

Poor Adherence to Oral Psychiatric Medication in Adults with Bipolar Disorder: The Psychiatrist May have More Influence than in Other Severe Mental Illnesses

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Objective: Medication adherence in bipolar disorder (BD) may be influenced by 6 self-reported dimensions: 1) high/low psychological reactance, 2) high/low internal health locus of control (HLOC), 3) high/low doctor HLOC, 4) pharmacophobia, 5) pharmacophilia, and 6) skepticism about a specific medication. This study in Spain, Argentina, and Venezuela included 142 outpatients with BD prescribed 320 psychiatric medications and 1230 other psychiatric outpatients prescribed 2134 medications. **Methods:** Logistic regression models included adherence for each psychiatric medication, measured by the Sidorkiewicz Adherence Tool as the dependent variable. The models provided adjusted odds ratios (ORs) of dichotomous independent variables: clinical variables and 6 self-reported dimensions. **Results:** ORs significant in both groups were: 1) high doctor HLOC (OR=1.87 in BD, OR=1.25 in other patients), 2) high psychological reactance (respectively OR=0.572, OR=0.798), 3) pharmacophobia (respectively OR=0.361, OR=0.614), and 4) skepticism about a specific medication (respectively OR=0.300, OR=0.556). Two ORs were only significant in BD patients: medication duration > 1 year (OR=0.449), and extreme polypharmacy (OR=2.49). The study included 104 BD patients prescribed 122 mood stabilizers and 136 other patients prescribed 140 mood stabilizers. Two ORs were significant for mood stabilizer adherence only in BD patients: high doctor HLOC and skepticism (respective ORs=2.38, OR=0.390). The study included 87 BD patients prescribed 97 antipsychotics and 417 other patients prescribed 458 antipsychotics. Four ORs were significant for antipsychotic adherence only in the BD group. **Conclusions:** Future studies of adherence to all/specific medications should explore the specificity/commonality of these dimensions, particularly doctor HLOC, in BD versus other psychiatric patients.

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INTRODUCTION

Bipolar disorder (BD) refers to a complex group of chronic affective disorders, which together are characterized by depressive and manic or hypomanic episodes (Phillips & Kupfer, 2013). BD affects more than 45 million people worldwide (GBD, 2018), represents one of the leading causes of disability worldwide and is associated with significant direct and indirect costs (Parker et al., 2013). Although psychosocial support is an important component of treatment, antipsychotics and mood stabilizers are the mainstays of acute treatment for mania and depression in BD (Grande & Vieta, 2015), and lithium is considered to be one of the most effective treatments for preventing both types of symptoms (Miura et al., 2014). Since BD is a lifelong illness with high risk of relapse and sustained disability, effective prophylactic pharmacological treatment is a highly prevalent component of treatment (Yee et al., 2019). However, about half of the patients diagnosed with BD become non-adherent during their long-term treatment (MacDonald et al., 2016; Prajapati et al., 2018), resulting in poorer long-term clinical outcomes that have economic implications for health-care providers (Hong et al., 2011).

The Health Belief Model (HBM) is a model developed to explain and predict health-related behaviors, which emphasizes the central role of the patients' subjective beliefs, understanding of illness, and treatment options in determining adherence to prescribed medications (Rosenstock, 1974; Sulat et al., 2018). Not unexpectedly, patients' beliefs and attitudes towards their treatment also influence medication adherence in psychiatric patients (De las Cuevas & de Leon, 2017; de Leon & De las Cuevas, 2017).

The HBM literature has not received enough attention in psychiatric journals. To simplify, we call these dimensions *self-reported dimensions* and divide them into those focused on personality styles and on medications. Personality style dimensions obtained by self-report comprise those included under the Health Locus of Control (HLOC), which refers to who is responsible for the management of a disorder, and psychological reactance (De las Cuevas & de Leon, 2019a). In psychiatric patients, two HLOC dimensions are important: patient (internal) HLOC and doctor HLOC (Wallston & Wallston, 1982; Wallston et al., 1994).

Psychological reactance can be defined as an

emotional reaction toward rules perceived as a threat (Rosenberg & Siegel, 2017); it is typically measured with the Hong Psychological Reactance Scale (Hong & Faedda, 1996).

The Drug Attitude Inventory (DAI-10) is a questionnaire that reports attitude toward all medications (Hogan et al., 1983). It has been used to define the concepts of pharmacophobia, or fear of the use of pharmacological treatments, and pharmacophilia, or a positive attitude toward using or testing medications (De las Cuevas & de Leon, 2019b).

