) greater specificity may be achieved from administrative databases by using diagnostic algorithms that require two or more visits with the specified diagnoses (28-30). In prospective studies, diagnoses obtained from chart review or claims data may be independently confirmed by clinicians. When diagnosis-specific AEIs are studied, semi-structured diagnostic interviews, such as the Structured Clinical Interview for DSM-IV (SCID) (31) or the Mini-International Neuropsychiatric Interview (M.I.N.I.) (32) are warranted.

## Targeting by Risk of Nonadherence

Many adherence studies include all patients meeting criteria for the disorder and/or treatment of interest without regard for levels of adherence (33, 34, 20, 35-37). This approach assumes that most patients could benefit from an adherence intervention. This assumption may be reasonable for disorders or treatments with high rates of nonadherence, but approximately half of psychiatric patients appear to adequately adhere to treatment without AEIs. Studies that deliver interventions to patients who may not need them (i.e., those whose baseline adherence is already at 70 to 80%) reduce the possibility of detecting improvements arising from interventions as there is little room for further improvement resulting in a "ceiling effect." Moreover, the power to detect proportional differences is lower in the middle of the proportion continuum (38). To illustrate, consider a study that includes all patients with a particular disorder where 50% are adherent at baseline. If 50% of controls versus 70% of intervention patients are adherent at the study's end, a sample of 75 patients per group or 150 total would be required to detect this 20% difference with 80% power. If, instead, only nonadherent patients were enrolled and 5% of control versus 25% of intervention patients were adherent at the study's end, the sample size could be reduced by over 50% to 68 (34 in each group) for comparable power. Although identifying and selecting nonadherent patients incurs additional costs, these costs may be offset by smaller sample size requirements to detect adherence differences.

To address these issues, we propose a three-tier AEI model (see Table 1) that is consistent with a stepped care treatment model and draws from the universal, selective, and indicated prevention model first presented by Gordon for general medical conditions and later adapted by the Institute of Medicine (IOM) for mental health conditions (39, 40). This three-tier model also is consistent with the NIH 4Ps model (Predictive, Personalized, Preemptive, and Participatory) for revolutionizing medicine (41). Similar models have been used to conceptualize and organize mental health services for geriatric and schizophrenia populations and to consider alternative suicide prevention services (42-46). However, to the panel's knowledge, this is the first use of this model to conceptually organize interventions to improve adherence with medication treatment.

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### Universal AEIs

Universal AEIs would include all patients receiving medication treatment for a general medical or psychiatric condition, regardless of current adherence—with the goal of *preventing* nonadherence in all patients. Services or environmental modifications that are appropriate for universal AEIs are likely to be less intensive and costly; less tailored,

**Table 1 Potential Adherence Interventions Based on the Three-Tiered Model of Adherence**

| Adherence Targeted Group | Examples of Appropriate Adherence-Enhancing Interventions |
|---|---|
| Universal (all patients) | psychoeducation, provider training in provider-patient communications, all systems-based interventions |
| Selected (high risk for nonadherence) | reminders, pill boxes, regular monitoring, family interventions |
| Indicated (currently nonadherent) | motivational interviewing, electronic monitoring, directly observed therapy |

and easily disseminated (e.g., psychoeducation). Due to ceiling effects, large sample sizes will often be needed to demonstrate the impact of universal interventions.

### Selected AEIs

Selected AEIs would target patients at risk for nonadherence. Because a number of studies have shown that clinicians are generally poor predictors of nonadherence, clinician judgment may not be a useful screen for at-risk individuals (47, 48). A variety of demographic and clinical factors may identify individuals at risk for adherence problems including a medication change initiated by the patient, treatment attitudes, prior adherence behavior, and nonhealth-related behaviors such as difficulties with personal finances and poor work performance (e.g., selected AEIs might include individually tailored psychoeducation, personalized motivational approaches, or distribution of more expensive medication assistive devices).

### Indicated AEIs

Indicated AEIs are recommended for patients who are currently nonadherent. Such interventions might be highly tailored to target the person's reason for nonadherence and, compared to the universal adherence intervention strategy, are usually more intensive and of longer duration. Examples of these approaches have included components such as home visits, extensive assistance with organizing medication-taking regimens, sophisticated assistive devices, ongoing care management, pharmacy-based medication management, and psychotherapeutic interventions. For studies assessing indicated AEIs, adherence could be assessed during a baseline period, and only those meeting nonadherence criteria would be included. Patients who have evidence of both current poor adherence and symptomatic exacerbation may be particularly important to target. Similar to a placebo lead-in, a baseline assessment period also could be used to exclude patients who become adherent due to measurement effects alone.

Challenges to implementation of an adherence enhancement stepped approach include determination of adequate versus inadequate adherence which may be difficult to specify for psychiatric treatments (3). In addition to a supportable rationale for defining adequate adherence, researchers also should consider the capabilities of clinicians and healthcare systems to easily or appropriately identify populations for an indicated AEI. Some methods of determining nonadherence, such as MEMs caps (electronic pill caps that monitor when a pill bottle is opened and shut), may be too cumbersome or difficult to employ in routine clinical settings.

In summary, it may be useful for adherence researchers to consider whether it is most appropriate and a better "research value" to select all patients in a treatment for a particular intervention (universal AEIs), patients at risk for nonadherence (selective AEIs), or patients who are currently nonadherent (indicated AEIs). Matching adherence selection criteria more closely to the purpose of the proposed intervention may result in more clearly targeted and efficient studies with greater clinical applicability.

