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Adherence to Antipsychotic Medication in Bipolar Disorder and Schizophrenic Patients

A Systematic Review

Sainza García, MSc,*† Mónica Martínez-Cengotitabengoa, PhD,*‡§
Saioa López-Zurbano, MD,* Iñaki Zorrilla, PhD, MD,*†‡ Purificación López, PhD, MD,*†‡
Eduard Vieta, PhD, MD,|| and Ana González-Pinto, PhD, MD*†‡

Abstract: Antipsychotics are the drugs prescribed to treat psychotic disorders; however, patients often fail to adhere to their treatment, and this has a severe negative effect on prognosis in these kinds of illnesses. Among the wide range of risk factors for treatment nonadherence, this systematic review covers those that are most important from the point of view of clinicians and patients and proposes guidelines for addressing them. Analyzing 38 studies conducted in a total of 51,796 patients, including patients with schizophrenia spectrum disorders and bipolar disorder, we found that younger age, substance abuse, poor insight, cognitive impairments, low level of education, minority ethnicity, poor therapeutic alliance, experience of barriers to care, high intensity of delusional symptoms and suspiciousness, and low socioeconomic status are the main risk factors for medication nonadherence in both types of disorder. In the future, prospective studies should be conducted on the use of personalized patient-tailored treatments, taking into account risk factors that may affect each individual, to assess the ability of such approaches to improve adherence and hence prognosis in these patients.

Key Words: adherence, antipsychotic, schizophrenia, bipolar disorder

(*J Clin Psychopharmacol* 2016;36: 355–371)

One of the greatest problems clinicians face when dealing with chronic illnesses is the effectiveness of treatment. This is determined by various different factors such as patient tolerance of the drug, the appropriateness of the regimen,¹ and, above all, adherence to the treatment prescribed. The best medication at the best dose can never be effective if the patient does not take it.

Medication adherence, previously known as compliance,² has been defined as “the extent to which a person's behavior coincides with the medical advice given.”³ This may include refusing to attend medical appointments or to start a treatment program or early discontinuation, as well as incomplete implementation of the doctor's instructions.⁴ Such behavior has a negative effect on the outcome of the illness and leads to higher rates of recurrence and hospitalization, worsening of signs and symptoms, and increases in hospital costs.⁵

At least half of patients who are prescribed long-term medication do not finish the course, this phenomenon representing a particularly serious problem in chronic psychiatric illnesses,^{6–10} in which treatment adherence rates are even lower than in other conditions.^{11,12} Specifically, considering 2 serious psychiatric disorders, bipolar disorder, and schizophrenia,¹³ mean rates of treatment adherence are approximately 42% in schizophrenia¹⁴ and 41% in bipolar disorder, with considerable variation between studies.¹⁵ This variation is mainly attributable to a lack of consensus on the best methodology for assessing adherence (qualitative vs quantitative research, patient self-reporting vs reports of clinicians, direct measurement of blood or urine parameters vs indirect measurements), the period of observation (from a week to several months), and the criteria for defining lack of adherence.¹⁶ Furthermore, medication adherence is a dynamic dichotomous behavior, influenced by multiple factors¹⁷ that may be related to patients (adverse effects of medication), their social relationships (family support and therapeutic alliance), cognitive problems such as impaired memory or attention,¹⁸ and the system for providing health services.¹⁹ Analysis of these factors has become a critical issue for clinicians and researchers, given that identification of specific risk factors will make it possible to carry out patient-targeted interventions.^{5,20} This is particularly important in early stages of severe mental illness, where it has been seen that treatment nonadherence is most critical for patient outcome.²¹

It has been reported that nonadherence to antipsychotic drugs in patients diagnosed with schizophrenia or schizophreniform psychosis is associated with a lower probability of a good response to treatment and significantly less improvement than in those who adhere to treatment,¹ a higher rate of positive and negative psychotic symptoms,²² and a greater risk of hospital readmission.²³ Similarly, it has been found that patients with bipolar disorder with good treatment adherence had less severe signs and symptoms, lower scores in the Clinical Global Impressions bipolar mania and hallucinations/delusions scales,²⁴ and a lower risk of suicide.²⁵ Martínez-Aran et al¹⁸ demonstrated that a history of nonadherence in adults with bipolar disorder was significantly associated with cognitive impairment.

The objectives of this systematic review are to provide a detailed and comprehensive description of the most important factors associated with lack of adherence to antipsychotic medication in patients with schizophrenia spectrum disorder and bipolar disorder and thereby to contribute to clarify our understanding of the factors underlying nonadherence.

MATERIALS AND METHODS

Literature Search

This systematic review was conducted and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.²⁶ We performed

From the *Department of Psychiatry, University Hospital of Araba (Santiago), Vitoria; †University of the Basque Country, Bizkaia; ‡Biomedical Research Centre in Mental Health Network (CIBERSAM), University Hospital of Araba, Vitoria; §National University of Distance Education (UNED), Madrid; and ||Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain.

Received June 2, 2015; accepted after revision April 20, 2016.

Reprints: Ana González-Pinto, PhD, MD, CIBERSAM, Department of Psychiatry, University Hospital of Araba (Santiago), Olaguibel 29, 01004-Vitoria, Spain (e-mail: Anamaria.gonzalez-pintoarrollaga@osakidetza.eus).

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ISSN: 0271-0749

DOI: 10.1097/JCP.0000000000000523

an electronic search in the PubMed (1990–2015) database, using the following MeSH terms: medication adherence, antipsychotic agents, mood disorder, psychotic disorder, and bipolar disorder. We selected 1990 as the start date for the search because of the reintroduction of clozapine in the following decade and the approval of risperidone by the Food and Drug Administration in the same period (1993).

In addition, we used the following filters: randomized controlled trial, meta-analysis, clinical trial, systematic review, controlled clinical trial, observational study, and humans. We reviewed all the articles published in English and Spanish. Subsequently, reference lists from the studies included in our systematic review were hand searched for additional relevant publications.

Inclusion Criteria

We included all the systematic reviews, meta-analyses, clinical trials, randomized clinical trials, and observational studies in which the study population was patients diagnosed with bipolar disorder, schizophrenia, schizoaffective disorder, or schizophreniform disorder who were being treated with antipsychotics and in whom factors associated with treatment adherence were assessed. Articles were excluded if patients had a diagnosis other than those mentioned previously or medical treatment with agents other than antipsychotics (eg, lithium or mood stabilizers), as well as if there was no assessment of factors associated with adherence to treatment with antipsychotics.

Data Collection and Extraction

From the set of articles selected in the systematic review, we excluded those that did not meet all the inclusion criteria or met any of the exclusion criteria. After reading the titles and the abstracts, we selected articles related to the objective of our study.

These were then summarized and assessed by 2 independent reviewers using the “Critical Reading Sheets” tool developed by the Basque Office for Health Technology Assessment,²⁷ and the most relevant data were retrieved. In the event of disagreement, a third researcher analyzed the article independently. The Basque Office for Health Technology Assessment tool facilitated the assessment of the methodological quality of the research described, classifying it as low, moderate, or high. In this review, we only included high-quality studies.

RESULTS

From the PubMed and manual backward searches, we identified a total of 96 articles. After screening and selection processes, we included 38 articles in this systematic review (Fig. 1). These corresponded to 22 cohort studies, 8 clinical trials, 6 reviews, 1 clinical guideline, and 1 meta-analysis. The characteristics of each study are summarized in Table 1.

A total of 51,796 patients were included, of whom 40,298 had been diagnosed with bipolar disorder, 10,385 with schizophrenia, 544 with schizoaffective disorder, 516 with schizophreniform disorders, and 53 with psychosis not otherwise specified.

