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.[9,10] 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

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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.[32] "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, psychoeducational 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).[22,35-38] 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.[23,48-50] 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 overestimate 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 1 Detailed description of studies identifying factors associated with nonadherence to medication or psychosocial treatment in first-episode psychosis

First author	Study design	Sample size	Study duration	Factors associated with nonadherence to medication or psychosocial treatment ($p \leqslant 0.05$)
Alvarez-Jiménez (2009)[39]	Randomized controlled trial; single-blind	81	2.5 years	Psychosocial (CBT) - predictive: longer DUP, poorer level of insight
Anderson (2013)[35]	Prospective cohort	324	24 months	Psychosocial (disengagement): older age, not living alone
Barbeito (2013)[43]	Prospective cohort	98	8 years*	Medication: family history of psychosis, lower functioning, lower levels of depressive symptoms, more alcohol use, involuntary first admission to hospital
Coldham (2002)[22]	Prospective cohort	200	1 year	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
Conus (2010)[36]	Retrospective longitudinal	660	18 months	Psychosocial (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 Associated: persistence of substance use disorder, living without family at discharge, higher severity at discharge, lower functioning at discharge
Fanning (2012)[40]	Prospective cohort	124	2 years	Psychosocial (CBT) - predictive: lower global attention, lower social self-consciousness, higher global bizarre behavior
Faridi (2012)[41]	Prospective cohort	192	1 year	Medication: discontinued cannabis use
Hill (2010)[21]	Prospective cohort	171	4 years	Medication - predictive: substance misuse, DUP Other associated factors: greater symptomatology, lower insight, lower global functioning, negative attitude toward medication, substance misuse
Kampman (2002)[57]	Retrospective longitudinal	59	3 months	Medication: experienced harmful side effects, male sex, lack of social activities, more positive symptoms, more symptoms in general, younger age
Lambert (2010)[23]	Retrospective longitudinal	605	18 months	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
Macbeth (2013)[58]	Cross-sectional cohort	64	12 months	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
Malla (2002)[44]	Prospective cohort	66	1 year	Medication: lower community functioning (social relations and activities of daily living)
Miller (2009)[59]	Prospective cohort	112	12 months	Medication and disengagement: cannabis use
Montreuil (2012)[47]	Prospective cohort	81	6 months	Medication - predictive: lower working alliance
Quach (2009)[45]	Prospective cohort	547	2 years	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
Rabinovitch (2009)[30]	Prospective cohort	100	6 months	Medication - predictive: low level of social support, single marital status, refusal of medication at the first offer of treatment

Table 1 Continued

First author	Study design	Sample size	Study duration	Factors associated with nonadherence to medication or psychosocial treatment ($p \leqslant 0.05$)
Rabinovitch (2013)[54]	Prospective cohort	152	6 months	Medication - predictive: any lifetime substance use diagnosis at baseline Other associated factors: increase in family support
Robinson (2002)[60]	Prospective cohort	112	1 year	Medication - predictive: poorer premorbid cognitive functioning
Schimmelmann (2006)[37]	Prospective cohort	157	18 months	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
Schimmelmann (2012)[50]	Prospective cohort	99	18 months	Medication: cannabis use Disengagement: persistent cannabis use (compared to baseline or decreasing use)
Schöttle (2012)[49]	Retrospective longitudinal	134	18 months	Medication: schizoaffective disorder diagnosis (compared to bipolar disorder)
Segarra (2012)[42]	Prospective cohort	577	1 year	Global treatment nonadherence - predictive: low insight into need for treatment, low level of education
Steger (2012)[52]	Prospective cohort	301	6 months	Medication - predictive: resolution of negative symptoms Others: no remission of positive symptoms
Stowkowy (2012)[31]	Prospective cohort	286	30 months	Psychosocial (disengagement) - predictive: lower negative symptoms at baseline, shorter DUP, not having a family member involved in the program Early dropout ($<$ 6 months): greater cannabis use, greater other drug use
Turner (2009)[38]	Prospective cohort	236	2 years	Psychosocial (disengagement) - predictive: unemployed at baseline, higher global functioning level at baseline, lower health and social functioning level at baseline
Verdoux (2002)[46]	Prospective cohort	35	2 years	Medication: higher cognitive flexibillity
Wade (2007)[53]	Prospective cohort	92	15 months	Medication: higher substance use disorder severity