## *Potential Selection Biases When Enrolling Study Participants*

In research on adherence, as in other clinical and health services research, a recurring methodological concern is the possibility of nonrepresentative study participants—either because of issues in recruiting or retention (3, 49-52). Nonadherent patients may be less likely to participate in research studies and, if they participate, may be less likely to adhere to study procedures. These biases in study enrollment and participation potentially limit both the internal validity and the external generalizability of study findings. Unfortunately, data documenting the extent of potential selection biases in adherence intervention research are lacking. To address this, adherence researchers need to consider innovative ways to both assess and reduce potential selection biases in their studies, and to report data that will allow readers to assess the extent of possible biases in their studies. Minimally, all adherence studies should follow CONSORT guidelines (http://www.consort-statement.org/) (53, 54) and provide data on patient attrition from screening through study completion to document the number of eligible patients who do not consent/enroll and who enroll but do not complete study assessments or procedures.

Assessing and minimizing selection biases arising from recruitment, enrollment, and retention issues will require innovative study designs and close collaboration with researchers' Institutional Review Boards (IRBs) in order to balance human participant protections with the pressing need to both minimize and characterize enrollment biases. For example, IRBs and researchers may need to consider procedures that would allow researchers to retain de-identified pre-enrollment screening data for patients who do not consent to study participation, protecting patient confidentiality while allowing assessment of potentially important differences between patients who do or do not consent to study participation. Refusal to consent to adherence research studies might be reduced if IRBs allowed researchers to use informed consent documents that describe study inclusion criteria without specifying diagnostic labels that may prevent psychiatric patients with limited insight or those who feel stigmatized by diagnostic labels from participating in these studies. Once patients are enrolled, researchers should have extensive, proactive procedures to minimize the risk of dropout from study assessments. Statistical analyses should include an intention-to-treat approach to reduce biases inherent in examining only AEI completers. Comparisons of study completers and noncompleters on baseline variables also should be used to assess potential attrition biases. When possible, adherence research should include adherence outcome data such as pharmacy records that can be obtained even if the patient is lost to follow-up.

*Selection biases are particularly important to consider in adherence research and efforts to assess and minimize these biases must always be part of research efforts.*

Adequate incentives (meaningful levels of compensation) for completing study assessments may improve retention. However, unless incentives are part of the adherence intervention itself (e.g., payment for adherence), it must be made clear to study participants that these incentives are for completing study measures and are not related to how closely participants adhere to either the AEIs or the treatments.

In summary, there are several important methodological issues to consider when defining the target population for adherence intervention research and when matching the study population with appropriate AEIs. Work is needed on the use of AEIs in real-world clinical populations, such as patients with multiple medical and psychiatric disorders. Participant selection based on risk of nonadherence should be informed by the three-tier model (universal, selected, indicated AEIs). Selection biases are particularly important to consider in adherence research and efforts to assess and minimize these biases must always be part of research efforts.

## Measurement Issues

### Defining Outcome

Sackett and Haynes (50) 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 morbidity and mortality (55-57) while in others it is not linked to poorer clinical outcomes (47). Clinical outcomes, including broader outcomes such as quality of life, can be impacted by factors other than treatment adherence such as the patient's environment (58). Therefore, proximal outcomes such as adherence behaviors and/or attitudes are important, and may be primary or secondary research outcome measures depending on study goals.

### Issues of Multiple Medications

When study participants take multiple medications, the average adherence for each drug class is often calculated as the variable of interest. However, assessing adherence for each medication may help determine the appropriateness of combining adherence rates for two medications and reveal differential adherence patterns. Consideration should be given to assessing all psychiatric medications, since adherence to one medication can affect adherence to others. However, the decision depends upon the goals of the study. Many individuals with psychiatric illness have medical comorbidities that contribute to adherence burden. In addition, many individuals use alternative medications or supplements. Assessing adherence to these medications or supplements can add considerable complexity, but may be appropriate when potential medication adherence interactions are hypothesized. Cost issues must be weighed against theoretical concerns in determining whether to assess adherence to single or multiple psychiatric medications, or to nonpsychotropic medications.

### Assessing Medication Adherence Attitudes

Adherence attitude is defined as the person's own thoughts and feelings about recommended medication. Ignoring the distinction between adherence *attitudes* and adherence *behaviors* has complicated the interpretation of many adherence studies published to date; yet, clarifying this distinction represents an opportunity to improve adherence research methodology. Patients can like but not take their medication, or not like their medication but still take it.

Furthermore, adherence attitudes are often complex and multidimensional. A patient can have both favorable and unfavorable attitudes toward taking medication; contradictory or ambivalent attitudes often coexist (59, 60). This complicates the relationship between adherence attitudes and behaviors. Variation in collective attitudes toward adherence, such as cultural expectations regarding how long or how consistently to take medications for particular disorders, also affects individual attitudes and their effect on adherence behavior. The attitudes of family and caretakers are also important because they may affect adherence behavior (61).

There are several threats to the validity of self-reported adherence attitudes. These include psychiatric symptoms such as paranoia or thought disorder, social desirability, and stigma. Methods have been developed to address these barriers, such as simplifying the interview, assessing patients when stable, nondisclosure to the treating clinician, and avoiding administering potentially stigmatizing assessments (e.g., a symptom rating scale) (62-64).

