# Prevalence of and Risk Factors for Medication Nonadherence in Patients With Schizophrenia: A Comprehensive Review of Recent Literature

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***Objective:*** Nonadherence to prescribed antipsychotic medications places patients with schizophrenia at a greatly increased risk of illness exacerbation and rehospitalization. Identification of risk factors for nonadherence is an initial step toward designing effective interventions. This article reviews recent literature on the prevalence of and risk factors for medication nonadherence in patients with schizophrenia.

***Data Sources:*** We searched the MEDLINE/HealthSTAR and PsycINFO databases using combinations of the keywords *risk factor(s)*, *adherence*, *compliance*, *antipsychotic*, *neuroleptic*, *schizophrenia*, and *psychosis* for articles published since 1980 that identified risk factors for medication nonadherence in schizophrenia patients. We included reports that (1) were published in English and (2) specifically examined risk factors for medication nonadherence. Thirty-nine articles met our selection criteria.

***Data Synthesis:*** Among the 10 reports that met a strict set of study inclusion criteria, we found a mean rate of nonadherence of 41.2%; the 5 reports that met a stricter set of inclusion criteria had a mean nonadherence rate of 49.5%. In the 39 articles reviewed, factors most consistently associated with nonadherence included poor insight, negative attitude or subjective response toward medication, previous nonadherence, substance abuse, shorter illness duration, inadequate discharge planning or aftercare environment, and poorer therapeutic alliance. Findings regarding an association between adherence and medication type were inconclusive, although few studies explored this relationship. Other factors such as age, gender, ethnicity, marital status, education level, neurocognitive impairment, severity of psychotic symptoms, severity of medication side effects, higher antipsychotic dose, presence of mood symptoms, route of medication administration, and family involvement were not found to be consistent predictors of nonadherence. Limitations of the published literature are discussed.

***Conclusion:*** Efforts to improve medication adherence in patients with schizophrenia should target relevant risk factors.

*(J Clin Psychiatry 2002;63:892–909)*

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*Supported in part by grants MH56938 (Dr. Lacro), MH43693 (Dr. Jeste), MH49671 (Dr. Jeste), MH59101 (Dr. Jeste), and MH19934 (Dr. Jeste) from the National Institute of Mental Health, Rockville, Md., and by the Department of Veterans Affairs, San Diego, Calif.*

*In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows: Drs. Dunn, Dolder, and Leckband have no significant commercial relationships to disclose relative to the presentation; Dr. Lacro is a consultant for and has received grant/research support and honoraria from AstraZeneca, Bristol-Myers, Lilly, Janssen, and Pfizer; Dr. Jeste is a consultant for and has received grant/research support and honoraria from AstraZeneca, Bristol-Myers, Lilly, Janssen, Pfizer, and Roche.*

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Nonadherence to prescribed treatment regimens jeopardizes the outcome of treatment for every medical and psychiatric condition and has been called "America's other drug problem."[1] A recent report from the National Institute of Mental Health emphasized the high prevalence of nonadherence in psychiatric populations, recommending further inquiry into all aspects of this problem.[2] Key tasks on this research agenda include clarifying patient characteristics associated with nonadherence, analyzing the clinician/patient alliance and its impact on adherence, developing and validating measures of adherence, and designing and evaluating interventions to change adherence behavior.[2]

In patients with schizophrenia, deviation from maintenance antipsychotic therapy places patients at risk for exacerbation of psychosis, increased clinic and emergency room visits, and rehospitalization.[3–6] Nonadherence to prescribed regimens can also compromise patients' daily functioning and quality of life. Fenton et al.[6] reported a median nonadherence rate of 55% in 15 investigations of patients on treatment with oral or depot antipsychotics. Other reviews of the literature have reported rates of nonadherence to antipsychotic medications ranging from 20% to 89%.[7]

These widely varying rates are explained, in part, by differences in research methods, including adherence measurement (e.g., qualitative vs. quantitative, self-report vs. informant-report, direct vs. indirect measurement), observation period (e.g., 1 week vs. several months), and criteria for nonadherence (e.g., any deviation from medication regimen vs. an acceptable range). Some investigators have categorized subjects dichotomously (adherent vs. nonadherent) on the basis of statistical measures such as the median or mean amounts of medication taken or measured.[8] Other authors have used past levels of medication-taking to categorize patients as adherent or nonadherent[8–10]; still others have relied on their own clinical impressions.[8]

Reliable measurement is a prerequisite for addressing nonadherence. Just as medical conditions wax and wane, patients' degrees of adherence may fluctuate over time. The ideal detection method would thus measure adherence at the time and place of the medication-taking event and would therefore possess perfect sensitivity and specificity. Obviously, no such method exists. Although direct measurements (e.g., blood or urine medication levels) are less subject to bias than indirect ones (e.g., self-reports, chart reviews, pill counts, or refill rates), practically every method has specific limitations.[11]

Identifying risk factors for nonadherence is a logical step toward improving treatment of this vast problem. Many variables that may predispose patients to nonadherence have been evaluated.[11,12] At this time, however, consensus is lacking regarding which risk factors are most strongly associated with poor adherence, especially in patients with chronic psychotic disorders. The health belief model provides a useful perspective for understanding how patients' beliefs and attitudes can affect adherence. In this schema, a patient's decision to be nonadherent stems from an implicit, subjective assessment of the relative costs and benefits of treatment.[13–16] When the perceived costs outweigh the perceived benefits, nonadherence becomes more likely. Thus, risk factors for nonadherence may include attitudes, beliefs, and degree of insight, in addition to factors such as effectiveness or side effects of medications. Identifying the full range of risk factors for nonadherence in patients with chronic psychotic disorders would enable clinicians and researchers to design and implement more specific interventions.

To assess the prevalence of nonadherence and identify risk factors consistently associated with it, we surveyed the literature on medication nonadherence in patients with schizophrenia. Our review differs from previous ones in that we calculated 3 mean rates of nonadherence—an all-inclusive rate and 2 additional rates: one using strict study selection criteria and the second based on even stricter criteria. Additionally, we provide a comprehensive table summarizing individual studies of risk factors for nonadherence (Table 1). For each risk factor, we provide a comprehensive listing of the instruments used to assess risk and identify those studies that did versus those that did not find an association with medication nonadherence (Table 2). Finally, we provide a list of factors that were more often than not associated with nonadherence in multiple studies; each study is weighted equally (Table 2). We also identify areas requiring additional research because of lack of or inconclusive data.

## DATA SOURCES

Studies published since 1980 that reported on medication nonadherence in patients with schizophrenia were identified using MEDLINE/HealthSTAR and PsycINFO databases using combinations of the keywords *risk factor(s)*, *adherence*, *compliance*, *antipsychotic*, *neuroleptic*, *schizophrenia*, and *psychosis*. We included reports that (1) were published in English and (2) specifically examined risk factors for medication nonadherence. References from the identified articles and citations from recent reviews[6,7] were examined for additional studies. Reports with fewer than 40 subjects were excluded.

At least 3 reviewers read each report. For each study, we noted the design, the subject characteristics, the assessments used to evaluate both risk factors and medication nonadherence, the rate of nonadherence recorded, and whether specific risk factors were found to be associated with nonadherence. As suggested by others,[6] risk factors were categorized as (1) patient-related, (2) medication-related, or (3) environment-related. We included a variable as a potential risk factor for nonadherence if 2 or more studies in our review examined the relationship between the variable and adherence. A variable was labeled as a risk factor if a majority (greater than 50%) of the studies reported an association between the variable and nonadherence.

## DATA SYNTHESIS

Thirty-nine articles met the inclusion criteria (Table 1). These investigations included a wide variety of patient populations, study designs, measures of adherence, and risk factors assessed, thus precluding us from performing a meaningful meta-analysis.

### Study Populations

For each article, the number of patients studied ranged from 40 to 423 (mean ± SD = 110 ± 80, median = 80). Thirty-four of the 39 studies reported the subjects' mean age (mean ± SD = 39 ± 6 years; median = 37 years; range, 31–63 years). Of these 34 reports, 25 included patients with a mean age between 31 and 39 years. In a majority of the articles, a greater number of men than women were studied. Of 16 articles reporting ethnicity of participants, approximately half included fewer than 50% minority sub-

jects, with the remainder including over 50% of subjects from ethnic minority groups. Eleven of 24 articles that provided subjects' educational level stated that the majority of participants had at least a high school education.