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

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

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.[35] 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.[59] 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 psychoeducation; 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.[42,45] 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.[40]

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.[45] 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.[60] 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 disconti-nuation), which suggests that lower cognitive ability could be associated with complete rather than partial non-adherence.

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 predic-tive 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 disengage-ment 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.[22] 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.[45] 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 control-ling 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 schizophrenic or schizoaffective disorder.[60]

A general lack of social activities and lower social functioning have also been associated both with non-adherence to medication and with disengagement.[44,57,58]

Living situation

Most studies have found living without family at hospital discharge or during treatment to be predictive of disen-gagement.[36,37] Conversely, in the most recent study on this factor, living alone reduced the likelihood of disen-gagement.[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 medica-tion, 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.[62]

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.[40] In a study by Alvarez-Jimenez et al.,[39] 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.[31] 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.[21,22,40,57,58] 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.[36,37,58]

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.[23,57]

Diagnosis

No significant differences were found between non-affective and affective psychosis in terms of adherence and nonadherence.[30] 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.[49]

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.[43,63]

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.[47]

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 non-adherence 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.[27,64] 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.

Disclosure

The authors report no conflicts of interest.

References

1 Birchwood M, Todd P, Jackson C. Early intervention in psychosis. The critical period hypothesis. Br J Psychiatry Suppl. 1998;172:53-9.

2 Abdel-Baki A, Lesage A, Nicole L, Cossette M, Salvat E, Lalonde P. Schizophrenia, an illness with bad outcome: myth or reality? Can J Psychiatry. 2011;56:92-101.

3 Abdel-Baki A, Ouellet-Plamondon C, Malla A. Pharmacotherapy challenges in patients with first-episode psychosis. J Affect Disord. 2012;138:S3-14.

4 Wood SJ, Brewer WJ, Koutsouradis P, Phillips LJ, Francey SM, Proffitt TM, et al. Cognitive decline following psychosis onset: data from the PACE clinic. Br J Psychiatry Suppl. 2007;51:s52-7.

5 Cotton SM, Gleeson JF, Alvarez-Jimenez M, McGorry PD. Quality of life in patients who have remitted from their first episode of psychosis. Schizophr Res. 2010;121:259-65.

6 Puri BK. Progressive structural brain changes in schizophrenia. Expert Rev Neurother. 2010;10:33-42.

7 Emsley R, Chiliza B, Asmal L. The evidence for illness progression after relapse in schizophrenia. Schizophr Res. 2013;148:117-21.

8 Noto MN, de Souza Noto C, de Jesus DR, Zugman A, Mansur RB, Berberian AA, et al. Recognition of bipolar disorder type i before the first manic episode: challenges and developments. Expert Rev Neurother. 2013;13:795-806.

9 McGorry PD, Killackey E, Yung AR. Early intervention in psychotic disorders: detection and treatment of the first episode and the critical early stages. Med J Aust. 2007;187:S8-10.

10 Brietzke E, Araripe Neto AG, Dias A, Mansur RB, Bressan RA. Early intervention in psychosis: a map of clinical and research initiatives in Latin America. Rev Bras Psiquiatr. 2011;33:s213-24.

11 Archie S, Rush BR, Akhtar-Danesh N, Norman R, Malla A, Roy P, et al. Substance use and abuse in first-episode psychosis: prevalence before and after early intervention. Schizophr Bull. 2007;33:1354-63.

12 Nielssen O, Large M. Rates of homicide during the first episode of psychosis and after treatment: a systematic review and meta-analysis. Schizophr Bull. 2010;36:702-12.