### Adherence Attitude Assessments

Adherence attitude scales for antipsychotics cover three general domains: 1) subjective response to antipsychotics (65-67); 2) insight and awareness measures (68-70); and, 3) comprehensive measures of adherence influences (71, 72). Subjective response measures include the Drug Attitude Inventory (DAI), which may show little or no correlation with current or future nonadherence. Examples of insight scales range from a single "insight" item on the Positive and Negative Syndrome Scale (PANSS) to more in-depth measures such as the Schedule of Unawareness of Mental Disorder (SUMD) (73), Insight and Treatment Attitudes Questionnaire (ITAQ) (74, 75), and the Schedule for Assessment of Insight (SAI) (76). Currently available insight scales have moderate correlations with adherence and evidence of predictive validity (63, 68, 74, 77-79). Scales that capture broader attitudinal domains such as therapeutic alliance, stigma, or opinions of family members include the Rating of Medication Influences (ROMI) Scale (72), which assesses a broad range of factors influencing a patient's decision to adhere to treatment, including subscales measuring reasons for adherence and for nonadherence.

Attitudinal assessment is critical for developing explanatory models of adherence, developing patient-centered interventions based upon shared decision making, and assessing AEIs that target adherence attitudes as mediators to changing adherence behaviors. Further qualitative research is needed to better understand the reasons for medication use and discontinuation, why some individuals are adherent despite numerous barriers, and the bidirectional influences between attitudes and behaviors. These qualitative data could serve as the basis for developing new adherence attitude scales consistent with recently published standards for patient-reported scale development and testing (FDA PRO guidance [http://www.fda.gov/CDER/GUIDANCE/5460dft.pdf]) (80).

## Assessing Medication Adherence Behavior

Many methods are available for assessing adherence behavior, but none completely measures each occurrence of an individual actually ingesting medication (3, 81). Therefore, all are inexact estimates of true adherence. For a given study, the appropriateness of specific methods for assessing adherence behaviors will depend upon the study context, the target population, and the types of nonadherence that are relevant.

### Pill Counts

Pill counts can be used to determine how many pills are missing from a container versus how many pills should have been taken within a specified time period, resulting in an estimated percentage of adherence (82). Although a deceptively simple approach, there are multiple variables to consider (3, 81, 83). Study participants typically need to bring in pill bottles for counting, which results in missing data, and the least adherent patients are the most likely to fail to bring in containers to count (3). Some studies report that pill counts overestimate adherence (84). If patients are aware that pills will be counted, they may dump pills before their visit to appear adherent (82). A novel, reliable and valid method for conducting pill counts is to count pills in the individual's home at unannounced and randomly scheduled visits (36, 47, 85). While such visits can be labor intensive and somewhat intrusive, an understanding of the home environment, the location and method of pill storage, and the availability of multiple bottles of the same medication can enhance overall adherence assessment. The accuracy of pill count data can be compromised when participants combine the contents of multiple bottles, throw away empty bottles, or are given medication samples (3, 81, 83). To minimize these problems, research participants should be prepared and trained on the home-based pill count procedure (e.g., keeping all empty bottles, counting, bagging and stapling old bottles so that pills are taken out of the current container, etc.), and random home visits should occur at short intervals (counting pills every three to four weeks) (85). To reduce the burden of random home-based pill counts, Kalichman and colleagues developed a phone-based pill count procedure which was shown to correlate with the home-based count for HIV adherence (86). This approach may also be appropriate for psychotropic adherence assessment, but testing in psychiatric samples is needed.

## Electronic 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 (3, 48, 82, 87). Older systems required that the cap be obtained by the researcher during an office or home visit, leading to substantial missing data, but newer systems transmit data via phone line (3, 87). In addition, manual data cleaning is required to eliminate openings that appear unrelated to taking medication (e.g., multiple openings over several minutes or openings to fill the container). If the caps are left off the bottle, data are lost (3, 82). The pitfalls noted for MEMS are also true for eCaps; however, eCaps can be programmed with blister packs (packages in which each pill is covered in a plastic casing backed by cardboard, and can be ejected using pressure from the thumb), can work with regular prescription bottles (less bulky than the MEMS bottles), and can be scanned into a computer.

The Med-eMonitor and Medsignals are devices capable of storing and simultaneously monitoring multiple medications (82, 85). 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 (85). 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 automatic data downloads.

Although electronic monitoring is often thought of as the "gold standard" for adherence measurement in nonpsychiatric populations and has clear benefit, these devices also have drawbacks (3, 82, 87). The expense of obtaining these devices and training in the use of the software may be prohibitive for limited-resource studies. 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 (3). With these devices, the investigator must consider pre-programmed day/date cutoffs (e.g., once per night dosing at 12:01 A.M. one day and 11:59 P.M. the next day would be represented as 0 doses in day 1 and 2 doses in day 2), and multiple openings that are not dose related (e.g., checking to see how many pills are left). Additionally, dates in which the patient has been hospitalized should typically be excluded in calculating adherence rates. Data cleaning procedures should be included in any report using electronic monitors.

Laws and IRB policies regarding who may fill these devices vary by jurisdiction, and may make use of these devices more complex and burdensome. Some policies require that containers are filled only by a licensed pharmacist, whereas other jurisdictions and IRBs allow nonpharmacist research staff to assist patients in placing the medication in the device or bottles or in picking up and bringing new bottles or trays prefilled by a pharmacist to the participant. Regardless of the procedure for filling these devices, requirements for using these devices include an initial setup of the device in the home, examination of all prescribed medications, determination of participant preferences, and training of participants in device use. In one study, 30% of participants trained in the hospital on the use of the monitor did not set up the electronic monitor when returning home (88).