Adherence to drug treatment can be measured by subjective methods, such as self-report and physician report, or objective methods, such as pill counting, blood or urine analysis, electronic monitoring, and electronic refill records.¹⁹ Of the 38 studies included in our review, 66% of the studies used subjective measures to assess adherence, 16% also used objective measures, 2% used only objective measures, and 16% of studies did not specify the measures used. The study by Lindenmayer et al¹ was the only one in which adherence was measured with objective measures only and patients had a mean adherence of 65.5%. In studies in which objective and subjective measures

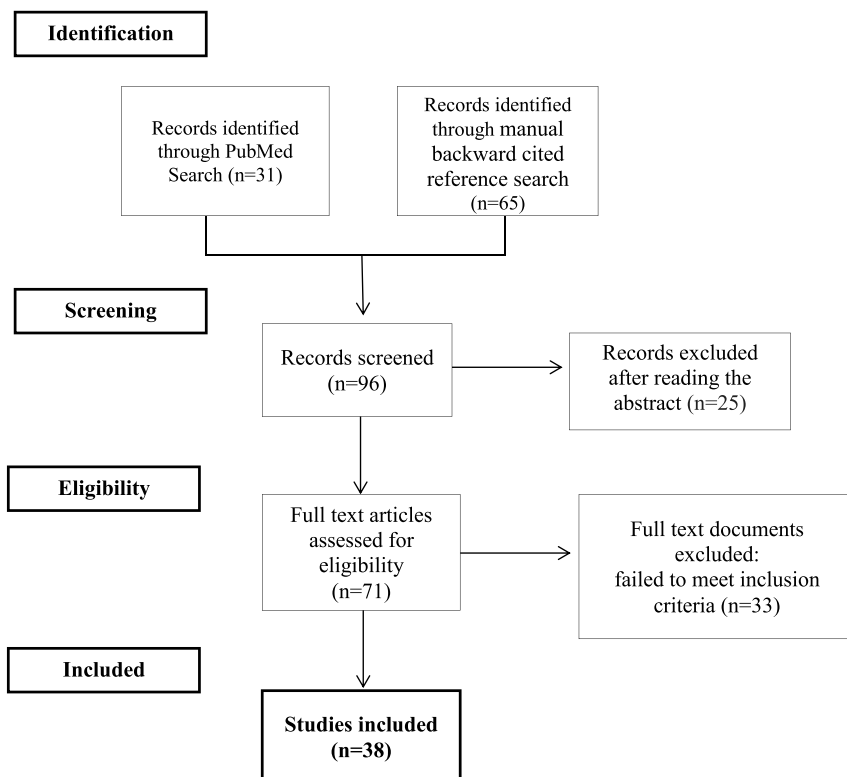


FIGURE 1. The PRISMA flow diagram figures.

were combined, adherence ranged from 60%¹⁸ to 81%,⁴³ whereas in studies in which only subjective methods were used, adherence ranged from 34%⁵² to approximately 80%.³⁹ Note that the reviews, meta-analysis, and guideline are not included in this description, because they are based on multiple studies using different methods and hence could have introduced bias into the analysis.

According to our findings, factors that influence treatment nonadherence are associated with patients themselves, the drug treatment, social issues, and the health system provider.

Patient-Related Factors

This category includes attitudes and behaviors, comorbidities and the severity of signs and symptoms, demographic and environmental factors, and the cognitive functioning of patients, as well as their relationship with their medication.

As part of the EMBLEM Project, González-Pinto et al²⁴ analyzed 1831 patients with bipolar disorder and found that the following factors were significantly positively associated with good adherence: good illness awareness (good adherence from the start of treatment) and a short duration of episodes. On the other hand, factors related to poor adherence were high scores in the Clinical Global Impressions hallucinations/delusions scale at baseline and depressive symptoms during mania. Regarding symptoms, a study including 128 patients diagnosed with schizophrenia⁵² observed that the time to discontinuation was significantly longer in those with an early nondysphoric response (7.3 months) than those with an early dysphoric response. In patients with schizophrenia and affective disorders, Verdoux et al²³ found that the intensity of delusional symptoms predicted poor treatment adherence ($P = 0.03$). In contrast, Patel et al⁴⁵ did not find symptom to be predictive of adherence.

Analyzing 469 patients with bipolar disorders, Johnson et al³⁷ found differences in adherence related to demographic characteristics; these included ethnic differences, with white patients having better treatment adherence than patients from other ethnic groups. These findings are in agreement with those of Zeber et al⁵⁴ and Fleck et al.³⁶ The authors found that Afro-American patients reported significantly more missed medication days and greater barriers to adherence than white patients. They also found a higher prevalence of patient-related factors influencing adherence (fear of becoming addicted and feeling that medication is a symbol of illness) in Afro-American patients than white patients, whereas the rates of treatment- or illness-related factors were similar in the 2 ethnic groups. Perkins et al⁴⁷ confirmed these findings, with black ethnicity again being associated with lower medication adherence in patients with schizophrenia. Among white patients, Perlis et al⁴⁸ observed in a cohort of 3460 patients with bipolar disorder that being Hispanic was associated with poor adherence, and, moreover, this association was not confounded by differences in other predictors such as household income or education. A similar pattern was observed in the study of Sajatovic et al,⁴⁹ in which patients with bipolar disorder from minority races had poorer adherence than other individuals with the same diagnosis. Education was another demographic characteristic related to adherence in the study of Johnson et al³⁷ in bipolar disorder (adherence decreased with level of education).

Young age has also been identified as a predictor of poor adherence in many studies, both in patients with schizophrenia and those with bipolar disorder.^{2,11,19} For the latter diagnosis, this association was found in the studies of González-Pinto et al,²⁴ Sajatovic et al,⁴⁹ Johnson et al,³⁷ who reported that adherence decreased to a mean age of 41 years and thereafter increased with

age, and Baldessarini et al²⁹ in which youth was a predictor of poor adherence, behind alcohol dependence and ahead of symptoms and adverse effects. In schizophrenia, Maeda et al⁴¹ noted that the age of patients was associated with increased awareness of disease prevention, older patients having more experience in the course of the disease, and possible relapses and hospital readmissions, and this led them to be more compliant with medication.

In addition to younger age, age at onset has also been cited as a risk factor for nonadherence to treatment, both in schizophrenia and bipolar disorder. Coldham et al³¹ found that nonadherent schizophrenic patients had an earlier age of onset, as well as being younger, and having poorer quality of life and premorbid functioning. Similarly, in a prospective study in 2010, Perlis et al⁴⁸ observed that 874 of 3640 patients with bipolar disorder (24%) reported nonadherence on 20% or more study visits and the clinical features that were significantly associated with this included earlier onset of illness, as well as suicide attempts and alcohol abuse.

Nevertheless, the association of age at onset and nonadherence might be related to younger age (ie, in first-episode studies, younger age, and age at onset are equivalent), and this has not been well investigated. Furthermore, there is no consensus on this association between age and adherence within the set of studies included in the review, some authors^{13,16,18,22,39,47,54} having observed no significant differences between patients in different age groups.