Twenty-four articles included primarily outpatients, while 15 involved inpatients only or a combination of inpatients and outpatients. Participants were generally chronically ill patients with schizophrenia or schizoaffective disorder. Mean duration of illness, provided in 8 articles, ranged from 9.6 to 23.9 years. In 6 studies, subjects were attending depot neuroleptic clinics. Only 7 of the investigations mentioned the use of atypical antipsychotics (generally by a minority of patients)[17–23]; most, however, were published prior to the widespread use of these medications.

### Study Designs

Designs were retrospective (N = 10), cross-sectional (N = 15), or prospective or longitudinal (N = 14). In the prospective investigations, length of follow-up varied from a few weeks to 2 years.

### Adherence Measures

A considerable heterogeneity of methods was used to evaluate adherence in these studies. Nine reports limited the adherence assessment to a dichotomous rating (adherent or nonadherent). Others used Likert-type scales. For example, several articles classified patients into 1 of 4 categories: "active compliance" ("patient comes readily for medication at the scheduled times"), "passive compliance" ("patient must be sought out for medication, but does not resist when told to take medication"), "resistance" ("patient 'cheeks' medication but takes medications when they are repeatedly offered"), and "overt refusal" ("medications can only be given against patient's wishes or are not given").[21,24,25]

Criteria and cutoff levels of adherence also varied, making it difficult to find any consistent pattern. In one examination, for example, patients who took their medications as prescribed at least 80% of the time were considered adherent.[26] In another article, patients who reported having stopped their medication for 1 week or longer after hospital discharge were deemed nonadherent.[23] Furthermore, patients in some investigations rated their own adherence or answered interview questions about their behavior. In other studies, clinicians, nurses, case managers, or family members rated patients' adherence. A few analyses (particularly those involving patients taking depot medications) provided a more objective measure, specifically the proportion of scheduled depot injection appointments kept by each subject.

### Risk Factor Measurement

Numerous measurement tools and rating scales were used. For example, level of insight, evaluated in 14 articles, was assessed by several authors[27,28] with the Scale to Assess Unawareness of Mental Disorder[24]; others employed the Schedule for Assessment of Insight,[22,29,30] the Awareness of Illness Interview,[31] insight self-report scales,[23,32] or a variety of other interview methods.[10,23,25,33–36,49] Instruments such as the Brief Psychiatric Rating Scale,[31,32,37–39] the Behavioral and Symptom Identification Scale,[21,40] the Global Assessment Scale,[17,19,23,32,41] the Scale for the Assessment of Positive Symptoms,[28,42,43] the Scale for the Assessment of Negative Symptoms,[28,42,43] the Positive and Negative Syndrome Scale for schizophrenia,[20,44] and the Schedule for Affective Disorders and Schizophrenia were used to rate psychopathology.[26,45,46] Neurocognitive status was evaluated with the Neurobehavioral Cognitive Status Examination,[29,31,47,48] the Mini-Mental State Examination,[50,51] and a neurocognitive battery.[28]

Attitudes toward medications were examined with a variety of measures, including the Drug Attitude Inventory,[17,22,27,52] structured assessments, and interviews.[19,24,33,35,36,53,54] Questionnaires or interviews regarding health beliefs were utilized in several articles.[10,14,25,34,55] Assessments of subjective response to medications were often included in these measures or were evaluated separately.[56,57] Surprisingly, only a few investigations reported using rating scales to evaluate medication side effects.[20,55]

### Study Results

***Rates of nonadherence.*** Reported rates of nonadherence ranged from 4% in a study of depot neuroleptic adherence[58] to 72% in an inpatient exploration that used a dichotomous adherence rating.[59] Most, but not all, of the 39 reports provided a nonadherence rate. The unweighted mean ± SD nonadherence rate for all studies reporting a nonadherence rate was 40.5% ± 18.5% (median = 40%). Some studies[9,10,55] intentionally selected an equal portion of adherent versus nonadherent patients and therefore were not used in our overall nonadherence calculation. Because of the high degree of variability in adherence measures and definitions, we calculated 2 additional mean rates for articles that met either of 2 sets of study inclusion criteria, the first using a strict set of criteria and the second employing stricter criteria. These criteria were selected to minimize underestimation of nonadherence and decrease the variability in nonadherence rates resulting from various definitions of adherence. In addition, these 2 rates of nonadherence were established to serve as a method that could be consistently applied to future investigations of medication adherence. Previous estimates of nonadherence, such as the rate reported by Young and colleagues,[7] defined nonadherence as any significant deviation from the prescribed medication regimen. Such an inclusive definition makes it difficult to extrapolate the clinical relevance of the nonadherence rate

**Table 1. Studies Evaluating Risk Factors for Treatment Nonadherence in Patients With Schizophrenia[a]**

| Authors | Study Type | Subjects | Other Characteristics | Risk Factor Measures |
|---|---|---|---|---|
| 1. Van Putten et al, 1981[56] | Prospective | N = 63 | Inpatients | Subjective response to medication (thiothixene) based on 4 questions about reaction, assessed at 4 and 24 h after test dose |
| 2. Hogan et al, 1983[52] | Cross-sectional | N = 150<br>Age = 41<br>M = 62% | Outpatients | Self-report scale of experiences related to medication |
| 3. Caton et al, 1984[71] | Prospective | N = 119<br>Age = 34<br>61% African American<br>20% Hispanic | Inpatients and outpatients | Chart review, interviews of patient and hospital staff regarding hospitalization, level of psychopathology, adequacy of discharge planning |
| 4. Van Putten et al, 1984[57] | Prospective | N = 105<br>Age = 32<br>M = 91% | Inpatients | Subjective response to medication (thiothixene or haloperidol) based on 4 questions about reaction, assessed shortly after test dose and weekly for next 4 wk |
| 5. Gaebel and Pietzcker, 1985[61] | Prospective, case series | N = 72<br>Age = 34<br>M = 53% | Outpatients | Assessed at baseline and 1 y |
| 6. Zito et al, 1985[9] | Retrospective | N = 60<br>Age = 34<br>M = 63% | Inpatients<br>60% high school graduates | Review of nursing summaries, psychiatrists' notes, order sheets over 1-mo period |
| 7. Kelly et al, 1987[14] | Cross-sectional | N = 107<br>Age = 42<br>M = 93%<br>56% White<br>44% African American | Outpatients<br>69% high school graduate or greater | Structured interview assessing components of Health Belief Model: severity, susceptibility, benefits, barriers, and cues to action |
| 8. Bartko et al, 1988[32] | Longitudinal | N = 58<br>Age = 42<br>M = 33%<br>D = 10 | Outpatients<br>Taking depot antipsychotic | Brief Psychiatric Rating Scale (BPRS), Global Assessment Scale (GAS), Clinical Self-Rating Scale (self-report) |
| 9. Drake et al, 1989[79] | Prospective | N = 115<br>Age = 38<br>M = 59% | Outpatients<br>66% high school graduates | Clinician ratings of alcohol and substance use |
| 10. McEvoy et al, 1989[25] | Case series | N = 52<br>Age = 34<br>M = 54% | Inpatients and outpatients<br>54% voluntarily admitted | Insight and Treatment Attitudes Questionnaire (ITAQ), interview scored 0 to 10 for degree of insight |
| 11. McEvoy et al, 1989[34] | Retrospective classification of information from case series (follow-up of McEvoy, 1989[25]) | N = 46<br>Age = 34<br>M = 54% | Outpatients | ITAQ, interview scored 0 to 10 for degree of insight, also rated aftercare environment at $2^1/_2$- to $3^1/_2$-y follow-up (facilitative, neutral, or problematic) |
| 12. Pan and Tantam, 1989[55] | Cross-sectional (regular vs irregular attenders at depot clinic) | N = 80<br>Age = 38<br>M = 73% | Outpatients<br>Taking depot antipsychotic | Interviewed regarding opinion about medications, health belief questionnaire, psychopathology scale, Abnormal Involuntary Movement Scale |
| 13. Frank and Gunderson, 1990[60] | Prospective 2-y study | N = 143 | Outpatients | Alliance assessed by psychotherapist |
| 14. Pristach and Smith, 1990[59] | Retrospective | N = 42<br>Age = 35<br>M = 67%<br>50% White<br>40% African American | Inpatients<br>77% high school or more education | Self-Administered Alcoholism Screening Test |
| 15. Drake et al, 1991[72] | Prospective 1-y study | N = 75<br>Age = 44<br>M = 48%<br>100% White | NR | Housing stability in previous 6 mo on 5-point scale |