Despite the disadvantages and difficulties, electronic monitoring has been widely used with many different populations to obtain extensive data on adherence behavior. 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 (89), 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.

## Pharmacy Refill Records

Electronic pharmacy records are an objective, unobtrusive method to determine level of adherence (2, 3, 5, 90). To estimate the percentage of days adherent, the number of days supply of a medication from a first prescription during a specified time period is examined in relation to the number of days that pass until a new prescription is filled. One can also calculate mean gap ratio or the number of days in a specified time period that an individual has been without medication. Increasing availability of electronic pharmacy records makes these data easier to obtain, but electronic records should not be assumed to be accurate or complete. In some systems, all records for the original prescription and the refills have the same fill date. In longitudinal studies, decisions must be made about which refills will count for which time period (2, 5). 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 (assessment of adherence does not encourage adherence) compared to more intrusive and burdensome monitoring procedures such as pill counts and electronic monitoring. Pharmacy records provide data for large numbers of individuals over long periods of time (2, 5). 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, and when individuals transfer in and out of a system.

*Since all adherence measures have strengths and weaknesses, it is generally recommended that investigations combine two or more potentially complementary measures of adherence (3, 91, 94).*

### Self-Reports

Self-reports of adherence behavior are sometimes considered less valid than other measures due to concern about the truthfulness of patient reporting and the demand characteristics that often positively bias self-reports. Despite these concerns, self-report of adherence behavior can often augment other adherence behavior measures, particularly when patients report nonadherence (81, 91).

### Biologic Measures

Measurements of a drug or its metabolite in serum, urine, saliva, and hair are possible for some medications (3, 92, 93). These measures are objective, and vary with respect to utility, degree of intrusiveness, cost and availability. Individual differences in metabolism and half-life make biologic markers useful for determining if a medication has been discontinued, but generally less useful for determining the amount of medication taken. Since the majority of individuals with adherence problems are partially adherent, biologic markers of a medication may not fully characterize this group of individuals (3).

Because of the problems with mapping medication levels to adherence, some adherence studies have used biologic tracers added to the medication (93). 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. Further research is needed on developing inexpensive tracers that are sensitive to small changes in adherence.

## *Combining Adherence Measures*

Since all adherence measures have strengths and weaknesses, it is generally recommended that investigations combine two or more potentially complementary measures of adherence (3, 91, 94). Selection and justification of assessment method should depend on type of adherence of interest (pattern vs. discontinuation), target of AEI, nature of research (epidemiologic, pilot, random controlled trial [RCT]), and the illness or treatment being investigated.

Multiple adherence measures also require an a priori analysis plan for combining these measures (94). 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 (94). 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. Finally, there needs to be a consideration of how to evaluate adherence attitudes as well as adherence behavior. It is important to make sure the attitude measure is clearly distinct from behavioral measures and to establish parallel assessment and analytic strategies in the study design.

# Adherence Interventions

## *Methodological Issues in Evaluating Adherence-Enhancing Interventions*

### Designing for Dissemination

Interventions intended to enhance medication adherence must address the competing priorities of efficacy versus dissemination. Early studies should focus appropriately on efficacy (what works under ideal or controlled conditions), but an overriding theme of adherence research must be approaches that are generalizable and able to be disseminated to a variety of treatment settings. A sustained, programmatic plan of research is needed to move adherence research from initial efficacy trials to effectiveness and dissemination trials, and to incrementally develop, refine and test interventions that are likely to benefit real-world patients. Dissemination and implementation research procedures can be used

to further adoption of evidence-based AEIs, but efficacy studies of new AEIs should consider dissemination beginning with the initial stages of intervention development (95).

### Adherence Intervention Fidelity

During the process of intervention development, testing, and dissemination, fidelity issues around care providers and systems become critical. Approaches that work in carefully controlled RCTs may become attenuated or ineffective without standardization processes to preserve the quality and format of the tested intervention. Manualization, increasingly common in psychosocial interventions for serious mental disorders (96, 97), improves fidelity in clinical trials, and allows for ready dissemination of the intervention. In addition to manualization, independent fidelity checks of AEI implementation, as well as oversight and supervision, can minimize deviations from the intended intervention both during the efficacy/effectiveness trials and during dissemination in real-world settings.

### Patient Adherence to the Adherence-Enhancing Interventions

For adherence-enhancing interventions (AEIs) requiring patient participation, adherence to the AEI itself becomes an important issue. If the AEI requires session attendance and patient participation, these need to be monitored to determine AEI exposure. The dose-response relationship between AEI exposure and medication adherence is often confounded, however, by the possibility that patients more adherent to the AEI are also more likely to be adherent to medication. Strategies to maximize adherence to the AEI should be considered, but researchers should be cautious about using financial incentives to increase patient participation in the AEI, since it can be difficult for patients to distinguish between incentives for adhering to the AEI versus adhering to the medication. This issue is separate from using contingency management as an intervention to increase adherence. This latter issue is discussed later in this report. Designing an AEI that encourages patient participation via minimizing patient burden and barriers is preferable to financial incentives for AEI participation.

### Comparison Condition

Participation in a research study may in itself modify medication adherence among individuals due to the additional monitoring, financial incentives, or other study procedures. An appropriate comparison condition should control for these study-related factors, particularly if the AEI is anticipated to affect patient expectancy of improving adherence. Although controlling for expectancy of change and other "nonspecific" factors is ideal, the problem with "controlling" for nonspecific factors early in the development and evaluation of new AEIs is that these factors may be "active" and lead to an underestimation of the treatment effects and a premature conclusion that a new intervention is ineffective. Therefore, more rigorous control conditions may be more appropriate after initial efficacy in comparison to usual care is established. In situations in which withholding AEI strategies produces ethical concerns (e.g., severe deterioration due to treatment discontinuation), the comparison condition should provide sufficient active AEI components to minimize participant risk.

