The Expert Consensus Guideline Series: Adherence Problems in Patients with Serious and Persistent Mental Illness

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Adherence Problems in Patients with Serious and Persistent Mental Illness

The Expert Consensus Panel on Adherence Problems in Serious and Persistent Mental Illness

The following participants in this Expert Consensus Survey were identified from recent research publications and funded grants on adherence problems in serious and persistent mental illness, work on guidelines on serious and persistent mental illness, and/or participation in previous Expert Consensus Surveys on psychotic disorders or bipolar disorder. Of the 48 experts to whom we sent the adherence survey, 41 (85%) replied. The recommendations in the guidelines reflect the aggregate opinions of the experts and do not necessarily reflect the opinion of each individual on each question.

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Introduction

ABSTRACT

Objectives. **Poor adherence to medication treatment can have devastating consequences for patients with mental illness. The goal of this project was to develop recommendations for addressing adherence problems to improve patient outcomes.**

Methods. **The editors identified important topics and questions concerning medication adherence problems in serious mental illness that are not fully addressed in the literature. A survey was developed containing 39 questions (521 options) asking about defining nonadherence, extent of adherence problems in schizophrenia and bipolar disorder, risk factors for nonadherence, assessment methods, and interventions for specific types of adherence problems. The survey was completed by 41 (85%) of the 48 experts to whom it was sent. Results of the literature review and survey were used to develop recommendations for assessing and improving adherence in patients with serious mental illness.**

Results. **Assessing adherence: The experts endorsed percentage of medication not taken as the preferred method of defining adherence, with 80% or more of medication taken endorsed as an appropriate cut-off for adherence in bipolar disorder and schizophrenia. Although self- and physician report are the most common methods used to assess adherence in clinical settings, they are often inaccurate and may underestimate nonadherence. The experts recommend that, if possible, clinicians also use more objective measures (e.g., pill counts, pharmacy records, and, when appropriate, serum levels such as are used for lithium). Use of a validated self-report scale may help improve accuracy.**

Scope of the problem: The majority of the experts believed the average patient with schizophrenia or bipolar disorder in their practices takes only 51%–70% of prescribed medication.

Factors associated with nonadherence: The experts endorsed poor insight and lack of illness awareness, distress associated with specific side effects or a general fear of side effects, inadequate efficacy with persistent symptoms, and believing medications are no longer needed as the most important factors leading to adherence problems in schizophrenia and bipolar disorder. The experts considered weight gain a side effect that is very likely to lead to adherence problems in patients with schizophrenia and bipolar disorder; sedation was considered a more important contributor to adherence problems in bipolar disorder than schizophrenia. The experts rated persistent positive or negative symptoms in schizophrenia and persistent grandiosity and manic symptoms in bipolar disorder as the most important symptomatic contributors to adherence problems in these illnesses.

Interventions: It is important to identify the specific factors that may be contributing to a patient's adherence problems in order to customize interventions to target those problems. Multiple problems may be involved, requiring a combination of interventions.

Conclusions. **Adherence problems are complex and multidetermined. The experts recommended customized interventions focused on the underlying causes.**

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BACKGROUND

Adherence to treatment is poor in patients with both physical and psychiatric disorders and is particularly problematic in persistent disorders, for which treatments are designed to prevent symptom recurrence and the consequences of stopping treatment are often delayed. Adherence to treatment plays an essential role in achieving best outcomes in the treatment of serious mental illnesses such as schizophrenia and bipolar disorder.[1] Although it was hoped that the advent of the newer second-generation (atypical) antipsychotics (SGAs), which produce fewer extrapyramidal side effects (EPS) than the first-generation antipsychotics (FGAs), would improve adherence, data to date do not support this.[2] For example, Dolder et al.[3] found slightly better rates of adherence among patients receiving SGAs, but those patients still had adherence rates of only 55%. Gianfrancesco et al.[4] found higher mean possession ratios (MPRs) for SGAs than FGAs, but they concluded that the differences were unlikely to be clinically meaningful. Given that prescription fill rates only identify when medication was *available* to individuals, not whether they actually *took* it, these studies may be underestimating rates of adherence problems. In a sample of 55 individuals with schizophrenia prescribed SGAs who were recently discharged from a state psychiatric facility, Velligan et al.[1] reported that, in the first 3 months after discharge, only 40% were adherent (defined as taking at least 80% of prescribed doses) based on pill counts in their homes. Adherence to antipsychotic medications continues to be a significant barrier to recovery in patients with serious mental illness.[1]

Mood stabilizers, such as lithium, divalproex, and carbamazepine, are the mainstay of treatment of bipolar disorders. Reported nonadherence rates for long-term prophylaxis range from 20%–66%,[5,6] with a median prevalence of 41%.[7] In clinical and community surveys,[8,9] use of prophylactic medication was often intermittent, with 50% of patients with bipolar disorders stopping and re-starting their lithium at least once, and 30% doing so at least twice, without medical advice. Similarly, the largest study of this issue in subjects prescribed carbamazepine and divalproex (N = 140) reported nonadherence rates in the maintenance phase of treatment of over 50%.[10]

Because poor adherence to treatment can have devastating consequences for patients with serious mental illness, the goal of this project was to develop recommendations for assessing and addressing adherence problems to promote improved outcomes. The guideline recommendations presented here are based on research and the consensus of a panel of experts.

EXPERT CONSENSUS AND PRACTICE GUIDELINES

The many variables involved in adherence to medication treatment and the widely varying definitions and assessment methods used in adherence studies make it difficult to provide comparative recommendations based entirely on research data.[11] A method for describing expert opinion in a quantitative, reliable manner to help fill gaps in evidence-based guidelines has been developed[12] and applied to a variety of psychiatric disorders,[13–30] as well as to the treatment of adult and pediatric epilepsy.[31–34]

METHOD

Creating the Survey

Based on a literature review, the editors identified questions concerning adherence problems in serious and persistent mental illness not adequately addressed in the research literature. They then developed a 39-question survey with 521 options that asked about how to define nonadherence, the extent of adherence problems in patients with schizophrenia and bipolar disorder, risk factors for adherence problems, assessment methods, and strategies for addressing specific types of adherence problems. The survey took approximately 2 hours to complete and a $250 honorarium was provided to each respondent. Surveys were completed online (n = 33) or on paper (n = 8).

The Rating Scale

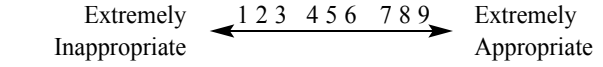
For 463 of the survey options, we asked raters to evaluate clinical appropriateness by means of a 9-point scale slightly modified from a format developed by the RAND Corporation for ascertaining expert consensus.[35] For the other 58 options, respondents filled in a blank or checked a box (e.g., to indicate a percentage). We presented the rating scale to the experts with the anchors shown in Figure 1 (for some questions, anchors of the scale were modified, e.g., to indicate level of agreement with a statement, with 7–9 = strongly agree, 4–6 = somewhat agree, and 1–3 = strongly disagree). Figure 2 shows a section of Survey Question 38 as an example of our question format.

Composition of the Expert Panel

We identified 48 leading experts on adherence problems in serious and persistent mental illness, most of whom were from the United States, with a small number of respondents from other countries. The experts were identified based on published research in this area and/or participation in previous expert consensus surveys that addressed issues related to the management of schizophrenia and bipolar disorder. Of the 48 experts to whom the survey was sent, 41 (85%) completed the survey.

Of the 41 respondents, 30 were male and 11 female. Two thirds of the respondents reported spending at least 25% of their time in clinical work with patients. All but 2 respondents (95%) worked in an academic clinical or research setting, of whom 4 also worked in the public sector and 3 in private practice or research; 2 respondents worked solely in the public sector. The respondents spent an average of 21% of their time treating or supervising the treatment of patients with schizophrenia and 25% of their time working with patients with bipolar disorder. Of the 41 experts, 39 (95%) had participated in a research project involving schizophrenia or bipolar disorder during the preceding 5 years, 35 (85%) had held an NIMH or NIH grant as principal investigator (PI), and 31 (76%) had been PI for an industry-sponsored grant. Respondents had received grants, speaking fees, and study funding from a variety of sources, including AstraZeneca (41%), Pfizer (39%), Bristol-Myers Squibb (34%), Eli Lilly (34%), Janssen (34%), National Institute of Mental Health (24%), and GlaxoSmithKline (17%).

Figure 1. The rating scale: Clinical appropriateness



9 = Extremely appropriate: this is your treatment of choice

7–8 = Usually appropriate: a first-line treatment you would often use

4–6 = Equivocal: a second-line treatment you would sometimes use (e.g., patient/family preference or if first-line treatment is ineffective, unavailable, or unsuitable)

2–3 = Usually inappropriate: a treatment you would rarely use

1 = Extremely inappropriate: a treatment you would never use

Support for the Survey and Guidelines

Although this project was supported by an educational grant from a commercial sponsor, the sponsor had no input into the selection of the panel, the formulation of survey questions, or the content of this publication. The expert consensus panel (with the exception of five of the guideline editors who completed the survey) was also kept blind to the source of support to avoid potential bias.

Data Analysis: Options Scored on the Rating Scale

For each option, we first defined the presence or absence of consensus as a distribution unlikely to occur by chance by performing a chi-square test ($p < 0.05$) of the distribution of scores across the 3 ranges of appropriateness (1–3, 4–6, 7–9).

Next we calculated the mean and 95% confidence interval (CI). A categorical rating of first-, second-, or third-line was designated based on the lowest category in which the CI fell, with boundaries of 6.5 or greater for first-line options, and 3.5 up to 6.5 for second-line options.

Data Analysis: Write-in Options

For write-in options, we present mean or modal values or report the percentage of respondents who endorsed different options.

Displaying the Survey Results

The results of the section of Question 38 presented in figure 2 are shown graphically in figure 3. The CIs for each treatment option are shown as horizontal bars and the number of respondents and the mean rating and standard deviation are given in the table on the right. Note that some respondents did not rate some options, so that the number of respondents does not always equal 41. An unshaded CI box indicates no consensus (i.e., based on chi-square test, responses on the item are randomly distributed across the ratings). In this question, the experts rated social work targeting logistic problems as the first-line strategy, with medication monitoring/environmental supports a high second-line option (because the CI bar crosses the boundary with first line). There was no consensus on the next four options, while the last four options were not generally recommended (i.e., there was consensus that they were third-line options).

Statistical Differences Among Treatments

While we did not perform tests of significance for most items, significance can generally be estimated based on whether the CIs overlap. When they overlap, this roughly indicates no significant difference between options by t-test. The wider the gap between CIs, the smaller the *p* value would be (i.e., the more significant the difference).

Development of Guidelines

Research data and other published findings concerning adherence were used along with the results of the expert survey to develop clinically useful recommendations on how best to define, assess, and manage problems with adherence in serious and persistent mental illness in order to promote the best outcomes for patients. Because of space limitations, only a small number of the actual graphic results from the survey could be included in this supplement. Instead, the experts' recommendations are often summarized in more concise tabular format or discussed in the text.

Readers can access the complete expert consensus survey results at:
www.psychiatrist.com/private/supplenet/v70s04/v70s0402.pdf.

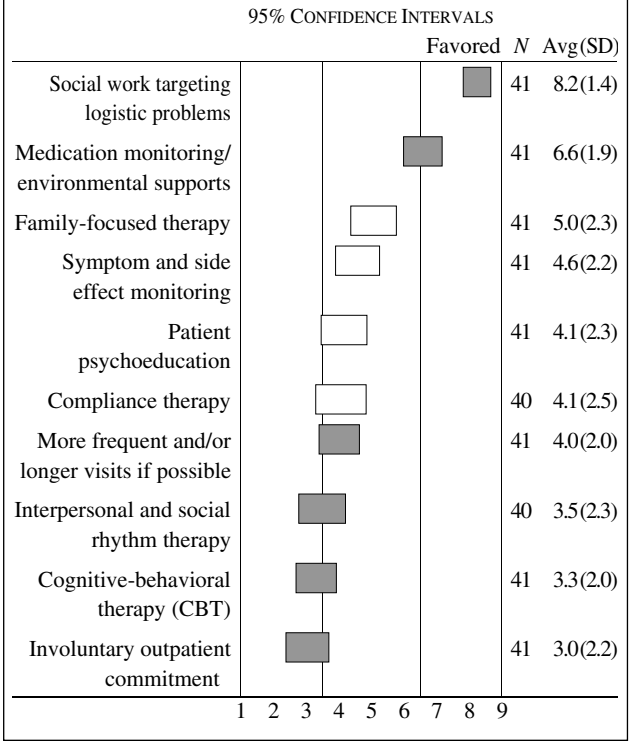
Figure 2. Sample question

38. PSYCHOSOCIAL SERVICES. Rate the appropriateness of the following psychosocial services for a patient with adherence problems primarily due to LOGISTIC PROBLEMS.

1) Cognitive-behavioral therapy (CBT)	1	2	3	4	5	6	7	8	9
2) Compliance therapy	1	2	3	4	5	6	7	8	9
3) Family-focused therapy	1	2	3	4	5	6	7	8	9
4) Interpersonal and social rhythm therapy	1	2	3	4	5	6	7	8	9
5) Involuntary outpatient commitment	1	2	3	4	5	6	7	8	9
6) Medication monitoring/ environmental supports	1	2	3	4	5	6	7	8	9
7) More frequent and/or longer visits if possible	1	2	3	4	5	6	7	8	9
8) Patient psychoeducation	1	2	3	4	5	6	7	8	9
9) Social work targeting logistic problems	1	2	3	4	5	6	7	8	9
10) Symptom and side effect monitoring	1	2	3	4	5	6	7	8	9

Figure 3. Graphic results of sample question

38. PSYCHOSOCIAL SERVICES. Rate the appropriateness of the following psychosocial services for a patient with adherence problems primarily due to LOGISTIC PROBLEMS.



I. Scope of the Problem: Definition and Epidemiology of Adherence Problems

Guideline 1: Defining Adherence

Treatment adherence may be regarded as the extent to which a person's behavior (taking medication, following a diet, lifestyle changes) corresponds to recommendations from a healthcare provider. Methods used to define and measure adherence vary widely across studies in serious mental illness. Yet consensus on how to define/assess medication adherence is needed to study the problem effectively, understand contributing factors, and develop and test interventions to improve adherence. If a patient is defined as adherent based on criteria in one study, but the same patient would be defined as nonadherent based on criteria in another study, one cannot combine information across studies.

LITERATURE REVIEW

Methods of Assessing Adherence

Velligan et al.[36] reviewed 161 publications from 1970 to 2006 to identify methods used to assess/define adherence in patients with schizophrenia. Of these studies, 93 were classified as adherence studies and 68 were general studies that included a measure of adherence to antipsychotics. They found that patient self-report was the most commonly used means of assessing adherence (Figure 1-1). Of the 161 studies, 124 (77%) used only subjective, indirect methods to assess adherence (e.g., reports from patients, providers, or significant others; chart review), while fewer than 23% (37/161) used direct or objective methods (e.g., pill count, blood/urine analysis, electronic monitoring, or refill records). Different types of errors occur with different types of assessments.[36] For example, in another study, Velligan et al.[1] found that, when adherence was defined as taking 80% of prescribed doses, only 40% of participants were adherent based on pill count at 3 months, while 55% of patients self-reported perfect adherence. Based on blood levels (less than 30% variability between samples used to define adherence), only 23% were judged adherent. Likewise, Tacchi and Scott suggested that estimates of mean lithium levels over several months more accurately reflect lithium adherence than single measures of serum lithium (especially since a minority of patients may take "loading doses" of lithium before testing).[7] Clearly, rates of adherence vary widely depending on assessment methods.

Defining Adherence

Even when studies used the same methodology, definitions of medication adherence varied greatly, so that it is still difficult to draw conclusions about the scope of adherence problems. Velligan et al.[36] found that percentages used ranged from taking 50% to 90% of prescribed medication, while categorical classifications ranged from taking any medication to taking nearly every dose. Other studies that used refill data defined adherence based on a gap or length of time during which no medication was available, but again specific time periods varied widely.[36]

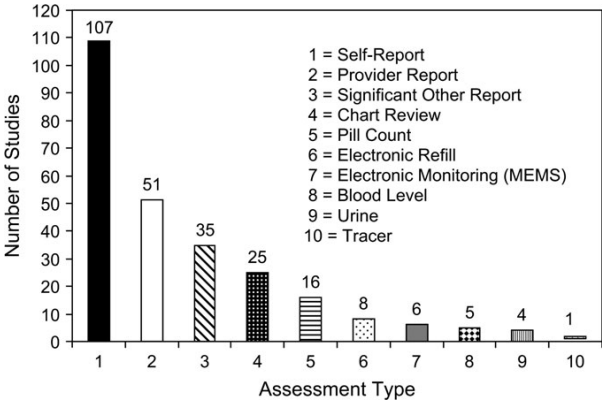
Some studies have used a pharmacy-based measure, the Medication Possession Ratio (MPR), to define levels of adherence. MPRs are calculated by dividing the number of days' supply of medication the patient received by the number of days' supply they needed to receive to take their medication continuously as prescribed. For example, in one study, Sajatovic et al.[37] defined patients with bipolar disorder as fully adherent with an MPR greater than 0.80, as partially adherent with an MPR of 0.50–0.80, and as nonadherent with an MPR of 0.50 or less.

Medication Event Monitoring (MEM), in which pill bottle caps record time and date whenever the bottle is opened, is often considered the "gold standard" for adherence monitoring, However, Velligan et al.[36] found that even MEM produced hard-to-assess results because of high rates of missing data.