| Adherence Measures | Adherence | Patient-Related Risk Factors for Nonadherence | Medication- and Environment-Related Risk Factors for Nonadherence |
|---|---|---|---|
| Dichotomous rating, based on immediate and eventual drug refusal | 30% nonadherent | Dysphoric initial response to medication | NR |
| Clinician rating of adherence based on prior year<br>Nonadherent if habitual to occasional refuser of medications | 54% nonadherent | More negative subjective response to medication<br>No association: knowledge or beliefs about medication | NR |
| Rated at 3 mo as "very compliant," "moderately compliant," or "noncompliant" | 47% nonadherent | NR | Inadequate discharge planning (trend) |
| Dichotomous rating based on cooperation with continued medication treatment in the hospital | 26% nonadherent | Dysphoric initial response to medication | NR |
| Patients and doctors were asked about patient's adherence; rated as continuous intake or not | 40% nonadherent | Fewer psychotic symptoms, lower degree of paranoid ideation or hallucinations, previous nonadherence, shorter duration of illness, ability to work, first break | NR |
| Patients who refused medications (N = 30) matched with patients who did not refuse medications (N = 30) | 50% nonadherent (by design) | Diagnosis of bipolar or schizoaffective disorder (compared with schizophrenia)<br>Samples matched for age and gender<br>No association: current or past threatening/assaultive behavior, self-reported substance abuse | Lower doses of prescribed neuroleptic<br>No association: adherence to other parts of the treatment program |
| Self-reported compliance: (a) reported compliance (*ever* neglecting to follow prescribed regimen, 0–9 score) and (b) reported errors (any of 6 specific types of errors at least once during week prior to interview, 0–6 score) | (a) Mean compliance, 7.6 out of possible 9<br>(b) Mean reported errors, 0.74 out of possible 6 | (a) 20% of variance in reported compliance explained by beliefs about susceptibility, benefits, and cues to action<br>(b) 17% of variance in reported errors explained by beliefs about susceptibility, benefits, and severity | NR |
| Dichotomous rating: Nonadherence based on missed appointments and deliberate discontinuation of injection treatments in the year following discharge | 54% nonadherent | Lower self-reported depressive symptoms, increased grandiosity (on BPRS), lack of feeling of illness, and lack of insight<br>No association: all other parts of BPRS, paranoia | NR |
| Clinician ratings of adherence on 5-point scale (for last 6 mo) | 26% nonadherent | Heavy alcohol use (vs mild) | NR |
| Nurse ratings of adherence every 2 wk: 1 = "active compliance," 2 = "passive compliance," 3 = "resistance," or 4 = "overt refusal" | Mean adherence in hospital: 1.35 at initial assessment and 1.23 at final assessment | Lower insight ratings on ITAQ | NR |
| Scored adherence at 30 d postdischarge and $2\frac{1}{2}$ to $3\frac{1}{2}$ y later: rated as adherent or not on the basis of regularity of outpatient visits and adherence with prescribed medications | 30-d: 25% nonadherent<br>Long-term: 47% nonadherent | Trend: lower insight (adherence at 30 d postdischarge) | Worse aftercare environment |
| 40 regular attenders (receiving injections regularly for at least 12 mo) matched with 40 irregular attenders (missed 2 or more appointments in last 12 mo) | 50% nonadherent (by design) | More frequent depression<br>Trend: longer history of psychiatric contact<br>No association: age, gender, health beliefs, psychotic symptoms | Trend: higher prescribed dose of depot neuroleptic<br>No association: severity of extrapyramidal symptoms, living situation |
| Dichotomous rating: nonadherent if changed own medication regimen, took less than full dosage, for shorter duration, or on a different schedule than prescribed | 61% nonadherent over course of 2-y study | NR | Poor or fair therapeutic alliance |
| Dichotomous rating based on self-report, chart review, information from significant others | 72% nonadherent | No association: alcohol use | No association: occurrence of or total number of side effects |
| Case manager's rating of adherence on 5-point scale from "highly significant" support/strength to "highly significant" stressor/weakness | NR | NR | Unstable housing |

continued

**Table 1. Studies Evaluating Risk Factors for Treatment Nonadherence in Patients With Schizophrenia[a] (cont.)**

| Authors | Study Type | Subjects | Other Characteristics | Risk Factor Measures |
|---|---|---|---|---|
| 16. Buchanan et al, 1992[33] | Longitudinal prospective | N = 61<br>Age = 36<br>M = 54%<br>66% White<br>28% African American<br>O = 27 | Outpatients<br>2/3 taking depot antipsychotic | Interview regarding insight and attitudes |
| 17. David et al, 1992[29] | Cross-sectional | N = 91<br>Age = 31<br>M = 67% | Inpatients and outpatients | Present State Examination, Schedule for Assessment of Insight |
| 18. Adams and Howe, 1993[53] | Cross-sectional | N = 42<br>Age = 36<br>M = 48%<br>E = 12 | Inpatients | Questionnaire about risk factors for nonadherence (checklist) and perceived benefits of medication |
| 19. Amador et al, 1993[24] | Cross-sectional | N = 43<br>Age = 31<br>M = 72%<br>E = 13<br>O = 21 | Inpatients | Scale to Assess Unawareness of Mental Disorder |
| 20. Sellwood and Tarrier, 1994[73] | Retrospective | N = 256<br>Age = 36<br>28% Afro-Caribbean<br>70% other ethnicity | Inpatients | Chart review for demographic information |
| 21. Razali and Yahya, 1995[35] | Retrospective | N = 225<br>Age = 2/3 ≤ 30<br>M = 32%<br>90% Malaysian | Outpatients<br>20% taking depot antipsychotic | Patient and family interviews, patient questionnaires, and chart review |
| 22. Budd et al, 1996[10] | Cross-sectional, case control | N = 40<br>Age = 49<br>M = 75%<br>D = 24 | Outpatients<br>Taking depot antipsychotic | Health Beliefs Questionnaire, Multidimensional Health Locus of Control scale, interview to assess level of insight |
| 23. Cuffel et al, 1996[31] | Case series, prospective | N = 89<br>Age range = 18–55 | Outpatients | BPRS, Neurobehavioral Cognitive Status Examination, Awareness of Illness Interview |
| 24. Macpherson et al, 1996[30] | Retrospective | N = 64<br>Age = 63<br>M = 42% | Inpatients<br>Mean length of stay = 22 y | Schedule for Assessment of Insight |
| 25. Owen et al, 1996[39] | Longitudinal (outcomes study) | N = 135<br>Age = 38<br>M = 89%<br>D = 16<br>57% African American<br>43% White | Inpatients and outpatients | Baseline and 6-mo follow-up: BPRS, information about drug and alcohol abuse and living arrangements, observed side effects |
| 26. Dixon et al, 1997[38] | Cross-sectional (for baseline assessment of adherence) | N = 77<br>Age = 41<br>M = 62%<br>62% African American | Outpatients<br>All patients homeless at baseline, 73% with lifetime substance use disorder diagnosis | BPRS, patient/clinician/family interviews |
| 27. Nageotte et al, 1997[36] | Cross-sectional | N = 202<br>Age = 35<br>M = 68%<br>D = 10<br>79% African American<br>21% White | Inpatients and outpatients<br>48% high school graduates | Structured interviews with patients and family members<br>Secondary analysis (study designed to look at readmission) |
| 28. Ruscher et al, 1997[54] | Cross-sectional (inpatients vs outpatients) | N = 148<br>Age = 37<br>M = 51% | Inpatients and outpatients<br>90% high school education or greater | Structured interview (Attitudes About Medications Questionnaire) to assess attitudes about medications |