*A sustained, programmatic plan of research is needed to move adherence research from initial efficacy trials to effectiveness and dissemination trials, and to incrementally develop, refine and test interventions that are likely to benefit real-world patients.*

Studies of AEIs in psychiatric populations are generally complementary or augmentative to usual care (98, 99), making usual care a convenient and often appropriate comparison condition. The primary question facing clinicians in real-world settings is not whether one new intervention is more effective than another, but rather whether adding a new intervention improves outcomes more than not adding it. However, usual care varies across providers and treatment settings in type and quality of the treatment. Adherence-enhancement interventions also overlap with selective techniques embedded in effective psychological therapies for individuals with serious mental illness (96, 100, 101), so it may be difficult to separate the effects of the adherence intervention from traditional psychosocial treatments. Therefore, it is important to describe in detail what "usual care" is, particularly any care that may impact adherence, and to utilize study procedures that will reduce the variability of usual care.

## Theoretical Basis of AEIs

Theory-based interventions, designed to increase knowledge, information and skills that individuals need to improve adherence, have been tested in a wide variety of psychiatric conditions including depression, schizophrenia, bipolar disorder and substance use disorders (36, 97, 102-105). Behavioral strategies designed to facilitate change in the actions of an individual are based upon theoretical models that conceptualize behavioral correlates of adherence (106). These include, but are not limited to, the Transtheoretical Model of Change (TMC), which proposes a series of stages that an individual moves through when adopting a

health-related behavior from contemplation through action and maintenance (107); the Health Beliefs Model (HBM), which suggests that an individual engages in a health-related behavior based upon beliefs about illness and its severity, as well as perceived costs and benefits of engaging in the behavior (108); the Theory of Reasoned Action (TRA), a cognitive theory to explain the decision to engage in a behavior which is based upon social norms and attitudes and beliefs about the potential outcomes (109); and, the Rational Choice Model (RCM), which proposes that an individual makes decisions about treatment by consciously evaluating evidence and considering the costs and benefits with respect to social conditions and their individual preferences and experiences (110).

*Designing an AEI that encourages patient participation via minimizing patient burden and barriers is preferable to financial incentives for AEI participation.*

Treatment strategies derived from these and other theoretical models include Motivational Interviewing and Contingency Management, which have been tailored to individuals with mental disorders (106, 111), and are intended to promote positive health behaviors including improved adherence. Despite common factors contributing to adherence across diseases and treatments, theoretical models for AEIs tend to be applied selectively (e.g., Information, Motivation, Behavior [IMB] in HIV adherence is seldom used in mental health adherence research).

Behavioral economics is another area of research which may have theoretical and practical implications for adherence interventions (112). One of the central tenets of behavioral economics is that individuals tend to be *present-biased*: they weigh current costs and benefits more heavily than future costs and benefits. This is not simply a preference for immediacy, but rather an indicator of inconsistency such that present-biased individuals may plan to take their medications as prescribed, but then fail to do so despite considerable negative future costs of nonadherence.

In terms of designing specific interventions for health behavior change, perhaps the most obvious from a behavioral economic perspective is simply to change the price of an outcome—usually via a tax or subsidy. Studies have demonstrated that medication adherence improves when copayments are lowered (113). One particular example of a price change that has garnered considerable recent attention is Contingency Management (CM), specifically conditional cash transfers. Cash payment for desired behaviors has also been used successfully in smoking cessation (114) and adherence to outpatient methadone treatment in addicts (115). An even more novel CM approach would be to use a monetary deposit by the patient which is returned if he adheres to the treatment (or follows through with any other chosen behavior change) (116). The application of behavioral economics theory to adherence research is one example of expanding the theoretical basis for understanding and modifying adherence attitudes and behaviors.

## Components of Adherence Interventions: From Patients to Healthcare Systems

Despite numerous studies assessing a variety of adherence-enhancing interventions (AEIs), there remains considerable controversy regarding best approaches to address nonadherence across a wide variety of disease states, patient populations and care settings (19, 106, 117). Multifaceted interventions that address the barriers to adherence and reinforce or emphasize positive behaviors appear most likely to succeed (19, 36, 106, 117). However, adherence interventions, like nonadherent individuals, differ widely and ideally should be tailored to the specific individual or care setting and incorporate culture-, gender- and age-specific issues. Interventions in populations with chronic disease states such as diabetes, or conditions requiring long-term medication usage to prevent clinical relapse such as HIV infection, can provide useful information to incorporate into adherence interventions for individuals with mental disorders.

Interventions that focus on specific needs, clinical/cognitive status, insight, and attitudes and beliefs toward illness and treatment are critical to optimize adherence (99, 106). For example, Keck and colleagues (118) noted that risk for nonadherence is particularly high for individuals with bipolar mania, suggesting that AEIs might be best implemented during euthymic or mildly depressed states with intensive monitoring and adherence maintenance efforts during manic states. Cognitive ability should also be a consideration guiding development of AEIs for neuropsychiatric populations.