13 Rinaldi M, Killackey E, Smith J, Shepherd G, Singh SP, Craig T. First episode psychosis and employment: a review. Int Rev Psychiatry. 2010;22:148-62.

14 Upthegrove R, Birchwood M, Ross K, Brunett K, McCollum R, Jones L. The evolution of depression and suicidality in first episode psychosis. Acta Psychiatr Scand. 2010;122:211-8.

15 Scott J, Fowler D, McGorry P, Birchwood M, Killackey E, Christensen H, et al. Adolescents and young adults who are not in employment, education, or training. BMJ. 2013;347:f5270.

16 Crespo-Facorro B, Pérez-Iglesias R, Mata I, Caseiro O, Martínez-Garcia O, Pardo G, et al. Relapse prevention and remission attainment in first-episode non-affective psychosis. A randomized, controlled 1-year follow-up comparison of haloperidol, risperidone and olanzapine. J Psychiatr Res. 2011;45:763-9.

17 Caseiro O, Pérez-Iglesias R, Mata I, Martínez-Garcia O, Pelayo-Terán JM, Tabares-Seisdedos R, et al. Predicting relapse after a first episode of non-affective psychosis: a three-year follow-up study. J Psychiatr Res. 2012;46:1099-105.

18 Alvarez-Jimenez M, Priede A, Hetrick SE, Bendall S, Killackey E, Parker a G, et al. Risk factors for relapse following treatment for first episode psychosis: a systematic review and meta-analysis of longitudinal studies. Schizophr Res. 2012;139:116-28.

19 Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry. 2011;168:6:603-9.

20 Gearing RE, Charach A. Medication adherence for children and adolescents with first-episode psychosis following hospitalization. Eur Child Adolesc Psychiatry. 2009;18:587-95.

21 Hill M, Crumlish N, Whitty P, Clarke M, Browne S, Kamali M, et al. Nonadherence to medication four years after a first episode of psychosis and associated risk factors. Psychiatr Serv. 2010;61:189-92.

22 Coldham EL, Addington J, Addington D. Medication adherence of individuals with a first episode of psychosis. Acta Psychiatr Scand. 2002;106:286-90.

23 Lambert M, Conus P, Cotton S, Robinson J, McGorry PD, Schimmelmann BG. Prevalence, predictors, and consequences of long-term refusal of antipsychotic treatment in first-episode psychosis. J Clin Psychopharmacol. 2010;30:565-72.

24 Malla A, Norman R, Schmitz N, Manchanda R, Béchard-Evans L, Takhar J, et al. Predictors of rate and time to remission in first-episode psychosis: a two-year outcome study. Psychol Med. 2006;36:649-58.

25 Petersen L, Thorup A, Øghlenschlaeger J, Christensen TØ, Jeppesen P, Krarup G, et al. Predictors of remission and recovery in a first-episode schizophrenia spectrum disorder sample: 2-year follow-up of the OPUS trial. Can J Psychiatry. 2008;53:660-70.

26 De Haan L, Linszen DH, Lenior ME, de Win ED, Gorsira R. Duration of untreated psychosis and outcome of schizophrenia: delay in intensive psychosocial treatment versus delay in treatment with antipsychotic medication. Schizophr Bull. 2003;29:341-8.

27 Acosta FJ, Hernández JL, Pereira J, Herrera J, Rodríguez CJ. Medication adherence in schizophrenia. World J Psychiatry. 2012;2:74-82.

28 McCabe R. Talking about adherence. World Psychiatry. 2013;12:231-2.

29 Stroup TS, Dixon LB. The enduring challenge of antipsychotic non-adherence. World Psychiatry. 2013;12:236-7.

30 Rabinovitch M, Béchard-Evans L, Schmitz N, Joober R, Malla A. Early predictors of nonadherence to antipsychotic therapy in first-episode psychosis. Can J Psychiatry. 2009;54:28-35.