Recommendations From the Literature Review

Based on their extensive review of the literature, Velligan et al.[36] recommended that, to increase comparability across studies, researchers report the estimated mean percentage of medication taken during the period in which patients were followed. They also recommended using at least 2 measures of adherence, one of which should be a direct or objective measure. Similar suggestions are found in the literature on bipolar disorder.[38]

Figure 1-1. Methodologies used to assess adherence



Reprinted with permission from Velligan et al. 2006.[36]

EXPERT CONSENSUS: DEFINING MEDICATION ADHERENCE

Given the variability in how studies have assessed and defined medication adherence, we asked the experts how adherence should best be defined and measured to facilitate research

on risk factors for adherence problems and effective interventions to improve adherence. We asked the experts what methods they considered most useful for defining nonadherence in schizophrenia and bipolar disorder, with 7–9 indicating methods they considered most useful, 4–6 somewhat useful methods, and 1–3 methods that are not very useful. Their responses were very similar for both disorders (Questions 1 and 6).

Percentage of medication. The panel endorsed percentage of medication not taken over a period of time as the preferred method of defining nonadherence, in keeping with the recommendations of Velligan et al.[36] discussed above.

Medication gaps. The experts also endorsed medication gaps as an alternative method to define nonadherence, commenting:

Partially adherent patients may still benefit from medication, depending on amount of medication taken and minimum therapeutic dose. Dichotomized adherence scores (e.g., cessation of medication, medication gaps) should if possible be avoided, although gaps can give important additional information.

Because most patients with bipolar disorder are on multiple medications, the concept of percentage of medications over time is probably more useful than an absolute metric because patients tend to stop medications differentially.

Complete cessation of medication. There was no consensus on using complete cessation of medication to define nonadherence, possibly reflecting the clinical reality that partial adherence is much more common. In addition, complete cessation may be viewed as less valuable because other methods may identify adherence problems at an earlier point allowing for more timely intervention. Respondents commented:

I believe the majority of patients have partial adherence.

Complete cessation or longer gaps are likely to be associated with more adverse outcomes than taking a less than specified amount over a longer period of time.

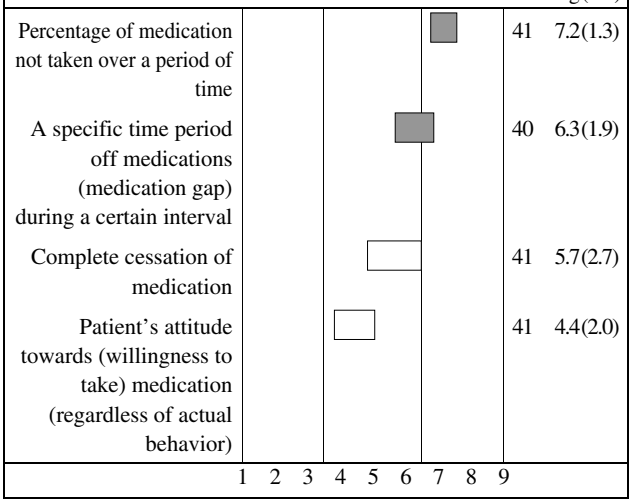
Cessation is difficult to assess if patients use multiple pharmacies or healthcare systems.

Attitude or willingness to take medication. There was only limited support for defining adherence in terms of the patient's attitude or willingness to take medication, probably because many environmental factors can interfere with medication taking even when a patient is willing to take medication as prescribed.[36] Nevertheless, the respondents indicated that they do consider attitude an important variable:

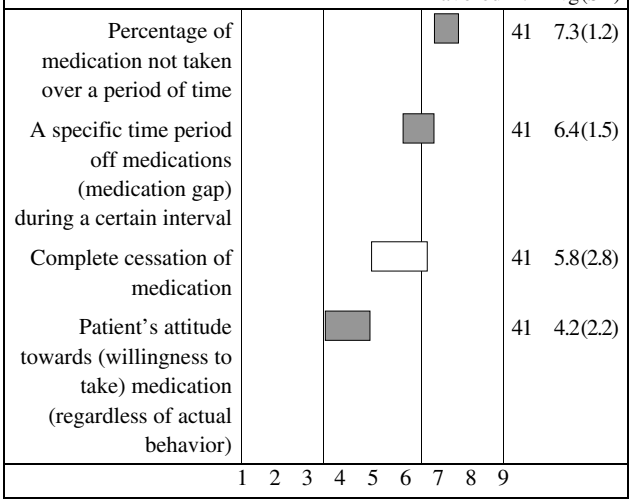
Attitude towards medication is one of many risk factors for nonadherence; however, it is not a valid indicator of adherence (e.g., patients may not like to take medication but may realize that they need to in order to avoid relapse and admission).

People who are willing to take medication (attitude) do not necessarily take it (behavior).

Question 1. Defining nonadherence in schizophrenia. Please rate the usefulness of the following ways of defining nonadherence to antipsychotic medication in clinical practice.



Question 6. Defining nonadherence in bipolar disorder. Please rate the usefulness of the following ways of defining nonadherence to medication in clinical practice.



Patient insight or willingness is crucial when placing poor adherence in context.

Use of multiple medications in bipolar disorder. We asked the experts if a patient with bipolar disorder who is prescribed both a second generation antipsychotic (SGA) and a mood stabilizer needs to take both as prescribed to be considered adherent. We specified that the doses were reasonable and there was an appropriate clinical rationale for the combination. Most of the respondents (85%, 34/40) believed that such a patient needs to take both medications to be considered adherent. The small number who indicated that one medication might be sufficient generally endorsed taking the mood stabilizer, but noted that

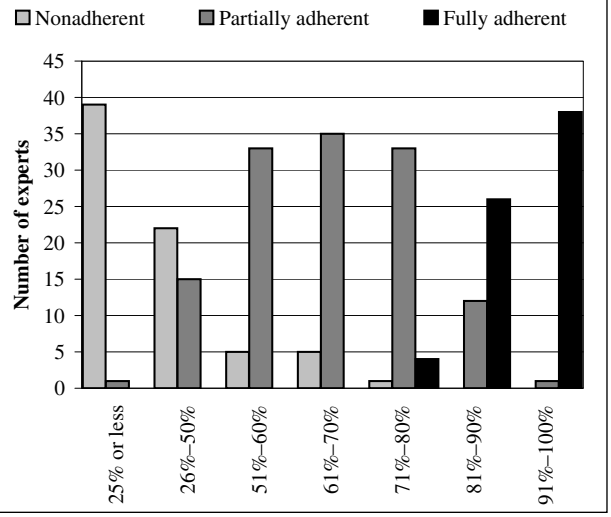
this might depend on phase of illness. These results are consistent with recommendations in the *Expert Consensus Guidelines on Treatment of Bipolar Disorder*, which stressed the importance of including a mood stabilizer in the treatment regimen of all patients with bipolar disorder.[27] Respondents commented:

Most patients with bipolar disorder are taking more than mood stabilizers—the greater the number of medications, the greater the chances for nonadherence (e.g., patients may take only one instead of two, may alternate depending on what they feel they need). Some different reasons for partial or nonadherence are associated with the nature of bipolar illness.

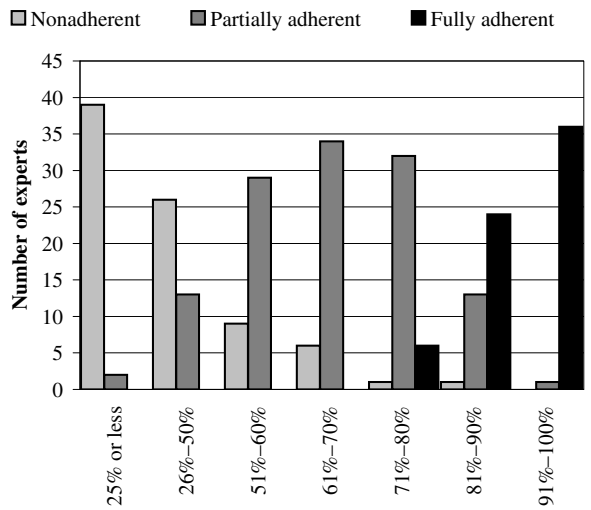
Adherence in patients with bipolar disorder may differ depending on the phase of the illness.

Both gaps and percentages often fail to capture potential adherence problems in bipolar disorder vs. schizophrenia. Current mania, anxiety, depression, or psychotic episodes, as well as complex regimens of mood stabilizers and atypical antipsychotics, may partially explain this. Patients' attitudes, health beliefs, and the therapeutic alliance may be equally important as objective adherence measures.

Question 3. Adherence in schizophrenia. Assuming you would define adherence in outpatients with schizophrenia as a ***percentage of antipsychotic medication consistently taken*** over the past 12 months, how would you define full, partial, and nonadherence?



Question 9. Adherence in bipolar disorder. Assuming you would define adherence in outpatients with bipolar disorder as a ***percentage of medication consistently taken*** over the past 12 months, how would you define full, partial, and nonadherence? Note we are asking about the primary psychiatric medication(s) the person is prescribed.



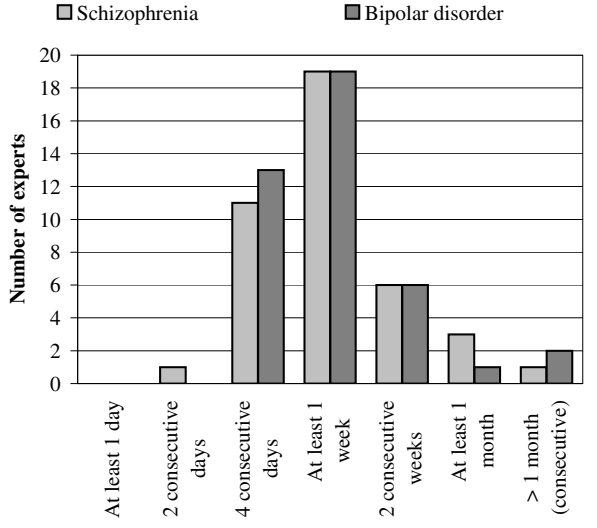
Adherence Defined as Percentage of Medication Taken

Most of the experts considered 80% or more an appropriate cut-off for considering patients with bipolar disorder or schizophrenia adherent, while they would generally rate those who take 50% or more of medication as partially adherent (Questions 3 and 9). This 80% cut-off is consistent with that used in many research studies.

Nonadherence Defined in Terms of a Medication Gap

Although there was less support for using medication gaps to define nonadherence, when asked what period off medication they would use if this method was employed, approximately three-quarters of the experts said 4 days to 1 week (median 1 week) without medication would represent nonadherence in patients with schizophrenia or bipolar disorder (Questions 5 and 11). The responses for schizophrenia and bipolar disorder were very similar and did not appear to reflect concern about rebound mania from lithium withdrawal, consistent with a recent retrospective case review that found early episode recurrence in bipolar disorder does not appear to be specific to lithium withdrawal but may occur following withdrawal of all classes of medication that are recommended for prophylaxis.[39]

Questions 5 and 11. Assuming you would use a period off medication to define nonadherence in outpatients with schizophrenia and bipolar disorder, which ***medication gap*** over the previous 3 months is the most useful definition for nonadherence?



Guideline 2: Epidemiology of Adherence Problems

LITERATURE REVIEW

Scope of Adherence Problems in Schizophrenia

Adherence to antipsychotic medications. As many as 75% of patients with schizophrenia become nonadherent within 2 years of hospital discharge.[40] Nosé et al.[41] reanalyzed data from 86 published studies involving 23,796 patients with psychosis being treated in community psychiatric services and found that approximately 1 in 4 patients was nonadherent with medication and scheduled appointments. Lacro et al.[42] reviewed 39 studies published between 1980 and 2000 that included data on the prevalence of medication nonadherence in patients with schizophrenia and found mean rates of nonadherence ranging from 20% to 89%, depending on methodology and patient population (recently hospitalized versus more stable outpatients), with rates of 40% to 50% in the studies with better methodology. Gilmer et al.[2] studied adherence to antipsychotic medications in Medicaid beneficiaries in San Diego County, California between 1998 and 2000, using cumulative MPRs and found that 41% were fully adherent, 16% were partially adherent, 24% were nonadherent, and 19% were excess fillers. Based on data from 49,003 patients with schizophrenia or schizoaffective disorder in the Veterans Affairs (VA) system who were prescribed one antipsychotic, Valenstein et al.[43] found that 40% had poor adherence (defined as MPR < 0.8). In a recent population-based study in Canada, Cooper et al.[44] reported that, of 6,662 individuals who began treatment with an SGA between 1997 and 1999, almost a third were no longer being treated with any SGA after 1 year. Of those who were still being treated, 20% were nonadherent.

Adherence to all medications. Dolder et al.[45] found that adherence rates in patients with psychotic disorders were equally problematic for antipsychotic *and* nonpsychiatric medications, with 12-month mean compliant fill rates for antipsychotics, antihypertensives, antihyperlipidemics, and antidiabetics ranging from 52% to 64%. Piette et al.[46] found that patients with schizophrenia were likely to be nonadherent both with antipsychotic medications *and* medications for diabetes and hypertension. These findings highlight the need to target medication adherence across the board in these patients.

First- and second-generation antipsychotics. Although it was hoped that the newer SGAs would lead to improved adherence, studies have found that adherence continues to be a problem for patients taking these newer agents.[3,43,47] A study of 298 California Medicaid recipients who began treatment with a first- (n = 93) or second- (n = 205) generation agent found that antipsychotic medication was available for about 60% of days over 1 year of follow-up in both groups.[48]

Stability of adherence. There is some disagreement about the stability of adherence patterns. In a sample of 1,906 patients with schizophrenia or schizoaffective or schizophreniform disorder followed for 3 years, Ascher-Svanum et al.[49] found that adherence was relatively stable, with 77.3% of patients maintaining the same adherence status from the first to the second year, and nonadherence in the first year predicting significantly poorer outcomes in the following 2 years. In a sample of 34,128 Veterans Affairs patients with schizophrenia, Valenstein et al.[50] found that the cross-sectional prevalence of poor adherence remained stable over a 4-year period, with 36%–37% poorly adherent in each year. However, 61% of patients had adherence difficulties at some point over the 4-year period. The authors found that approximately 18% had consistently poor adherence, 43% were inconsistently adherent, and 39% had consistently good adherence. They concluded that the majority of patients have adherence problems at some point and should therefore receive interventions to enhance adherence.

Scope of Adherence Problems in Bipolar Disorder

Although there are many similarities, there are certain important differences in patterns of medication adherence between patients with bipolar disorder and schizophrenia that have important clinical implications. Like patients with schizophrenia, patients with bipolar disorder may have cognitive problems and difficulties with disorganization and lack of insight; however, cognitive problems may be more severe in patients with schizophrenia.[51–55] Substance abuse problems are also a particularly important contributor to adherence problems in patients with bipolar disorder. In a sample of 115 patients with bipolar disorder, Manwani et al.[56] found that lifetime adherence with mood stabilizers was 66% in those with substance use disorders and 83% in those without.

In a large-scale study of over 1500 patients, Johnson and McFarland reported that the median duration of continuous use of lithium after it was first prescribed, before it was stopped without advice, was approximately 2 months.[57] Maarbjerg et al.[58] found that 25% of a group of 133 patients prescribed long-term prophylactic lithium discontinued treatment prematurely within the first 6 months. In a sample of 101 patients hospitalized for acute mania, Keck et al.[59] found that 65 patients (64%) were nonadherent to their pharmacologic regimen in the month prior to admission, based on responses to a questionnaire administered to patients, treaters, and significant others and plasma concentrations of mood-stabilizing agents at admission. In a sample of 98 patients being treated with mood stabilizers (lithium, carbamazepine, and/or divalproex), 78 of whom were diagnosed with bipolar disorder and 20 with major depressive disorder, Scott and Pope[8] found that almost 50% of the patients acknowledged some degree of medication nonadherence in the preceding 2 years, and 32% reported only partial adherence (missing 30% or more of their prescribed medication) in the preceding month. Over 18 months, admission rates were 90% in those who were nonadherent compared with 10% in those who were adherent.

In a study involving 21 older outpatients with bipolar disorder, Depp et al.[60] found that 55% reported recent nonadherence to psychiatric medications. Based on a secondary analysis of data from two randomized, double-blind studies of mood stabilizer treatment in patients with rapid cycling bipolar disorder, Sajatovic et al.[61] reported fairly high rates of adherence problems (20% overall, with higher rates in those with substance use disorders) even in a highly structured clinical trial setting. These rates occurred despite substantial efforts to promote treatment adherence and study completion using close monitoring, appointment reminders, and rapid follow-up for missed appointments. In a recent study, Baldessarini et al.[62] reported that, of 429 patients with DSM-IV bipolar disorders, 34% reported missing one or more doses of psychotropic medication within 10 days, 20% missed entire daily doses at least once, and 2.5% missed all doses for 10 days. However, their prescribing psychiatrists considered only 6% of these patients nonadherent. In the study discussed in Guideline 1, involving data from 44,637 Veteran's Affairs patients with bipolar disorder being treated with lithium or anticonvulsant medication, Sajatovic et al.[37] found that 54.1% were fully adherent (MPR > 0.80), 24.5% were partially adherent (MPR = 0.51–0.80), and 21.4% were nonadherent (MPR of 0.50 or less). Thus, nearly one in two individuals with bipolar disorder in this study who were given prescriptions for lithium or anticonvulsant medication did not take their medications as prescribed. In another study, using MPR data from 73,964 patients with bipolar disorder in the VA National Psychosis Registry, Sajatovic et al.[63] found that approximately 45% (n = 32,993) were prescribed antipsychotic medication and just over half (51.9%) appeared to be fully adherent, while 48.1% were either partially adherent or nonadherent with antipsychotic medications.

