REVIEW ARTICLE

Determinants of adherence to treatment in first-episode psychosis: a comprehensive review

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Objective: To conduct a comprehensive review of current evidence on factors for nonadherence to treatment in individuals with first-episode psychosis (FEP).

Methods: MEDLINE, LILACS, PsycINFO, and SciELO databases were searched with the keywords first episode psychosis, factor, adherence, nonadherence, engagement, disengagement, compliance, and intervention. References of selected studies were consulted for relevant articles.

Results: A total of 157 articles were screened, of which 33 articles were retained for full review. The factors related to nonadherence were: a) patient-related (e.g., lower education level, persistent substance use, forensic history, unemployment, history of physical abuse); b) environment-related (e.g., no family involved in treatment, social adjustment difficulties); c) medication-related (e.g., rapid remission of negative symptoms when starting treatment, therapeutic alliance); and d) illness-related (e.g., more positive symptoms, more relapses). Treatment factors that improve adherence include a good therapeutic alliance and a voluntary first admission when hospitalization occurs.

Conclusion: The results of this review suggest that nonadherence to treatment in FEP is multifactorial. Many of these factors are modifiable and can be specifically targeted in early intervention programs. Very few studies have assessed strategies to raise adherence in FEP.

Keywords: Medication adherence; patient dropouts; risk factors; schizophrenia; bipolar disorder

Introduction

In 1998, Birchwood et al.1 proposed the hypothesis of the “critical period” of psychosis, during which symptomatic and psychosocial deterioration progresses quickly. Studies have shown that the outcome of the first 2 years past a first episode of psychosis (FEP) predicts the long-term outcome in terms of symptoms and disability.2,3 Prevention of new episodes is crucial, as severe mental disorders such as schizophrenia or bipolar disorder feature progression of symptoms, cognitive impairment, and brain damage over time.1,4-8

In the last decade, early intervention has become the dominant paradigm in identification and treatment of psychosis.3,10 Early treatment is associated with less disruption in personal and professional life, reduced severity of depressive symptoms, and reduction in the risk of substance abuse and suicidal or aggressive behavior.11-15

The risk of relapse after the FEP is high, and the most robust predictor of this occurrence is nonadherence to medication.3,16-18 Tiihonen et al.19 performed a nationwide cohort study of 2,588 patients hospitalized for the first time with schizophrenia in Finland and found that only a minority of patients adhered to their initial antipsychotic during the first 60 days after discharge. Individuals nonadherent to medication have higher rates of hospital readmission, lower rates of symptom remission, and lower quality of life.20-23 In early intervention programs, medication adherence is significantly associated with full recovery at 2 years after a FEP.18,24,25 Beyond medication adherence, delay to initiation of intensive psychosocial treatment has been correlated with duration of psychiatric hospitalization and negative symptoms, even after controlling for age at onset, gender, and duration of antipsychotic medication use.26 In recent publications, treatment engagement has been emphasized in addition to adherence to medication, since, alongside shared decision-making, it can provide better quality of life and beneficial lifestyle changes, such as regularity of habits or reduced drug and/or alcohol use.27-29

Achieving and maintaining adherence is a challenge in the treatment of any mental health condition. For FEP patients, overall rates of nonadherence to antipsychotic medication are estimated at over 50% in the first year.22,23,30 Disengaged individuals are often excluded from adherence studies, but they represent between 30 and 57% in FEP programs.23,31 In this context, improving adherence to medication and psychosocial treatment as early as possible after the FEP could be crucial in modifying the course of illness.24 Thorough knowledge of factors related to medication adherence and psychosocial
treatment can help maximize the efficiency of early intervention services.

Reinforcing the concept of a broad definition of adherence, the World Health Organization (WHO) defines it as “the extent to which a person’s behavior… corresponds with agreed recommendations from a health care provider,” including but not limited to medication adherence.30 “Adherence” thus differs from the previous concept of “compliance” used in the literature by including the patient’s participation in the decision-making process.