| Adherence Measures | Adherence | Patient-Related Risk Factors for Nonadherence | Medication- and Environment-Related Risk Factors for Nonadherence |
|---|---|---|---|
| Rated adherence as good, average, or poor on the basis of inspection of records and analysis of urine | 41% "poor" or "average" medication adherence at 1 y<br>49% "poor" or "average" medication adherence at 2 y | Negative attitude toward medications, previous nonadherence, involuntary hospitalization<br>No association: age, gender, ethnicity, employment, belief in having been unwell during admission or in becoming ill again, Mini-Mental State Examination score, psychotic symptoms, mood change, thought disorder | Trend: living alone, presence of akinesia<br>No association: number of drugs being taken, number of doses per day, depot vs oral, akathisia, drowsiness, tremor, dystonia, destination on discharge, treatment setting |
| Adherence rated 0 to 4 (measure within insight scale) | NR | Less ability to recognize illness<br>Not associated: ability to relabel delusions and hallucinations as abnormal | NR |
| Interview assessing % of medications taken in month prior | 43% took 50% or less of medications in month prior | Lower endorsement of symptom relief and indirect benefits (eg, staying out of hospital, allowing patient to make friends) | No association: side effects, difficulty obtaining medication, reinforcement for not taking medication |
| Rating of adherence by nurses on unit: "active compliance," "passive compliance," "resistance," or "overt refusal" | NR | Moderately correlated with poorer awareness of mental disorder and current awareness of effects of medication (subscales of instrument) | NR |
| Psychiatrists' recall of patients who were "very noncompliant," ie, persistent refusal of medication while in hospital | 17% nonadherent | Male gender, Afro-Caribbean ethnicity (British study)<br>No association: age | NR |
| Dichotomous rating: nonadherent if missed more than 2 doses over a period of 2 wk and defaulted on more than 1 follow-up visit | 73% nonadherent | Treatment duration more than 5 y, negative attitude toward medication<br>No association: age, gender, income, view of past severity of illness | Once or twice daily dosage (vs 3 times daily), supervised medication usage<br>No association: family involvement in follow-up |
| Dichotomous rating: nonadherent if failed to attend and/or accept medication at 1/3 or more of all scheduled appointments over past year | 50% nonadherent (by design) | Feeling less susceptible to relapse, not perceiving relapse to be severe, not feeling medications beneficial<br>Not associated: knowledge and insight | NR |
| Interview at baseline and at 6-mo follow-up regarding past 30 d of outpatient adherence to medication on 5-point self-report scale (higher score = less adherent) | Mean rating 1.7 at baseline and 1.9 at follow-up | Lower awareness<br>Lower neurocognitive impairment associated with less positive self-report of adherence at baseline | NR |
| Keyworker evaluation of attitudes to treatment (actively pursued, passively accepted, or actively refused) and of acceptance of treatment (always, usually, not usually, or never) over past 2 wk | Attitudes: 23% "actively refused"<br>Acceptance: 20% "not usually," 0% "never" | Attitudes: lower insight scores (for comparison of "actively pursued" vs "actively refused")<br>Acceptance: higher insight scores (for "always" vs "not usually") | NR |
| Dichotomous rating taken from self-rated adherence on 5-point scale: nonadherent if missed several times, took fewer than half of prescribed doses, or stopped altogether<br>Informant (family member or health professional) also reported on patient's adherence using same scale | Baseline: 36% nonadherent<br>6-mo follow-up: 15% nonadherent | Substance abuse<br>No association: gender, ethnicity | Trend: less outpatient contact, fewer observed side effects<br>No association: stability of living arrangements |
| Patients deemed nonadherent if they refused a beneficial psychotropic medication or missed more than 1 wk of medication (at baseline) | Baseline: 71% nonadherent | Higher psychotic symptom subscale and total BPRS scores<br>No association: age, gender, ethnicity | NR |
| Dichotomous rating based on ratings of patients and family members about degree of antipsychotic adherence on 5-point scale<br>Coded as adherent if took all medications or only missed occasionally | 47% nonadherent | Lack of belief that they have a mental illness<br>No association: gender, ethnicity, marital status, perceived medication efficacy, inpatient status, substance abuse | No recent mental health care (within 3 mo)<br>No association: oral vs depot medication, urban/rural residence, side effects, access to care |
| Structured interview assessing history of adherence, based on patient's responses to questions about changing or stopping medications without discussing with psychiatrist | 66% changed way they were taking medications<br>47% had stopped taking medications at some point | Higher education, opposition to idea of taking medications, belief that medications not working, inpatient status<br>No association: age, gender, marital status, diagnosis, other attitudes toward medications (both positive and negative) | Side effects<br>No association: current medication |

**Table 1. Studies Evaluating Risk Factors for Treatment Nonadherence in Patients With Schizophrenia[a] (cont.)**

| Authors | Study Type | Subjects | Other Characteristics | Risk Factor Measures |
|---|---|---|---|---|
| 29. Agarwal et al, 1998[27] | Cross-sectional | N = 78<br>Age = 37<br>M = 68%<br>D = 23<br>E = 12 | Outpatients | Scale to Assess Unawareness of Mental Disorder, Drug Attitude Inventory, Knowledge About Schizophrenia Interview (given to key relative identified by patient) |
| 30. Duncan and Rogers, 1998[26] | Cross-sectional | N = 90<br>Age = 43<br>M = 68%<br>61% White<br>37% African American | Outpatients<br>Majority with ≥ 1 y of college | Schedule for Affective Disorders and Schizophrenia |
| 31. Garavan et al, 1998[22] | Cross-sectional | N = 70<br>Age = 39<br>M = 56%<br>D = 11 | Outpatients<br>31% taking depot antipsychotic | Drug Attitude Inventory, Insight Scale (self-report), Schedule for Assessment of Insight (interview) |
| 32. Heyscue et al, 1998[58] | Retrospective | N = 98<br>D = 19 | Outpatients<br>Taking depot antipsychotic | Evaluation of urban (N = 75) vs rural (N = 23) location and sociodemographic characteristics |
| 33. Corriss et al, 1999[21] | Cross-sectional | N = 87<br>Age = 35<br>M = 64%<br>E = 13<br>73% White<br>10% African American<br>O = 19 | Outpatients | Ratings by clinical staff: Behavior and Symptom Identification Scale (subscales on psychosis, depression/anxiety, impulsive/addictive behavior, relation to self and others, daily living skills), Working Alliance Inventory |
| 34. Smith et al, 1999[28] | Cross-sectional | N = 46<br>Age = 39<br>M = 63%<br>94% White<br>O = 18 | Outpatients | Scale to Assess Unawareness of Mental Disorder, Scale for the Assessment of Positive Symptoms, Scale for the Assessment of Negative Symptoms, BPRS, neurocognitive battery |
| 35. Cabeza et al, 2000[17] | Retrospective | N = 60<br>Age = 35<br>M = 72% | Inpatients<br>27% high school graduates<br>53% with duration of illness ≥ 6 y | Interviews by psychiatrists prior to discharge from hospital, Drug Attitude Inventory, BPRS, GAS |
| 36. Olfson et al, 2000[23] | Prospective | N = 213<br>Age = 37<br>M = 61%<br>54% African American<br>43% White | Outpatients<br>43% < 12 y education | Inpatient and follow-up (3 mo postdischarge) assessments: BPRS, GAS, level of insight (assessed with 2 probes and follow-up to positive response), side effects, therapeutic alliance, family involvement, substance use disorders |
| 37. Rosenheck et al, 2000[20] | Prospective, double-blind, haloperidol vs clozapine | N = 423<br>Age = 44<br>M = 98%<br>E = 12<br>66% White<br>30% African American | Outpatients<br>Mean ± SD days of hospitalization during year prior to study entry = 110 ± 89 | Positive and Negative Syndrome Scale, Heinrichs-Carpenter Quality of Life Scale, Barnes Akathisia Scale, Abnormal Involuntary Movement Scale, Simpson-Angus Scale for extrapyramidal syndromes |
| 38. Grunebaum et al, 2001[19] | Retrospective | N = 74<br>Age = 47<br>M = 40%<br>46% African American<br>45% White | Outpatients in supported residential housing facilities | Medication supervision status, regimen complexity, patient opinion about antipsychotic, Global Assessment of Functioning (GAF), substance abuse |