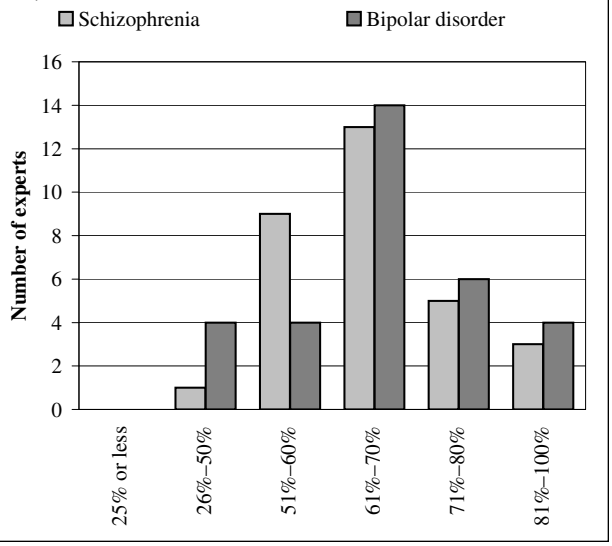
Summary

It is clear from this review of the literature that rates of nonadherence to medication are high among patients with both schizophrenia and bipolar disorder.

EXPERT CONSENSUS

The majority of experts who see patients with schizophrenia and bipolar disorder believed that the average patient in their practices (including those who dropped out of treatment) took 51%–70% of prescribed medication (Questions 4 and 10). Only a very small percentage (10% of those treating patients with schizophrenia and 13% of those treating patients with bipolar disorder) thought their patients took 80%–100% of prescribed medication. These results represent a change from previous surveys, in which clinicians have tended to report better adherence in their own patients than is found in general surveys. For example, in an expert consensus survey in 2003 concerning the treatment of psychotic disorders, the experts estimated that 43% of their patients were adherent (defined as missing less than 20% of their medication) and that 38% were partially adherent (defined as taking 20%–80% of their medication).[25] The results of the current survey should reassure clinicians that problems with adherence occur throughout the mental health care system and that even experts on these problems have difficulty achieving high rates of adherence in patients with serious and persistent mental illness. The results of the survey may also reflect an increasing awareness among mental health researchers and clinicians of the pervasive nature of adherence problems.

Questions 4 and 10. Levels of adherence of the average patient in your practice. What percentage of antipsychotic medication do you think the average outpatient with schizophrenia in your practice and what percentage of his or her primary psychiatric medication(s) do you think the average outpatient with bipolar disorder has taken over the past 12 months (include patients who have dropped out of treatment)?



II. Consequences of Adherence Problems

Problems with medication adherence are important not in themselves, but because of the very negative impact they can have on patients' health and functioning and on society as a whole.[64] Improving adherence is important because it can help prevent relapse, reduce rehospitalization, improve long-term outcomes and productivity, and reduce healthcare costs. In this section, we discuss consequences of adherence problems from three different perspectives—those of the patient, the clinician, and the healthcare system and society—but it is important to keep in mind that the issues discussed are closely interrelated.

Guideline 3: The Patient's Perspective

Patients with Schizophrenia

When a patient with schizophrenia has poor adherence to antipsychotic medications, this can lead to:

- Partial or no response to treatment
- Increased rates of symptomatic relapse
- Increased rates of hospitalization
- Negative impact on functioning and course of illness.

Rates of symptomatic relapse and rehospitalization. Nonadherence to antipsychotic medications greatly increases risk of relapse in patients with schizophrenia.[42] A number of early studies[65–69] found that continuous medication was associated with reduced risk of relapse, while intermittent medication use increased relapse rates, leading researchers to abandon work on intermittent dosing schedules. In 1993, Davis et al.[70] reported that more than 35 double-blind trials involving over 3,500 patients and many different agents confirmed the role of antipsychotic medications in preventing symptom exacerbation and rehospitalization. In 1995, Hirsch and Barnes[71] reported that more than 50% of patients with schizophrenia who discontinue antipsychotics relapse in 3 to 10 months. This effect is seen even in patients with a first psychotic episode, among whom relapse rates have been reported to be 5 times higher in nonadherent than adherent patients.[72] In a sample of nearly 70,000 U.S. veterans with schizophrenia who received antipsychotic medication over a 12-month period, Valenstein et al.[73] found that patients with medication possession ratios (MPRs) closest to 1.0 had the lowest hospital admission rates and that rates increased progressively with smaller MPRs. Among 49,000 patients prescribed one antipsychotic, those with poor adherence (MPRs < 0.8) were 2.4 times as likely to be admitted as those with good adherence (MPRs = 0.8–1.1): 23% of poorly adherent patients were admitted compared with 10% of adherent patients.[73] Poorly adherent patients also had longer durations of hospitalization. In a study of California Medicaid data, Gilmer et al.[2] found lower rates of psychiatric hospitalization in patients who were adherent (14%) than nonadherent (35%) or partially adherent (24%). Rates of medical hospitalization were also lower among adherent (7%) than nonadherent (13%) patients. Based on California Medicaid data from more than 4,000 outpatients with schizophrenia, Weiden et al.[74] found that risk of hospitalization was significantly correlated with adherence problems, no matter how they were defined (e.g., gaps in medication, medication consistency and persistency, MPRs). Thus, hospitalization risk increased with longer medication gaps (odds ratio = 1.98 for a 1–10 day gap; 2.81 for a 11–30 day gap; 3.96 for a gap longer than 30 days).

Impact on functioning and course of illness. In a study of 565 patients in 17 states, Docherty et al.[47] found that decreased adherence resulted in symptom exacerbation, with a regression model predicting 0.16 change in PANSS score for every 1% difference in MPR. Nakonezny et al.[75] found that poorer adherence to antipsychotic medications was related to greater symptom severity in 61 patients followed for 6 months. Using patient reports and MPRs to monitor 1,906 patients with psychotic disorders for 3 years, Ascher-Svanum et al.[49] found that nonadherence was associated with poorer functional outcomes (increased psychiatric hospitalizations, use of emergency psychiatric services, arrests, violence, and victimizations), poorer mental functioning and life satisfaction, and more substance use and alcohol-related problems. Treatment nonadherence is also associated with increased suicide risk in schizophrenia.[76]

Patients with Bipolar Disorder

Adherence problems also increase relapse and rehospitalization rates in patients with bipolar disorder. Johnson and McFarland[57] found that lithium discontinuation was associated with increased rates of psychiatric hospitalization in 1,594 patients with bipolar disorder. Keck et al.[59] found that nonadherence to medication was significantly associated with greater severity of mania in 101 patients hospitalized for acute mania. In a sample of 200 patients with bipolar disorder, Colom et al.[77] found that those with good adherence had fewer hospitalizations over the course of 2 years. Scott and Pope[8] explored the relationship between medication adherence, plasma levels of mood stabilizers, and psychiatric hospitalizations in 98 patients with mood disorders and found significantly higher admission rates in partially adherent patients with subtherapeutic plasma levels than in adherent subjects with therapeutic plasma levels. In a sample of patients with bipolar disorder, Svarstad et al.[78] found that the 33% who were irregular users of medication had significantly higher hospitalization rates than regular users (73% vs. 31%), more hospital days (37 vs. 4 days), and higher hospital costs. Based on 38 studies in bipolar disorder, Altman et al.[79] reported that medication adherence was associated with reduced risk of relapse. Martinez-Aran et al.[80] also demonstrated that cognitive impairment in adults with bipolar disorder was significantly associated with a history of nonadherence.

Discontinuation of lithium treatment by individuals with bipolar disorder has been reported to be associated with

increased risk of suicide and suicidal behavior.[81] It is difficult to give definitive data concerning any association between adherence rates and mortality, but, based on collaborative study data from over 5,500 patient years, Müller-Oerlinghausen reported that adequate long-term lithium treatment significantly reduced and even normalized excess mortality rates in patients with mood disorders and produced a significant reduction in suicide attempts/year.[82] A meta-analysis of pooled data from 17,000 patients in 28 studies demonstrated that the rate of suicidal acts was 8.6 times higher in patients not receiving long-term lithium than in those receiving regular lithium treatment.[82] Gonzalez-Pinto et al.[83] confirmed these findings in 2006, reporting a lower risk of suicidal acts during closely monitored, highly adherent, long-term lithium treatment. It is not known whether any of the newer mood stabilizers have a similar protective effect, since no studies of this question are yet available.

Summary

Increased rates of relapse and hospital readmission have repeatedly been found to be associated with poor adherence to medication in both schizophrenia and bipolar disorder.

Guideline 4: The Clinician's Perspective

Adherence problems make it very difficult, if not impossible, for the prescribing clinician to evaluate treatment response and determine if dosing is appropriate or whether concomitant medication is needed.[84] It has been found that physicians are more likely to change or add medications for patients who are not fully adherent.[85] Using electronic monitors and pill counts conducted in the home, Velligan et al.[84] assessed adherence every 2 weeks in 50 individuals with schizophrenia or schizoaffective disorder residing in the community and found little relationship between physicians' ratings of adherence and other measures. Byerly et al.[86] also found that physicians tend to significantly underestimate adherence problems in patients with schizophrenia. Tacchi and Scott[7] noted that, while patients with bipolar disorder tend to overestimate their adherence by about 17%, variability among clinicians assessing the same patient is considerably greater, with overall clinical judgment found to be only 50% reliable. In 2008, Baldessarini et al.[62] reported high rates of nonadherence among U.S. patients with bipolar disorder and striking underestimation of the problem by prescribing clinicians. They expressed concern that this could lead to prescription of increasingly complex treatment regimens of untested value that would increase costs and risk of adverse effects.

In summary, clinicians working with patients with schizophrenia or bipolar disorders often have trouble determining whether lack of response is related to the medication regimen itself or to lack of adherence, and they often have only patient self-report of adherence and the person's clinical state to guide them. Thus, physicians may continue to prescribe additional medications for patients who are not showing desired improvement, even though the real cause of the lack of response may be that patients are not taking medication as prescribed.[85,87]

Guideline 5: The Perspective of the Healthcare System and Society

From the perspective of society, serious mental illness that is inadequately treated increases both direct medical costs (e.g., for emergency interventions and hospitalization) and indirect costs (e.g., lost productivity). As noted in preceding sections, poor adherence is one of the main contributors to poor treatment outcomes and thus increased costs. One must also consider the economic impact of all the filled but unused prescriptions for expensive antipsychotic agents. A study of 68 patients with schizophrenia who had recently been discharged from a state psychiatric facility found that the patients had between 2 and 22 bottles of untaken antipsychotic medications in their possession.[1]

In 2004, Almond et al.[88] reported that costs in patients with schizophrenia who relapsed were more than four times higher than those in a control group who did not relapse. Given that adherence problems are the most common cause of relapse in schizophrenia,[89] nonadherence is a significant contributor to increased costs in this patient population. In 2004, Gilmer et al.[2] reported that patients with schizophrenia who were adherent with medications had significantly lower hospital costs than other groups, although their pharmacy costs were higher than for those who were nonadherent. Based on data from patients with schizophrenia in the Medicaid program, Sun et al.[90] estimated that the national rehospitalization cost related to antipsychotic nonadherence was $1479 million in the United States in 2005. Based on data from a large sample of patients treated for schizophrenia in the United States between 1997 and 2003, Ascher-Svanum et al.[91] reported that adherence to antipsychotics was associated with lower utilization of acute care services and greater engagement in outpatient mental health treatment.

Higher costs are also associated with adherence problems in bipolar disorder. In a sample of 1,399 patients with bipolar disorder, Lew et al.[92] reported that reduced adherence to traditional mood-stabilizing therapy was associated with significantly increased risk of mental-health-related emergency room visits and hospitalizations. Based on claims data from a large sample of patients with bipolar disorder treated with antipsychotic medications, Gianfrancesco et al.[93] reported that improved adherence to antipsychotic treatment was associated with lower total and outpatient mental healthcare expenditures, especially for patients with predominantly manic or mixed symptoms. A case series reported by Durrenberger et al.[94] demonstrated that the cost of care over 6 years for a nonadherent patient with frequent manic relapses (about $4,000/month) was equal to that for 13 patients who were adherent with their mood stabilizers ($320/month each). Begley et al.[95] suggested that the lifetime cost of care for chronic unresponsive bipolar disorders (frequently characterized by comorbid substance misuse and nonadherence) was approximately $264,785/person compared with $11,720 for a person who experiences only a single manic episode.

In summary, problems with adherence have been found to be associated with greater healthcare costs for those with severe and persistent mental illness.

III. Factors That Affect Medication Adherence

Guideline 6: Research on Factors That Affect Adherence

To design effective interventions to address adherence problems in patients with serious and persistent mental illness, one must first identify the factors that are contributing to those problems.[42] Many studies have attempted to identify predictors of medication nonadherence. These studies have varied in design, potential predictors and samples examined, and manner in which adherence was defined and measured.[36] Given this variability, it is remarkable that consistent predictors of adherence have emerged. A number of review articles have summarized this literature, including a 2002 paper by Lacro et al.,[42] who reviewed 39 articles published between 1980 and 2000 that included data on risk factors for medication nonadherence, and a systematic review and re-analysis of data from 86 published studies by Nosé et al.[41] published in 2003. Factors affecting adherence can reside 1) within the patient, 2) within the patient's relationship to healthcare providers and family and other caregivers, or 3) within the service delivery system. Patient-related factors include attitudes toward treatment, comorbid conditions, and environmental problems and stressors. The strength of the patient's therapeutic alliance with his or her doctor can strongly influence adherence. Caregivers may support or oppose use of medication and have differing views about the effect of medication on their loved one. The poorly funded, over-burdened service delivery system can contribute to adherence problems by having extremely long waiting times to see a prescriber, not providing funding for necessary medications, and being unable to provide appointments when medications need to be renewed or changed.

FACTORS THAT AFFECT ADHERENCE IN SCHIZOPHRENIA

Patient-Related Factors

Attitudes and past behaviors. Some of the most consistent predictors of adherence problems include lack of illness awareness and insight into having a mental illness and negative attitudes toward medication.[41,42,96–101] Individuals who are opposed to taking medication and believe medication does not work are likely to stop taking it.[97] Lack of insight and negative attitudes toward medication have been suggested as a possible target of intervention.[64,98] In addition to attitudes, behaviors such as previous patient-initiated changes in the medication regimen or previous nonadherence consistently predict poor future adherence to medication.[42,97,102]

Comorbidity and symptom severity. Research has consistently supported an association between co-occurring substance abuse and problems with medication adherence.[41,42,102–107] Among patients with schizophrenia who are nonadherent with antipsychotic medications, comorbid substance use disorders are associated with more severe symptoms[106] and a greater risk of relapse.[101,108] In a recent 52-week randomized, double-blind, multicenter study in 400 patients with a first episode of schizophrenia treated with olanzapine, quetiapine, or risperidone, Perkins et al.[109] found that ongoing substance abuse was a significant predictor of poor medication adherence. Other comorbid conditions (e.g., mood symptoms) have also been found to be related to adherence problems,[109] although fewer data support this relationship. Some studies have also suggested that severity of psychotic symptoms may relate to poor adherence,[41,99,110,111] and Perkins et al.[109,112] found that failure to respond to treatment was associated with greater likelihood of nonadherence.

Demographic factors. While there is some variability in the literature, possibly due to sampling differences, studies have generally found that younger age, male gender, lower socioeconomic status, minority status, and poorer social functioning are associated with adherence problems.[41,43,113,114] For example, Nosé et al.[41] reported that both younger age and male gender were consistent predictors of adherence problems. However, while these groups are *statistically* at higher risk, clinicians need to be wary of jumping to conclusions when assessing adherence in an individual patient (e.g., middle aged women of higher economic status are not immune from medication nonadherence, and indeed they often have more faith in complementary medicines than traditional treatments[115]).

Environmental factors. Factors such as a disorganized or chaotic living situation, financial problems (e.g., lack of health insurance, low income), housing problems, in particular homelessness, and a variety of logistic problems can interfere with patients' ability to take their medication as prescribed even if they are motivated to do so.[1]

Cognitive impairment. In a study of patients with schizophrenia or schizoaffective disorder, Jeste et al.[116] found that cognitive functioning, especially conceptualization and memory, were the strongest patient-related predictors of ability to manage medications. They suggested that studies be done to test interventions to improve, or at least compensate for, specific cognitive deficits in patients with schizophrenia. Approaches designed to bypass deficits in cognition using environmental supports (e.g., pill boxes with alarms) have been found to improve adherence to medication in patients with schizophrenia and schizoaffective disorders.[117] Studies have also shown that decreased ability to take medication in patients with schizophrenia, as measured by a performance-based test, is related to cognitive impairments as well as actual amount of medication taken.[118]

Medication-related factors. The burden of side effects has been extensively explored as a predictor of poor medication adherence.[100,119–121] While Lacro et al.[42] did not find consistent evidence that severity of side effects predicted adherence problems, some studies have reported an association.[120–123] In a sample of patients with first-episode schizophrenia, parkinsonian side effects significantly increased the likelihood that patients would discontinue medication during the first year of treatment.[123] In a study of 81 patients with schizophrenia, McCann et al.[124] found that 70% experienced notable side effects, which contributed significantly to missed doses. Perkins noted that those side effects that cause subjective distress to the patient are the most likely to affect willingness to take medication and that the subjective tolerability of antipsychotics varies considerably from one patient to another.[98] Thus, the perceived burden of side effects in relation to the perceived benefits of medication may have a negative impact on adherence in some individuals.