31 Stowkowy J, Addington D, Liu L, Hollowell B, Addington J. Predictors of disengagement from treatment in an early psychosis program. Schizophr Res. 2012;136:7-12.

32 Sabaté E, World Health Organization (WHO). Adherence to long-term therapies: evidence for action. Geneva: WHO. 2003.

33 Bromet EJ, Kotov R, Fochtmann LJ, Carlson GA, Tanenberg-Karant M, Ruggero C, et al. Diagnostic shifts during the decade following first admission for psychosis. Am J Psychiatry. 2011;168:1186-94.

34 Remington G. Rational pharmacotherapy in early psychosis. Br J Psychiatry Suppl. 2005;48:s77-84.

35 Anderson KK, Fuhrer R, Schmitz N, Malla AK. Determinants of negative pathways to care and their impact on service disengagement in first-episode psychosis. Soc Psychiatry Psychiatr Epidemiol. 2013;48:125-36.

36 Conus P, Lambert M, Cotton S, Bonsack C, McGorry PD, Schimmelmann BG. Rate and predictors of service disengagement in an epidemiological first-episode psychosis cohort. Schizophr Res. 2010;118:256-63.

37 Schimmelmann BG, Conus P, Schacht M, McGorry P, Lambert M. Predictors of service disengagement in first-admitted adolescents with psychosis. J Am Acad Child Adolesc Psychiatry. 2006;45:990-9.

38 Turner MA, Boden JM, Smith-Hamel C, Mulder RT. Outcomes for 236 patients from a 2-year early intervention in psychosis service. Acta Psychiatr Scand. 2009;120:129-37.

39 Alvarez-Jiménez M, Gleeson JF, Cotton S, Wade D, Gee D, Pearce T, et al. Predictors of adherence to cognitive-behavioural therapy in first-episode psychosis. Can J Psychiatry. 2009;54:710-8.

40 Fanning F, Foley S, Lawlor E, McWilliams S, Jackson D, Renwick L, et al. Group cognitive behavioural therapy for first episode psychosis: who's referred, who attends and who completes it? Early Interv Psychiatry. 2012;6:432-41.

41 Faridi K, Joober R, Malla A. Medication adherence mediates the impact of sustained cannabis use on symptom levels in first-episode psychosis. Schizophr Res. 2012;141:78-82.

42 Segarra R, Ojeda N, Pena J, Garcia J, Rodriguez-Morales A, Ruiz I, et al. Longitudinal changes of insight in first episode psychosis and its relation to clinical symptoms, treatment adherence and global functioning: one-year follow-up from the Eiffel study. Eur Psychiatry. 2012;27:43-9.

43 Barbeito S, Vega P, Ruiz de Azúa S, Saenz M, Martinez-Cengotitabengoa M, González-Ortega I, et al. Cannabis use and involuntary admission may mediate long-term adherence in first-episode psychosis patients: a prospective longitudinal study. BMC Psychiatry. 2013;13:326.

44 Malla AK, Norman RM, Manchanda R, Townsend L. Symptoms, cognition, treatment adherence and functional outcome in first-episode psychosis. Psychol Med. 2002;32:1109-19.

45 Quach P Le, Mors O, Christensen TØ, Krarup G, Jørgensen P, Bertelsen M, et al. Predictors of poor adherence to medication among patients with first-episode schizophrenia-spectrum disorder. Early Interv Psychiatry. 2009;3:66-74.

46 Verdoux H, Liraud F, Assens F, Abalan F, van Os J. Social and clinical consequences of cognitive deficits in early psychosis: a two-year follow-up study of first-admitted patients. Schizophr Res. 2002;56:149-59.

47 Montreuil TC, Cassidy CM, Rabinovitch M, Pawliuk N, Schmitz N, Joober R, et al. Case manager- and patient-rated alliance as a predictor of medication adherence in first-episode psychosis. J Clin Psychopharmacol. 2012;32:465-9.