This is the first study to review the literature regarding risk factors associated with a broad definition of adherence to treatment after FEP, including both medication adherence and adherence to psychosocial treatment. The results of this review may support further studies, help design effective psychosocial programs, and provide elements to improve adherence to treatment in clinical practice.

Method

The research question that directed this review was: “Which factors are associated with adherence or non-adherence among individuals after FEP?” To conduct this review, we searched the MEDLINE (via PubMed), LILACS, PsycINFO, and SciELO electronic databases. The keywords used were first episode psychosis, factor, adherence, nonadherence, engagement, disengagement, compliance, and intervention. In addition, the reference lists of selected studies were hand-searched for relevant articles. Only peer-reviewed articles written in English, French, Spanish, or Portuguese and published from 2000 to 2013 were included. Well-conducted randomized controlled trials (RCT), case-control studies, and longitudinal studies were considered.

Definition of FEP

Different definitions of FEP were found among the studies. We used a broad definition by including studies that had considered FEP the first onset of psychotic symptoms or the first time of being treated for psychosis, up to 5 years retrospectively. We retained publications referring to both affective and non-affective psychosis, considering that it is often difficult to establish a clear diagnosis in the first years and that the diagnosis can shift.33,34

Definition of adherence

Different definitions of the term “adherence” were adopted among the studies. For the purposes of this review, these definitions were regrouped as: 1) adherence to medication; 2) adherence to psychosocial treatment (engagement in services, attendance of medical appointments, psychosocial interventions, cognitive behavioral therapy [CBT], etc.); or 3) both, as a continuous measure of adherence, with the worst outcome being treatment dropout. To reflect more adequately the broad definition of adherence recommended by the WHO, this review will cover both medication adherence and adherence to psychosocial treatment. They are presented as somewhat separate outcomes, yet minimal adherence to psychosocial treatment (i.e., attendance of follow-up appointments with a clinician) is obviously a prerequisite to medication adherence when taking into consideration the need for a prescription. When both psychosocial adherence and medication adherence were included in the results, we simply used the term adherence.

Measures of adherence

Adherence to psychosocial treatment was measured variously across the studies. For example, service disengagement was considered if patients dropped out for a minimum of 1 month despite need for treatment, actively refused contact, or were untraceable (the last contact in person was considered the date of disengagement).32,35-38 Some studies did not classify as disengaged patients who returned in the following 6 months or before the end of the program duration.31,38 For CBT, patients who did not start treatment, left without therapist advice, or attended fewer than 80% of appointments were considered nonadherent.39 Another study used attendance of five or fewer out of 12 CBT sessions as the cutoff point for nonadherence.40

For medication adherence, subjective and objective measures were used. Subjective measures included self-reporting, ratings by clinicians or other treatment providers, consensus of the whole treatment team, family members, or a combination of the above.16,41-44 Objective measures of medication adherence included plasma levels of antipsychotic medication and/or mood stabilizers, pill counts, and prescription renewals.45-47 A frequent method to measure medication adherence subjectively was to consider patients nonadherent when they failed to take medication for a period of 1 or 2 weeks.29,46-50 A majority of studies also used a dichotomous subjective measure of adherence in the analysis, whereby an individual was considered nonadherent to medication when he or she reported taking less than 75% of the medication as prescribed.21,41,51-54 This has been shown to be comparable to the results of pill counting for FEP patients, although any subjective report tends to underestimate adherence to medication, as is the case in other psychiatric disorders.55 The informers that tend to overestimate adherence the most are family members, followed by patients themselves and, to a much lesser extent, clinicians.55 In fact, even psychiatrists may underestimate nonadherence when compared to objective methods, such as pill counting or electronic monitoring.56