Because the second generation (atypical) antipsychotics (SGAs) appear to have less liability than the first generation agents (FGAs) to cause movement side effects, it was hoped that increased use of SGAs would improve treatment adherence.[125] However, studies to date have found little clinically significant difference in rates of adherence between FGAs and SGAs.[3,4,43,47,48,126] The SGAs also have metabolic and weight gain side effects that may have a negative effect on adherence.[127]

Relationship Factors

Therapeutic alliance. Lecomte et al.[128] reported that difficulties in building a therapeutic alliance were significantly related to problems with medication adherence and engagement in services. Tunis et al.[129] reported that a positive relationship with clinical staff and fulfillment of life goals were two significant predictors of persistence with initial antipsychotic medication over the course of 1 year. Based on a review of the literature, Masand and Narasimhan[103] concluded that a poor clinician-patient relationship is a significant risk factor for nonadherence. Based on a concept-mapping study involving patients, caregivers, and professionals, Kikkert et al.[130] reported a positive influence on adherence if professionals focus on positive aspects of medication, on enhancing insight, and on fostering a positive therapeutic relationship with patients and carers. The findings described here confirm the results of numerous earlier studies and reviews concerning the importance of the therapeutic alliance in promoting adherence to treatment in patients with schizophrenia.[42,119,131]

Family and social support. Family and social support have consistently been shown to have a beneficial effect on treatment adherence in patients with schizophrenia,[119] while lack of such support has been found to have a significant association with adherence problems.[103,132] Studies have also found that family education and support is associated with improved adherence and better outcomes for patients with schizophrenia.[133,134]

Factors Related to the Service Delivery System

Factors in the service delivery system can have an important effect on adherence, although these often vary internationally. In a U.S. study of 38,983 veterans, refill rates declined by 25% and costs for psychiatric admissions and hospital days increased slightly after the co-payment was increased from $2 to $7.[135] Velligan et al.[1] found that patients discharged from a state psychiatric facility to board and care homes where medications were ostensibly supervised received only 60% of their medications during the first 2 weeks after discharge. In a recent study, McCann et al.[124] found that many patients with schizophrenia reported dissatisfaction with level of access to their mental healthcare providers, especially psychiatrists, and that lack of access significantly predicted medication omission. Clearly, adherence is not always a patient-related phenomenon.

FACTORS THAT AFFECT ADHERENCE IN BIPOLAR DISORDER

Patient-Related Factors

Attitudes and past behaviors. Denial of illness and previous adherence problems also predict poor adherence in individuals with bipolar disorders. Scott and Pope[8] found that poor adherence to mood stabilizer treatment was associated with a history of adherence problems and denial of the severity of illness. They also found that attitudes and behaviors of individuals with bipolar disorder were better predictors of nonadherence than medication side effects. Clatworthy et al. suggested that using a "necessity-concerns" framework may help clinicians understand the complex relationship between perceptions of treatment benefits and barriers.[136] In a sample of more than 200 individuals being treated for bipolar disorders, they demonstrated that low adherence (30%) was predicted by greater doubts about personal need for treatment (OR = 0.50; 95% CI, 0.31–0.82) and stronger concerns about potential negative effects (OR = 2.00; 95% CI, 1.20–3.34). These predictors were independent of current mood state and illness and demographic characteristics. Copeland et al.[137] also reported that poor adherence in patients with bipolar disorder was associated with lack of insight into the need for medication. Sajatovic and Jenkins[138] also expressed concern that individuals with bipolar disorder may perceive antipsychotic medications as stigmatizing and as "schizophrenia drugs" that are inappropriate for their condition.

Comorbidity and symptom severity. Comorbid substance abuse has been found to be a significant risk factor for adherence problems in bipolar disorder.[37,56,63,139] For example, in a study of 115 patients with bipolar disorder, Manwani et al.[56] found that lifetime adherence with mood stabilizers was 65.5% in the 58 patients with comorbid substance use disorders compared with 82.5% in the 57 patients without substance use disorders ($p < .05$). In a study of patient-related risk factors, Baldessarini et al.[62] found that alcohol dependence accounted for the greatest variance in adherence in patients with bipolar

disorder. They also found that greater affective morbidity, various side effects, comorbid obsessive-compulsive disorder, and recovering from mania/hypomania were predictors of adherence problems. Copeland et al.[137] reported that manic symptoms and hazardous drinking were associated with nonadherence in bipolar disorder. Colom et al.[77] reported that comorbid personality disorders were strongly associated with poor adherence in patients with bipolar disorder.

Demographic factors. Studies have found that the following demographic factors appear to be significantly associated with adherence problems in bipolar disorder: minority ethnicity,[37,61,137] lower educational level,[61] a history of legal problems,[61] and being younger,[37,62] unmarried,[37] homeless,[37] and female.[137] In a sample of more than 32,000 patients with bipolar disorder from the VA National Psychosis Registry who were prescribed antipsychotic medications, Sajatovic et al.[63] found that younger age, minority ethnicity, and homelessness were associated with nonadherence. However, as noted in the discussion of schizophrenia, while these groups are *statistically* at higher risk, clinicians need to be wary of jumping to conclusions when assessing adherence in an individual patient. For example, Sajatovic et al.[140] found that, while older patients with bipolar disorder were more adherent with antipsychotic medications than younger individuals, a substantial proportion (39%) still had adherence problems.

Environmental factors. The same types of environmental factors discussed above for schizophrenia can also make it difficult for patients with bipolar disorder to be adherent.

Cognitive functioning. Martinez-Aran et al.[80] found a robust association between cognitive functioning and medication adherence in patients with bipolar disorders.

Medication-related factors. Tacchi and Scott[7] noted that studies in which patients are allowed to rank order factors (other than just side effects) that lead to nonadherence do not find a robust association between medication side effects and adherence, although fear of side effects and lack of knowledge of how to manage side effects can be an issue.[8] Thus, a European survey of over 3,000 patients found that side effects were ranked only seventh in a list of concerns about treatment.[9] In a web survey examining the stated preferences of 469 patients with bipolar disorder, Johnson et al.[141] found that efficacy of a medication for reducing severity of depressive episodes strongly influences patients' adherence to treatment and that, among side effects, weight gain and cognitive effects are the ones most likely to adversely affect adherence to hypothetical medications.

Relationship Factors

Therapeutic alliance. Strauss and Johnson[142] found that a stronger treatment alliance was associated with less negative attitudes about medication and less sense of stigma about having bipolar disorder. Zeber et al.[143] found that adherence to medication in patients with bipolar disorder was associated with strength of the therapeutic alliance. Thus, patients whose providers encouraged them to stay in regular contact and regularly reviewed their progress were more likely to be adherent.

Family and social support. In a sample of 100 individuals with bipolar disorder, of whom 50 were considered adherent and 50 nonadherent to medication, Darling et al.[144] found that the adherent group had fewer health problems and more resources for coping with stress, possessed a stronger belief that their own behaviors controlled their health status, and had higher life contentment than the nonadherent group. In this study, internal health locus of control had the greatest total effect on life contentment, followed by family coping.

Factors Related to the Service Delivery System

In a sample of 306 persons with severe bipolar disorder, of whom 240 (78%) were largely adherent and 37 (12%) were largely nonadherent to treatment, Sajatovic et al.[145] found that the nonadherent individuals received less intensive pharmacologic treatment, had more suicide attempts, and experienced more barriers to care than adherent individuals. They concluded that both patient and system factors contribute to adherence problems in bipolar disorder and should be a target of intervention. Another study found that individuals with bipolar disorder who were dissatisfied with the quality and amount of information about medications they received, particularly about potential problems and side effects, had lower levels of adherence.[146]

SUMMARY

Adherence problems in patients with schizophrenia or bipolar disorder are likely to be multi-determined and related to different factors in different individuals. It is important to identify the factors that may be contributing to a specific patient's adherence problems in order to select the most appropriate strategy to address those problems for that particular patient. A helpful method of conceptualizing these factors is to divide them into those that affect patients' *willingness* to take medications (Table 3-1, p. 22) and those that affect their *ability* to take medications (Table 3-2, p. 22), a distinction that can have important treatment implications.

Guideline 7: Experts Consensus on Factors That Affect Adherence

7A. Potential Contributors to Adherence Problems

In order to develop a hierarchy of risk factors for clinicians to consider in evaluating their patients, we asked the experts to rate the general importance of a number of potential contributors to adherence problems suggested by the literature, We asked them to rate these factors separately for populations of patients with schizophrenia and bipolar disorder, since the literature suggests that some differences in causes of adherence problems between the two disorders may have implications for clinical management. The experts were asked to give a rating of 7–9 to those factors they believed were often very important, a 4–6 to those factors they believed were somewhat important, and a 1–3 to those they did not believe played much of a role in adherence problems. Their ratings are summarized in the table below by order of mean ranking. The table lists all items that received a mean rating of 5.0 or higher. Note that there was little statistical difference among the top-rated options.

The experts' ratings agreed with the findings in the literature about the importance of poor insight and lack of illness awareness, belief that medications are no longer needed, and lack of treatment efficacy as key factors that can contribute to adherence problems. It is interesting that the experts gave more prominence to side effects as a contributor to adherence problems than has been reported in surveys of patients and other studies in the literature.[7–9,42]

Note that, in this question, the experts were asked to rate these factors in terms of their general importance *in populations of patients with schizophrenia or bipolar disorder*. Clinicians should keep in mind, however, that some of the factors that were rated as only somewhat important in populations of patients, such as stigma associated with mental illness and medications, may be *very important* for a specific patient.[115]

Findings from the expert consensus survey: Potential contributors to adherence problems

In Schizophrenia	*In Bipolar Disorder*
Poor insight into having an illness (7.2)	Distress associated with persistent side effects (7.6)
Distress associated with persistent side effects (or fear of potential side effects (7.2)	Believing medications are no longer needed (7.1)
Lack of/partial efficacy with continued symptoms (6.9)	Poor insight into having an illness (7.1)
Believing medications are no longer needed (6.7)	Lack of/partial efficacy with continued symptoms (6.9)
Ongoing substance use problems (6.6)	Ongoing substance use problems (6.7)
Cognitive deficits (6.5)	Problems with therapeutic alliance (6.4)
Lack of social support to help with medication-taking (6.4)	Psychological reactions to symptomatic improvement (6.0)
Practical problems (e.g., transportation, financial) (6.4)	Complexity of treatment regimen (5.9)
Problems with therapeutic alliance (6.3)	Stigma associated with mental illness and medication (5.8)
Lack of daily routines (6.2)	Lack of daily routines (5.7)
Complexity of treatment regimen (6.0)	Significant others ambivalent/opposed to medication (5.7)
Significant others ambivalent/opposed to medication (5.5)	Negative attitudes towards medications in general (5.4)
Stigma associated with mental illness and medication (5.3)	Practical problems (e.g., transportation, financial) (5.4)
Negative attitudes towards medications in general (5.3)	Lack of social support to help with medication-taking (5.4)
	Preference for alternative treatments (5.2)

Mean rating from the expert panel shown in parentheses. The experts were asked to give a rating of 7–9 to those factors they believed were often very important, a 4–6 to those factors they believed were somewhat important, and a 1–3 to those they did not believe played much of a role in adherence problems.

7B. Side Effects as Contributors to Adherence Problems

As noted in Guideline 7A, the experts considered persistent side effects (or fear of side effects) one of the most important risk factors for nonadherence in populations of patients with schizophrenia and the most important contributor to adherence problems in populations of patients with bipolar disorder. This rating is not consistent with a number of studies and patient surveys, which found that side effects were not as important as lack of illness awareness and insight and negative attitudes towards medication as contributors to adherence problems.[7–9,42] However, when asked to rate the different types of side effects (anticipated or actual) in terms of how much they believe they contribute to adherence problems in schizophrenia and bipolar disorder, the experts' ratings generally agreed with research showing that weight gain and cognitive side effects tend to be particularly distressing to patients and thus likely to make them less willing to take medication.[98,141] It is interesting, although not surprising, that the experts considered excessive sedation a more important contributor to adherence problems for patients with bipolar disorder than schizophrenia, reflecting clinical experience that patients with bipolar disorder strongly dislike being sedated.

The experts were asked to give a rating of 7–9 to those side effects they believed were often very important, a 4–6 to those side effects they believed were somewhat important, and a 1–3 to those they did not believe played much of a role in adherence problems. Their ratings are summarized in the table below by order of mean ranking. The table lists all items that received a mean rating of 5.0 or higher. Note that there was little statistical difference among the top-rated options.

Note also that, as in the previous question, here again the experts were asked to rate these factors in terms of their general importance *in populations of patients with schizophrenia or bipolar disorder*. Clinicians should, however, keep in mind that some of the side effects listed as somewhat important in populations of patients may be *very important* for a specific patient.

Findings from the expert consensus survey: Side effects as contributors to adherence problems

In Schizophrenia	*In Bipolar Disorder*
Weight gain (women) (7.0)	Weight gain (women) (7.5)
Excessive sedation (6.4)	Excessive sedation (7.0)
Akathisia (6.2)	Sexual dysfunction associated with medication (men) (6.8)
Weight gain (men) (6.1)	Cognitive problems associated with the medication (6.6)
Sexual dysfunction associated with medication (men) (6.0)	Weight gain (men) (6.6)
Parkinsonian symptoms (5.7)	Sexual dysfunction associated with medication (women) (5.6)
Cognitive problems associated with the medication (5.7)	Akathisia (5.6)
	Gastrointestinal side effects (e.g., nausea, diarrhea) (5.5)
	Nonparkinsonian tremor (5.1)
	Parkinsonian symptoms (5.1)

Mean rating from the expert panel shown in parentheses. The experts were asked to give a rating of 7–9 to those side effects they believed were often very important, a 4–6 to those they believed were somewhat important, and a 1–3 to those they did not believe played much of a role in adherence problems.

7C. Persistent Symptoms as Contributors to Adherence Problems

The experts indicated that partial efficacy of treatment with persisting symptoms is an important factor contributing to adherence problems in both schizophrenia and bipolar disorder. We therefore asked them which types of persistent symptoms were the greatest contributors to adherence difficulties in the two disorders. The experts were asked to give a rating of 7–9 to those symptoms they believed were often very important, a 4–6 to those symptoms they believed were somewhat important, and a 1–3 to those they did not believe played much of a role in adherence problems. Their ratings are summarized in the table below by order of mean ranking. The table lists all items on which the experts reached consensus. Note that there was no statistical difference among the top-rated options.

Schizophrenia. Persistent negative symptoms can affect both willingness and ability to take medications. For example, a patient may be apathetic and not care about potential benefits of taking medication (lack of willingness) or may lack the motivation or initiative to follow through with the treatment regimen (lack of ability).

Persistent positive symptoms may interfere with a person's understanding of the need to take medications (voices tell the person not to take medication), making the person unwilling to do what he or she does not believe is needed. Positive symptoms can also interfere with the person's ability to follow the treatment regimen (e.g., the person may be too paranoid to go to the pharmacy and pick up the prescription).

The experts did not give much support to depressive symptoms as a contributor to adherence problems.

Bipolar Disorder. The experts considered persistent grandiosity and manic symptoms as more important contributors to adherence problems than psychotic or depressive symptoms in patients with bipolar disorder. Again, these symptoms can interfere with a patient's willingness to take medication (persistent grandiosity that makes the person believe that he is doing very well and does not need medication) or ability (manic behavior that makes the person too busy to go to the pharmacy and get the prescription filled).

Findings from the expert consensus survey: Persistent symptoms as contributors to adherence problems

In Schizophrenia	*In Bipolar Disorder*
Persistent negative symptoms interfering with patient's motivation or ability to take medication (6.7)	Persistent grandiosity (6.5)
Persistent positive symptoms interfering with patient's understanding of need to take medications (6.2)	Persistent manic symptoms (too busy to go to the pharmacy) (6.1)

Mean rating from the expert panel shown in parentheses. The experts were asked to give a rating of 7–9 to those symptoms they believed were often very important, a 4–6 to those they believed were somewhat important, and a 1–3 to those they did not believe played much of a role in adherence problems.