There are a growing number of psychological therapies that have shown promise in improving treatment adherence, usually incorporating a patient-centered, interactional approach. Motivational Interviewing (MI), based upon the Transtheoretical Model of Change (119), has been successfully utilized in populations with addiction and with other psychiatric conditions (120, 121), but continued development and evaluation of MI approaches for psychiatric treatment adherence are needed. Early results of MI in schizophrenia by Kemp et al. (102) were promising, but subsequent research failed to confirm these findings (122).

A Collaborative Care Model (CCM), which is adapted from treatments for chronic medical disorders, may be par-

**Table 2 Facilitators and Barriers to Medication Adherence among Individuals with Serious Mental Illness**

| Facilitators of Treatment Adherence |
|---|
| • perceived benefit of medication on overall illness outcome and personal goal attainment |
| • perceived immediate benefit on specific symptoms |
| • fear of illness relapse |
| • reminders or cues to treatment adherence |
| • structured daily routine |
| • family/friend support for adherence |
| • acceptable financial costs |
| • few logistical barriers to refilling |
| **Barriers to Treatment Adherence** |
| • perceived lack of benefit of medications |
| • lack of insight into illness/problems |
| • medication-related adverse effects |
| • misunderstanding of medication effects and interactions |
| • logistic burdens to medication taking |
| • forgetting, distractibility, lack of a routine to support taking regular medication |
| • direct recommendations not to take medications from family, friends or others |
| • stigma related to psychotropic medication taking |
| • psychological issues related to long-term use of medications |

Adapted with permission from: Sajatovic M, Jenkins JH, West JA, Cassidy KA, Meyer WJ, Lamkin N, et al. Subjective aspects of medication treatment and medication adherence among individuals with bipolar disorder. New Research in Mental Health (Ohio Department of Mental Health); 2006-2007 Biennium, Vol. 18:324-332.

ticularly efficacious in mental disorders where symptoms wax and wane in type and intensity, such as bipolar disorder (123, 124). While the CCM, which stresses illness self-management, empowerment, and communication and collaboration with treatment providers, appears to be generally associated with better illness outcomes, the effects of a CCM approach on adherence remain unclear (123-125).

Disease-based interventions that focus on a specific illness and feature interactive education and disease management training have been demonstrated to help promote adherence across a variety of conditions (106). Psychoeducation is a psychosocial intervention that is usually focused on a particular disorder and disorder-based intervention. The potential value of psychoeducation is based on the premise that informed patients are more likely to take an active role in managing their illness, resulting in better health outcomes (7). Psychoeducation appears to produce modest improvements among individuals with eating disorders (126), anxiety/panic disorder (127), addictive disorders (128), schizophrenia (129), depressive disorders (130) and bipolar disorder (131). However, additional research is needed to identify how, and in which populations, psychoeducation and other disease-state specific interventions enhance adherence.

Family and social support appear to enhance adherence in populations with mental disorders (97). However, family environments that are chaotic, overly crowded, or place excessive dependence on the individual may adversely affect treatment adherence (132). Adherence interventions should maximize positive influences while neutralizing negative influences to adherence in the context of the individual's social and cultural environment.

Depot formulations have been found to improve adherence (133, 134). However, group differences in randomized trials have been less robust than anticipated. A meta-analysis based upon data from the Cochrane systematic reviews concludes that those on depot have an advantage in global outcome over those on orals (51). However, in a review of six randomized, double-blind trials comparing depot and oral medications, Glazer and Kane (52) report only a 15% difference in relapse rates favoring the depot drugs. Authors argue that this figure substantially underestimates the benefits of depot medications. Both reviews suggest that sampling bias may be a significant problem in studies using injectable medications in one of the treatment arms.

Directly Observed Therapy (DOT) has been used extensively for improving adherence to tuberculosis (TB) treatment. Although recent meta-analyses have questioned the

effectiveness of DOT for curing TB (135), modified forms of DOT have been shown effective in improving HIV treatment adherence and reducing viral loads and CD4 counts (136). Directly Observed Therapy has not been evaluated specifically for psychiatric treatments, although it is sometimes a component of assertive community outreach programs for patients with serious mental illness. Given the cost and intrusion, DOT would probably be most appropriate for those at high risk for nonadherence and subsequent serious deterioration.

Numerous barriers to, and facilitators of, adherence in psychiatric populations have been identified, including limited access to care, poor health literacy and cultural biases against specific types of treatments (137-140). Both quantitative and qualitative studies may help to identify and understand the full spectrum of barriers to, and facilitators of, treatment adherence in psychiatric populations. Table 2 identifies selected patient-reported barriers to, and facilitators of, adherence. Compton and colleagues identified characteristics associated with psychotropic medication nonadherence among 1,843 individuals receiving psychiatric care using logistic regression modeling to identify independent predictors of nonadherence. A predictive model of eight demographic and clinical domains was developed that included substance use, medication side effects, psychotic symptoms, personality disorder, financial problems, previous hospitalizations, functional status and duration of treatment. This eight-domain predictive model identified 91% of individuals who had adherence problems (139). Identification of the most common risk factors for nonadherence (examined in multiple studies over the past three decades) can be a useful starting place to address the issue of modifiable barriers to care.

In contrast to barriers to care, several factors may facilitate adherence (106). Approaches that may improve treatment adherence across many disease states include medication dosage simplification and cues or reminders to take medication or follow-up with appointments (106, 141). Behavioral tailoring to include taking medications into the daily routine of the individual has also been effective (142-144). Studies that examine dosing specifics—such as dosing titration, dose effects, and timing in relation to lifestyle and daily activities—as well as variable formulations of medications, are needed to guide evidence-based recommendations for clinicians treating suboptimally adherent psychiatric populations.