48 Weiden PJ, Schooler NR, Weedon JC, Elmouchtari A, Sunakawa A, Goldfinger SM. A randomized controlled trial of long-acting injectable risperidone vs continuation on oral atypical antipsychotics for first-episode schizophrenia patients: initial adherence outcome. J Clin Psychiatry. 2009;70:1397-406.

49 Schöttle D, Schimmelmann BG, Conus P, Cotton SM, Michel C, McGorry PD, et al. Differentiating schizoaffective and bipolar I disorder in first-episode psychotic mania. Schizophr Res. 2012;140:31-6.

50 Schimmelmann BG, Conus P, Cotton S, Kupferschmid S, Mcgorry PD, Lambert M. Prevalence and impact of cannabis use disorders in adolescents with early onset first episode psychosis. Eur Psychiatry. 2012;27:463-9.

51 Lepage M, Bodnar M, Joober R, Malla A. Is there an association between neurocognitive performance and medication adherence in first episode psychosis? Early Interv Psychiatry. 2010;4:189-95.

52 Steger KA, Cassidy C, Rabinovitch M, Joober R, Malla A. Impact of symptom resolution on medication adherence in first episode psychosis. Psychiatry Res. 2012;196:45-51.

53 Wade D, Harrigan S, McGorry PD, Burgess PM, Whelan G. Impact of severity of substance use disorder on symptomatic and functional outcome in young individuals with first-episode psychosis. J Clin Psychiatry. 2007;68:5:767-74.

54 Rabinovitch M, Cassidy C, Schmitz N, Joober R, Malla A. The influence of perceived social support on medication adherence in first-episode psychosis. Can J Psychiatry. 2013;58:59-65.

55 Cassidy CM, Rabinovitch M, Schmitz N, Joober R, Malla A. A comparison study of multiple measures of adherence to antipsychotic medication in first-episode psychosis. J Clin Psychopharmacol. 2010;30:64-7.

56 Marder SR. Overview of partial compliance. J Clin Psychiatry. 2003;64:3-9.

57 Kampman O, Laippala P, Väänänen J, Koivisto E, Kiviniemi P, Kilkku N, et al. Indicators of medication compliance in first-episode psychosis. Psychiatry Res. 2002;110:39-48.

58 Macbeth A, Gumley A, Schwannauer M, Fisher R. Service engagement in first episode psychosis: clinical and premorbid correlates. J Nerv Ment Dis. 2013;201:359-64.

59 Miller R, Ream G, McCormack J, Gunduz-Bruce H, Sevy S, Robinson D. A prospective study of cannabis use as a risk factor for non-adherence and treatment dropout in first-episode schizophrenia. Schizophr Res. 2009;113:138-44.

60 Robinson DG, Woerner MG, Alvir JM, Bilder RM, Hinrichsen GA, Lieberman JA. Predictors of medication discontinuation by patients with first-episode schizophrenia and schizoaffective disorder. Schizophr Res. 2002;57:209-19.

61 Leeson VC, Sharma P, Harrison M, Ron MA, Barnes TR, Joyce EM. IQ trajectory, cognitive reserve, and clinical outcome following a first episode of psychosis: a 3-year longitudinal study. Schizophr Bull. 2011;37:768-77.

62 Kane JM, Kishimoto T, Correll CU. Assessing the comparative effectiveness of long-acting injectable vs. oral antipsychotic medications in the prevention of relapse provides a case study in comparative effectiveness research in psychiatry. J Clin Epidemiol. 2013;66:S37-41.

63 Opjordsmoen S, Friis S, Melle I, Haahr U, Johannessen JO, Larsen TK, et al. A 2-year follow-up of involuntary admission's influence upon adherence and outcome in first-episode psychosis. Acta Psychiatr Scand. 2010;121:371-6.

64 Kane JM, Kishimoto T, Correll CU. Non-adherence to medication in patients with psychotic disorders: epidemiology, contributing factors and management strategies. World Psychiatry. 2013;12: 216-26.