Guideline 8: Summary: Most Important Risk Factors for Adherence Problems

Expert consensus on most important risk factors for adherence problems*

In Schizophrenia	*In Bipolar Disorder*
Poor insight into having an illness or needing medication	Distress associated with persistent side effects (particularly weight gain, sedation, sexual dysfunction, and cognitive problems)
Distress associated with persistent side effects (particularly weight gain, sedation, akathisia, and sexual dysfunction)	Poor insight into having an illness or needing medication
Persistent positive and negative symptoms	Persistent grandiosity or manic symptoms
Substance use problems	Substance use problems
Cognitive deficits	Problems with therapeutic alliance
Lack of social support	
Problems with the therapeutic alliance	
Practical problems (financial, environmental, lack of routine)	

**Note that the results in this table reflect the experts' ratings of these factors* in populations of patients with schizophrenia or bipolar disorder. *Clinicians should keep in mind that some of the factors that were rated as only somewhat important in populations of patients (see p. 19), such as stigma associated with mental illness and medications, may be* very important *for a specific patient.*[115]

Table 3-1. Findings from the literature: Risk factors likely to affect *willingness* to take medication

Negative attitudes toward medications or believing medication not needed
Lack of insight
Lack of illness awareness
Lack of efficacy of current treatment (uncontrolled symptoms)
Poor therapeutic alliance
Lack of family/social support
Fear of side effects or developing dependence
Unmanageable or unacceptable side effects

Table 3-2. Findings from the literature: Risk factors likely to affect *ability* to take medication

Cognitive deficits and dysfunction
Substance use problems
Disorganized environments
Psychosocial issues
Financial (e.g., lack of health insurance)
Housing problems, homelessness
Lack of social support
Resource and logistic problems
Comorbid psychiatric conditions
Comorbid medical conditions

IV. Assessing Level of Adherence

Guideline 9: Research on Tools for Measuring Adherence

9A. ACCURACY OF MEASUREMENT TOOLS

Problems with adherence in patients with serious mental illness that are not identified can lead to unnecessary increases in dosage, addition of unnecessary adjunctive medications, unwarranted changes in primary medication, and increased rates of relapse and hospitalization.[1,84,85] Patients whose adherence problems have been missed may also be incorrectly labeled as having treatment-resistant illness. Conversely, if the physician believes a patient's lack of response is due to nonadherence when that person is in fact taking the medication as prescribed, the doctor may not make changes in the regimen that could improve outcomes.[84] Studies have shown that physicians are frequently unable to accurately determine whether patients are adherent to treatment.[84] Thus, researchers have undertaken studies to test different methods—both subjective and objective—for evaluating patients' current level of adherence and identifying the potential for future adherence problems. In this section, we first review findings from this research and then present the experts' recommendations for strategies for assessing adherence. The majority of studies in this area have focused on patients with schizophrenia; however, some studies have also examined adherence in bipolar disorder and other serious mental illness.

Subjective Methods of Assessing Adherence

Self-report and *physician report* are the most common ways of assessing adherence to medication. Velligan et al.[36] reviewed literature published between 1970 and 2006 on adherence to oral antipsychotic medications in patients with schizophrenia and found that patient self-report was the most common method used to assess adherence. They found that subjective and indirect methods (self-report, provider report, significant other report, chart review) were the only strategies used to assess adherence in more than 77% (124/161) of the studies they examined, while direct or objective measures (such as pill count, blood or urine analysis, electronic monitoring, electronic refill records) were used in fewer than 23% (37/161) of studies (see Figure 1-1 p. 9).

Unfortunately, although they are the most commonly used methods, subjective assessments are likely to be inaccurate and tend to overestimate levels of adherence. For example, in a study published in 2005, Byerly et al.[86] compared an objective measurement of adherence to antipsychotic medication, the Medication Event Monitoring System (MEMS) cap (pill bottle caps that record time and date of opening) and a clinician rating scale of adherence in patients with schizophrenia and found that clinicians dramatically underestimated levels of nonadherence. In this study, the MEMS system identified nonadherence in 48% of the 30 participants, while the clinicians identified none of these individuals as nonadherent. A follow-up study by Byerly et al.[147] published in 2007 confirmed these findings, with MEMS detecting 57% nonadherence compared with 7% reported by prescribers and 5% based on patient self-report.

In a 12-week study of 52 outpatients with schizophrenia, Velligan et al.[84] found that neither physician report nor patient self-report accurately identified adherence when compared with data from electronic monitoring or pill counts. Based on these findings, the investigators in this study cautioned against using self-report or physician impression alone for assessing adherence. These researchers concluded that physicians' inability to accurately identify adherence is likely to have important consequences for prescribing behavior, healthcare costs, and patient outcomes. For example, without accurate data on adherence (i.e., how much medication a patient is actually taking), it is very difficult for a clinician to know if the dosage he or she is prescribing is appropriate for that patient.

Objective Methods of Assessing Adherence

As noted above, the use of new technologies, such as the MEMS and other types of "smart" pill containers that are capable of both prompting and monitoring adherence and downloading data on adherence to a secure website, has the potential to provide clinicians with much more accurate information on which to base their prescribing decisions.[84]

Nakonezny et al.[75] evaluated the use of electronic monitoring (EM) of medication bottle opening for assessing adherence with oral antipsychotic medication in 61 outpatients with schizophrenia or schizoaffective disorder. They found the EM had high test-retest reliability and high predictive validity (greater adherence was significantly related to lower mean symptom severity).

However, even the use of more objective measures, such as pill counts, pharmacy records, electronic monitors, and plasma concentrations, can be associated with significant errors.[36] For example, the use of samples or old medications can compromise the results obtained using pill counts and pharmacy refill records. Patients may also fill prescriptions in other locations for which there is no record. In addition, just because patients have filled a prescription and have medication on hand does not mean that they will take the medication as prescribed or at all. Although electronic monitors are generally considered the gold standard for assessing adherence, results can be compromised by a number of problems—patients may take more than one dose out of the bottle at a time, not take any pills out at all, or fail to replace the cap, resulting in missing data. Even the use of plasma drug levels can be problematic. For example, the patient's behavior in the days immediately before the sample is taken may not accurately represent the person's usual behavior over a longer period of time. Thus, with regard to monitoring

lithium levels, opinions differ as to the value of measuring plasma levels alone or the ratio of lithium concentration in red blood cells (RBC) to serum levels. Alternatively, Harvey and Peet[148] recommended using serial measures of RBC lithium levels during a fixed dosage regimen to measure changes in adherence (using the lithium level/dose ratio). Scott and Pope[8] found that calculating the mean variation in lithium level over time gave a useful indication of nonadherence, as stability of the plasma level may be a better indicator of adherence rather than fluctuating levels. There is also great variability in individual blood levels of antipsychotics across patients and very few data on what blood levels of the newer antipsychotics would be considered therapeutic. For example, in a study involving olanzapine, medication blood levels were taken but were not used as the primary measure of adherence because few data about therapeutic blood levels are available to use as a criterion.[149] Therefore, until more sophisticated techniques become available to understand blood level data for different second generation antipsychotics, this method may not be very useful as an adherence measure, particularly for patients who are partially adherent.

Velligan et al.[1] assessed adherence to treatment for 3 months in a sample of 55 patients prescribed antipsychotics using blood level analysis, pill counts, pharmacy records, and self-report. Based on a definition of adherence as taking 80% of prescribed doses, this study found that only 40% of participants were adherent based on pill count and only 9% took all doses prescribed over the 3 months. Analysis of blood levels suggested that the adherence rate in this sample was even lower—23%. In contrast, 55% of the participants self-reported perfect adherence. Despite ensuring that all needed medication was in patients' possession during the 2-week baseline period, these investigators still found adherence problems, even among patients living in group-home settings, making it clear that availability is necessary but not sufficient for adherence and confirming that, as noted above, fill and refill rates are likely to underestimate levels of nonadherence.

9B. FEASIBILITY OF USE IN DAY-TO-DAY CLINICAL PRACTICE

The research reviewed in the preceding sections makes it clear that most physicians are poor judges of how much medication their patients are actually taking and that even time-consuming and expensive objective measures of medication adherence may be inaccurate.[36,84] Even under the best of circumstances in rigorous research, it is very difficult to tell how much medication a patient is actually taking. It is therefore not surprising that it is difficult to make such a determination in a 15-minute medication check.

It is also important that methods used to assess adherence distinguish "medication refusers" (i.e., patients who take only some or none of their medication by choice) from those who are willing to take their medication but miss doses due to factors such as forgetting, misunderstanding instructions, or financial or environmental problems,[36] since the focus of intervention will differ considerably for these two groups. (See Tables 3-1 and 3-2 p. 22 for factors that can affect willingness versus ability to take medications.) What steps can clinicians take to more accurately assess their patients' adherence to treatment that are feasible for use in real-world clinical settings?

A recent study by Woltmann et al.[150] found that MPRs constructed from pharmacy data can be a useful first screen for identifying patients with schizophrenia and bipolar disorder who are partially adherent with medication, with bipolar patients more likely to be incorrectly identified as partially adherent based on pharmacy records. Given the current interest in increasing the standardization and computerization of medical records in the United States, assessment based on pharmacy records is likely to become more accessible to clinicians in the near future.

The use of electronic monitors is not currently a practical means of monitoring adherence in large clinic settings. However, newer devices that prompt adherence and download adherence data to a website that can be examined by a provider have been used in health maintenance organizations (HMOs) to improve outcomes.[151] These devices may be cost effective in HMO settings in the treatment of individuals who have complex regimens and long-standing illnesses for whom poor treatment adherence has serious and expensive consequences. Pill counts are very practical if clients are seen in their homes by a provider. If this is not the case, pill counts in the office can be done. However, clinicians must stress to patients the importance of bringing in *all* bottles of medication (old and new). Individuals who don't remember to bring in the bottles are more likely to have adherence problems. In addition, this process can help the patient dispose of expired products. The physician or another member of the treatment team can bag and staple unused bottles and not count them on the next visit if the seal is not broken. While this is a time-consuming process, particularly at the initial counting, the method provides reasonably good data on which to base decisions about treatment changes.

9C. RECENT STUDIES OF SELF-REPORT SCALES

As noted above, patient self-report is the most commonly used method of assessing adherence and is certainly the easiest method to use in the average practice setting. Thus, a number of researchers have investigated methods for improving the accuracy of results obtained from patient self-report.

Dolder et al.[152] developed and tested the Brief Evaluation of Medication Influences and Beliefs [BEMIB] Scale, an assessment tool for identifying patients likely to be nonadherent to their antipsychotic medication. Respondents rate their level of agreement with 8 statements derived from the health belief model on a 5-point Likert-type scale. These researchers found that total scores on the BEMIB were significantly correlated with results of an established questionnaire used to assess adherence, the Drug Attitude Inventory, so that the BEMIB

demonstrated adequate construct validity. However, these data must be interpreted cautiously because both of these are self-report measures and no objective measures of adherence were investigated.

Fialko et al.[153] evaluated the psychometric properties of the Medication Adherence Rating Scale (MARS), a 10-item self-report measure of medication adherence in psychosis,[154] in a large sample of 277 individuals with psychosis and found only weak correlation with adherence as rated by the patients' key-workers. Based on factor analysis, these researchers suggested that the factor 1 score, which corresponds to the Medication Adherence Questionnaire,[155] may be a preferable measure of medication adherence behavior compared with the total scale score.

Validity in the studies described above was examined by correlating self-reported adherence with other self-report measures or clinician reports. This methodological weakness is common in studies examining the validity of adherence assessments based on self-report. However, in a recent study, Byerly et al.[156] used electronic monitoring as the reference standard to evaluate the reliability, validity, sensitivity, and specificity of a brief, pencil-and-paper, clinician-administered adherence instrument, the Brief Adherence Rating Scale (BARS), for assessing adherence to oral antipsychotic medications in outpatients with schizophrenia and schizoaffective disorder. They found that, relative to electronic monitoring, the BARS appears to provide valid, reliable, sensitive, and specific estimates of antipsychotic medication adherence in outpatients with schizophrenia and schizoaffective disorder. Thus, the BARS appears to be a promising candidate for use as a brief adherence assessment in community-based settings. However, additional research, including evaluation of the use of the BARS in clinical settings, is needed. The BARS, which is in the public domain and available for free use, is presented in Table 4-1.

Table 4-1. Brief Adherence Rating Scale

Patient identification: _____ Date: _____

The following information is obtained by the clinician:

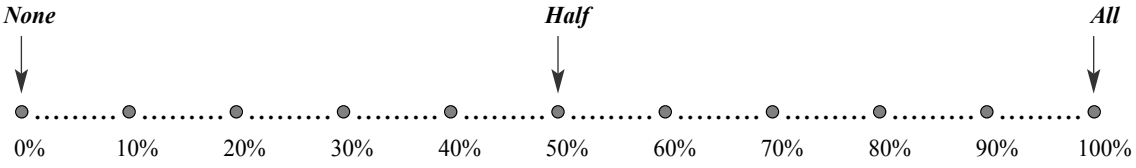
1. How many pills of _____(name of antipsychotic) did the doctor tell you to take each day? _____

2. Over the month since your last visit with me, on how many days did you NOT TAKE your _____(name of antipsychotic)?
   - Few, if any (< 7) _____
   - 7–13 _____
   - 14–20 _____
   - Most (> 20) _____

3. Over the month since your last visit with me, how many days did you TAKE LESS THAN the prescribed number of pills of your _____(name of antipsychotic)?
   - Always/almost always = 1 (76%–100% of the time) _____
   - Usually = 2 (51%–75% of the time) _____
   - Sometimes = 3 (26%–50% of the time) _____
   - Never/almost never = 4 (0–25% of the time) _____

Note: 1 = poor adherence
4 = good adherence

Please place a single vertical line on the dotted line below that you believe best describes, out of the prescribed antipsychotic medication (_____) doses, the proportion of doses taken by the patient in the past month.



Response struck on above line (%) = _____

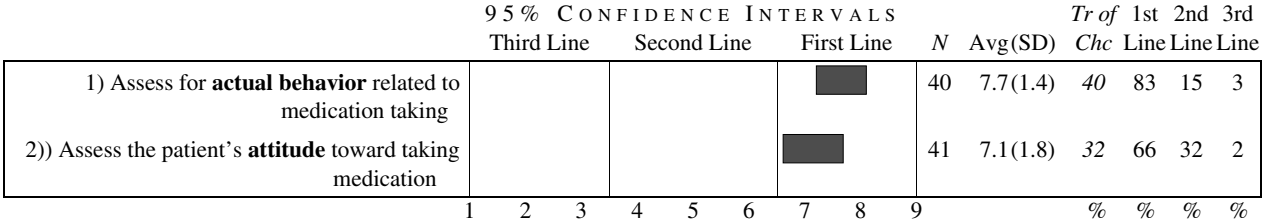
Rater's initials: _____

The BARS scale is available in the public domain, allowing unrestricted use of this scale. An electronic copy of the BARS scale can be requested from Dr. Byerly at matt.byerly@utsouthwestern.edu.

Guideline 10: Expert Consensus on Tools for Assessing Adherence

Research reviewed in Guideline 9 indicates that methods currently being used to assess adherence in patients with serious and persistent mental illness are not adequate, but the research provides only limited guidance on how to improve the situation. We therefore asked the experts about methods and tools for assessing adherence. The experts indicated that it is important to assess both behavior and attitude, although they considered assessment of actual behavior the most important component (Question 26).

26 **Overall strategies for assessing adherence.** Please rate the appropriateness of the following strategies in assessing for adherence problems.



The tables below present the experts' responses concerning how ***frequently*** different sources of information are used in routine clinical practice and how ***accurate*** they are. Not surprisingly, the experts believe clinicians are much more likely to use self-report than any other method, although they are aware that other techniques are likely to be more accurate. They indicated that more accurate information will be obtained by asking about any problems patients are having or anticipate having taking their medication than just asking if they have been taking their medication. The table on the right lists other steps clinicians can use when they suspect adherence problems may be present, depending on availability of time and staff. In keeping with findings in the literature, the experts did not believe that a patient's level of symptoms is likely to be a very accurate indicator of adherence.

Frequency
with which physicians use different sources of information on adherence

Very frequent	Ask the patient about recent adherence to medication (behavior)
Frequent	Ask about any problems patient has been having or anticipates having taking medications
Somewhat frequent	Ask about attitude towards medication
	Use level of symptoms to estimate adherence
	Speak with other members of treatment team
	Ask patients to bring in medication for review and/or pill count
	Call patient's family or caregiver to ask about adherence, if patient gives permission
Rarely	Obtain plasma levels of medications
	Review pharmacy refill records
	Use standardized instrument (e.g., BARS)
	Use technological tools (e.g., smart pill containers)

Usefulness
of different sources of information in obtaining an accurate assessment of adherence

Useful	Ask about any problems patient has been having or anticipates having taking medications
	Call patient's family or caregiver to ask about adherence, if patient gives permission
	Obtain plasma levels of medications
	Ask patients to bring in medication for review and/or pill count
	Review pharmacy refill records
	Use technological tools (e.g., smart pill containers)
	Ask about attitude towards medication
Sometimes useful	Speak with other members of treatment team
	Ask the patient about recent adherence to medication (behavior)
	Use standardized instrument (e.g., BARS)
Not useful	Use level of symptoms to estimate adherence

Clinicians should keep the following key points in mind in discussing adherence to medication with their patients[64]:

- How you ask is important
- Your relationship with the patient is key
- Avoid appearing punitive or authoritarian
- Let the patient know that it is ok to disagree
- Be willing to take a flexible approach
- Exploring practical problems that interfere with adherence can help sort out reasons for less than optimal medication response.

Guideline 11: Frequency and Duration of Adherence Assessments

For patients who appear to be adherent to medications, the experts recommended monthly assessments for adherence problems, as well as additional assessment whenever there is a noticeable change in the patient's symptoms. However, when there is concern about adherence, they would recommend more frequent (e.g., weekly) adherence assessments.

Expert consensus on frequency and duration of adherence assessments

Clinical situation	Recommended frequency	Recommended duration	Actual clinical frequency*
A patient you know well and believe is regularly adherent to medication	Noticeable change in symptoms Monthly Every 3 months	5 minutes	7.4 ± 5.5 weeks
A patient who is relatively new to you but at initial evaluation was regularly adherent to medication	Noticeable change in symptoms Monthly	5–10 minutes	3.0 ± 2.1 weeks
A patient whose adherence is already known to be problematic	Weekly Noticeable change in symptoms *Consider daily (e.g., PACT)*	10–30 minutes	2.1 ± 1.2 weeks
A patient who is not responding to medication	Weekly Daily (e.g., PACT) Noticeable change in symptoms	10–30 minutes	1.3 ± 0.7 weeks

**The experts were asked to indicate the actual frequency with which the different types of patients would usually be seen in their practices.*

Guideline 12: Clinical Interview Techniques for Assessing Adherence

An adherence interview has three primary goals:
- To determine whether, or confirm that, the person is not taking medication as prescribed
- To assess how much medication is actually being taken
- To identify factors that are causing the patient not to take medication as prescribed.