Each type of measure of medication adherence (objective/subjective) has its weaknesses, and the method recommended by the WHO is to combine both,32 as was done in a few studies included in this review. Studies that did not specify how they measured adherence or that measured adherence solely on the basis of subjective reports by a family member were excluded, as this method is a relatively poor estimate in FEP.55
<table>
<thead>
<tr>
<th>First author</th>
<th>Study design</th>
<th>Sample size</th>
<th>Study duration</th>
<th>Factors associated with nonadherence to medication or psychosocial treatment (p ( \leq 0.05 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvarez-Jiménez (2009)[^39^]</td>
<td>Randomized controlled trial; single-blind</td>
<td>81</td>
<td>2.5 years</td>
<td>Psychosocial (CBT) - predictive: longer DUP, poorer level of insight</td>
</tr>
<tr>
<td>Anderson (2013)[^35^]</td>
<td>Prospective cohort</td>
<td>324</td>
<td>24 months</td>
<td>Psycchosocial (disengagement): older age, not living alone</td>
</tr>
<tr>
<td>Barbeito (2013)[^43^]</td>
<td>Prospective cohort</td>
<td>98</td>
<td>8 years[^*^]</td>
<td>Medication: family history of psychosis, lower functioning, lower levels of depressive symptoms, more alcohol use, involuntary first admission to hospital</td>
</tr>
<tr>
<td>Coldham (2002)[^22^]</td>
<td>Prospective cohort</td>
<td>200</td>
<td>1 year</td>
<td>Medication: younger age, earlier age at onset, poorer premorbid functioning, no family member involved in treatment, more positive symptoms, more relapses, more alcohol and cannabis use, reduced insight, poorer quality of life</td>
</tr>
<tr>
<td>Conus (2010)[^36^]</td>
<td>Retrospective longitudinal</td>
<td>660</td>
<td>18 months</td>
<td>Psycchosocial (disengagement) - predictive: lower premorbid functioning, forensic history before treatment, shorter duration of prodrome, no work or school, living without family, lower severity of illness at baseline, higher baseline functioning, diagnoses other than schizophrenia spectrum or bipolar disorder</td>
</tr>
<tr>
<td>Fanning (2012)[^40^]</td>
<td>Prospective cohort</td>
<td>124</td>
<td>2 years</td>
<td>Psychosocial (CBT) - predictive: lower global attention, lower social self-consciousness, higher global bizarre behavior</td>
</tr>
<tr>
<td>Faridi (2012)[^41^]</td>
<td>Prospective cohort</td>
<td>192</td>
<td>1 year</td>
<td>Medication: discontinued cannabis use</td>
</tr>
<tr>
<td>Hill (2010)[^21^]</td>
<td>Prospective cohort</td>
<td>171</td>
<td>4 years</td>
<td>Medication - predictive: substance misuse, DUP Other associated factors: greater symptomatology, lower insight, lower global functioning, negative attitude toward medication, substance misuse</td>
</tr>
<tr>
<td>Kampman (2002)[^57^]</td>
<td>Retrospective longitudinal</td>
<td>59</td>
<td>3 months</td>
<td>Medication: experienced harmful side effects, male sex, lack of social activities, more positive symptoms, more symptoms in general, younger age</td>
</tr>
<tr>
<td>Lambert (2010)[^23^]</td>
<td>Retrospective longitudinal</td>
<td>605</td>
<td>18 months</td>
<td>Medication - predictive: male sex, fewer years of schooling, low premorbid functioning, history of physical abuse, forensic history, lifetime substance use disorder, longer duration of untreated illness, no previous contact with psychiatric care, any substance use disorder at baseline, unemployment at baseline, low insight, severity of illness</td>
</tr>
<tr>
<td>Macbeth (2013)[^58^]</td>
<td>Cross-sectional cohort</td>
<td>64</td>
<td>12 months</td>
<td>Psychosocial (poor engagement) - predictive: negative symptoms Other associated factors: more positive symptoms, more negative symptoms, higher general psychopathology, lower late-adolescence academic adjustment, lower early- and late-adolescence social adjustment</td>
</tr>
<tr>
<td>Malla (2002)[^44^]</td>
<td>Prospective cohort</td>
<td>66</td>
<td>1 year</td>
<td>Medication: lower community functioning (social relations and activities of daily living)</td>
</tr>
<tr>
<td>Miller (2009)[^39^]</td>
<td>Prospective cohort</td>
<td>112</td>
<td>12 months</td>
<td>Medication and disengagement: cannabis use</td>
</tr>
<tr>
<td>Montreuil (2012)[^45^]</td>
<td>Prospective cohort</td>
<td>81</td>
<td>6 months</td>
<td>Medication - predictive: lower working alliance</td>
</tr>
<tr>
<td>Quach (2009)[^46^]</td>
<td>Prospective cohort</td>
<td>547</td>
<td>2 years</td>
<td>Medication - predictive: negative attitudes toward medication, lack of consistent family support, not have grown up with both parents, no key relative to interview at entry, no vocational education, younger patients, no key relative at 1-year follow-up interview, fewer negative symptoms, lower insight</td>
</tr>
<tr>
<td>Rabinovitch (2009)[^30^]</td>
<td>Prospective cohort</td>
<td>100</td>
<td>6 months</td>
<td>Medication - predictive: low level of social support, single marital status, refusal of medication at the first offer of treatment</td>
</tr>
</tbody>
</table>