In the study carried out by Lindenmayer et al,¹ in 599 patients with schizophrenia, no baseline characteristics of patients, including demographic characteristics, initial body weight, and history of substance abuse, seem to be good predictors of adherence, whereas the severity of the depressive symptoms at baseline and a high level of hostility during the study were risk factors for nonadherence. In contrast to the aforementioned findings of Lindenmayer et al,¹ alcohol and cannabis use and abuse have been found to be significantly associated with nonadherence to medication in several studies. In the 2015 meta-analysis of Czobor et al,³³ in which they combined 2 studies, the European First-Episode Schizophrenia Trial (EUFEST) and the Clinical Antipsychotic Trials of Intervention Effectiveness, yielding a cohort of 1154 patients diagnosed with schizophrenia, they found that nonadherence to treatment was associated with substance abuse and hostility. This was consistent with earlier studies in schizophrenia, namely, those of van Nimwegen-Campailla et al,⁵² who found that patients who did not consume cannabis during treatment had a significantly longer treatment period (mean, 6.4 months) than cannabis users (mean, 4.3 months), and those of Miller et al,⁴³ who found that the use of cannabis was associated with a 2.4-fold lower rate of adherence, independent of age, socioeconomic status, sex, and the medication prescribed. Similarly, in patients with bipolar disorder, González-Pinto et al²⁵ observed that the use and abuse of cannabis were key factors for nonadherence. Furthermore, Coldham et al³¹ found that schizophrenic patients who were nonadherent (73 of 186 patients) consumed significantly more cannabis and alcohol than an adherent group, and Verdoux et al²³ described lower adherence in patients with schizophrenia and bipolar disorder who had alcohol abuse problems. Notably, in a clinical trial with 400 schizophrenic patients, ongoing substance abuse significantly predicted poor adherence,⁴⁷ and Sajatovic et al⁴⁹ found similar results in their study with veterans with bipolar disorder.

Regarding cognitive factors, Martínez-Aran et al¹⁸ found that nonadherent bipolar patients showed greater cognitive impairment in verbal learning tasks and some executive functions, as well as greater deterioration in spatial memory and in their ability to inhibit interference than adherent patients. Also in patients with bipolar disorder, Perlis et al⁴⁸ found that cognitive

TABLE 1. Summary of the Characteristics of the 38 Articles Included in the Review

| | Study | Diagnosis | Definition of Adherence/Nonadherence | Classification of Adherence | Methodology | % Adherent/Nonadherent | Type of Antipsychotic |
|---|---|---------------------------------|---|---|---|---|-----------------------|
| Adams and Scott (2000) ²⁸ | Clinical trial | SZ and affective disorders | Adherence: levels of adherence >75% | Adherent, partially adherent (<70%), uncertain adherence. | Subjective: Adherence measured at 3 times: 1. Verbal (Rating of Medication Influences scale) and written (Tablets Routine Questionnaire) self-report 2. Independent psychiatric assessment | Adherent: 49% Partially adherent: 38% Not classified: 21% | NR |
| Baldessarini et al (2008) ²⁹ | Randomized, prospective, cross-sectional cohort study | BPD | Nonadherence: ≥ 1 doses missed in a period of 10 d | Adherent vs nonadherent | Subjective: 1. Patient record form completed by participating psychiatrist 2. Patient self-completion form completed by the patient | By self-report: 56.5% nonadherent By psychiatrists: 6% nonadherent | NR |
| Bond et al (2007) ³⁰ | Review | BPD | NR | NR | NR | NR | Depot FGA and SGA |
| Coldham 2002 ³¹ | Prospective cohort study | SZ or schizoaffective disorders | Nonadherence: discontinuation of treatment before 1 y and/or taking the medication incorrectly or not all | Good adherence, inadequate adherence, nonadherence | Subjective: scale adapted from Hayward et al 1995 ³² | Adherent: 41% Inadequately adherent: 20% Nonadherent: 39% | NR |
| Czobor et al (2015) ³³ | Meta-analysis | SZ | NR | Adherence vs nonadherence | NR | NR | NR |
| Davis et al (1994) ³⁴ | Review | SZ | NR | NR | NR | NR | Depot FGA |
| Day et al (2005) ¹⁷ | Prospective, cross-sectional cohort study | SZ or schizoaffective disorder | NR | NR | Subjective: Drug Attitude Inventory, Morisky Medication Adherence Scale | NR | FGA and SGA |
| Faries et al (2012) ³⁵ | Randomized double-blind clinical trial | SZ or schizoaffective disorders | NR | NR | Subjective: Schizophrenia Care and Assessment Program Health Questionnaire | NR | Oral SGA |
| Fleck et al (2005) ³⁶ | Cross-sectional cohort study | BPD | Highly adherent: those who had taken the pharmacological treatment $\geq 75\%$ of the time | Highly adherent, partially adherent, nonadherent | Subjective: Structured questionnaire administered by the clinician | Highly adherent: 40% Partially adherent: 12% Nonadherent: 48% | FGA and SGA |

| Author | Study Design | Population | Nonadherence: answering "adheres about half of the time" or "almost never adheres" at ≥ 1 completed observations during the maintenance phase (3–24 mo) | Adherence vs nonadherence | Subjective: Adherence assessed by the clinician by selecting the response that best described adherence in the past 4 wk: 1. The medication was not prescribed to the patient 2. Patients almost always take the medication 3. Patient takes the medication half the time 4. Patients hardly ever take the medication | Adherent: 76.6% Nonadherent: 23.4% | Medication |
|---|---|---------------------------------|--|---|---|---|------------------|
| González-Pinto et al (2010) ²⁴ | Prospective, observational cohort study | BPD | | | | | Oral FGA and SGA |
| Jeste et al (2003) ⁵ | Cohort study | SZ or schizoaffective disorders | NR | NR | Subjective: Medication Management Ability Assessment: a measure of an individual's ability to adhere to treatment, adherence being assessed in relation to performance in a simulated medication management task | NR | Oral |
| Johnson et al (2007) ³⁷ | Cohort study | BPD | Adherence ("always adherent"): "I never forget my dose" | Always adherent, usually adherent, sometimes adherent, never adherent | Subjective: stated-preference web survey | Always adherent: 23% Usually adherent: 37% Sometimes adherent: 23% Never adherent: 17% | NR |
| Jónsdóttir et al (2013) ¹³ | Cross-sectional cohort study | BPD and SZ | Adherence ("full adherence"): taking all the medication the previous week and having a serum drug concentration within the reference range and a correct concentration-to-dose ratio | Full adherence, partial adherence, nonadherence | Objective: blood test Subjective: self-report of each patient using a Likert scale (0%-100%) | Schizophrenia: Full adherence: 55% Partial adherence: 34% Nonadherence: 11% Bipolar disorder: Full adherence: 57% Partial adherence: 26% Nonadherence: 17% | FGA and SGA |