| Adherence Measures | Adherence | Patient-Related Risk Factors for Nonadherence | Medication- and Environment-Related Risk Factors for Nonadherence |
|---|---|---|---|
| Dichotomous rating. Nonadherent if: patient claimed had stopped medications, took medications only when had supply, or discontinued medications when symptoms disappeared, or if patient's family member, case worker, or doctor stated patient had not been taking medications regularly | 38% nonadherent | Younger age, shorter duration of illness, episodic (vs continuous) course of illness, more negative subjective response to medications<br>Trend: poorer awareness of disorder and symptoms<br>No association: gender, education, marital or employment status | Fewer side effects; having key relative who is employed<br>No association: knowledge of family member about schizophrenia |
| Staff nurses rated adherence as "compliant" (took medications as prescribed 80% or more of the time), "noncompliant" (less than 50% of the time), or "mixed" (between 50% and 80% of the time) | 42% "noncompliant"<br>13% "mixed" | Younger age, severity of hallucinations and delusions, subjective anger<br>No association: gender, ethnicity, education, marital status, employment, depressive and manic symptoms | NR |
| Adherence rated on 4-point scale: no or consistently irregular, frequently irregular, rather irregular, or regular | 20% consistently, frequently, or rather irregularly nonadherent | More negative subjective response to medications, lower scores on "recognition of need for treatment" subscale of Insight Scale<br>No association: age, duration of illness, number of admissions, attitudes toward medication, or overall insight | Higher neuroleptic dose, oral (vs depot) neuroleptic use<br>No association between adherence and dose of medication when mode of administration controlled for |
| Chart review: number of kept appointments divided by number of scheduled appointments over the previous year | 4% nonadherent | Shorter duration of illness, history of substance abuse<br>No association: age, gender, ethnicity, education | No association: geographic location, having a case manager, type of transportation used |
| Rated by clinicians on 4-point scale: "active compliance," "passive compliance," "resistance," and "overt refusal" | NR | More severe psychotic symptoms, poor sense of relation to self/others | Low agreement between patient and therapist on tasks of treatment |
| Rated using 100-point visual analog scale (0 = no adherence, 100 = perfect adherence) for adherence during 2 wk after hospital discharge | NR | Poor insight regarding current and past symptoms<br>No association: positive or negative symptoms, depression, neurocognitive measures | NR |
| Adherence over prior year rated as adequate, irregular (taking medications in different way from prescribed or missing appointments), or dropouts | NR | Less positive attitudes toward medications | No association: use of typical vs atypical medications |
| At 3-mo follow-up, interviewed about medication adherence<br>Nonadherent if reported having stopped medication for 1 wk or more since discharge | 19% nonadherent | Medication nonadherence in 3 mo prior to hospitalization, substance use disorder in past 6 mo, lack of recognition of diagnosis of schizophrenia, lack of recognition of symptoms<br>No association: GAS, BPRS score | Poorer therapeutic alliance, family refusal of involvement during hospitalization, use of typical vs atypical medications (trend)<br>No association: experiencing medication side effects within 3 mo prior to hospitalization, family visits during hospitalization |
| Medication continuation measured as the number of weeks of participation in double-blind treatment<br>Weekly pill counts performed | Mean ± SD weeks of participation: clozapine 35.5 ± 19.9 vs haloperidol 27.2 ± 20.2<br>No difference in pill counts between groups | Older age, African American (possibly secondary to increased weight gain vs white subjects), substance abuse history<br>Improved adherence: reduction in psychopathology, improved quality of life<br>No association: education level | Haloperidol > clozapine (by duration of study participation)<br>Note: clozapine = haloperidol for nonadherence as determined by pill count<br>Improved adherence: receiving public support<br>No association: reduction in side effects (beyond effect of taking clozapine) |
| Total number of days in the past month in which patient did not take antipsychotic | NR | Negative views about medication<br>Trend: lower GAF score<br>No association: age, gender, ethnicity, diagnosis, substance abuse | Atypical antipsychotic use<br>Trend: less medication supervision, increased medication regimen complexity |

continued

Table 1. Studies Evaluating Risk Factors for Treatment Nonadherence in Patients With Schizophrenia[a] (cont.)

| Authors | Study Type | Subjects | Other Characteristics | Risk Factor Measures |
|---|---|---|---|---|
| 39. Dolder et al, 2002[18] | Retrospective | N = 286<br>Age = 50<br>M = 90%<br>65% White<br>20% African American | Outpatients | Antipsychotic type. Compared patients receiving antipsychotic monotherapy with haloperidol, perphenazine, risperidone, olanzapine, or quetiapine |

[a]Age is in mean years.
Abbreviations: D = mean years of duration of illness, E = mean years of education, M = percent male, NR = not reported, O = mean age at onset in years.



because nonadherence could range from taking no medications to only missing several doses.

For the "strict" criteria, the working definition for adherence was "regularly taking medications as prescribed." In addition, we included only those studies in which trained personnel measured adherence. We excluded analyses in which adherence was calculated based solely on subjects' willingness to take medications. Where patients' self-reports were used to determine adherence rates, these estimates needed to have agreed with another estimate from an additional source (e.g., family members, care providers, or individual clinicians). Ten articles met these "strict" criteria; their weighted (by sample size) mean nonadherence rate was 41.2% (unweighted mean ± SD = 39.1% ± 11.4%; median = 39%; range, 20.0%–55.6%).[22,26,27,33,34,36,39,53,60,61]

For the "stricter" criteria, we restricted the inclusion of articles further by including only those (from among the above mentioned 10 investigations) in which adherence met the following working definition: "taking medications as prescribed at least 75% of the time." We also required that investigations using Likert-type scales must have explained adherence in a way that matched this definition. This criterion was based on the notion that a requirement that one take 100% of medications as prescribed was too rigorous, whereas requiring only that one take medication "regularly" was not strict enough. This "stricter" set of criteria yielded 5 studies whose weighted mean nonadherence rate was 49.5% (unweighted mean ± SD = 47.3% ± 7.4%; median = 47%; range, 37.7%–55.6%).[26,33,36,39,53]

## Risk Factors for Nonadherence

In Table 2, we list the specific articles that evaluated each potential risk factor. Each study is classified as either (1) having demonstrated an association or (2) having found little or no association. To be included in the table, 2 or more reports must have evaluated the particular factor in relation to adherence. Below, we summarize the associations between specific risk factors and nonadherence. (Please see Table 2 for references to individual studies; those risk factors not listed in Table 2 but discussed below include citations to the relevant articles.)

***Patient-related risk factors for nonadherence.*** We identified the following patient-related risk factors as being consistently associated with nonadherence to antipsychotic medication: poor insight, negative attitude toward or subjective response to medication, previous nonadherence, and shorter duration of illness. A current or past history of substance abuse was associated with nonadherence in 5 of 9 analyses; those studies employing more rigorous methodology were more likely to find an association. Severity of psychotic symptoms, presence of mood symptoms (or diagnosis of schizoaffective or bipolar disorder), and current inpatient status gave mixed results regarding associations with nonadherence. A majority of the articles in which data were analyzed for an association of age, gender, ethnicity, marital status, or education level with nonadherence found no such associations. Measures of neurocognitive impairment were relatively scarcely used in the research reviewed; those investigators who did analyze their data for associations between cognitive measures and nonadherence reported inconsistent findings.

***Medication-related risk factors for nonadherence.*** Higher antipsychotic dose was associated with nonadherence in 2 of 4 reports. The use of typical (vs. atypical) medications was not consistently associated with nonadherence in the 5 studies that compared these agents. Rosenheck et al.[20] found that patients taking clozapine continued their medication for a significantly longer time period (mean = 35.5 weeks) compared with patients taking haloperidol (mean = 27.2 weeks). There was no difference, however, between the groups in the number of pills returned each week. Olfson and colleagues[23] found a nonsignificant trend suggesting that patients taking clozapine or risperidone were less likely to become nonadherent with their treatment, while Cabeza and associates[17] reported finding no association between type of medication and medication adherence. Grunebaum and col-

| Adherence Measures | Adherence | Patient-Related Risk Factors for Nonadherence | Medication- and Environment-Related Risk Factors for Nonadherence |
|---|---|---|---|
| Analyzed refill records for up to 12 mo<br>Calculated compliant fill rate (CFR) and cumulative mean gap ratio (CMGR)<br>CFR = (Number of Adherent Fills/Total Number of Fills) × 100<br>CMGR = [(Total Number of Days of Study Period) – (Total Number of Days of Medication Obtained)/Total Number of Days of Study Period] × 100 | Based on CMGR: Mean days per month without medication for atypical and typical antipsychotic groups was 4 and 7 d, respectively<br>Based on CFR: Patients were noncompliant with fills of medications 47% of the time | No association: age, gender, ethnicity, diagnosis, presence of mood symptoms | Typical antipsychotic<br>No association: antipsychotic dose, number of adjuvant psychotropic medications |



leagues[19] found that patients prescribed atypical antipsychotics had significantly more days of missed medication compared with those patients receiving typical agents; however, clinical comparisons were not made between groups on the basis of antipsychotic type, and conclusions drawn from regression analyses suggested medication supervision status was a more important predictor in the study sample. In our own recent study[18] of the effect of antipsychotic type on adherence, refill records of 288 outpatients prescribed monotherapy with a conventional or atypical agent were examined and adherence rates for up to a 12-month period were calculated. While those patients receiving atypical agents had significantly higher adherence rates on some of the measures used, adherence remained problematic regardless of antipsychotic type. While the data are still limited and inconclusive, these findings may suggest a trend toward atypical antipsychotics being associated with greater adherence. Clearly, further research will be necessary to better understand this relationship and to evaluate the importance of side effect profiles of different medications for adherence behavior.

The presence and/or severity of medication side effects and use of oral versus depot medication did not consistently correlate with degree of adherence. There were only 3 analyses of the relationship of medication regimen complexity to medication adherence, and these provided mixed findings. The paucity of studies analyzing medication supervision status in relation to adherence prevented us from drawing any conclusions about this potential risk factor, although 1 study[35] did find that adherence improved when patients were supervised in their medication usage.