12A. ASSESSING LEVEL OF ADHERENCE

Clinicians should keep in mind that patients often overestimate their level of adherence.[84,147] A classic response is: "How do you expect me to remember when I forgot to take my medicine?" Rather than asking "Are you taking your medication?" it is more useful to ask about *how* the person takes medication:
- *When do you take your medication?*
- *Where do you keep your medication?*
- *What does your medication look like?*
- *We all forget to take our pills sometimes. Do you ever forget to take your medication?*
- *In the last week, how many doses do you think you may have missed?*

Asking patients to bring in medications for a pill count or obtaining pharmacy refill data can also be helpful.

12B. IDENTIFYING FACTORS THAT AFFECT ADHERENCE

If you believe your patient is not taking medication as prescribed, the next step is to find out *why*. In 2007, Weiden[64] outlined five theories about adherence (Table 4-2), which highlight that the true goal of treatment is not adherence, but symptom control, improved health, and a better chance of recovery. Keeping these theories in mind can help clinicians communicate more effectively with patients, uncover issues relevant for specific patients, and individualize treatment interventions.

Table 4-2. Principles regarding medication adherence in patients with schizophrenia*

Theory	Clinical implications
1. Adherence is not a clinical outcome and only matters as it interferes with outcome.	Symptom control, functioning, and remission are outcomes; adherence is not. Adherence is a means to an end (e.g., symptom control, remission). Clinicians should consider nonadherence a barrier to achieving mutually desired outcomes and express this to the patient, as well as fostering realistic expectations about medication.
2. Adherence problems are often entangled with efficacy limitations of antipsychotic medications.	Clinicians should not automatically assume that nonresponse/breakthrough symptoms are due to nonadherence. In mental illness, lack of efficacy can lead to nonadherence; abrupt changes in cooperation may be symptoms of relapse. Misattributing poor outcomes to nonadherence rather than lack of effectiveness or a comorbid problem (e.g., substance use) can keep the clinician from seeking a more effective treatment.
3. Adherence can be viewed as a behavior (taking/not taking) or an attitude (prefers taking/prefers stopping medication).	A patient may be willing to take medication but unable to because of logistic problems. Or a patient may not believe medication is needed but takes it because a family member administers it. Clinicians need to assess behavior *and* attitudes.
4. When considering adherence attitudes, patient belief is always reality.	Clinicians should encourage patients to express their feelings about medication honestly, practice active listening, be nonjudgmental, take the patient's beliefs at face value, and avoid interrupting to correct mistaken perceptions.
5. Adherence behavior changes and fluctuates over time and should be considered part of the illness in the context of the long-term trajectory of desired clinical outcomes such as recovery.	Clinicians should expect nonadherence, use it as a learning tool for the patient, and maintain the therapeutic alliance while the patient learns to accept and integrate medication into life as part of the recovery process and a tool to achieve life goals.

**Adapted with permission from Weiden*[64]

12C. ASSESSING PATIENT-RELATED FACTORS

Within the context of these overarching principles, it is important to identify specific issues that are causing adherence problems. The suggestions for interviewing presented below are organized based on factors that affect adherence (see Section III, pp. 16–18). We present a variety of questions that may be used to elicit similar information, so that clinicians can select a subset of questions that seem most appropriate for use with a specific patent.

Attitudes and past behaviors

The questions listed below address insight into having an illness (illness awareness) and the need for medication, as well as past adherence problems that may predict future problems.

- *How do you feel about taking this medication?*
- *What do you think are reasons to take this medication? What about reasons not to take it?*
- *Do you believe you benefit from taking your medication?*
- *Do believe you need to take medicine?*
- *What do you like (or dislike) about your medication?*
- *Do you plan to keep taking your medication in the future?*
- *Has there been a day when you intentionally decided not to take your medication? What was that about?*
- *Do you ever think about stopping your medication? Why? Do you feel better when you stop your medication?*
- *Have you ever stopped taking your medication in the past or cut it down without telling your doctor? What led you to do that?*

Comorbidity and symptom severity

Problems with substance use often lead to adherence problems. If you suspect your patient has substance-related problems, it is important to determine the extent of the problem(s) and how it is affecting adherence to antipsychotic medication. Ask:

- *How much alcohol do you drink during a typical day? What about on the weekends?*
- *What kind of street drugs or prescription drugs that you have not told me about are you using?*
- *How much do you use during a typical week? What about on the weekend?*
- *How much money do you spend on the drug each week or month?*
- *Do you find that you are more likely to miss taking your medication when you are using?*

Lack of response or persistent symptoms can also cause patients to stop medication (Guideline 7C, p. 21). Ask:

- *Do any of your symptoms make it harder for you to take medication?* (Insert examples pertinent to the specific patient—e.g., persistent negative symptoms, paranoia, excessive sedation, persistent grandiosity.)

Demographic factors

Patients who are younger, from lower socioeconomic classes, with less education, of minority ethnicity, or homeless are more likely to have adherence problems.[37,41,43,61–63,113,114,137] Higher rates of nonadherence have been reported in male patients with schizophrenia[41] and female patients with bipolar disorder[137] (Section III Demographic factors, pp. 16 and 18). While these are not factors that clinicians can change, clinicians should be especially alert for adherence problems in such patients.

Environmental factors

Practical problems (e.g., logistic, financial, organizational) can interfere with medication taking, especially in patients with schizophrenia (see Guideline 7A, p. 19) and are amenable to intervention. To identify problems related to the patient's ***routine or home environment,*** you can ask:

- *Do you anticipate any trouble in taking your medication as prescribed? What might get in the way?*
- *Where do you keep your medication?*
- *Do you find it difficult to have to take medication every day?*
- *How do you remember to take your medication? Do you have a regular schedule that you keep? What about on weekends?*
- *Does anyone help you or remind you to take your medication?*

The following questions can help identify ***financial and logistic problems*** related to obtaining medication.

- *How do you get your medication refills?*
- *What do you do when you see you are running out of pills?*
- *Can you easily get to your pharmacy?*
- *How do you pay for your medicine? Do you have a co-pay? How do you manage to pay it?*

Cognitive impairment

Cognitive deficits in patients with schizophrenia can be an important cause of problems with medication taking.[116,118] Patients may not understand the instructions they are given or may have difficulty following them. The following questions, some of which are also listed elsewhere, may help to identify these types of difficulties.

- *What is the name of the medication you are taking? What does your medication look like?*
- *How are you supposed to take the medication? How do you usually take it?*
- *Where do you keep your medication?*
- *How many pills are you taking?*
- *How do you remember to take your medication?*

Medication-related factors

Side effects can make patients unwilling to take medications.[123,124,141] As Perkins[98] noted, those side effects that cause subjective distress are the most likely to lead to adherence problems. Assess how problematic a side effect is for the specific patient, since this is a very personal matter. In general, the experts indicated that weight gain , sedation, akathisia, and sexual dysfunction are particularly bothersome for patients with schizophrenia. They identified weight gain, sedation, sexual dysfunction, and cognitive problems as side effects most likely to distress patients with bipolar disorder (see Guideline 7B, p. 20). The following questions may encourage your patient to tell you about any problematic side effects.

- *Are you experiencing any problems or side effects due to your medication?*
- *Are you having any trouble with* (ask about side effects common with the specific medication the person is taking)*?*
- (If the person reports a side effect) *How much does that bother you? Is there anything you do that helps with that problem?*

12D. ASSESSING RELATIONSHIP FACTORS

Therapeutic alliance

Research findings[103,128,129,143] and the experts' responses both indicated that the quality of the therapeutic alliance between prescriber and patient plays a key role in patients' attitudes toward treatment and willingness to take medication as prescribed. As Weiden stressed,[64] clinicians need to make it clear that they are not promoting treatment adherence for its own sake (i.e., that this is not a matter of control and obedience), but should link treatment adherence with achieving life goals. The following questions may help patients be open about their feelings concerning the treatment team:

- *Do you think your doctor and your treatment team understand your concerns about your medication?*
- *Is there anything your doctor or treatment team is doing that makes you less willing to take your medicine?*
- *Is there anything that your doctor or treatment team could do that would make you more willing to take your medication?*

Family and social support

Because of the important role family members and significant others often play in patients' lives, they can have a big effect on how the person feels about taking medication. Lack of family and social support can lead to adherence problems and poorer outcomes.[103,119,132] These questions can help you get a better idea of how the patient's family feels about the prescribed treatment and if they provide support to help the person stick with treatment:

- *How does your family feel about your medication?*
- *Do family members encourage you to take your medication? Does anyone help you remember to take your medication?*
- *Is there anyone important to you who thinks you shouldn't take medicine? Why do they think so?*
- *Do you ever have disagreements with your family about taking medication?*

12E. ASSESSING FACTORS RELATED TO THE SERVICE DELIVERY SYSTEM

Clinicians may not be aware of problems patients have in accessing care or may not be aware that patients feel that the level of access is not adequate. Patients may also feel they have not received enough information about their illness and its treatment or may not have understood what was provided. The following questions may help identify such issues:

- *Did you ever have any trouble getting an appointment when you felt you needed to see me? How long did you have to wait? Did that cause you any problems?*
- *Have you or your family ever called the office with a question about your illness or medication? Did you get an answer? How long did that take?*
- *Do you feel you have good information about your illness? Do you feel you have good information about the medication you are taking? Is there more information you would like us to give you?*

V. Strategies for Addressing Adherence Problems

Guideline 13: Research Findings

After identifying factors that may be contributing to a patient's adherence problems, it is important for clinicians to initiate strategies specifically targeted to those problems. For example, cognitive strategies may be helpful for those with poor insight into having an illness and the need to take medication. Social work interventions may be most appropriate if the person cannot pay for medication or lacks transportation to the pharmacy.

Research has increasingly focused on psychosocial, pharmacological, and programmatic interventions to improve outcomes in patients with schizophrenia and bipolar disorder. In 2009, Julius et al.[157] reviewed the literature on adherence in psychiatric disorders, and concluded that many research models for interventions to improve adherence are time- and staff-intensive and are often not feasible for use by individual clinicians. We therefore asked the experts about the appropriateness of different psychosocial and pharmacological strategies for addressing specific adherence problems in real-world clinical settings (note that programmatic interventions, such as assertive community treatment [ACT] and intensive case management, were included as a type of medication monitoring/environmental support). This guideline describes the strategies we asked about and research on these interventions, some of which focused specifically on adherence and some on a variety of outcomes.

13A. PSYCHOSOCIAL AND PROGRAMMATIC INTERVENTIONS

Cognitive-behavioral therapy (CBT) is a psychotherapy intervention focused on understanding patients' perception of their problems and treatment. In theory, it is possible to undertake this approach even if the patient does not accept a diagnosis (as long as there is a shared understanding of the problems). CBT techniques include assessing patient perspective, examining evidence, and rolling with resistance. *Rolling with resistance* means not challenging the patient's resistance to taking medication but exploring this resistance to better understand the patient's viewpoint and help the patient re-evaluate beliefs about medication.[157] CBT therapists help patients identify and modify negative automatic thoughts about medications and use guided discovery to help strengthen patients' beliefs that taking medication is associated with staying well and achieving goals.[158] In schizophrenia, CBT to improve adherence often incorporates motivational interviewing techniques. First developed for use in addiction treatment, these techniques assess patients' motivation to make changes in behavior related to adherence. In bipolar disorders, patients often prefer a model that encompasses the principles of concordance,[159] although motivational techniques are useful in those with comorbid substance use problems. CBT has been found to improve adherence and symptom management and increase insight in patients with schizophrenia[157,160,161] and brief[162] and extended models of CBT can improve adherence in patients with bipolar disorder.[163]

Compliance therapy is a CBT intervention that targets adherence issues and incorporates psychoeducation and motivational interviewing to help patients understand the connection between relapse and medication nonadherence to improve motivation for taking medication. In a small-scale study, Kemp et al.[164,165] found that compliance therapy significantly improved insight, attitudes to treatment, and adherence in patients with schizophrenia. A study in Thailand found that adherence therapy, a brief intervention based on compliance therapy and motivational interviewing, delivered by nurses who received intensive training, significantly improved psychotic symptoms and attitude towards and satisfaction with medication compared with treatment as usual,[166] but a large scale effectiveness study in Europe yielded disappointing results.[167]

Interpersonal and social rhythm therapy focuses on stabilizing daily routines and resolving interpersonal problems. It uses motivational interviewing and CBT techniques to help individuals learn the benefits of maintaining a regular schedule in managing their illness, accomplishing life goals, and resolving key interpersonal problems. This strategy has primarily been investigated in bipolar disorder and has been found to improve adherence and help prevent relapses.[163,168,169]

Involuntary outpatient commitment involves compulsory, community-based treatment for mental illness, with regulations and criteria differing from state to state. In a 2005 Cochrane review of randomized controlled trials, Kisely et al.[170] found that compulsory community treatment resulted in no significant difference in service use, social functioning, quality of life, or cost effectiveness compared with treatment as usual; they concluded that it is "difficult to conceive of another group in society that would be subject to measures that curtail the freedom of 85 people to avoid one admission to hospital or of 238 to avoid one arrest" and recommended further randomized controlled studies.

Medication monitoring/environmental supports include dispensing doses; directly observing medication taking; providing environmental supports in the home as reminders to take medications and fill prescriptions; helping people deal with practical barriers to coming to appointments or refilling prescriptions; as well as programmatic interventions such as ACT.

A program called ***cognitive adaptation*** appears to be a promising strategy to improve adherence.[117] Cognitive adaptation focused on medication adherence uses individually tailored environmental supports (e.g., signs, checklists, electronic cuing devices, organization of belongings) to cue adaptive behavior in the patient's home environment and help compensate for cognitive deficits. It also addresses logistic issues related to obtaining

medication (e.g., picking up prescriptions) and getting to appointments. In a study published in 2008, Velligan et al.[117] found that a full cognitive adaptation program (focused on many aspects of community adaptation including grooming, care of living quarters, leisure skills, social and role performance, and medication adherence) and a cognitive adaptation program focused only on adherence to medication and appointments were both superior to treatment as usual in improving adherence, reducing relapse rates, and increasing time to relapse or exacerbation of symptoms. The full program produced greater improvements in functional outcome than the other two interventions. Improvements in adherence persisted after home visits stopped. The authors concluded that targeted supports can improve adherence and reduce relapse rates, but that comprehensive supports targeting multiple domains are necessary to improve functional outcomes.

Recent research has focused on new technology. Spaniel et al.[171] tested an information technology aided relapse prevention program (ITAREPS) that uses a mobile phone-based telemedicine strategy to remotely monitor patients with schizophrenia on a weekly basis to identify prodromal symptoms of relapse, enable early intervention, and reduce hospitalizations. ITAREPS produced a statistically significant 60% decrease in hospitalizations over a mean of 9 months compared with the same period before entry in the program. Variables influencing number of hospitalizations after entry in ITAREPS were adherence to medication and the program and involvement of a family member.

ACT and ***case management*** were developed in the 1970s in response to closing of psychiatric hospitals. In 2000 Cochrane reviews on these interventions, Marshall et al. reported that patients in ACT were more likely to stay in contact with services, were less likely to be hospitalized, and were more satisfied with care than those in standard community care; however, they found case management to be of questionable value and doubted it should be offered by community psychiatric services.[172,173]

More frequent and/or longer visits, if possible, may help foster an improved therapeutic alliance. Sajatovic et al.[163] reported that most effective therapies involve an interactional component between patients and care providers/therapists.

Psychoeducation

Patient psychoeducation involves strategies (e.g., individual and group counseling, use of written/audiovisual materials) to teach patients about their illness, medication and side effects, and relapse prevention. Some studies have found that psychoeducation used alone is not effective in improving medication adherence in schizophrenia.[133] However, this may be a function of the model of psychoeducation employed, as those which use techniques to promote changes in behavior, skills, and/or attitudes (e.g., using homework or practice) have been found significantly more likely to improve adherence in bipolar disorder.[7] Based on data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, Mohamed et al.[174] found that a change to more positive medication attitudes (on the Drug Attitude Inventory) in patients with schizophrenia was associated with significantly greater medication adherence, decreases in psychopathology, and improvement in functioning. They concluded that it may be important to include educational interventions targeting these attitudes in psychosocial rehabilitation and recovery services. A recent pilot study in patients with early psychosis found that an intervention called adherence-coping-education was associated with a significant decrease in symptoms and a trend toward improved attitudes toward treatment compared with supportive therapy.[175]

Relatively few studies have focused on psychoeducation in bipolar disorders compared with schizophrenia. However, psychoeducational interventions appear effective in improving adherence in bipolar disorder,[87,163] especially when provided in the context of long-term illness management that incorporates good understanding of medications and their risks and benefits and education about illness awareness and self-management.[163] In a 2007 literature review, Rouget and Aubry[176] reported that psychoeducation, alone or as a component of more complex interventions, can improve the course of bipolar disorder by increasing patients'/families' knowledge of the disorder and its treatment, decreasing risk of relapse and hospitalization, and improving adherence. They concluded that, as a complement to pharmacotherapy, individual/group psychoeducation is a first-line psychological intervention applicable to a majority of patients and families, which can be delivered by a range of health professionals trained in this approach. Bowskill et al.[146] recommended that clinicians evaluate what information patients with bipolar disorder need and tailor education to the specific patient in a way appropriate for the person's cognitive functioning at that phase of illness to facilitate informed choice and adherence.