Continued next page

TABLE 1. (Continued)

| | Study | Diagnosis | Definition of Adherence/Nonadherence | Classification of Adherence | Methodology | % Adherent/Nonadherent | Type of Antipsychotic |
|-------------------------------------|--|--|--|---|--|---|-----------------------------|
| Kahn et al (2008) ³⁸ | Open randomized controlled trial, 12-mo follow-up. | SZ, schizopreniform disorder or schizoaffective disorder | <p>Nonadherence was defined as:</p> <ol style="list-style-type: none"> The use of a dose below the predefined range including complete discontinuation; The use of a dose greater than the predefined range; The use of another antipsychotic drug each for >14 days for 6 mo; The use of any parenteral antipsychotic drug when the drug was active for >14 d for 6 mo. | Adherence vs nonadherence | <p>Subjective: Treatment discontinuation was defined as occurring on the 15th day as soon as 1 of the 4 criteria for discontinuation was met.</p> | <p>Nonadherence: Haloperidol: 72% Amisulpride: 40% Olanzapine: 33% Quetiapine: 53% Ziprasidone: 53%</p> | Oral FGA and SGA |
| Karow et al (2007) ³⁹ | Multicenter, observational cohort study | SZ | Adherence ("the patient almost always takes medication"); patients and clinician report that the patient has taken almost always the medication, in an assessment after 12 mo | Patient takes the medication: almost always, sometimes, hardly ever; classified at 12 mo | <p>Subjective: independently rated by patients and by physicians</p> | <p>Adherence by physicians: 82.9% Adherence by themselves: 88.3%</p> | Oral SGA Depot and oral FGA |
| Kemp and David (1996) ¹¹ | Randomized, double-blind, placebo-controlled trial | SZ and BPD | NR | Complete refusal, reluctant acceptance, occasional reluctance about treatment, passive acceptance, moderate participation, active participation | <p>Subjective: 1. Schedule for Assessment of Insight, a semistructured interview; Drug Attitude Inventory, a self-report measure; Attitudes to Medication Questionnaire, a semistructured interview</p> <p>2. Adherence was measured using an observer-rated scale</p> | NR | NR |
| Lacro et al (2002) ¹⁶ | Review | SZ | Adherence definition by: Strict criteria: "regularly taking medications as prescribed." "Stricter" criteria: "taking medications as prescribed at least 75% of the time." | NR | <p>Subjective: Likert-type assessment scale</p> | <p>For the strict criteria: 58.8% adherence For the stricter criteria: 49.5% adherence</p> | Oral and depot FGA and SGA |

| | | | | | | |
|--|--|---------------------------------|---|--|--|--|
| Lieberman (2007) ⁴⁰ | Randomized, controlled trial, 18-mo follow-up. | SZ | NR | Objective: monthly pill counts Subjective: 1. Direct interview with patients 2. Reports by their families, and clinicians | 74% of patients discontinued the medication (nonadherent) 64% of those assigned to olanzapine 75% of those assigned to perphenazine 82% of those assigned to quetiapine 74% of those assigned to risperidone 79% of those assigned to ziprasidone | Oral FGA and SGA |
| Lindenmayer et al (2009) ¹ | Randomized prospective double-blind clinical trial | SZ or schizoaffective disorders | Nonadherence: not taking the complete dose of the prescribed medication | Adherence vs nonadherence | Objective: 1. Daily pill counts for each patient 2. Measurement of olanzapine concentration in plasma (1/2 of the study patients) | Adherent: 65.5% Nonadherent: 24.5% Oral SGA |
| Maeda et al (2006) ⁴¹ | Cross-sectional cohort study | SZ | Nonadherence: not taking the medication for at least 1 wk in the last month | Adherence vs nonadherence | Subjective: Rating of Medication Influences scale | NR |
| Martinez-Aran et al (2009) ¹⁸ | Prospective, cross-sectional cohort study | BPD | Nonadherence: if at least 1 of the 3 assessments suggested nonadherence. | Adherent vs nonadherent | Three adherence assessments: Subjective: 1. Direct interview with patients 2. Interviews with first-degree relatives or a partner Objective: 3. Plasma concentrations of mood stabilizers measured during the previous 2 y. | Adherent: 60% Nonadherent: 40% NR |
| Menzin et al (2003) ⁴² | Retrospective cohort study | SZ | Nonadherence: patients who were identified on the basis of having no record of a prescription refill for the medication in the last 6 mo of the 1-y follow-up period. | Adherence vs nonadherence | Subjective: records from paid medical and pharmacy claims for a random sample of California Medicaid ("Medi-Cal") recipients | Discontinuation in patients who initiated the therapy with FGA: 58% Discontinuation in patients who initiated the therapy with SGA: 33% Oral FGA and SGA |

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TABLE 1. (Continued)

| | Study | Diagnosis | Definition of Adherence/Nonadherence | Classification of Adherence | Methodology | % Adherent/Nonadherent | Type of Antipsychotic |
|-------------------------------------|---|--|---|----------------------------------|--|--|-------------------------------|
| Miller et al (2009) ⁴³ | Longitudinal prospective cohort study | SZ, schizophreniform or schizoaffective disorder | Adherence: average of weekly adherence for 1 mo was $\geq 50\%$ of adherence | Adhering patients vs nonadhering | Three adherence assessments: Objective: 1. Plasma levels of antipsychotics after 16, 24, 36, and 52 wk. 2. Additional blood tests Subjective: 3. Reports by patients and their families, as well as clinicians | Adherent: 81% Nonadherent: 19% | Oral SGA |
| Mutsaers et al (2003) ²² | Prospective, cross-sectional cohort study | Schizophreniform disorder | NR | Good vs poor adherence | Subjective: Compliance from the patient's doctors, nurses, caregivers and family members, etc, as well as from their medical record | Good adherence: 56% Poor adherence: 44% | Oral FGA and SGA |
| Nosé et al (2003) ² | Review | SZ, psychosis, and severe mental disorders | Nonadherence: not attending scheduled appointments and not taking the medication as prescribed | Adherence vs nonadherence | Subjective: 1. Patient interview (9% studies) 2. Review of case notes; physician interview (77% studies) 3. Rating scales (14%) Objective: 4. Classification scale: urine test (1%) | Adherent: 27% Nonadherent: 73% | NR |
| Olivares et al (2008) ⁴⁴ | International, long-term, ongoing, observational cohort study | SZ | NR | Compliance vs noncompliance | NR | Noncompliance group 12-mo follow-up: 30.8% Noncompliance group 24-mo follow-up: 31.3% | Depot SGA |
| Patel et al (2008) ⁴⁵ | Cross-sectional cohort study | SZ or schizoaffective disorders | NR | Compliance vs noncompliance | Subjective: Rating of Medication Influences | NR | FGA depot FGA and SGA oral |
| Perkins (2002) ⁴⁶ | Review | SZ | Nonadherence: includes errors in filling the prescription form, refusal to take the medication, early medication discontinuation, and taking medication at incorrect doses or at the wrong time | NR | NR | NR | NR |
| Perkins (2008) ⁴⁷ | Multicenter, randomized double-blind clinical trial | SZ, schizophreniform or schizoaffective disorder | Nonadherence: patient discontinuation of medication before completing 1 y of treatment | Adherent vs nonadherent | Subjective: Insight and Treatment Attitude Questionnaire | Adherent: 49% Nonadherent: 51% | Oral SGA |

