Journal of Affective Disorders 149 (2013) 247–252

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

# Determinants of adherence to treatment in bipolar disorder: A comprehensive review

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ARTICLE INFO

*Article history:*
Received 6 December 2012
Accepted 29 January 2013
Available online 13 March 2013

*Keywords:*
Bipolar disorder
Adherence
Psychoeducation
Risk factors
Intervention

ABSTRACT

*Objective:* Comprehensively review studies evaluating factors associated with adherence to treatment in bipolar disorder (BD), as well as the results of interventions developed to enhance adherence in this population.

*Methods:* The following search engines were consulted: PubMed, Scielo, LILACS and PsycINFO. The keywords used were "Bipolar Disorder", "Factor", "Adherence", "Nonadherence", "Compliance" and "Intervention". In addition, references list of selected studies were consulted searching for relevant articles.

*Results:* Adherence has been defined in various ways, with some considering adherence vs. nonadherence, and other including a "partial" adherence measure. In addition, methods to assess adherence differ for each study. Several factors were related to poor adherence, including patient-related factors (e.g. younger age, male gender, low level of education, alcohol and drugs comorbidity), disorder-related factors (e.g. younger age of onset, severity of BD, insight and lack of awareness of illness) and treatment-related factors (e.g. side effects of medications, effectiveness). To improve adherence, the main recommendations are to provide customized interventions focusing on the underlying causes of nonadherence, strong therapeutic alliance and different modalities based on psychoeducation.

*Conclusion:* Our results indicate that nonadherence is a multicausal phenomenon and strategies to prevent and approaches them must include enhanced therapeutic alliance, flexible topics, early intervention, group setting, and psychoeducation.

*Limitations:* Different definitions and measures of adherence in the literature currently moderate the generalization of the findings in this review. Further studies are necessary regarding factors of adherence in BD and interventions to improve it, especially on social factors like stigma and family.



## 1. Introduction

Bipolar disorder (BD) is a common and often severe mood disorder, which affects multiple dimensions of the life of the patients (Colom et al., 2006). Functioning in BD is impaired in several domains, such as social, occupational and/or educational, and self-care (Michalak et al., 2008). One of the most robust determinants of level of functioning in BD is a history of multiple episodes, which impacts disability, chronicity and severity of subsyndromal symptoms and quality of life (Magalhaes et al., 2012).

The recurrence of episodes has been associated with deterioration in clinical and neurobiological parameters, including cognitive performance, response to pharmacological and psychosocial treatments and brain structures (Kapczinski et al., 2009; Taylor et al., 2011). These findings are in agreement with the recent paradigm of BD that considers this disorder not only a cyclic, but also a progressive one (Berk et al., 2011). Nevertheless, effective interventions focusing on reduction and delay of progression are not currently available. Because of this, to prevent new mood episodes is the only alternative to presumably delay evolution to disability (Brietzke et al., 2012).

Poor adherence to treatment is one of the main challenges to control the symptoms and prevent the recurrence in BD. Treatment nonadherence occurs at a rate between 12% and 64% among individuals with the disorder (Suppes et al., 1991; Keck et al., 1997; Schumann et al., 1999; Adams and Scott, 2000; Colom et al., 2000; Vega et al., 2011). Poor adherence increases the likelihood of relapse and neuroprogression, while it reduces the quality of life of patients and increases the risk of suicide (Colom et al., 2005; Gonzalez-Pinto et al., 2006; Lopez-Castroman et al., 2009).

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http://dx.doi.org/10.1016/j.jad.2013.01.036

The first aspect to be considered when adherence is the object of study is the different definitions of adherence that are found in the literature. The most widely accepted is the one developed by the World Health Organization (WHO) (Colom et al., 2005). The WHO basically defines "treatment adherence" as the extent to which a patient follows the medical instructions of their healthcare provider, and plays a key role in coming to an agreement about its own treatment (Velligan et al., 2009). The inclusion of an active engagement of the patient in the treatment is the differentiation with the previously used and similar concept of "compliance" (Colom et al., 2005). Additionally, the WHO recognizes that adherence necessarily reflects not only to take medication appropriately, but also to adopt a wider set of recommended behaviors with the objective to prevent, maintain and/or restore health. Examples of behavioral modifications that can be recommended in BD to minimize mood instability are to reduce or avoid substance/alcohol use and to regulate sleep/awake cycle. Attendance to psychosocial treatment, time to drop-out or attendance to psychiatrist follow-up appointments have already been used to measure the treatment adherence from a broader perspective (Even et al., 2007; Cakir et al., 2009; Proudfoot et al., 2012). Nonetheless, several authors still keep the emphasis on adherence regarding solely medication and use the term "adherence" just in that aspect (Jonsdottir et al., 2012).