Family psychoeducation has been shown to reduce relapse rates and facilitate recovery in persons with mental illness.[177] Psychoeducation for patients with schizophrenia that includes family members has been found to be more effective in reducing symptoms and preventing relapse than psychoeducation involving the patient alone.[133,178] In a controlled trial, Chan et al.[179] found that a psychoeducational intervention for patients with schizophrenia and family caregivers significantly improved medication adherence, mental status, and insight into illness in patients, and self-efficacy, satisfaction, and perception of family burden in caregivers, but that these benefits were not sustained after 12 months. They concluded that psychoeducation should be an ongoing intervention. A 2006 Cochrane review[180] found that family interventions for schizophrenia may encourage adherence with medication and decrease relapses and hospitalizations, but they do not appear to affect the tendency of individuals/families to drop out of care. The authors noted the need for more trials of interventions applicable for use in routine care.

In a literature review, Sajatovic et al.[163] reported that group sessions with partners of individuals with bipolar disorder and patient and family psychoeducation improved medication adherence in bipolar disorder. Reinares et al.[181] found that a psychoeducation group intervention for caregivers significantly reduced risk of manic recurrences in bipolar disorder.

Family-focused therapy involves providing psychoeducation, emotional support, and resources during crises; teaching problem-solving skills to identify and resolve family conflict; and strategies to improve communication. The goal is to reduce stress and conflict in families of patients.[168] Although family-focused therapy does not specifically target medication adherence, adherence has been evaluated in studies of this intervention. Results of studies of family-focused therapy have been promising, especially in bipolar disorder. Miklowitz et al.[182] found that family-focused therapy (21 sessions of psychoeducation, communication training, and problem-solving skills training) produced greater reductions in mood symptoms and better adherence over 2 years than a crisis management intervention (2 family education sessions plus crisis intervention as needed) in patients with bipolar disorder receiving medication.

Social work targeting logistic problems focuses on identifying barriers related to transportation, insurance benefits, and finances that can interfere with ability to attend appointments and refill medication. In a study involving 349 VA patients with an exacerbation of schizophrenia, Hudson et al.[183] found that patients who received an enhanced guideline implementation strategy, in which a research nurse worked with them to identify and develop patient-specific strategies to overcome barriers to medication adherence, were almost twice as likely to be adherent at follow-up as those who did not receive this intervention.

Symptom/side effect monitoring is important because lack of response can lead to poor adherence and discontinuation of medication against medical advice.[109] It is important for clinicians to monitor symptom response on an ongoing basis (e.g., using a daily checklist or mood chart) and be alert for adherence problems in patients who do not achieve an adequate response. Tacchi and Scott[7] reported that giving detailed information on how to manage specific side effects should they occur can increase the likelihood of sustained adherence.

With regard to side effects, in another recent survey,[30] experts stressed the importance of matching interventions to the specific side effect the person is experiencing and considering how distressing the symptom is for *that* patient (e.g., amenorrhea may be very distressing for some women but not others). Some side effects that patients find distressing may be transient (e.g., nausea or other gastrointestinal effects that occur early in treatment with some medications), so that all that may be required is to provide support and encouragement to the patient to stick with treatment and see if the problem goes away on its own. Some side effects (e.g., extrapyramidal symptoms [EPS], amenorrhea due to prolactin elevation) may be amenable to dose adjustments or treatment with adjunctive medications. However, other side effects that can occur with antipsychotics and mood stabilizers, such as weight gain, do not appear amenable to dose adjustments. The experts in the survey cited above recommended that, if diet and lifestyle changes are not successful in controlling weight, clinicians may want to suggest switching to an agent with less liability to cause weight gain.

13B. PHARMACOLOGICAL INTERVENTIONS

Clinicians must first determine if the cause of the adherence problem is amenable to a pharmacological intervention. If so, the following strategies, used alone or in combination, may help:

- Decrease or increase dose of the current antipsychotic
- Add an oral or long-acting injectable antipsychotic
- Add another type of adjunctive medication for side effects
- Switch to a different oral antipsychotic
- Switch to a long-acting antipsychotic
- Monitor plasma levels of medication
- Simplify medication regimen.

Side effects that may be amenable to dose adjustments include EPS, sedation, amenorrhea, agitation, and activation. Dose adjustment strategies for side effects differ from one medication to another. For example, early agitation/activation with aripiprazole is best addressed by lowering the dose. However, when these side effects occur with ziprasidone, they are best addressed by raising the dose.[30] Some side effects (e.g., EPS) may improve with a dose reduction. If response cannot be maintained at a lower dose, adding an anticholinergic agent may help manage the EPS.

First- and second-generation long-acting injectable antipsychotics may improve treatment adherence and reduce relapse risk in patients with schizophrenia.[184,185] Based on data from the Schizophrenia Treatment Adherence Registry (e-STAR) study in Spain, a long-term observational study of patients with schizophrenia who started a new antipsychotic treatment in the course of real-world clinical treatment, Olivares et al.[185] reported that long-acting injectable risperidone reduced rates of relapse and rehospitalization and reduced costs per month per patient. Preliminary findings from the Prevent First Episode Relapse (PreFER)[186] study indicate that patients with a first episode of psychosis will accept the recommendation for treatment with a long-acting injectable antipsychotic if delivered in a psychoeducational format and that such a recommendation did not appear to threaten the therapeutic alliance. The results of this study suggested that the main reason patients appeared to take their medication is their relationship with their clinicians, not whether they believe they needed medication or were having side effects. One caveat in reviewing results of these studies is that patients who are adherent to treatment may be more likely to enter and complete randomized clinical trials, so that trials that use a mirror group design may produce more accurate results.[187]

Improvement in adherence with long-acting agents may not persist without other interventions that promote adherence (e.g., educating patients about importance of medication and associating it with achieving life goals).[40,188] Patel et al.[189] reported that beliefs and attitudes are more important than side effects in predicting adherence and that a depot agent will not ensure adherence without a discussion of the benefits of adherence.

Long-acting formulations of first- and second-generation antipsychotic medications (FGAs and SGAs) have also been evaluated in bipolar disorder. Based on 8 reports, Bond et al.[190] concluded that depot FGAs are efficacious in preventing manic episodes during maintenance treatment of bipolar disorder but

may be associated with increased time with depressive symptoms, particularly in patients with a predominantly depressive course of illness. Bond et al.[190] also described 6 preliminary reports suggesting that depot SGAs reduced frequency of manic and depressive episodes during maintenance treatment and were well tolerated. They concluded that, after careful risk-benefit analyses, depot antipsychotics may be considered for long-term control of mood episodes in bipolar patients who have failed to respond to standard therapies or relapsed due to medication nonadherence. They recommended avoiding depot FGAs in patients with a high burden of illness from depressive symptoms, particularly in those judged to be at high risk of suicide. They concluded that preliminary data on depot formulations of SGAs indicate that they are efficacious in maintenance treatment of bipolar illness without increasing the burden of the depressive pole of the illness, but that further systematic studies are needed. See Guideline 15 for recommendations on long-acting antipsychotics.

Simplifying medication regimen. The literature provides some support for simplifying medication regimens. Pfeiffer et al.[191] found that increases in dosing frequency may result in modest decreases in adherence in patients with schizophrenia who were on less stable dosing regimens, but they did not find significant differences in adherence in patients who were on stable regimens receiving once-daily or more than once-daily dosing, The literature hints at the notion that patient preference for a specific regimen (even for more frequent dosing), rather than number of medications or doses may be an important mediator.[158]

13C. MULTIFACETED INTERVENTIONS

Because adherence problems tend to be related to multiple factors, researchers often recommend multi-faceted interventions.

Schizophrenia

Based on a review of literature from 1980 to 2002, Perkins[98] suggested that management of schizophrenia could be greatly improved by considering factors leading to nonadherence and adopting a comprehensive strategy that included psychosocial interventions and optimum choice of medication. Dolder et al.[178] reviewed studies of 23 educational, behavioral, affective, or combination approaches to improve adherence in schizophrenia, 15 of which produced moderate improvements in adherence. The greatest improvement was seen with combination strategies. Reduced relapse, hospitalization, and psychopathology and improved social function, gains in medication knowledge, and improved insight into need for treatment were also found. Longer interventions and a good therapeutic alliance were important for successful outcomes. Based on the literature, Masand and Narasimhan[103] recommended the following strategies to improve adherence in schizophrenia: optimizing antipsychotic therapy, minimizing adverse events, encouraging participation in psychoeducational programs, treating substance abuse, involving family members, and fostering good therapeutic relationships. Valencia et al.[134] reported that a strategy that included psychosocial skills training, family therapy, and antipsychotic medication improved symptomatology and psychosocial and global functioning; reduced relapse, rehospitalization, and drop-out rates; and increased adherence compared with treatment as usual after 1 year in outpatients with chronic schizophrenia.

Bipolar Disorder

Reilly-Harrington and Sachs[192] reviewed psychosocial strategies that can improve adherence in patients with bipolar disorder, including CBT to modify dysfunctional thinking/behavior, treatment contracts to help patients develop plans to identify and cope with symptoms, daily mood charting to help patients identify and seek intervention when changes occur, and teaching patients to use weekly activity schedules to encourage them to participate in positive and avoid destructive activities. Depp et al.[60] reported that a 12-week manualized group intervention combining educational and motivational interventions, medication management skills, and symptom management training for older adults with bipolar disorder (medication adherence skills training [MAST-BD] was associated with high levels of satisfaction and improvement in medication adherence. management ability, depressive symptoms, and health-related quality of life. Miklowitz[193] reviewed studies of psychoeducation, systematic care, family therapy, interpersonal therapy, and CBT for bipolar disorder and found that effects of different interventions varied depending on patients' clinical condition at the time. Family therapy, interpersonal therapy, and systematic care were most effective in preventing recurrences after an acute episode. CBT and group psychoeducation were most effective while the patient was in remission. Individual psychoeducation and systematic care programs were more effective for manic than depressive symptoms, while family therapy, CBT, and interpersonal coping strategies were more effective for depressive than manic symptoms.

General Recommendations

Weiden[186] stressed the importance of using appropriate pharmacological options that are effective for individual patients and administered by the proper route in the context of a positive therapeutic relationship. He advised "Don't end your relationship with a patient in a power struggle over adherence; work toward helping the patient understand the importance of medication adherence as a part of recovery." Tacchi and Scott[7] highlighted the need to normalize adherence problems, noting that no one can expect to be 100% successful in trying to sustain a new behavior (e.g., trying to diet, lose weight, stop smoking, or exercise more) and that, in a similar way, there may be understandable setbacks when trying to stick with a medication regimen. They emphasized the importance of creating an atmosphere in which the patient can admit it if they have not been taking all of their medication as prescribed. Based on their comprehensive review of the literature, Julius et al.[157] recommended the following strategies for addressing adherence problems in patients with psychiatric illness: focus on strengthening the therapeutic alliance, devote time in treatment specifically to address medication adherence, assess patients' motivation to take prescribed medication, and identify and assess potential barriers to treatment adherence.

Guideline 14: Expert Recommendations for Addressing Specific Adherence Problems

In this guideline, we present the experts' first-line and high second-line recommendations for strategies targeted to specific types of adherence problems and comment on how these recommendations relate to available research findings. The experts' recommendations reflect the importance of individually tailoring medication regimens to improve adherence, as supported by the National Alliance on Mental Illness in a recent discussion of the results of the CATIE study.[194] In reviewing these guidelines, keep in mind that, in many cases, adherence problems are multiply determined so that a number of different factors may be involved and a variety of strategies may be needed. In the tables that follow, interventions of choice (rated a 9 by more than 50% of the experts) are in bold italics and first-line options are in bold (note that in some cases, no interventions received first-line ratings, probably reflecting limited data concerning their effectiveness).

14A. PATIENT-RELATED FACTORS

Insight and attitudes

The support for CBT to address lack of insight reflects findings from controlled trials showing that CBT significantly improves insight into the need for treatment,[195] and that even a brief CBT intervention provided by community psychiatric nurses can significantly improve symptomatology and insight.[196] Although there is less compelling evidence for bipolar disorders, a similar model may be beneficial, especially because insight or lack of illness awareness can fluctuate across phases of bipolar illness and the risk of nonadherence may be greater at times when the patient is most acutely and severely unwell.

Problem	***Psychosocial/programmatic***	***Pharmacological***
Lack of insight	Medication monitoring/environmental supports Patient psychoeducation More frequent/longer visits if possible CBT Family-focused therapy	Switch to a long-acting antipsychotic
Concern about stigma	Patient psychoeducation CBT Family-focused therapy	No change in medication; intensify psychosocial interventions

Comorbidity and symptom severity (lack of efficacy)

The experts stressed the importance of targeting comorbid substance use and optimizing medication treatment to address persistent symptoms. A recent double-blind randomized study of adherence in 400 patients with a first-episode of schizophrenia treated with olanzapine, quetiapine, or risperidone highlighted the importance of treatment response in predicting discontinuation against medical advice and poor adherence to medication.[109] The researchers in this study also concluded that interventions targeting substance use disorders and depressive symptoms have the potential to improve adherence problems.

Problem	***Psychosocial/programmatic***	***Pharmacological***
Substance use	Patient psychoeducation Involuntary outpatient commitment Medication monitoring/environmental supports Integrated dual diagnosis treatment program*	Switch to a long-acting antipsychotic No change in medication; intensify psychosocial interventions
Persistent symptoms	**Symptom and side effect monitoring** Medication monitoring/environmental supports More frequent and/or longer visits if possible CBT	Increase dose of current antipsychotic Switch to a long-acting antipsychotic or a different oral antipsychotic

**Recommendation from earlier expert consensus guidelines that asked specifically about programmatic interventions.*[18]

Environmental factors

The experts endorsed social work and medication monitoring/environmental supports to address environmental factors. Patients with schizophrenia receiving an intervention in which a research nurse worked with them to identify and develop patient-specific strategies to overcome barriers to medication adherence were almost twice as likely to be adherent as those who received basic care without this intervention.[183] These recommendations are consistent with previous expert consensus guidelines on schizophrenia and bipolar disorder.[18,27] The 1999 *Expert Consensus Guidelines on the Treatment of Schizophrenia* recommended programmatic interventions (e.g., ACT, partial hospitalization, rehabilitation services), especially for severely impaired and unstable patients.[18]

Problem	*Psychosocial/programmatic*	*Pharmacological*
Logistic problems	***Social work targeting logistic problems***	
	Medication monitoring/environmental supports	Simplify medication regimen
		Switch to a long-acting antipsychotic
Lack of routines	**Medication monitoring/environmental supports**	No change in medication; intensify psychosocial interventions
	Social work targeting logistic problems	
	Interpersonal and social rhythm therapy	

Cognitive impairment

The experts considered medication monitoring/environmental supports the first-line choice for addressing cognitive deficits. A cognitive adaptation intervention (see p. 31) focused on medication adherence has been found to improve adherence, reduce relapse rates, and increase survival time to relapse or exacerbation of symptoms.[117] Clinicians should note that environmental supports are not likely to be used unless they are customized for the individual patient and set up in the home environment.[197]

Problem	*Psychosocial/programmatic*	*Pharmacological*
Cognitive deficits	**Medication monitoring/environmental supports**	Simplify medication regimen
	Social work targeting logistic problems	
	Symptom and side effect monitoring	

Medication-related factors

Clinicians need to distinguish side effects that may be addressed through simple self-management strategies (e.g., dry mouth) or are amenable to dose adjustments. adjunctive medications, or life style changes from those that may require a medication change.[30]

Problem	*Psychosocial/programmatic*	*Pharmacological*
Persistent side effects	**Symptom and side effect monitoring**	**Decrease dose of current antipsychotic**
		Switch to a different oral antipsychotic

14B. RELATIONSHIP FACTORS

The experts stressed the importance of improving the therapeutic alliance and involving family members. Research supports the importance of a partnership between patient and clinician and shared decision making when treating patients with antipsychotic medications in order to improve outcomes and increase patient satisfaction and willingness to adhere to treatment.[7,198–200]

Problem	*Psychosocial/programmatic*	*Pharmacological*
Poor therapeutic alliance	More frequent and/or longer visits if possible	No change in medication; intensify psychosocial interventions
	Patient psychoeducation	
	Compliance therapy	
	Medication monitoring/environmental supports	
Lack of family and social support	Family-focused therapy	No change in medication; intensify psychosocial interventions
	Social work targeting logistic problems	Switch to a long-acting antipsychotic
	Medication monitoring/environmental supports	Simplify medication regimen

14C. FACTORS RELATED TO THE SERVICE DELIVERY SYSTEM

We did not ask about service delivery problems in the survey. However, the editors suggest that the following strategies can be helpful in identifying and addressing service delivery problems in clinical treatment settings:

- Ensure that telephone calls from patients/family members receive a timely response and requested information is provided.
- Ensure that patients can schedule appointments in a timely manner, especially if experiencing a new onset of problems.
- If a patient has a crisis when it is not possible to schedule an immediate appointment, refer for emergency care and follow-up.
- Ensure that staff communicate and document information received during phone calls from patients.
- Regularly ask patients (and family members if appropriate) if they are satisfied with the access they have to the treatment team.
- Regularly ask patients (and family members if appropriate) if they need more information about the illness and their treatment.
- Ask patients (and family members if appropriate) if they need additional support or community assistance. If so, refer to social services agencies and advocacy groups (e.g., National Alliance on Mental Illness, Depression and Bipolar Support Alliance).
- Ask about paying for medication and, if needed, refer patients to compassionate programs at pharmaceutical companies.
- Ask about paying for care and, if needed, refer patients to social services (e.g., for Medicaid, Social Security Disability).