***Environmental risk factors for nonadherence.*** Factors that emerged as being predictive of nonadherence included a poor alliance with therapist or clinician or less outpatient contact, and inadequate discharge planning or poor aftercare environment. Factors for which there were mixed results regarding the predictive value for nonadherence were family involvement during hospitalization or follow-up and stability of living arrangements. Too few studies examined the relationship between nonadherence and the following factors for us to be able to draw any conclusions: knowledge of family members regarding schizophrenia,[27] medication supervision status,[19,35] type of living situation,[33,55] urban versus rural location,[36,58] having a case manager,[58] type of transportation used,[58] access to care,[36] and adherence to other parts of an inpatient treatment program.[9] Further investigation is needed into potential associations between the factors in patients' environments and adherence behavior.

## DISCUSSION

This article represents an updated review of risk factors for medication nonadherence. It adds a number of studies that were published after the scholarly reviews by Perkins (1999),[13] Fenton et al. (1997),[6] and Young et al. (1986).[7] Additionally, the tables listed in our review that allow for the side-by-side comparison of individual studies and risk factors represent an advancement over recent reviews. Our review presents data for all potential risk factor variables identified in 2 or more studies, rather than highlighting just those variables that appear to be consistent risk factors for nonadherence. Lastly, we have compiled an extensive list of measurement tools that have been used to examine risk factors for nonadherence.

We observed a wide range of reported prevalence rates of nonadherence in the articles reviewed, probably reflecting the extensive variability in adherence methodology. One of the difficulties in adherence research is the methodological inconsistency within the literature. Some investigations, for example, used patients' self-reports, which are less reliable and tend to overestimate adherence. In an attempt to level out the variability and to identify a clinically relevant nonadherence threshold, we derived weighted mean prevalence rates of nonadherence using 2 sets of study selection criteria ("strict" and "stricter"). When we calculated 2 mean nonadherence rates using our "strict" and "stricter" study selection criteria, however, the derived rates remained disappointingly

**Table 2. Studies Finding and Not Finding Associations Between Specific Risk Factors and Nonadherence***

| Risk Factor for Nonadherence | Measure(s) | Total Number | Demonstrating Association | Demonstrating Little or No Association |
|---|---|---|---|---|
| Patient-Related Risk Factors for Nonadherence | | | | |
| Poor insight | Scale to Assess Unawareness of Mental Disorders,[a] Present State Examination,[b] Schedule for Assessment of Insight,[c] Insight and Treatment Attitudes,[d] structured interview,[e] Knowledge About Schizophrenia Interview,[f] Health Belief Questionnaire,[g] self-report scale[h] | 14 | 10/14 studies<br>Amador et al,[24f] Bartko et al,[32h] Cuffell et al,[31e] David et al,[29b,c] Macpherson et al[30c] (mixed findings), McEvoy et al[34d] (trend only), McEvoy et al,[25d] Nageotte et al,[36e] Olfson et al,[23h] Smith et al[28a] | 4/14 studies<br>Agarwal et al,[27a,f] Budd et al,[10e,g] Garavan et al,[22c] Razali and Yahya[35e] |
| Negative attitude toward medications | Questionnaire,[a] interview,[b] Drug Attitude Inventory,[c] Attitudes About Medication Questionnaire[d] | 10 | 8/10 studies<br>Adams and Howe,[53a] Amador et al,[24b] Buchanan,[51b] Budd et al,[10b] Cabeza et al,[17b,c] Grunebaum et al,[19b] Razali and Yahya,[35b] Ruscher et al[54d] | 2/10 studies<br>Hogan et al,[52a] Nageotte et al[36b] |
| Negative subjective response to medication | Drug Attitude Inventory,[a] questionnaire[b] | 4 | 4/4 studies<br>Agarwal et al,[27a] Garavan et al,[22a] Hogan et al,[52b] Van Putten et al[56b] | |
| Previous nonadherence | Chart review,[a] interview[b] | 3 | 3/3 studies<br>Buchanan,[51b] Gaebel and Pietzcker,[61a] Olfson et al[23b] | |
| Substance abuse | Structured interview,[a] chart review,[b] Self-Administered Alcoholism Screening Test,[c] self-report,[d] clinician rating[e] | 9 | 5/9 studies<br>Drake et al,[79e] Heyscue et al,[58b] Olfson et al,[23a] Owen et al,[39a,b] Rosenheck et al[20a] | 4/9 studies<br>Grunebaum et al,[19a] Nageotte et al,[36a] Pristach and Smith,[59c] Zito et al[9d] |
| More severe psychotic symptoms | Interview,[a] BASIS-32,[b] Schedule for Affective Disorders and Schizophrenia,[c] SAPS/SANS,[d] BPRS,[e] PANSS,[f] unspecified[g] | 8 | 4/8 studies<br>Corriss et al,[21b] Dixon et al,[38a,e] Duncan and Rogers,[26c] Rosenheck et al[20f] | 4/8 studies<br>Buchanan,[51a] Gaebel and Pietzcker,[61g] Pan and Tantam,[55g] Smith et al[28d] |
| Presence of mood symptoms or diagnosis of schizoaffective disorder or bipolar disorder vs schizophrenia *(see specific studies)* | Chart review,[a] self-report scale,[b] interview,[c] Schedule for Affective Disorders and Schizophrenia[d] | 7 | 3/7 studies<br>Bartko et al[32b] (increased grandiosity but decreased depressive symptoms), Pan and Tantam[55c] (increased depressive symptoms), Zito et al[9a] (diagnosis of schizoaffective disorder or bipolar disorder vs schizophrenia) | 4/7 studies<br>Dolder et al,[18a] Duncan and Rogers,[26d] Grunebaum et al,[19c] Smith et al[28] |
| Shorter duration of illness or treatment | Chart review | 5 | 3/5 studies<br>Agarwal et al,[27] Gaebel and Pietzcker,[61] Heyscue et al[58] | 2/5 studies<br>Garavan et al,[22] Razali and Yahya[35] |
| Current inpatient status | Structured interview | 2 | 1/2 studies<br>Ruscher et al[54] | 1/2 studies<br>Nageotte et al[36] |
| Higher education level | Structured interview | 5 | 1/5 studies<br>Ruscher et al[54] | 4/5 studies<br>Agarwal et al,[27] Duncan and Rogers,[26] Heyscue et al,[58] Rosenheck et al[20] |
| Nonwhite ethnicity | Structured interview, chart review | 9 | 2/9 studies<br>Rosenheck et al,[20] Sellwood and Tarrier[73] | 7/9 studies<br>Buchanan,[51] Dolder et al,[18] Dixon et al,[38] Grunebaum et al,[19] Heyscue et al,[58] Nageotte et al,[36] Owen et al[39] |
| Younger age | Structured interview, chart review | 13 | 2/13 studies<br>Agarwal et al,[27] Duncan and Rogers[26] | 11/13 studies<br>Buchanan,[51] Dolder et al,[18] Dixon et al,[38] Garavan et al,[22] Grunebaum et al,[19] Heyscue et al,[58] Pan and Tantam,[55] Razali and Yahya,[35] Rosenheck et al[20] (older age), Ruscher et al,[54] Sellwood and Tarrier[73] |
| Male gender | Structured interview, chart review | 12 | 1/12 studies<br>Sellwood and Tarrier[73] | 11/12 studies<br>Agarwal et al,[27] Buchanan,[51] Dixon et al,[38] Duncan and Rogers,[26] Grunebaum et al,[19] Heyscue et al,[58] Nageotte et al,[36] Owen et al,[39] Pan and Tantam,[55] Razali and Yahya,[35] Ruscher et al[54] |