| | | | | | | | |
|---|---|----------------------------|---|---|--|--|---------------------------------|
| Perlis et al (2010) ⁴⁸ | Multicenter, observational prospective cohort study | BPD | Nonadherence: missing at least 25% of total doses of any 1 medication. | Adherent vs nonadherent | Subjective: Clinical Monitoring Form: patients were asked to report the total no. missed doses of each medication that they were prescribed in the preceding week and this was recorded by the clinician as mg per wk missed. Subjective: MPR for patients receiving any antipsychotic medication. | Adherent at all visits: 46.40% Nonadherent < 10% of visits: 13.8% Nonadherent between 10% and 20% of visits: 15.8% Nonadherent ≥ 20% of visits: 23.9% | NR |
| Sajatovic et al (2006) ⁴⁹ | Retrospective cohort study | BPD | (Fully) adherence: patient has received all medication needed to take their AP as prescribed. | Fully adherent, partially adherent, nonadherent | Subjective: MPR for patients receiving any antipsychotic medication. | Fully adherent: 51.9% Partially adherent: 21.2% Nonadherent: 26.9% | Oral FGA and SGA |
| Sajatovic et al (2009) ⁵⁰ | Cross-sectional cohort study | BPD | NR | NR | Subjective: 1. Insight and Treatment Attitude Questionnaire 2. Subjective Medication Interview: illness attitudes, attributions and behaviors, social relations, treatment history and medication experience, self-medication, quality of life, stigma, culture/ethnicity, and health care logistics | NR | NR |
| Sendt et al (2015) ⁵¹ | Systematic review | SZ | No consensus: the definition varying between studies reviewed | No consensus: the classification varying between studies reviewed | The method varied between studies | Rates varied between studies, no mean rate reported | Oral and depot FGA and SGA |
| van Nimwegen-Campailla et al (2010) ⁵² | Randomized double-blind placebo-controlled clinical trial | SZ | NR | NR | Subjective: Life Chart Schedule | Adherence: 34% Nonadherence: 6% | Oral SGA |
| Velligan et al (2009) ¹⁹ | Guidelines | SZ and BPD | Adherence (most broadly used definition): ≥80% of the medication taken, both for SZ and BPD | NR | Subjective: 7% of the studies (eg, self-reports) Objective: <23% of the studies (eg, blood tests) | NR | Oral and depot FGA and SGA oral |
| Verdoux et al (2000) ²⁵ | Prospective longitudinal cohort study | SZ and affective disorders | Poor adherence: medication discontinuation for at least 2 wk in a period of 6 mo | Good vs poor adherence | Subjective: interviews with patients themselves, their relatives and clinicians, and data collection from hospitals every 6 mo for 2 y. | Interrupted their medication at least once for the 2-y follow-up. 53.1% Poor medication adherence: 33%-44%. | Depot and oral |

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TABLE 1. (Continued)

| Study | Diagnosis | Definition of Adherence/Nonadherence | Classification of Adherence | Methodology | % Adherent/Nonadherent | Type of Antipsychotic |
|-----------------------------------|-----------|---|-----------------------------|---|--|-----------------------|
| Weiden et al (2004) ³³ | SZ | Nonadherence: missing any antipsychotic medication in the previous month. NR | Adherence vs nonadherence | Subjective: self-reports | Adherence: 63% Nonadherence: 37% | Oral FGA and SGA |
| Zeher et al (2008) ³⁴ | BPD | NR | Good vs poor adherence | Subjective: 2 complementary self-report measures: 1. Missed medication days (no. days in the last 4 d on which the patient forgot to take the medication at least once) 2. Intrapersonal barriers (Morisky Medication Adherence) | 1. No missed doses: Good adherence: 50.9% Poor adherence: 49.2% 2. Morisky: Good adherence 51.2% Poor adherence 48.7% | NR |

BPD indicates bipolar disorder; MPR, medication possession ratio; NR, not reported; SZ, schizophrenia.

impairment was the only adverse effect significantly associated with nonadherence. In line with this, in patients with schizophrenia, Jeste et al⁵ found that deterioration in cognitive functions, in particular conceptualization and memory, had greater predictive value of poor patient medication self-management than other factors, namely, sex, age, level of education, symptom severity, and attitudes toward medication. In contrast to these findings, in patients with schizophrenia, Perkins et al⁴⁷ found the highest level of adherence to be significantly associated with lower executive functioning, and in the review by Send et al,⁵¹ neurocognitive functioning did not seem to impact medication adherence.

Some adverse effects, such as secondary extrapyramidal symptoms (akathisia, pseudoparkinsonism, dyskinesia, and acute dystonic reactions), neuroleptic dysphoria, sexual dysfunction, and weight gain are associated with nonadherence in schizophrenic patients.⁴⁶ Subjective distress, weight gain, and body mass index (BMI) were found to be predictive of therapeutic nonadherence, specifically, obese individuals being twice as likely to report nonadherence as patients with a normal BMI.⁵³ Weight gain was also a fear in patients with bipolar disorder and a better predictor of nonadherence than adverse effects such as excessive sedation and tremors.²⁹

In both types of disorders, illness awareness and trust in the medication have been found to be predictive factors for good adherence.^{2,19,31,33,46,51} In schizophrenia, according to patients, the most important reasons for continuing with their medication are the beneficial effects in terms of control of positive symptoms, a perception of improvement,^{35,39} a reduction in the rate of hospital readmissions, and the prevention of relapses.⁵² With regard to the reasons for discontinuing treatment, patients have cited insufficient improvement or actual worsening of symptoms, adverse effects of the medication,^{19,35,37} denial of the illness, and not considering medication to be necessary.^{19,45} In the clinical trial carried out by Adams and Scott,²⁸ including 39 patients with schizophrenia, it was found that perception of illness severity and benefits of the treatment explained 43% of the variance in adherence.

Administering structured interviews about concerns and expectations regarding medication to 90 patients with bipolar disorder, Sajatovic et al⁵⁰ found that 39% of patients were not concerned about their medication; 29% had specific concerns (worrying about developing more health problems); 6% feared becoming addicted; and 5% were worried about the economic costs. Patients' expectations ranged from hoping that the medication would be able to decrease their symptoms and stabilize their mood (23%) to helping them to become "normal" (20%) and even curing them (20%), individuals reporting a feeling of disappointment when this did not happen.

Drug Treatment-Related Factors

First- Versus Second-Generation Antipsychotic Drugs

The Clinical Antipsychotic Trials of Intervention Effectiveness compared effectiveness of first-generation antipsychotic (FGA) and second-generation antipsychotic (SGA) drugs in patients with chronic schizophrenia. Differences in time to discontinuation of treatment due to ineffectiveness were lower with olanzapine, although there were no differences between the FGA perphenazine and SGA drugs such as risperidone or quetiapine.⁴⁰ The EUFEST study also found that the risk of discontinuation was lower with olanzapine than with haloperidol (33% vs 72%). In fact, the risk of discontinuation due to any cause was higher with haloperidol than with all SGAs. With respect to discontinuation due to nonadherence, there were also no differences between first- and second-generation drugs.³⁸

Another study compared 298 schizophrenic patients starting antipsychotic treatment with FGAs (n = 93) or SGAs (n = 205), the SGAs being associated with significantly less treatment switching and less use of concomitant medications than FGAs. On the other hand, in the 1-year follow-up, it was observed that both groups of patients took the drugs on 60% of days.⁴² In line with these findings, in a review of the risks of nonadherence, Lacro et al¹⁶ reported that there was inconclusive evidence of a relationship between nonadherence and the type of treatment.

In a recent systematic review, that only included studies in schizophrenia, Send et al⁵¹ found no significant differences in rates of adherence between the 2 types of antipsychotics. On the other hand, in bipolar disorder, Sajatovic et al⁴⁹ observed that patients who take FGAs were more adherent than those taking SGAs.

To sum up, it seems that some SGAs give some advantages in relation to adherence versus FGA. Nevertheless, the rates of nonadherence are high, and new therapeutic approaches are required.

Depot Versus Oral

Formulation type has been found not to be a consistent predictor of nonadherence.^{45,51} The main reasons for changing from an oral to an intramuscular or depot antipsychotic^{30,34,44} are usually nonadherence and resistance to oral antipsychotics.^{34,44,45} Prescription of a depot medication must, however, be accompanied by discussion with the patient about personal benefits, because beliefs and attitudes have an important influence on adherence to depot medication.⁴⁵

Factors Associated With Social Relationships

A good therapeutic alliance between the patient and the physician^{17,54} and the level of family support^{31,46} have been found to be significantly associated with good treatment adherence in both pathologies.¹⁹ In the multivariate analysis carried out by Zeber et al,⁵⁴ with patients with bipolar disorder, the overall score on

the Health Care Climate Questionnaire (a measure of therapeutic alliance) was found to be significantly positively associated with the number of days on which medication was not missed. Furthermore, in schizophrenic patients, Coldham et al³¹ found a higher level of family involvement in the adherent group (80%) than the nonadherent group (51%).