Additional facilitators to adherence include environmental supports and memory aids such as alarm devices, signs and checklists, e-mail reminders, portable multidose medication envelopes, refill reminder postcards/telephone calls and automatic medication home delivery (36, 106). Technological advances not only provide automated reminders to increase adherence, but also monitor adherence and can provide real-time alerts to the clinician when nonadherence is a concern. The use of these and other technologies for improving adherence of those with mental disorders has only recently begun to be explored (85).

**Table 3 Qualities of an Ideal Adherence-Enhancement Intervention**

| |
|---|
| • patient-centered, fostering empowerment and self-management |
| • incorporates consideration of illness type and severity, cognitive status and relevant clinical variables |
| • tailored to the individual's **current attitudes** toward treatment |
| • longer-term as opposed to one-time intervention, recognizing that adherence is a process/may change over time |
| • incorporates culture-, gender-, age-specific issues regarding adherence |
| • considers both barriers and facilitators to adherence |
| • may blend multiple types of approaches (behavior+care system+ memory aid) |
| • incorporates both quantitative and qualitative assessments as appropriate |

Healthcare system- or organizational-level facilitators of adherence, such as pharmacy-based or hospital-discharge programs targeting individuals known to be at risk for future nonadherence, may be a useful and practical focus of both study and intervention (106). Hospital discharge provides an important transition and critical time period for addressing treatment adherence. One-time and noninteractive interventions, however, are unlikely to be of benefit (145). Adherence drug utilization review (DUR) flags at point-of-medication dispensing or in the medical record, telecommunication, e-Health websites, and adherence incentives for professionals are all organizational-level possibilities requiring additional study in populations with mental illnesses (106, 117, 146). Drug utilization reviews can address issues such as polypharmacy that can increase the complexity of treatment and negatively impact adherence (147, 148). Most psychiatric adherence interventions have targeted primarily the patient, not the environment or system in which they function. An ecological model (149) of adherence would argue for a more balanced approach in which the patients, provider, health system, family and social support network, community, and society/policy should all be targets of an intervention to improve adherence.

In summary, despite the pervasiveness and severe negative consequences of treatment nonadherence in populations with mental disorder, the literature on treatments to enhance adherence in these individuals is quite limited.

Table 3 outlines features of an "ideal" adherence-enhancing intervention for individuals with mental disorders. Based upon the available data, interventions with the best chance of success should be tailored to an individual's needs, paying attention to cultural-, gender- and age-related factors as well as comorbidity and type/quality of the social support network. Interventions must be patient-centered, fostering empowerment and self-management while at the same time taking into consideration clinical/cognitive status, capabilities, barriers, and facilitators specific to the individual. Interventions may require the use of multiple or blended approaches, such as behavioral (MI, CM or others), memory aids or adherence prompts, and healthcare system- or organizational-level techniques.

## Conclusions

Adherence to medications used to treat schizophrenia, bipolar disorder, depression, and other mental disorders is a critical factor in improving outcomes for these serious and potentially disabling conditions. This expert panel convened by NIMH outlined a number of methodological challenges and potential directions for future adherence research. Selection bias, an important challenge in all clinical research, is particularly important to address in adherence research. There are numerous valid measures of adherence, but each has weaknesses that can be partially overcome by rationally combining adherence measures. Adherence-enhancing interventions (AEIs) for mental illness treatments have shown efficacy, but can be substantially improved by drawing upon a wider array of theoretical perspectives, developing more patient-centered or tailored approaches, and taking a more ecological perspective that addresses not only the patient but the broad environmental context that facilitates or impedes adherence. Matching intervention intensity to a stepped model of intervention for all patients (universal), patients at risk for nonadherence (selected) and those nonadherent (indicated) has the potential to improve the effect sizes of adherence intervention trials, and provide a structure that facilitates dissemination and implementation in real-world settings.

## Appendix

### *Definition and Assessment of Adequate Adherence*

Defining what constitutes adequate medication adherence in psychiatry is a complex issue and much work remains to be done in this area (3). Its complexity is due in part to the difficulty of defining adequate treatment, as this can vary across disorders, population subgroups (e.g., children, elderly, racial/ethnic subgroups), and individuals, and is also influenced by social factors, such as access to ongoing mental healthcare.

In clinical practice, a working general definition of adequate adherence is the minimum level of adherence required for each person to achieve adequate treatment response and avoid relapse that is mutually agreed upon by patient and provider. This definition locates adherence at the intersection of evidence-based practice and person-centered care, and can be conceptualized as a form of ***concordance*** between patients and clinicians. It emphasizes the collaborative nature of medication management and allows for individual, and even subgroup (e.g., cultural), variation in dosing and pattern of medication taking (3, 150).

To date, multiple research approaches have been used to define adequate adherence, hindering cross-study comparisons due to lack of standard definitions (3, 151). There is no clear consensus at present on which cutoff to use, and the choice may depend on the specific aims of each study.

Research involving specific disorders or medications may further tailor a categorical definition using evidence-based treatment parameters by adding a minimally effective dose to the percent use over time or to a minimal duration of treatment (152). Other categorical definitions used in adherence research vary from taking any of the prescribed medication to taking nearly every dose. In addition, Likert-type scales that are not divided into percentage of medication taken are also used, ranging from 3 points to 7 points, with a variety of different terms for each point (3).