continued

**Table 2. Studies Finding and Not Finding Associations Between Specific Risk Factors and Nonadherence (cont.)**

| Risk Factor for Nonadherence | Measure(s) | Total Number | Demonstrating Association | Demonstrating Little or No Association |
|---|---|---|---|---|
| Neurocognitive impairment | MMSE,[a] Neurocognitive battery,[b] Neurobehavioral Cognitive Status Examination[c] | 3 | | 3/3 studies<br>Buchanan,[51a] Cuffel et al,[31c] Smith et al[28b] |
| Marital status | Structured interview, chart review | 4 | | 4/4 studies<br>Agarwal et al,[27] Duncan and Rogers,[26] Nageotte et al,[36] Ruscher et al[54] |
| Medication-Related Risk Factors for Nonadherence | | | | |
| Higher antipsychotic dose | Chart review,[a] provider summary,[b] interview[c] | 4 | 2/4 studies<br>Garavan et al,[22a] Pan and Tantam[55c] | 2/4 studies<br>Dolder et al,[18a] Zito et al[9a,b] |
| Medication regimen complexity | Structured interview | 3 | 2/3 studies<br>Razali and Yahya,[35] Grunebaum et al[19] (trend) | 1/3 studies<br>Buchanan[51] |
| Use of typical vs atypical antipsychotic | Chart review[a]<br>Structured interview | 5 | 3/5 studies (see notes)<br>Dolder et al,[18a] Rosenheck et al[20] (partial), Olfson et al[23] (trend) | 2/5 studies<br>Cabeza et al,[17] Grunebaum et al[19] |
| Oral (vs depot) administration route | Structured interview | 3 | 1/3 studies<br>Garavan et al[22] | 2/3 studies<br>Buchanan,[51] Nageotte et al[36] |
| More severe side effects | Structured interview,[a] unspecified,[b] AIMS,[c] Simpson-Angus Scale,[d] Barnes Akathisia Scale[e] | 9 | 1/9 studies<br>Ruscher et al[54a] | 8/9 studies<br>Agarwal et al,[27a] Buchanan,[51b] Nageotte et al,[36a] Olfson et al,[23a] Owen et al,[39a] Pan and Tantam,[55c] Pristach and Smith,[59b] Rosenheck et al[20c,d,e] (beyond effect of clozapine) |
| Environment-Related Risk Factors for Nonadherence | | | | |
| Poor therapeutic alliance or less outpatient contact | Working Alliance Inventory,[a] therapist assessment[b] | 5 | 5/5 studies<br>Corriss et al,[21a] Frank and Gunderson,[60b] Nageotte et al,[36b] Olfson et al,[23b] Owen et al[39b] | |
| Inadequate discharge planning or poor aftercare environment | Chart review, interviews | 2 | 2/2 studies<br>Caton et al[71] (trend only), McEvoy et al[34] | |
| Unstable living arrangement | Structured interview,[a] questionnaire[b] | 6 | 2/6 studies<br>Drake et al,[72b] McEvoy et al[34b] | 4/6 studies<br>Buchanan,[51a] Nageotte et al,[36a] Owen et al,[39a] Pan and Tantam[55a] |
| Poor family involvement during hospitalization or follow-up | Knowledge About Schizophrenia Interview,[a] interview[b] | 3 | | 3/3 studies<br>Agarwal et al,[27a] Olfson et al,[23b] Razali and Yahya[35b] |

*Superscript letters in the "Demonstrating Association" and the "Demonstrating Little or No Association" columns correspond to the measures identified in the "Measure(s)" column. Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BASIS-32 = Behavioral and Symptom Identification Scale, BPRS = Brief Psychiatric Rating Scale, MMSE = Mini-Mental State Examination, PANSS = Positive and Negative Syndrome Scale for schizophrenia, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms.

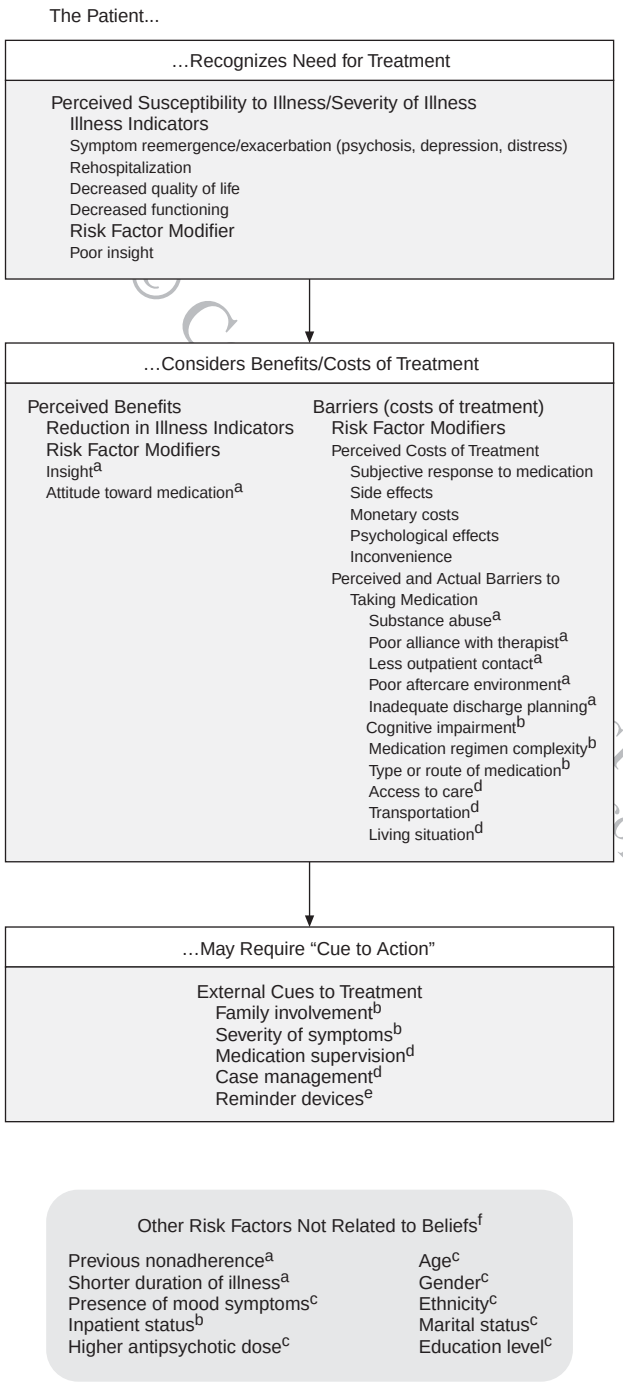


higher (41.2% and 49.5%, respectively) than our all-inclusive rate (40.5%). While using relatively strict criteria reduced the number of studies included in both weighted mean rates, these carefully constructed criteria also appeared to decrease the variability in the reported nonadherence rates and most likely provide a better estimate of a population that is likely at risk for negative outcomes owing to nonadherence.

Among the investigations we reviewed, factors most consistently associated with nonadherence were poor insight into having a mental illness, negative attitude or subjective response toward medication, previous nonadherence, current or past substance abuse, shorter duration of illness, inadequate discharge planning or aftercare environment, and poor therapeutic alliance. The findings of our review support a multifactorial, etiopathologic model of medication nonadherence in patients with schizophrenia.

Factors that may affect a patient's decision to adhere to a medication regimen can be considered in the context of the Health Belief Model (HBM). The HBM considers health behavior a result of the interplay among a number of construct factors.[13–16] These factors include perceived susceptibility to illness, perceived severity of illness, perceived benefits of taking health action, perceived barriers (or costs) of taking action, and various cues to action. In this sense, the HBM can be applied to nonadherence to antipsychotic medication in people with schizophrenia or schizoaffective disorder.[13,15] According to the HBM, 2 major factors influence the likelihood that patients will

**Figure 1. Health Belief Model Framework for Antipsychotic Adherence***




*Based on Perkins,[13] Kelly et al.,[14] Weiden et al.,[15] and Janz and Becker.[16]
[a]Consistently associated with nonadherence.
[b]Mixed findings.
[c]Not consistently associated with nonadherence.
[d]Not enough studies to reach a conclusion.
[e]Not examined in our review.
[f]A limitation of the Health Belief Model is that there may be factors other than health beliefs that may also influence adherence behavior in patients.

accept maintenance antipsychotic treatment. First, they must feel personally threatened by their susceptibility to the serious nature of schizophrenia or another chronic psychotic disorder. Second, patients must believe that the benefits of taking medications outweigh the perceived barriers to (and/or costs of) taking antipsychotic medication. In some cases, however, a "cue to action" may be required for the desired adherence to antipsychotic medication to take place. The factors that may affect a patient's decision to adhere to a medication regimen are illustrated in the HBM framework (Figure 1). Using a framework such as a behavior change model (e.g., the HBM) can aid in the development of interventions designed to improve adherence by altering the cost:benefit ratio of antipsychotic medications in favor of the benefits. A limitation of the HBM in explaining patient adherence is the recognition of factors other than health beliefs that may also influence adherence behavior in patients. These factors may include socioeconomic status, cultural factors, and previous experiences. These factors have been added to our HBM model to explain patient adherence behavior. The finding that impaired insight was consistently related to nonadherence supports the work of investigators and colleagues such as McEvoy et al.,[34] who have emphasized the key role of insight in treatment adherence. The HBM highlights this pivotal relationship. When patients lack an appreciation of the nature of their disorder, the risks of not taking medications, or the benefits of taking medications, the perceived cost:benefit ratio tends to be weighted against adherence.