Factors Associated With the Health Service Provider

Barriers to or difficulties accessing treatment (lack of economic resources for buying medication or lack of transport to reach health service providers) were found to be predictive of nonadherence in schizophrenic and bipolar patients in the reviews conducted by Perkins⁴⁶ and Velligan et al,¹⁹ respectively. Patient experience with the health system was also found to be associated with subsequent adherence to drug treatments in both types of disorder.^{17,19}

To summarize the findings in a clear way, Table 2 lists all factors associated with nonadherence rates found in literature by diagnosis. We can observe that a number of factors are common to both types of disorders, whereas other factors are more closely related to the clinical symptoms of each diagnosis.

DISCUSSION

Adherence to antipsychotics by patients diagnosed with psychosis is notably low; a review found a mean rate of 42%.¹⁴ This has negative consequences for patients, their families, and communities. For clinicians, it makes treatment nonadherence one of the most important challenges in treating these highly prevalent psychiatric conditions. Overall, it is clear that great efforts are needed to enhance adherence. From this review, we conclude that the most important factors to consider are associated with patients themselves and with the medication.

The nonmodifiable factors associated with patients themselves include young age, and although results differed between

TABLE 2. Factors Common to Both Pathologies and Specific Factors by Diagnosis

Factors Commonly Involved in Nonadherence

- Low level of education
- Young age
- Cognitive impairment
- High intensity of delusional symptoms and suspiciousness
- Substance abuse/dependence
- Minority ethnicity
- Poor insight
- Poor therapeutic alliance
- Low socioeconomic status
- Barriers to treatment, bad patient experience of admission

Factors Potentially Involved in Nonadherence in Bipolar Disorder

- Psychotic symptoms
- High severity of depressive episodes
- Rapid cycling
- High affective morbidity
- Comorbidity with other conditions (anxiety, obsessive compulsive disorder)
- Adverse effects: weight gain, cognitive effects
- Longer duration of episodes suicide attempts

Factors Potentially Involved in Nonadherence in Schizophrenia

- Positive symptoms
- High severity of depression at baseline
- Early dysphoric response
- Short illness duration
- Adverse effects: extrapyramidal symptoms, neuroleptic dysphoria, akathisia, sexual dysfunction, and weight gain.
- Poor response to or tolerance of treatment
- Early treatment discontinuation rate
- Hostility to treatment

studies, as we have said previously, we found this association in most cases.³¹ In particular, adolescents may be less tolerant to the adverse effects of antipsychotics (sexual dysfunction, sedation), more concerned about the stigma of the illness, or more impulsive and impatient if treatment is complex or does not improve symptoms sufficiently fast, and these attitudes can lead to treatment discontinuation.⁵⁵ Furthermore, ethnicity is associated with significant differences in adherence, antipsychotic adherence rates tending to be lower in black than white patients.^{36,37,54} On the other hand, level of education and quality of life also have an impact on adherence; patients with a low level of education or poor quality of life are more prone to nonadherence.³⁷

Regarding modifiable factors, a psychological model has been proposed, the Health Belief Model, which aims to explain and predict health behaviors, focusing on attitudes and beliefs of individuals that may have an influence on adherence.¹⁶ This model indicates 2 behaviors that play a very important role in medication acceptance: (1) patients must be aware of their own condition (they must perceive their vulnerability and the seriousness of the illness) and (2) they must know and interiorize the benefits of treatment adherence.^{24,31,46} These 2 requisites are of particular importance in patients with first psychotic episodes, given that they tend to occur during adolescence,⁵⁶ a critical period of development at biological, personal, and social levels.^{45,57} For this reason, a specialized early intervention program is needed at this stage of the illness in young patients,^{58,59} to attempt to minimize the consequences of the psychosis.⁶⁰ A study on adolescents, all treated with antipsychotics, assessed their subjective experience with medication with the “Drug Attitude Inventory” and found that a change to more positive medication attitudes was associated with significantly greater medication adherence, decreases in psychopathology, and improvement in functioning.⁶¹ To achieve this change in patient attitude, it is essential to include psychoeducation in the treatment program, to teach patients about their illness, medication and adverse effects, and relapse prevention.¹⁹

Cognitive Behavioral Therapy is a model of psychotherapy intervention focused on understanding patient's perception of their problems and treatment. Cognitive Behavioral Therapy therapists help patients identify and modify negative automatic thoughts about medications and strengthen their belief that taking their medication is a step toward recovery and improving their well-being. This type of therapy has been found to improve adherence and symptom management and to enhance insight in patients with schizophrenia.¹⁹

In addition, psychoeducation may be extended to include the patient's family, as seen in previous studies,^{31,46} and then treatment becomes more effective in reducing relapse rates and the symptoms of the illness than if psychoeducation is given only to the patient.⁶² As long as the patient consents, involvement of a family member would help improve the management of the patient's treatment program, providing support through the course of the disease and reminding the patient take medications, attend health appointments, etc, and improving the patient environment.

Therapeutic alliance has also been identified as a relevant factor for improving adherence to antipsychotics.^{17,54,63} A study on patients with bipolar disorder found that patient collaboration was significantly associated with good adherence, that is, patients being involved as a comanager of their own illness, with the psychiatrist considering their opinions and comments during the intervention process, helped improve the management of the illness, and hence led to better treatment adherence.⁶⁴ These 2 factors, therapeutic alliance and patient collaboration, together with social support and a positive environment^{31,46} are also predictive of good adherence during treatment.

Therefore, the first contact between the patient and the health system is a key factor because it influences patient perception. The following factors help patients develop a more positive perception of their illness and drug treatment: approachable clinicians, who discuss the beliefs, fears, and needs of patients regarding their illness and treatment; continuity of care provided by a single health care team; more frequent and/or longer visits¹⁹; and easy access to their health center.⁶⁵ Regarding the last of these factors, physical or economic barriers, such as a lack of public transport to reach the health center or difficulties meeting the costs of new antipsychotics, clearly hinder patients' capacity to adhere to medication.^{19,46} Health centers should explore ways to facilitate access, and clinicians should provide support and advice as part of the treatment, being proactive in the breaking down of barriers, for example, offering free samples of drugs to start the treatment,⁶⁶ or informing patients and families about the drugs, and helping them obtain grants to cover the cost of drugs, especially in the case of people with low economic resources. These gestures could also contribute to improve patient-clinician relationships.

In line with these ideas for improvement, new strategies for therapeutic interventions include offering economic rewards to patients with a psychotic disorder to investigate whether financial incentives would affect their adherence to antipsychotic medication. A study with 73 patients with schizophrenia and bipolar disorder demonstrated the effectiveness of this type of intervention, showing benefits in adherence, contact, monitoring, and patient trust in 77% of cases.⁶⁷ Further research is needed into this type of intervention; however, benefits were only found in the short-term, intrinsic demotivation being observed in the long term.⁶³

Other important modifiable risk factors are alcohol and drug abuse, which can be said to have an almost direct relationship with nonadherence to antipsychotic drugs.^{23,33,43,47,52} Notably, in a study with patients with bipolar disorder, alcohol dependence was the factor most strongly associated with nonadherence, above and beyond being young, and even the potential adverse effects of treatment.²⁹ The findings of Barbeito et al⁶⁸ in the first psychotic episodes support the view that there is a link between nonadherence and cannabis use, and interestingly, they found not only that patients who had never used cannabis had better adherence but also that patients who were nonusers with a history of dependence were also good adherers to treatment. These results are in line with those of the 2006 study of Sajatovic et al,⁶⁹ in which past substance use disorder did not differ between adherent and nonadherent patients. Hence, we conclude that cannabis abuse does not cause irreversible damage in patients and that the aim of interventions should be to create a targeted and personalized treatment, not only to increase medication adherence but also to encourage the cessation of substance abuse.