Because adherence is a at the same time a complex phenomenon and a crucial step to acquire good outcomes in BD, to understand which aspects of the patient, the treatment and the healthcare provider have an impact on adherence is important to design new interventions to obtain and maintain adherence during treatment of individuals with BD.

The objective of this study is to conduct the first broad overview regarding determinant of adherence in BD and efficacy of interventions designed to improve adherence in this population.

## 2. Methods

The research questions that directed this review were: "Which factors are associated to adherence among individuals with BD?" and "Which interventions are effective to enhance adherence to treatment of individuals with BD?". To conduct this review, the following search engines were consulted: PubMed, Scielo, LILACS and PsycINFO. The keywords used were "Bipolar Disorder", "Factor", "Adherence", "Nonadherence", "Compliance" and "Intervention". In addition, references list of selected studies were consulted searching for relevant articles. Well-conducted observational studies, randomized controlled trials (RCT), cross-sectional and case-control studies were considered. Expert consensus reviews were also included. Articles from 1980 to 2012 were included from peer-reviewed publications only. We included articles published in English, French and Portuguese. We excluded review article and articles with data in repetition.

## 3. Results

A total of 115 articles were identified, and after screening 27 were kept.

### 3.1. Measures of medication adherence

Medication adherence has been measured in various ways in the different studies with some authors considering adherence vs. nonadherence, and others including one or more "partial" adherence measures (Jonsdottir et al., 2012). Several different objective and/or subjective measures have also been used in the literature. However, even with the best design each type of measure has its drawbacks and no measure alone can be considered optimal (World Health Organization and Sabate´, 2003).

Direct measures of medication adherence encountered were pills count (Gonzalez-Pinto et al., 2010; Sajatovic et al., 2012) or blood sampling to evaluate the plasma levels of medications, such as lithium, valproate or carbamazepine (Gonzalez-Pinto et al., 2006; Colom et al., 2009; Mazza et al., 2009; Pacchiarotti et al., 2009; Jonsdottir et al., 2012).

Indirect measures commonly used were self-report questionnaire (Baldessarini et al., 2008; Barraco et al., 2012) or clinical assessment filed out by the psychiatrist (Gonzalez-Pinto et al., 2010; Jonsdottir et al., 2012). Johnson et al. (2007) used a more original approach with a stated-preference web-survey combining medication attributes preference of BD patients and current self-reported adherence, verified for internal validity. Another example is the study from Jonsdottir et al. (2012) that used a validated Likert scale (0–100%) filled out by patients, about how much of their prescribed medication they have taken in the past week. Eker and Harkin (2012) used a multifaceted approach, with a combination of scores from three standardized instruments: the McEvoy Treatment Observation Form, the Medication Adherence Rating Scale (MARS), and the Attitude toward Neuroleptic Treatment (ANT). Even though self-report measures are subjective, they were proven valid by Jonsdottir et al. (2010). Still, both subjective measure (i.e. self-reported and rated by

**Table 1**
Factors associated to poor adherence.

| | Medication | Psychosocial treatment |
|---|---|---|
| **Patient-related factors** | Gender—Men<br>Younger age<br>Low level of education<br>Being single | Gender—Men<br>Older age<br>Low level of education |
| | **Psychology**<br>Poor insight | **Psychology**<br>Lack of awareness of the disease |
| | Lack of awareness of their disease<br>Negative attitude to treatment<br>Fear of side-effects<br>Negative attitude to medication<br>Low overall life satisfaction<br>Low cognitive functioning | External locus of control |
| | **Comorbidity**<br>Comorbid use of alcohol and cannabis<br>Obsessive-compulsive disorder | |
| **Social** | No social activities<br>Work impairment | No family history of BD and/or suicide |
| **Chronology** | Younger age of onset<br>Current inpatient status<br>Hospitalization or suicide attempt in past 12 months | |
| **Disease characteristics** | Mixed episode<br>Rapid cycling<br>Delusions and hallucinations<br>Severity of the illness<br>BD I diagnosis<br>Higher number of episodes | Depressive/manic episode<br>Longer duration of illness<br>Higher number of episodes |
| **Treatment related** | Side effects of medications<br>Inadequate efficacy of medication<br>Use of antidepressant<br>Low treatment dosage | Poor response to medication<br>Poor medication and medical follow-up adherence |