Continued on next page
### Table 1 Continued

<table>
<thead>
<tr>
<th>First author</th>
<th>Study design</th>
<th>Sample size</th>
<th>Study duration</th>
<th>Factors associated with nonadherence to medication or psychosocial treatment (p ≤ 0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabinovitch (2013)</td>
<td>Prospective cohort</td>
<td>152</td>
<td>6 months</td>
<td>Medication - predictive: any lifetime substance use diagnosis at baseline Other associated factors: increase in family support</td>
</tr>
<tr>
<td>Robinson (2002)</td>
<td>Prospective cohort</td>
<td>112</td>
<td>1 year</td>
<td>Medication - predictive: poorer premorbid cognitive functioning</td>
</tr>
<tr>
<td>Schimmelmann (2006)</td>
<td>Prospective cohort</td>
<td>157</td>
<td>18 months</td>
<td>Psychosocial (disengagement) - predictive: lower severity of illness at baseline, higher global functioning at baseline, living without family at baseline Other associated factors: living without family during treatment, persistent substance use, lower global functioning at discharge</td>
</tr>
<tr>
<td>Schimmelmann (2012)</td>
<td>Prospective cohort</td>
<td>99</td>
<td>18 months</td>
<td>Medication: cannabis use Disengagement: persistent cannabis use (compared to baseline or decreasing use)</td>
</tr>
<tr>
<td>Schöttle (2012)</td>
<td>Retrospective longitudinal</td>
<td>134</td>
<td>18 months</td>
<td>Medication: schizoaffective disorder diagnosis (compared to bipolar disorder)</td>
</tr>
<tr>
<td>Segarra (2012)</td>
<td>Prospective cohort</td>
<td>577</td>
<td>1 year</td>
<td>Global treatment nonadherence - predictive: low insight into need for treatment, low level of education Others: no remission of positive symptoms Psychosocial (disengagement) - predictive: lower negative symptoms at baseline, shorter DUP, not having a family member involved in the program Early dropout (&lt; 6 months): greater cannabis use, greater other drug use</td>
</tr>
<tr>
<td>Steger (2012)</td>
<td>Prospective cohort</td>
<td>301</td>
<td>6 months</td>
<td>Medication - predictive: resolution of negative symptoms Others: no remission of positive symptoms Psychosocial (disengagement) - predictive: lower negative symptoms at baseline, higher global functioning level at baseline, lower health and social functioning level at baseline</td>
</tr>
<tr>
<td>Stowkowy (2012)</td>
<td>Prospective cohort</td>
<td>286</td>
<td>30 months</td>
<td>Medication: higher cognitive flexibility</td>
</tr>
<tr>
<td>Turner (2009)</td>
<td>Prospective cohort</td>
<td>236</td>
<td>2 years</td>
<td>Medication: higher substance use disorder severity</td>
</tr>
<tr>
<td>Verdoux (2002)</td>
<td>Prospective cohort</td>
<td>35</td>
<td>2 years</td>
<td></td>
</tr>
<tr>
<td>Wade (2007)</td>
<td>Prospective cohort</td>
<td>92</td>
<td>15 months</td>
<td></td>
</tr>
</tbody>
</table>