Among the adverse effects of antipsychotics, weight gain is probably the health problem that is most likely to result in nonadherence.¹⁹ In fact, there is an association between adherence and patient BMI, adherence being lower among those with higher BMIs, and more subjective distress was related to weight gain.⁵³ Extrapyramidal adverse effects such as pseudoparkinsonism, akathisia, dyskinesia, and sexual dysfunction were also found to be of great importance in nonadherence.⁴⁶ One way to address this type of factor would be to create strategies for offering specific treatments depending on patients' characteristics, carefully considering the risk-benefit ratio of each drug and selecting those least likely to have relevant adverse effects in given patients.^{70–74} Type of antipsychotic may be a factor underlying loss of adherence in some patients, related to low efficacy or severe adverse effects, but results were mixed across the articles reviewed. Specifically, not all studies found significant differences in adherence between FGA and SGA drugs that would be able to guide our

choice, and more importantly, loss of adherence was observed with both types of antipsychotic.

Regarding the route of administration, depot formulations are the type most widely chosen for patients with severe lack of adherence, although again data are mixed, results differing by trial design.⁷⁵ Despite the use of depot medication, patient lack of insight or poor therapeutic alliance over time and among others factors mean that patients tend to become nonadherent again.

We conclude that neither lack of medication effectiveness nor the choice of route of administration is the real factor that prevents patients from continuing treatment. If possible, it is important to accompany treatment with an informative and explanatory discussion about the benefits thereof and to reduce polypharmacy (which increases the risk of adverse events and pharmacokinetic interactions, thereby increasing the likelihood of nonadherence). In addition, reducing the number of pills, when possible, is a good way to increase adherence, making the treatment easier for patients to remember and follow.⁶⁶

Regarding adverse events, there are innovations in personalized medicine, with growth in the area of pharmacogenetics. Numerous studies have found polymorphism in genes that are involved in the metabolism of antipsychotics. Moreover, in relation to adherence, there is a direct relationship between some polymorphisms and the development of adverse events. For example, it has been found that genetic polymorphisms in the genes encoding cytochrome P450 enzymes CYP2D6 and CYP2C19 provide an explanation as to why some patients do not respond to drugs as expected, whereas others show an exaggerated response or serious adverse effects after receiving a standard dose that should have been safe for them. These differential responses to treatment are related to 2 phenotypes in the population, the extensive metabolizer and the poor metabolizer. The gene coding for CYP2D6 is highly polymorphic, and several mutations have been identified in poor metabolizers, all leading to the absence of functional CYP2D6. It is relatively common that poor metabolizers of CYP2D6 and CYP2C19 show an exaggerated drug response and adverse effects when they receive standard doses, whereas at the other extreme, so-called ultrarapid metabolizers do not respond to standard doses. Recently, the molecular basis of ultrarapid metabolism has been identified as the CYP2D6 gene amplification.^{76,77} Given this, new personalized medicine has the potential to reduce adverse events and indirectly increase adherence.⁷⁸

Another new area of knowledge has emerged, namely, pharmacogenovigilance.⁷⁹ The most common adverse effects of drug therapy are observed before approval for clinical use. The less common adverse effects may not be observed, however, until after regulatory approval in clinical practice; in some cases, serious effects may be discovered many decades after a drug receives regulatory approval.⁸⁰ The aim of pharmacovigilance is to monitor drug safety and effectiveness after approval and understand the epidemiology and mechanisms of vast heterogeneity in drug-related outcomes, at individual and population levels. This area together with pharmacogenomics, seeking to explain the genomic basis of interindividual differences in efficacy and safety of drugs, creates the new term “pharmacogenovigilance.” This union enables a more mechanical approach, allowing extrapolation of early signs of drug-related events from 1 population to another, when the worldwide distribution of pharmacogenomics biomarkers linked to a given drug safety or efficacy event is known.⁷⁹ It also helps us understand the pharmacokinetic and pharmacodynamic performance of drugs in population extremes, such as poor and ultrarapid metabolizers, mentioned previously and thus prompts a population-scale overview during postmarketing surveillance.⁸¹

A third new area of knowledge is pharmamicrobiomics. In relation to the Human Microbiome Project, it has been observed that drug-microbiome interactions may shed light on the influence that individual microbiota can have on the effects and adverse events of therapies in individuals. Gut microbiota can vary from 1 person to other because of differences in diet, health, use of medicines, place of residence, or age. Some drugs are particularly affected by gut microbes, and this is a little explored area that may help us understand patterns of adherence.⁷⁸ For instance, it has been demonstrated that the gut microbiota has a role in the metabolic dysfunction associated with olanzapine in an animal model.⁸² In the future, the microbiome will be taken into account along with other factors, in personalized medicine. It is likely that considering the microbiome in the development of personalized medicine will initially be too expensive. Nevertheless, the use of this new tool may be justified and provide benefits in some patients with serious adverse events.

On the other hand, it has been observed that long hospital stays favor medication adherence. In particular, they allow pharmacotherapy to be optimized and to be more effective, given that patients' beliefs and attitudes regarding their illness and medication can slowly change during admission, enabling a therapeutic alliance to develop, and this subsequently helps maintain treatment adherence.⁸³ In relation to this, psychoeducation therapies mentioned previously play a very important role in the preparation of patients for the type of response they should expect, how their symptoms will improve, the management of adverse effects, and how to adjust their medication dosage.

Another very important area in which there is margin for improving practice relates to cognitive impairment in patients with psychiatric illnesses. In recent years, several studies have been conducted in an attempt to clarify the relationship between cognitive dysfunction and nonadherence. Jeste et al⁵ indicated that memory and conceptualization dysfunction were very good predictors of poor medication management. However, the results regarding predictive factors are mixed. On the one hand, Martinez-Aran et al¹⁸ analyzed cognitive dysfunction in a sample of patients with bipolar disorder and found that patients with the lowest levels of adherence had greater cognitive impairments. In this type of patients, adherence can be improved with the use of electronic pill boxes or alerts, to remind them to take their medication and hence adhere to their treatment.⁸⁴ Furthermore, Perlis et al⁴⁸ observed that memory impairment was the only significant predictor of nonadherence in 3460 patients with bipolar disorder, which might suggest that nonadherence is likely to result, at least in part, from the cognitive deficits that are increasingly recognized in these patients.⁸⁵

In line with this, a study by Torrent et al⁸⁶ in patients with bipolar disorder and moderate to severe cognitive disability showed functional improvement after a functional remediation program compared with usual care and psychoeducation. In this new type of intervention, patients perform exercises to improve memory, attention, problem solving and reasoning, multitasking, and organization, to strengthen their cognitive and general functioning. With the same objective, Velligan et al⁸⁷ developed a program called cognitive adaptation training, which seems to be a promising strategy to improve adherence. Cognitive adaptation training focused on medication adherence uses individually tailored environmental supports (eg, 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 (eg, picking up prescriptions) and getting to appointments. In a study published in 2008 involving patients with schizophrenia, Velligan et al⁸⁷ found that a full cognitive

adaptation training program, focused on many aspects of community adaptation, and a cognitive adaptation training program, focused only on adherence to medication and appointments, were both better than 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 2 interventions.