14.D APPLYING RECOMMENDATIONS IN REAL-WORLD TREATMENT SETTINGS: CASE VIGNETTES

We presented two cases to the experts and asked about primary contributors to the problems and strategies to address them.

Patient 1. *Mr. A, a 38-year-old unmarried Hispanic male with a 20-year history of bipolar disorder with psychotic features, began hearing voices while at university. He was able to graduate but has never worked or supported himself financially. His parents pay his rent and give him an allowance, which Mr. A uses to travel. Mr. A comes to the mental health clinic because his parents told him they would not continue to support him unless he seeks treatment. Mr. A's speech is pressured and tangential, he makes inappropriate sexual comments to the doctor, and he appears distracted and excited. He refuses medication and says that years ago his mother put olanzapine in his coffee and that is what caused him to hear voices. At present, he hears voices continuously. The voices of famous people such as Duke Ellington and Benjamin Franklin do not bother him and he enjoys his scholarly interactions with them. However, he hears the voice of his father continually criticizing him. He reports that he cannot handle the continual badgering and wants it to stop immediately. Mr. A attacked members of his family in the past because the voices told him these family members wanted to have sex with him. He is loud and speaks in a threatening manner about his family, but he does not meet criteria for involuntary hospitalization in this state. The clinician is not sure how to help this patient accept medication treatment.*

The experts identified **poor insight into the illness and need for medication** as the primary problem, followed by **problems with the therapeutic alliance**. They endorsed the following interventions for Mr. A (none rated first line): family-focused therapy, patient psychoeducation, more frequent and/or longer visits, compliance therapy, involuntary outpatient commitment (if the patient comes to meet criteria), symptom and side effect monitoring, and medication monitoring and environmental supports.

Patient 2. *Ms. B, a 42-year-old unmarried Caucasian women with a 20-year history of schizoaffective disorder, comes in for an unscheduled visit due to increasing symptoms. She attends about half of her scheduled appointments, but often arrives very late or very early. When she misses appointments, she comes into the clinic on a walk-in basis. Ms. B reports excellent adherence to her medications, but continues to hear voices and is so frightened by her neighbors that she refuses to leave her apartment. In addition, she complains of depression and loneliness. She is tearful during the interview. Ms. B guesses the day as Tuesday, but it is Friday. She does not wear a watch or have a cell phone. The patient's social worker reports that the apartment where Ms. B lives alone is in extreme disarray, so that she often cannot find her appointment cards and frequently searches for items she has misplaced.*

The experts identified **cognitive deficits** and **a lack of routines that make it hard to take medication accurately** and **lack of social support** as the primary problems in this case. They also believed that inadequate efficacy of the current medication leading to persistent symptoms and logistic problems were contributors. Thus this case involved both environmental barriers and symptomatic problems. The experts recommended first helping the patient compensate for her cognitive deficits and providing social support to overcome practical logistic problems, endorsing medication monitoring/environmental supports and social work targeting logistic problems as first-line strategies. They endorsed more frequent and/or longer visits and symptom and side effect monitoring as high second-line strategies, which would be helpful in addressing Ms. A's persistent symptoms.

14E. AVAILABILITY OF TREATMENT RESOURCES

The guidelines thus far recommend interventions without regard to their availability in real-world settings. We therefore asked the experts what interventions were available (as of 2008) to the patients they treat. The responses of the 41 experts have important implications for healthcare policy and funding and for the training of providers. It is clear that many interventions that were endorsed as extremely helpful in improving adherence and treatment outcomes are not adequately available to practicing clinicians.

	n		*n*
Long-acting injectable first generation antipsychotics	37	Cognitive-behavioral therapy targeted for schizophrenia	18
Long-acting risperidone injections	35	Involuntary outpatient commitment	18
Assertive community treatment	29	Family-focused therapy	13
Family psychoeducation (e.g., NAMI Family-to-Family)	29	Compliance therapy	6
Intensive case management involving home visits	27	Interpersonal and social rhythm therapy	6
Cognitive-behavioral therapy targeted for bipolar disorder	22		

14F. IS IT APPROPRIATE TO PRESCRIBE OTHER MEDICATIONS FOR PATIENTS WHO REFUSE PRIMARY MEDICATION?

Patients sometimes refuse to take the primary medication recommended for their condition, but will request or accept other medications or treatments. We asked the experts about the appropriateness of prescribing different treatments for a patient who is cooperative about coming in for regular appointments and is not showing acute psychotic or manic symptoms. Their recommendations are presented in the table below. They would consider (although there was no consensus) using lorazepam for insomnia or anxiety. The only difference in the recommendations for the two conditions is that the experts would consider monotherapy with a selective serotonin reuptake inhibitor (SSRI) for depressive symptoms in a patient with schizophrenia (although again there was no consensus) but not for a patient with bipolar disorder. As reflected in the experts' ratings presented in the table, consensus and evidence-based guidelines all agree that patients with bipolar disorder should never receive antidepressants as monotherapy because of concerns about triggering a switch to mania/hypomania.[27,201] Although stimulants are sometimes used as adjunctive agents in the treatment of patients with bipolar disorder,[202,203] there are few data regarding the use of these medications in bipolar disorder, likely due in part to concerns regarding potential stimulant-induced switching and stimulant abuse.[202] As shown in the table, the experts would avoid monotherapy with stimulant medications in patients with schizophrenia and bipolar disorder, probably because these medications can trigger psychosis and might also trigger a switch to mania/hypomania in bipolar disorder, as well as concern about the potential for substance abuse with these agents.

Interventions for a patient who refuses maintenance antipsychotic treatment in schizophrenia or mood stabilizer treatment in bipolar disorder

Recommended	*Possibly consider (second line, no consensus)*	*Avoid (third line—not recommended)*
Ongoing psychotherapy	Lorazepam	Anticonvulsant not approved for use in bipolar disorder
	SSRI (depressive symptoms in schizophrenia *only*)	Natural/vitamin treatment
		SSRI (bipolar disorder)*
		Modafanil
		Stimulant (methylphenidate, amphetamine)*

**Monotherapy with antidepressants is contraindicated in patients with bipolar disorder because of concern about triggering a switch to mania/hypomania. Monotherapy with stimulants is not recommended in patients with bipolar disorder because of concern about triggering psychosis or a switch to mania/hypomania and the potential for substance abuse.*

Guideline 15: Use of Long-Acting Injectable Antipsychotics

Potential benefits

We asked the experts to rate the importance of a number of potential benefits of long-acting antipsychotics that have been discussed in the literature. In this question, we asked them to consider all the currently available long-acting agents, including haloperidol decanoate, fluphenazine decanoate, and long-acting injectable risperidone.

First line	*High second line*
Immediate recognition of nonadherence by the treatment team	Regular contact between patient and treatment team
Knowing when relapse has occurred despite adequate pharmacotherapy	Peace of mind for family members
Reduced risk of relapse	More consistent plasma levels than short-acting formulation
Convenience for the patient (not having to take a pill every day)	Better efficacy in long-term treatment than short-acting
Some continuing medication coverage after a missed dose	

Availability in Formulary for Different Indications

Of the 23 experts who indicated that they deal with a formulary in their practices, nearly all indicated that haloperidol decanoate and fluphenazine decanoate were available for the treatment of schizophrenia (100%), schizoaffective disorder (100%), and bipolar disorder (96%). The percentages who indicated that long-acting injectable risperidone was available in their formularies were slightly lower: schizophrenia 91%, schizoaffective disorder 83%, and bipolar disorder 65%.

Current Level of Use: Percentage of Patients Prescribed Long-Acting Antipsychotics

Only one long-acting injectable SGA (risperidone) is available in the United States, although long-acting formulations of other SGAs are in development. Studies have found lower rates of use of long-acting antipsychotics in the United States than in other countries, which did not change as was anticipated when the first long-acting SGA became available.This table shows the percentage of patients being treated with long-acting antipsychotics at the experts' practice sites.

	Long-acting first generation depot medications						**Long-acting injectable risperidone**					
Percentage of patients	**Bipolar disorder**		**Schizoaffective disorder**		**Schizophrenia**		**Bipolar disorder**		**Schizoaffective disorder**		**Schizophrenia**	
	n*	***%***	***n****	***%***	***n****	***%***	***n****	***%***	***n****	***%***	***n****	***%***
< 10%	33	94%	27	77%	23	66%	34	94%	28	82%	26	74%
10%–20%	1	3%	7	20%	10	29%	1	3%	6	18%	8	23%
> 20%	1	3%	1	3%	2	6%	1	3%	0	0%	1	3%

**n = number of experts responding*

Barriers to Use

Given the low rates of use found in the preceding question, we asked the experts about potential barriers to use of long-acting injectable risperidone. They did not rate any factor we asked about as a significant barrier to use of this formulation, although they indicated that the following issues sometimes interfere with their willingness to prescribe it:

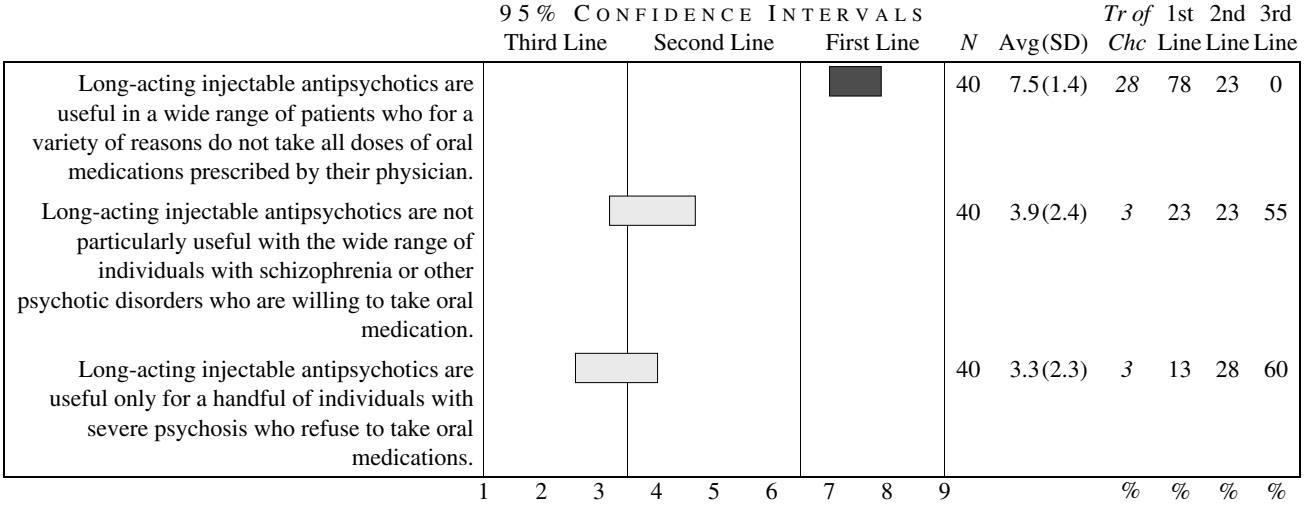
- Negative attitudes towards injections by patients
- Inability to stop medication immediately should side effects become a problem
- Frequency of injections (e.g., every 2 weeks)
- Problems with reimbursement for medication or injection visits.

Interestingly, the experts did not endorse factors such as lack of availability of nursing staff to give injections, stigma associated with injections or depot clinics, the assumption that patients will refuse injections, or negative perceptions of injectable antipsychotics, as barriers to their willingness to use this agent. However, these factors have been reported in the literature as barriers to use of the whole class of long-acting injectables. Unfortunately, we only asked the experts about their own prescribing practices rather than how much they believed these factors limit the use of these agents in routine clinical practice.

Role of Long-Acting Antipsychotics

We asked the experts to evaluate three statements concerning use of long-acting injectable antipsychotics. Their responses indicate that they feel these agents can play a role in a wider variety of situations than those in which they are generally currently used.

22 We are interested in how strongly you agree or disagree with a number of statements concerning the use of long-acting injectable antipsychotics. Please give a rating of 7–9 to those statements with which you strongly agree, a rating of 4–6 to those statements with which you somewhat agree, and a rating of 1–3 to those statements with which you strongly disagree.



Reasons for Using Long-Acting Antipsychotics

We then asked the experts about the appropriateness of switching a patient from an oral to a long-acting injectable antipsychotic in different situations. Their recommendations are shown in the table below. The experts endorsed using these agents in a broad range of situations, even though these agents are not currently often used in these situations. Guidelines for depot antipsychotic treatment published in 1998 indicated that depot antipsychotics should be considered for any patient with schizophrenia for whom long-term antipsychotic treatment is needed.[187] Expert consensus guidelines on antipsychotic treatment published in 2003 also endorsed the use of long-acting agents in a wide variety of situations.[25] This leads to the conclusion that long-acting injectable antipsychotics should be available to a broad range of patients and raises the question of why their use is currently so limited. Long-acting injectable risperidone was recently approved by the U.S. Food and Drug Administration for use, adjunctively and as monotherapy, in the maintenance treatment of bipolar disorder; this may change clinical practice patterns towards a more frequent use of long-acting risperidone in populations with bipolar illness.

Reasons of choice	*First line*	*High second line*
Patient expresses preference for long-acting antipsychotic	Patient has done well with depot antipsychotic in the past	Persistent lack of insight/denial of illness
Patient prescribed oral antipsychotic who is experiencing relapse because he or she stopped taking medication	Involuntary outpatient commitment	History of or potential for aggressive or violent behavior
Evidence that relapses are frequently associated with nonadherence but that patient functions well when taking medication as prescribed (patient is responsive to medication but not always adherent)	Chronically relapsing patient prescribed oral antipsychotic	Homelessness
		Patient prescribed oral antipsychotic who is experiencing relapse for reasons that are unclear
		Lack of social supports
		Comorbid substance abuse problems
		History of or potential for suicidal behavior
		Patient being seen by a visiting nurse for home visits
		Patient experiencing persistent symptoms despite treatment with oral antipsychotic

Guideline 16: Working with Families

Clinicians frequently face dilemmas in knowing how to advise family members of patients with serious mental illness. The table below presents the experts' recommendations for what they would do (and not do) if a family member calls asking for advice about a patient's lack of adherence to medication (e.g., asks about putting medication in the patient's food without his or her knowledge).

Recommended (high second line)	*Possibly consider (second line, no consensus)*	*Not recommended (third line)*
Ask the patient if you could invite family members to the next appointment or visit them at home to see how everyone is coping (without reporting the call). Advise family against putting medication in the food and tell them it is not a good idea to medicate someone without their knowledge. Use what the family has told you to construct questions that are likely to elicit the same information from the patient. Refer the parents to the National Alliance on Mental Illness for advice.	Review criteria and process for involuntary outpatient or inpatient treatment with the family. Refuse to talk with family because of confidentiality and HIPAA regulations unless the patient gives permission.	Suggest that the parents inform the patient that he or she must take medication regularly to live in their house. Suggest that the parents set strong limits on the patient's behavior, warning that this may provoke the patient to violence but may also increase the likelihood that he or she will meet criteria for involuntary hospitalization. Tell the parents they should do whatever they feel is necessary to be safe in their home, including putting medication in the patient's food.

Guideline 17: Outpatient Commitment and Involuntary Hospitalization

Of the 41 experts, 17 (42%) indicated that patients in their treatment setting had received outpatient commitment. In keeping with the findings reviewed by Kisely et al.,[170] there was no consensus among the experts as to the effectiveness of this intervention, with 55% giving involuntary commitment first-line ratings and 15% giving it third-line ratings for effectiveness. They noted a number of problems with the implementation of involuntary commitment, including:

- Inconsistent criteria for implementation
- Unwillingness of court systems (and law enforcement) to hold hearings, enforce requirements, and follow through
- Difficult to obtain due to paperwork and lack of integration of systems
- May be perceived as coercive by patients and have a negative effect on the therapeutic alliance
- Only temporarily effective
- Very inconsistent quality of care after court decision.

Guideline 18: Recommendations for Improving Clinician Training

Both the research findings and expert responses reviewed in this publication indicate that clinicians have difficulties accurately assessing and effectively intervening for adherence problems in patients with serious mental illness. Weiden and Rao[204] noted that training in the understanding and management of adherence problems does not neatly fall within the domain of psychopharmacology or other core curricula areas, such as clinical interviewing or psychotherapy training. They also noted that the American Board of Psychiatry and Neurology (ABPN) core curriculum does not mention medication compliance/adherence as a specific training goal and that many residency programs do not include a course focusing on this topic. They therefore developed and pilot tested a curriculum that addresses the following five core components:

- Definition of adherence and nonadherence
- Understanding how adherence depends on efficacy
- Assessment of adherence and nonadherence
- Importance of the therapeutic alliance
- Pharmacological and psychosocial strategies to improve adherence.

The authors reported that the course was very well received.[204]

Scott and Tacchi[205] undertook a series of national 1-day workshops around the United Kingdom and trained over 150 staff in key issues in understanding, identifying, and managing adherence problems. Using self-rated questionnaires, they found that staff attitudes, knowledge, and skills improved after the intervention and that, at 3-month follow-up, the majority of workshop attendees continued to use most of the key techniques they had practiced.[205] The editors of these guidelines encourage residency and other training programs to give serious consideration to incorporating elements such as these in their curricula.

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