CBT = cognitive behavioral therapy; DUP = duration of untreated psychosis; FEP = first-episode psychosis. * In accordance with the definition of FEP, only results from < 5 years were used.

### Table 2 Main factors associated with nonadherence to treatment in first episode psychosis

<table>
<thead>
<tr>
<th>Nonadherence to medication</th>
<th>Nonadherence to psychosocial treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-related factors</td>
<td></td>
</tr>
<tr>
<td>Younger age</td>
<td>Older age</td>
</tr>
<tr>
<td>Lower level of education</td>
<td>Lower level of education</td>
</tr>
<tr>
<td>Persistent substance use</td>
<td>Persistent substance use</td>
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<tr>
<td>Any lifetime substance use</td>
<td></td>
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<tr>
<td>No previous contact with psychiatric care</td>
<td></td>
</tr>
<tr>
<td>Lack of insight</td>
<td></td>
</tr>
<tr>
<td>Negative attitude toward treatment</td>
<td></td>
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<tr>
<td>Lower cognitive abilities</td>
<td></td>
</tr>
<tr>
<td>Poor quality of life</td>
<td></td>
</tr>
<tr>
<td>Forensic history</td>
<td>Forensic history</td>
</tr>
<tr>
<td>Unemployment</td>
<td>Unemployment</td>
</tr>
<tr>
<td>History of physical abuse</td>
<td>History of physical abuse</td>
</tr>
<tr>
<td>Lower functioning level</td>
<td>Higher functioning level</td>
</tr>
<tr>
<td>Environment-related factors</td>
<td></td>
</tr>
<tr>
<td>No family involved in treatment</td>
<td></td>
</tr>
<tr>
<td>To have grown up without one or both parent</td>
<td></td>
</tr>
<tr>
<td>Lack of social activities</td>
<td>Living without family</td>
</tr>
<tr>
<td>Medication-related or treatment-related factors</td>
<td></td>
</tr>
<tr>
<td>Rapid remission of negative symptoms</td>
<td></td>
</tr>
<tr>
<td>Therapeutic alliance</td>
<td></td>
</tr>
<tr>
<td>Voluntary first admission (when hospitalized)</td>
<td></td>
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<tr>
<td>Disorder-related factors</td>
<td></td>
</tr>
<tr>
<td>More positive symptoms</td>
<td>More positive symptoms</td>
</tr>
<tr>
<td>Longer duration of untreated psychosis</td>
<td></td>
</tr>
<tr>
<td>More relapses</td>
<td></td>
</tr>
</tbody>
</table>
Results

A total of 157 articles were identified. After screening, 33 were retained. We excluded review articles, articles with no description of the method used to measure adherence or only family report as a measure of adherence, and articles with duplicate data. Table 1 presents a detailed description of the articles included in this review.

Factors associated with nonadherence in a first episode of psychosis

Several factors were associated with nonadherence in early psychosis, including patient-related, environment-related, medication-related, disorder-related, and other treatment-related factors. A summary of the most relevant factors for nonadherence in each category is presented in Table 2.

Patient-related factors: sociodemographic variables

Age

Different types of adherence were associated in different ways with age. Younger age was related with medication nonadherence in first episode of schizophrenia-spectrum disorder.22,45,57 In a recent study of similar design and duration, older age (in a sample aged 14 to 30 years) was associated with service disengagement to an early intervention program.36 Early intervention programs tend to target adolescents and young adults, and this could explain the lower engagement of older individuals.