Interestingly, a number of factors one might expect to be related to nonadherence were not found to be significant predictors in a majority of studies that examined them. These factors included age, gender, ethnicity, marital status, education level, neurocognitive impairment, severity of psychotic symptoms, severity of medication side effects, route of medication administration, and family involvement. In some cases, the lack of association was surprising. It is a widely held view, for example, that aging is associated with poorer medication adherence, although the literature offers conflicting data.[62] While we did not find consistent evidence for such an association, this may have been due to the limited range of ages included in many of these reports. We also did not find a clear association between neurocognitive impairment (examined explicitly in only a few of the studies) with nonadherence, although further work is clearly needed to clarify this relationship. One such study was recently conducted by Patterson and colleagues.[63] The outcomes of a performance-based measure of hypothetical medication management in a group of older patients with schizophrenia were compared with normal controls. In addition to patients with schizophrenia committing more errors in medication management, those patients with more severe cognitive deficits also performed worse in terms of medi-

cation management, suggesting an association between neurocognitive impairment and nonadherence.[63]

We were also surprised at the lack of association we found between medication-induced side effects and nonadherence, particularly given the predominant use of typical antipsychotics in the studies reviewed. One way to explain this negative finding is to note that systematic ratings of side effects, particularly of the associated subjective levels of distress, were rarely obtained. It is possible that the investigators did not capture significantly the impact of side effects on patients' adherence behavior. Our review confirms observations of Van Putten and colleagues[56,57] and Buchanan,[51] among others, that subjective response and negative attitudes toward medication are key risk factors for nonadherence. The HBM provides a framework for understanding how adverse effects relate to subjective factors, in turn influencing adherence. Side effects, whether or not they are observable, can negatively affect patients' attitudes toward medications, thus increasing the perceived costs of taking medication and tipping the cost:benefit ratio against adherence.[13] In addition, subjective distress associated with extrapyramidal symptoms (EPS) does not always correlate with objective ratings used to evaluate the severity of these side effects.[15,64] Yet, EPS-induced distress may interfere with patients' perceptions of medication benefits by impairing the ability to learn about benefits, by disrupting the therapeutic alliance, and by heightening the stigma associated with medication (e.g., as a result of visible medication side effects such as tremor).[65,66]

A current and widespread assumption is that adherence should be greater in patients who are prescribed atypical antipsychotics, due to the more advantageous side effect profile of these drugs. As our review demonstrates, few published studies have compared adherence data on typical versus atypical antipsychotics. In those studies that did compare these agents, there was an overall trend toward greater adherence among patients taking atypical antipsychotic agents. While 3 of the 5 studies that examined medication type as a risk factor found atypical agents to be associated with greater adherence, 2 of these studies found only a partial association or nonsignificant trend.[20,23] In another (unpublished) comparison of typical and atypical agents not included in this review, Menzin and colleagues[67] evaluated treatment switching, discontinuation, and adherence over a 1-year period using Medicaid claims for almost 2500 patients prescribed conventional antipsychotics, risperidone, or olanzapine. Compared with patients taking conventional agents, those receiving atypical antipsychotics were significantly less likely to switch medications; in addition, those receiving olanzapine were significantly less likely to discontinue pharmacotherapy. Nevertheless, despite the benefits of the atypical agents, fewer than 60% of patients received "persistent" therapy, regardless of medication type. While the risk of neurologic side effects such as EPS[68] and tardive dyskinesia[69,70] is greatly reduced with these newer agents, other side effects such as sedation, weight gain, postural hypotension, and sialorrhea may contribute to the observed level of nonadherence in patients prescribed atypical agents.

We should point out limitations of this review. It is possible that we missed a few relevant articles, and we did not include those published in languages other than English. Also, subject selection biases are likely in individual studies. For example, over a similar observation period, the potential for antipsychotic discontinuation or deviation differs significantly for a patient on a regimen of a "monthly depot injection" compared with "3 tablets 4 times daily." Limitations of this review also involve the previously described limitations of the studies themselves. These include issues of study design, definitions and measures of adherence rates, and methods of assessing risk factors for nonadherence. The variability of methods and measures of adherence precluded us from performing a meaningful meta-analysis. Furthermore, our categorization of variables as risk factors for nonadherence was based on a majority of studies specifically examining those variables and finding an association with nonadherence, thereby weighting the findings of each study equally. It could be argued that because investigations vary in quality and rigor of methods, it is inappropriate to weight their findings equally. Examples of more qualitatively rigorous study designs include adherence measures with input other than just patient self-report (i.e., objective measures such as pill counts or drug levels, subjective measures in addition to self-report, or multiple adherence measures involving combinations of subjective and objective measures); validated, standardized or structured instruments to evaluate a risk variable; and study designs that prospectively evaluate risk factors for nonadherence in a large number of subjects. We believe, however, that to judge the quality of each study would require a subjective decision about aspects such as the soundness of measures used, about which there is likely to be some disagreement. Furthermore, in our review, applying the above mentioned qualitative standards would have placed emphasis on the findings of relatively few studies.[20,25,32,60,71–73] Table 1 may be useful for others who wish to apply qualitative judgments to investigations while examining risk factors of antipsychotic nonadherence.

Further research is needed into the types of interventions that would most effectively improve treatment adherence in patients with schizophrenia. Moreover, the associations of specific risk factors with nonadherence demonstrated in this review highlight the need for targeted interventions. Some investigators have begun to develop these sorts of interventions. For instance, "compliance therapy," developed by Kemp and colleagues,[74] targets insight as a key risk factor for nonadherence. Uti-

lizing the technique of motivational interviewing, therapists help patients to reshape their beliefs about their illness and to recognize the benefits of taking medications. In a randomized study of compliance therapy, patients participating in the intervention demonstrated improved adherence to treatment, more positive attitudes toward medications, and enhanced insight into their illness.

Intervention strategies may be considered educational, behavioral, or affective.[75] Education may assist the patient in increasing his or her awareness of the seriousness of schizophrenia or other chronic psychotic disorders. Further, with education the patient may recognize that behaviors such as treatment nonadherence or substance abuse may increase susceptibility for an adverse outcome. Educational strategies include those emphasizing the provision of information, whether by verbal or written means. Behavioral strategies include skill building, behavioral modeling and contracting, packaging and dosage modifications or tailoring, and reminders. These strategies help to reduce barriers and may cue patients to appropriate adherence behavior. Affective strategies focus on influencing medication adherence through appeals to emotions or by enlisting social relationships or supports. Motivational interviewing may be employed to facilitate changes in attitude and behaviors.[76] While each of these strategies alone has shown some benefit, all have their limitations—particularly, it appears, when provided in isolation from the other strategies. The appreciation that more than one factor may facilitate patient adherence highlights the need for combined strategies.[3–6]

Future studies evaluating the prevalence of and risk factors for nonadherence should be large-scale, prospective trials. Optimal measurement of adherence remains a fundamental issue for such investigations. Until we identify a "gold standard" for measuring medication nonadherence, a combination of assessments utilizing self-reports and objective measures should be employed, as no single measure of adherence is appropriate for all settings.[77] Electronic adherence monitors, while providing detailed information regarding medication administration, are expensive and do not measure actual consumption. Pill counts are commonly utilized, inexpensive, and theoretically provide information about the number of pills taken; it is impossible to determine, however, whether patients have actually taken the medications as prescribed. Patient interviews, while straightforward, are clearly limited by their subjective nature. Medication refill records provide unobtrusive information regarding refill histories and can be valuable in determining gaps in therapy, but this method is indirect and cannot confirm actual medication consumption. Performance-based tests to evaluate medication management skills, such as the Medication Management Ability Assessment,[63] may be a part of a larger battery of adherence measures. Blood and urine medication levels, while direct measures of actual medication taking, may be unpopular with patients and can be manipulated to an extent if subjects were to know when testing would be performed.[77] Furthermore, the value of blood levels as an indicator of drug intake is questionable for some antipsychotics.[77,78]

In conclusion, this review found that a variety of risk factors were consistently associated with medication nonadherence in patients with schizophrenia. Other potential risk factors, such as neurocognition and medication supervision status, require further study to elucidate associations with nonadherence. Interventions targeting known risk factors should be designed and empirically validated. Future research should also be aimed at identifying specific risk factors in individual patients as well as developing methods for matching patients to adherence interventions on the basis of patients' particular needs.

*Drug names:* clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane and others).

*Disclosure of off-label usage:* The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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