An alternative method for measuring adequate adherence relies on the percentage of doses taken over a specified period. However, the variability in adherence percentages can be substantial, requiring large sample sizes in order to find a significant effect. An alternate approach altogether is to focus on a definition of nonadherence based on gaps in days between doses (5). While robust, however, this simpler approach is not sensitive to more subtle changes in adherence that characterize partial adherence measures, and imposes a dichotomous (rather than ordinal or continuous) structure to the data.

Definitions of adequate adherence should also take into account the possibility of excessive use of medication, or overdosing (1). A review of adherence behavior reported that 10 to 15% of individuals prescribed long-term psychiatric medications may be excess fillers of their prescriptions (7, 153).

It remains to be determined to what extent these alternative definitions of adequate adherence identify similar or distinct aspects of suboptimal medication taking. The results would help tailor adherence interventions for particular individuals or patient subgroups, since different patterns of inadequate adherence would likely require distinct intervention approaches.

## Adequate Adherence in Specific Psychiatric Populations

### Adherence in Populations with Schizophrenia

Rates of full and partial nonadherence, including excess filling of medication prescriptions, remain very high in patients with schizophrenia. Exact rates of inadequate adherence differ according to the adherence definition used, assessment method, and duration of follow-up, but over time they exceed 60% (1-3). Moreover, there is a clear relationship between inadequate adherence and relapse and hospitalization (4). Even a gap of one to ten days in antipsychotic therapy over the course of a year is associated with a two-fold risk of hospitalization, after adjusting for age, race/ethnicity, and insurance characteristics (5). In addition, all forms of nonadherence are associated with elevated healthcare costs (1).

Definitions of adequate adherence in schizophrenia must include the role of partial adherence. Measuring adherence, however, especially partial adherence, among patients with schizophrenia is challenging (3). Numerous barriers complicate simpler assessments, including clinical state, level of insight, cognitive impairment, and living situation. Unfortunately, blood plasma concentrations for the atypical antipsychotics do not assist in the assessment of partial adherence, given the lack of correlation between this biological test and other adherence measures (3), as well as the complex relationship between blood level data and treatment outcome (47).

### Adherence in Populations with Bipolar Disorder

As in the case of schizophrenia, rates of inadequate adherence are also elevated in bipolar disorder, with similar variation over time (20 to 60%) as a function of measurement, clinical, and secular factors (6, 7). Two recent reviews of bipolar disorder studies found median rates of inadequate adherence of 41 to 42% (6, 8). The chronic, relapsing nature of the illness, with intervening periods of euthymia, contributes to the usual challenges of achieving long-term adherence. Type of mood stabilizing medication does not appear to affect adherence rates, however, which are consistently low for lithium, anticonvulsants, and atypical antipsychotics (150, 90). Inadequate adherence in bipolar disorder, as in schizophrenia, is generally associated with poorer outcomes, including elevated rates of relapse, hospitalization, suicidal behavior, and greater cost of care (7, 9, 10).

Inadequate adherence in bipolar disorder has been defined in various ways, including categorical variables, serum levels, Likert scales, and combinations thereof (10, 150, 151). The most typical categorical definitions parallel those used in schizophrenia, with ≥80% indicating full adherence, 51 to 79% partial adherence, and ≤50% full nonadherence (149). However, more work needs to be done to compare across these diverse definitions and assessment methodologies.

Unlike for antipsychotics or antidepressants, adherence to mood stabilizers may also be traced with serum levels. However, these levels show substantial subgroup variation, being lower in the elderly, having a different relationship to toxicity in certain ethnic groups, and varying with the effect of diet, smoking, and other medications (154, 155). Attitudinal markers of medication taking also constitute a useful complement to definitions of adequate adherence (156, 157) and may also help identify groups at high risk for nonadherence.

### Adherence in Populations with Unipolar Depression

Adequate adherence findings in unipolar depression are similar to those in schizophrenia and bipolar disorder. Nonadherence in major depression is elevated, with a median rate of 53% (6). On average, about 30% of patients stop taking antidepressants after one month and 45 to 60% after three months of treatment. Among those who enter maintenance therapy, up to 50% discontinue prematurely (6). The risks of inadequate adherence include increased recurrence, severity, disability, poorer responsivity to future treatment, and greater healthcare cost (11-18). Relapse is lowest among patients who remain on their initially effective dose during the maintenance phase, rather than a lower dose, suggesting the negative effect of partial adherence (12).

One factor that may affect adherence specifically in unipolar depression is direct-to-consumer advertising, which is nearly absent in schizophrenia and bipolar disorder. Direct to consumer advertising may increase adherence if it increases patients' conviction of the efficacy of the medication or it may decrease adherence if more patients with marginal indications are placed on these medications. In addition, heightened popular attention has been paid to the emergence of discontinuation symptoms when antidepressant doses are abruptly stopped or markedly reduced (158). The impact of both of these factors on community levels of adherence to antidepressant therapy deserves further study.

Most research on major depression utilizes a categorical definition of adequate adherence. This can take the form of a combined measure of dose and duration (e.g., ≥80% of *X* mg over *X* time) or retention status (percentage drop vs. completer at treatment endpoint) (11). Some studies utilize continuous measures, such as proportion of the treatment period with full adherence as measured by electronic counts, or number of treatment days prior to discontinuation (159). Interest in attitudinal measures also is growing in unipolar disorder due to findings such as the association between baseline concerns about stigma and higher nonadherence

(160). Other potential attitudinal factors include baseline perceptions of addictiveness, treatment duration, and need for medication after improvement of the acute episode (161, 162). Serum assays have also been used to complement adherence measures, but are complicated by considerable interindividual variation and nonlinear pharmacokinetics (163, 11).

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