Education

Fewer years of schooling and no vocational education were also related to medication nonadherence and treatment dropout.23,45 Furthermore, Segarra et al.42 showed that the level of education was predictive of treatment adherence at 1-year follow-up.

Others

Although studies tend to point out that nonadherence is associated with male sex, when controlling for possible confounding factors such as substance use, the majority of studies found no sex difference in medication nonadherence or engagement in treatment.22,23,30,45,54,57 It is not clear whether marital status has an influence on adherence, but some authors suggest that any purported association could actually be related to other factors, such as living alone and/or lack of social support.54

Patient-related factors: comorbidity

Substance use

Several studies have linked concomitant substance use and poor treatment adherence in FEP.22,36,45,59 Individuals with persistent substance abuse problems are more likely to drop out of treatment or be nonadherent to medication.21,31,50,53 In first-episode schizophrenia, adolescents with continuous substance use have a 2.6-fold increased risk of disengagement,37 and specifically for cannabis use, a 6.4-fold increase in risk.59 Cannabis use also increases the risk of nonadherence to medication by a factor of 2.4.21 This association can be reversed with behavior modification, as demonstrated in a 8-year cohort study: patients who dropped cannabis use (compared with no cannabis use or declining use) were among those whose adherence to medication improved the most over the years.43 Nevertheless, findings regarding cannabis are not homogeneous. In a 12-month prospective cohort study involving 192 patients with first-episode schizophrenia, stable cannabis users became more adherent to medication than those who stopped using cannabis.41 The authors believed that those differences were related to the specific context of their service, which provides a high level of psychosocial intervention; thus, patients were more likely to recognize cannabis as a risk factor for psychotic symptoms and tended to either stay adherent to medication (to minimize risk) or stop both cannabis and their medication. In addition, a very large cohort study of 605 patients with affective or non-affective FEP showed that the severity and frequency of substance use had differential impacts on adherence.23 In terms of predictive value, substance use disorder (SUD) at baseline is significantly associated with a higher rate of nonadherence to medication, but is not predictive of poor engagement in treatment.21,31,37,50,54 In fact, any lifetime SUD also predicts poor adherence, and is a better predictor than SUD at baseline.23,54

Psychiatric characteristics

No previous contact with the psychiatric health system distinguished total medication refusal from partial medication nonadherence, as only individuals refusing any medication were more likely to have had no previous contact with the psychiatric health system.23

Patient-related factors: psychological variables

Insight

At baseline, lack of insight at the beginning of treatment, especially unawareness of the effect of medication, specifically predicted nonadherence to medication after 1 year.21,45 Lack of insight has consistently been associated with nonadherence to medication.21,22 Lambert et al.23 found that lack of insight specifically predicted total medication refusal, but not partial nonadherence or disengagement.

The few studies conducted thus far on lack of insight as a predictor of disengagement have yielded inconsistent findings,37,39 but patients with a higher level of insight are more likely to be referred to a specific psychosocial treatment such as CBT, and this could minimize the significance of the difference between subjects.30

Attitude toward medication

A negative attitude toward treatment is one of the most robust predictors of nonadherence to medication in the first 2 years of treatment for a first-episode
schizophrenia-spectrum disorder. In a 4-year cohort study, negative attitude toward medication was also related to nonadherence in both affective and non-affective FEP. 21

Cognitive abilities

Overall, no strong association has been suggested between specific or global cognitive abilities and medication adherence. 51,61 One study suggested that a lower premorbid cognitive function could predict medication nonadherence during the first year in schizophrenia-spectrum disorders. 62 A 2-year cohort study with a small sample (n=35) suggested higher cognitive flexibility could raise the risk of nonadherence to medication, regardless of categorical diagnosis, probably by reinforcing the tendency to try different behaviors to control symptoms. 46 The cutoff point of nonadherence in these positive studies were high (1 week and 2 weeks of medication discontinuation), which suggests that lower cognitive ability could be associated with complete rather than partial nonadherence.