On the other hand, unlike the aforementioned studies, Perkins et al⁴⁷ and Maeda et al⁴¹ found that patients with the poorest adherence had better cognitive performance. Such contradictions between studies make it necessary to conduct further research in this area and, in turn, identify techniques that are useful for patients.

In several studies, symptom at baseline was found to be a relevant factor. In particular, the duration of episodes was observed to be a key factor in patients with bipolar disorder, adherence being better in patients with short episodes than those with longer ones.²⁴ In patients with schizophrenia, Lindenmayer et al¹ found that the time to medication discontinuation was significantly longer in patients with high levels of hostility toward the study and those with poor insight.^{33,88} Taking into account these results, characterizing the symptom, monitoring symptom response on an ongoing basis (eg, using a daily checklist or mood chart),¹⁹ and reducing patient hostility may contribute to preventing future nonadherence.

Table 3 summarizes factors that it might be feasible to modify through interventions to improve patient adherence. A psychoeducational intervention in which patients are provided with a global overview of all these factors, with emphasis on aspects that are most relevant to their own profiles, may help encourage them to take a proactive role in the management of their illness.

Limitations

The findings of the review are limited by the wide range of rates of adherence found in the scientific literature (from 10 to 76% in schizophrenia¹⁴ and 20 to 66% in bipolar disorder),¹⁵ this being attributable to the different measures and definitions of

adherence used. The percentages of studies included in our review that used subjective (66%), objective (2%), or both (16%) kinds of measures are consistent with figures in other studies described in the clinical guidelines developed by Velligan et al.¹⁹ These authors¹⁹ evaluated 161 studies on adherence, and 77% used only subjective measures. Nosé et al² also found that only 1% of studies used objective measures (urine tests).

As we explained previously, the rate of adherence differs markedly between studies that use subjective measures (34%^{52–80%}³⁹). Errors associated with this approach can be seen in the study of Baldessarini et al²⁹: adherence measured by self-report resulted in more than half (56%) of patients being classified as nonadherent, whereas in assessments carried by psychiatrists, only 6% of patients were classified as nonadherent.

There are also sources of error when using objective measures. Plasma or urine measures only determine whether the patient is taking the medication at the time but cannot be considered proof of their usual behavior.⁴³ If the patient only took the medication before the test, adherence would be overestimated.¹³ In particular, it is essential to use objective measures for testing adherence, when nonadherence is denied by the patient and ignored by the family.¹⁸

Pill counting can also overestimate adherence, because patients can throw away pills without ingesting them.¹ In brief, by describing these results, we want to underline the wide range of measurements in the literature and the need for agreeing on an appropriate methodology, to enable more accurate research in this field and comparisons between studies.

In terms of our methodology, another limitation is that the assessment of the quality of each article using critical reading sheets is open to a degree of subjective interpretation, although we have attempted to compensate for this to some extent by 2 different researchers reviewing each article independently.

Despite these limitations, in this systematic review, we have been able to classify the multiple factors associated with adherence to antipsychotics, in patients from the 38 selected studies, into 4 groups related to patients themselves, the drug treatment, their environment (social issues), and the health system provider. Finally, all factors were grouped by diagnosis to clarify the results,

TABLE 3. Potential Areas for Intervention to Improve Adherence

Factors associated with patients

- Pay special attention to young patients for early intervention programs.
- Tackle dependence on alcohol and other drugs, encouraging cessation.
- Increase awareness of the illness and of the benefits of antipsychotic treatment (eg, through psychoeducation and psychotherapy interventions).
- Prevent or minimize adverse effects of antipsychotics, implementing personalized treatment.
- In cases of cognitive dysfunction, use programs and/or technical devices to support treatment adherence.
- Assess patient education and quality of life and take the results into account in planning treatment.
- Characterize the symptom at onset and during the course of the illness.
- Consider patient ethnicity as a potential risk factor for nonadherence.

Factors associated with pharmacological treatment

- Accompany treatment with an informative and explanatory discussion about the benefits of treatment.
- Reduce polypharmacy, making the treatment easier for patients to remember and follow.

Factors associated with social relationships

- Improve the patient-physician relationship (strengthening the therapeutic alliance).
- Involve the family in the illness of the patient.

Factors associated with the service provision system

- Avoid patients' first contact with the health system being a traumatic experience.
- Reduce access barriers to treatment and health centers (eg, offering free samples of medications to start the treatment or inform patients of grants available to cover the medication costs).

allowing us to produce a summary of all the key factors that may affect patients in the management of their medication.

We can conclude that great efforts must be made to enhance adherence in patients with schizophrenia and bipolar disorder. Among the most important factors influencing this behavior, there are nonmodifiable factors, such as young age (adolescents having lower levels of adherence) and ethnicity but also many potentially modifiable factors, and these include the following: symptom at baseline, alcohol and drug abuse, illness awareness, therapeutic alliance and family support, adverse effects (weight gain and extrapyramidal adverse effects being the most important for patients), quality of life, level of education, previous experience with health services, and level of cognitive impairment.

Improvements in patient symptoms and quality of life are dependent on good adherence to drug treatment. In the era of precision psychiatry, the choice of the right treatment for the right patient may be an affordable unmet need,⁸⁹ and this may be particularly relevant when trying to predict poor treatment adherence. Hence, early interventions focused on adherence enhancement may be particularly relevant.⁹⁰ Accordingly, this systematic review seeks to facilitate efforts to improve patient behavior, by identifying factors associated with adherence in specific diagnoses and proposing potential strategies to address modifiable factors.

AUTHOR DISCLOSURE INFORMATION

This study was supported by health research funds from the Spanish Government, cofinancing FEDER (PI12/02077, PI11/01977, PI14/01900); the Basque Foundation for Health Innovation and Research (BIOEF); Networking Center for Biomedical Research in Mental Health (CIBERSAM); and the University of the Basque Country (GIC12/84). The psychiatric research department in University Hospital Araba is supported by the Stanley Research Foundation (03-RC-003). Dr Gonzalez-Pinto has received grants and served as consultant, advisor, or CME speaker for the following entities: Almirall, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Glaxo-Smith-Kline, Janssen-Cilag, Jazz, Johnson & Johnson, Lundbeck, Merck, Otsuka, Pfizer, Sanofi-Aventis, Servier, Shering-Plough, Solvay, the Spanish Ministry of Science and Innovation (CIBERSAM), the Ministry of Science (Carlos III Institute), the Basque Government, the Stanley Medical Research Institute, and Wyeth. Dr Vieta has received grants and served as consultant, advisor, or CME speaker for the following entities: AB-Biotics, Actavis, Allergan, AstraZeneca, Bristol-Myers Squibb, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, Telefónica, the Brain and Behaviour Foundation, the Spanish Ministry of Economy and Competitiveness (CIBERSAM and PI 12/00910), the Seventh European Framework Programme (ENBREC), the Stanley Medical Research Institute, and the Comissionat per a Universitats i Recerca del DIUE de la Generalitat de Catalunya (2014 SGR 398), Aequus, Adamed, Alexza, Bial, Daiinippon Sumitomo Pharma, Elan, Eli Lilly, Gedeon Richter, Janssen-Cilag, Jazz, Johnson & Johnson, Merck, Novartis, Organon, Pierre-Fabre, Qualigen, Shering-Plough, Solvay, Sumitomo Daiinippon, Telenofica, Teva, the Spanish Ministry of Science and Innovation (CIBERSAM), United Biosource Corporation, and Wyeth. The other authors declare no conflicts of interest.

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