Patient-related factors: other individual variables

A few other individual factors have been associated with nonadherence to medication, such as a poor quality of life. 22 In some studies, forensic history was predictive of later medication refusal and disengagement. 23,36 Unemployment at baseline and a history of physical abuse were predictive of both complete nonadherence and service disengagement. 23,38 Lower global functioning has frequently been considered a possible risk factor for medication nonadherence, and studies tend to confirm this. 21-23,36,43,44 On the other hand, studies on disengagement show the opposite association, with disengagement linked to higher global functioning. 37,38 One explanation for these contrasting results could be that some individuals tend to be nonadherent because they lack the necessary functioning to use medication regularly, whereas others are nonadherent because they are functional and do not feel a need for follow-up.

Environment-related factors

Social support

Many studies have addressed the impact of family or social support on adherence, and their results mostly show an association. For example, patients who are nonadherent to medication are less likely to have a family member involved in their treatment. 25 In a study of 100 patients, a good level of social and family support at entry was a significant predictor of adherence at 6 months (OR = 3.552, p = 0.03), 30 and a large cohort study found a lack of consistent family support to be among the strongest predictors of medication nonadherence at 2 years. 46 Likewise, there is strong evidence that family support and involvement in treatment have a positive impact on engagement. A cohort study of 286 subjects found that those without a family involved in treatment at baseline were at higher risk of disengagement before the end of a 30-month early-psychosis follow-up, even after controlling for other confounders. 31 Conversely, the family’s attitude toward treatment seemed to have no influence on adherence to medication during the first year of a schizophrenia or schizoaffective disorder. 60

A general lack of social activities and lower social functioning have also been associated both with nonadherence to medication and with disengagement. 14,57,58

Living situation

Most studies have found living without family at hospital discharge or during treatment to be predictive of disengagement. 36,37 Conversely, in the most recent study on this factor, living alone reduced the likelihood of disengagement. 35 The authors suggested that the more attentive follow-up given by clinicians to socially isolated patients might have stimulated engagement and explained this diverging result. Age could also be a factor, as the Schimmelmann et al. 37 study focused on adolescents, who are unlikely to live without their family. The authors estimated that patients (15 to 18 years old) living without family during treatment had a 4.8-fold greater risk of treatment dropout. 37 To have grown up without one or both parents is among the strongest predictors of nonadherence to medication at 1 year. 45

Medication-related factors

Tolerability

Although well-tolerated medications are usually considered to be associated with better adherence, this outcome did not differ between different medications in non-affective FEP, even in the presence of motor side effects. 16,60

Effectiveness

In a cohort study by Steger et al. 52 of patients with a diagnosis of either affective or non-affective psychosis, remission of negative symptoms by the third month of treatment was associated with nonadherence to medication, but a rapid remission of positive symptoms showed no relationship with adherence. This means that even patients who seem to benefit from medication could be at a higher risk of nonadherence.

Previous medication refusal

Refusal of medication at the first offer of treatment is predictive of nonadherence to medication 6 months after. 30

Route of administration

The route of administration of medication is another important factor implicated in nonadherence. In a small RCT (n=37), Weiden et al. 48 found that administering a long-acting injectable antipsychotics (LAIA) (in this case, risperidone) instead of traditional oral antipsychotics had no significant difference on survival time to a 2-week refusal of medication, since it delayed nonadherence for the duration of the effect, but did not prevent it. It has
been largely discussed whether RCTs are the best option to evaluate LAIAs, as this design generally tends to increase adherence compared with clinical practice and, therefore, might not be representative of real-world patients.\(^6^2\)

**Disorder-related factors associated with nonadherence**

**Severity**

More negative symptoms, especially in relation to global attention, were related to nonadherence to group CBT in one study.\(^5^9\) In a study by Alvarez-Jimenez et al.,\(^3^9\) negative symptoms did not predict nonadherence to individual CBT. It is possible that the greater attention provided by the therapist in an individual setting counteracted negative symptoms, which would explain these different results. Were this the case, negative symptoms could make it harder to adhere to a group program, but not to an individual one. In the same vein, a 30-month follow-up of an early psychosis program showed that having lower scores on a negative symptoms scale predicted disengagement before the completion of the program.\(^3^1\) Although the study was large, using full 30-month engagement as a measure could dissolve the results of subjects who are nonadherent to psychosocial treatment but need it nonetheless. It is possible, for example, that subjects with lower negative symptom scores did not need the full 30 months of treatment and thus left the program earlier.

Another influence of disorder severity is that more positive symptoms and more relapses are mostly associated with medication nonadherence and disengagement.\(^2^1,2^2,4^0,5^7,5^8\) Other results of studies on the link between general psychopathology and nonadherence have been divergent, which suggests that, as for specific adherence to CBT, the type of symptoms might be more influential than global severity.\(^3^6,3^7,5^8\)

**Duration of untreated psychosis (DUP)**

Although results have been inconsistent, the most robust studies conducted thus far show that longer DUP is associated with poorer adherence to medication and, possibly, to CBT, even when controlling for confounders.\(^2^3,5^7\)

**Diagnosis**

No significant differences were found between non-affective and affective psychosis in terms of adherence and nonadherence.\(^3^0\) Patients with a diagnosis of schizoaffective disorder (SAD) compared to a bipolar type 1 disorder (BD-I) diagnosis are more likely to be nonadherent to treatment, but individuals with SAD have a longer DUP and a history of more traumatic events, which could explain this finding.\(^4^9\)

**Strategies or treatment-related factors to improve adherence**

**First hospitalization**

One of the treatment factors that can enhance adherence when a hospitalization is involved is whether it is voluntary. Involuntary first hospitalization has a negative effect on short- and medium-term medication adherence (< 2 years), although adherence later improved for 96% of these patients.\(^4^3,5^3\)

**Strategies during outpatient care**

In regular follow-up, one strategy that has been found to raise adherence is a good therapeutic alliance. The therapeutic alliance is a significant predictor of future medication adherence in FEP.\(^4^7\)

**Discussion**

To the best of our knowledge, this was the first review to consider factors predictive of broadly define adherence (including adherence to medication and treatment engagement) in FEP. Our findings reveal many different levels of factors associated with or predictive of nonadherence in FEP. These findings have important implications for the development of psychosocial interventions designed to increase adherence to medication or engagement in treatment. A negative attitude, lack of insight, substance use or abuse, unemployment, and poor quality of life are examples of modifiable individual factors that could be targeted by such interventions. Encouraging social relationships or the involvement of family members in treatment would probably be efficient as well. Although our results suggest that differences in medication have little impact on medication adherence in a research setting, having access to different forms of medication such as LAIA can be helpful in clinical practice, especially for patients who have difficulties with medication adherence caused by cognitive weaknesses (e.g., memory) or lack of structure rather than clear refusals.\(^2^7,6^4\) It might also help the clinician monitor adherence more clearly. Furthermore, when hospitalization is unavoidable, taking some steps to encourage voluntary admission is recommended. Concerning engagement, it is our understanding that the intensity of psychosocial intervention needs to fit the severity of illness as perceived by the individual so as to maximize adherence. More studies are needed on factors that influence adherence, especially adherence to psychosocial treatment, and effective strategies to increase adherence in FEP.

Regarding the limitations of the present study, this review considered associated risk factors; unless otherwise specified, they do not necessarily indicate a causal relationship. Moreover, divergences in how adherence was measured between studies could explain the heterogeneity in results. The review was conducted as systematically as possible, but was designed to be comprehensive. For these reasons, its results should be interpreted and generalized with caution.

Most studies on adherence in FEP have focused on individual risk factors, but evidence suggests that other types of factors are relevant as well; evidence from clinical practice, for instance, indicates that social stigma might be of relevance. Future investigations could study in greater detail the impact of social and family factors on...
treatment adherence, especially since FEP occurs in younger subjects.

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Disclosure
The authors report no conflicts of interest.

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