In summary, medication adherence in any psychiatric disorder, including bipolar disorder, may be influenced by 5 self-reported dimensions describing the patient: pharmacophobia, pharmacophilia, high/low psychological reactance, high/low doctor HLOC and high/low internal HLOC. To complete the four scales that refer to the patient, the DAI-10, Hong Psychological Reactance Scale and Multidimensional HLOC, requires from 1-1.5 hours of the patient's time. We have developed the Patient Health Beliefs Questionnaire on Psychiatric Treatment (De las Cuevas & de Leon, 2019a). It includes major items from the 4 scales and has 5 subscales: 1) positive aspects of medication, 2) negative aspects of medication 3) psychological reactance, 4) internal HLOC, and 5) doctor HLOC. It has recently been translated into other languages (Pogany et al., 2021).

The Beliefs about Medicines Questionnaire (BMQ) focuses on each medication individually and measures perception of necessity and concerns that the patient has regarding that specific medication (Horne et al., 1999). This is not a self-reported dimension based on the individual but on each individual drug. It can be used to define the concept of skepticism, which is high concern about adverse reactions and low belief in the drug's necessity (De las Cuevas et al., 2018a)

Box 1 describes our PubMed search that identified 92 articles on psychological aspects of medication adherence in BD and briefly summarizes 15 review articles (Davies et al., 2008; Miklowitz & Scott, 2009; Velligan et al., 2009; Berk et al., 2010; Maurel et al., 2010; Velligan et al., 2010; Macneil et al., 2011; Vega et al., 2011; Crowe et al., 2012; Laasko, 2012; Látalová, 2012; Malhi et al., 2012; Mago et al., 2014; Hartung et al., 2017; Boyce et al., 2018).

Box 2 describes our systematic PubMed search on adherence and BD which led to 14 articles using at least one of these 5 psychological scales. They include: HLOC: 5 articles (Darling et al., 2008; Sajatovic et

al., 2009a; Sajatovic et al., 2011; Chang et al., 2015; Hatzioannou et al., 2021); Psychological Reactance Scale: 0 articles, DAI: 9 articles (Pollice et al., 2008; Sajatovic et al., 2009b; Teter et al., 2011; Barraco et al., 2012; Medina et al., 2012; Montes et al., 2013; Rej et al., 2016; Lee et al., 2019; Maurin et al., 2020) and BMQ: 2 articles (Jónsdóttir et al., 2009; Klein et al., 2020). Of these 16 articles, none combined more than one scale and only 4 used some kind of control patients (Pollice et al., 2008; Jónsdóttir et al., 2009; Medina et al., 2012; Lee et al., 2019).

We conducted an ethnopsychopharmacology study in psychiatric outpatients in Spain, Argentina, and Venezuela including 1,372 patients using 2,454 psychiatric drugs. Prior analyses (De las Cuevas et al., 2018a; 2019; 2021) focused on the sample in general and included fewer patients.

In these new analyses, we divided the sample in two, 142 patients with BD (prescribed 320 psychiatric medications) and 1230 other psychiatric outpatients (prescribed 2134 medications), to explore which self-reported psychological dimensions and clinical variables are specifically associated with adherence in BD versus those common to other psychiatric disorders.

METHODS

Study design and participants

The ethics committee of the Canary Islands Health Service approved this study, and all the participating patients provided written informed consent approved by the corresponding institutional review boards. This 2017 cross-sectional cross-cultural psychopharmacology study included psychiatric outpatients in 3 centers in the Canary Islands (Spain), Mendoza (Argentina) and Mérida (Venezuela). The inclusion criteria for the psychiatric outpatients were as follows: (1) 18 years or older, (2) able to read and understand Spanish, (3) diagnosed with a psychiatric disorder, (4) treated with at least 1 psychiatric drug, and (5) participating voluntarily. Clinical diagnoses were based on the International Classification of Diseases, 11th revision. The patient completed the scales for each drug used and then the research team entered these records in the database and categorized the drugs based on their class. After consecutive recruitment at each center we had a final sample of 1372 psychiatric outpatients using 2454 psychotropic drugs.

Scales

The Patient Health Beliefs Questionnaire on Psychiatric Treatment has 17 items and 5 subscales referring to the patient: positive aspects of medications, negative aspects of medications, psychological reactance, internal HLOC and doctor's HLOC (De las Cuevas & de Leon, 2019a).

The BMQ-Specific measures the necessity and concerns beliefs about the potential negative effects of taking medicines, by which each drug in each patient was assessed for the accompanying presence or absence of skepticism (low necessity, high concern).

Polypharmacy is increasingly common in psychiatric patients. In this situation, measurement of treatment adherence is a really complex task because patients with BD could adhere differently to the various drugs prescribed, so it becomes essential to assess adherence to each individual drug. This was not possible until the introduction of the Sidorkiewicz Adherence Tool (Sidorkiewicz et al., 2016;). In this sample, adherence to every prescribed psychiatric drug was assessed using the Spanish validated version of the Sidorkiewicz adherence tool which has 5 questions leading to 6 levels of adherence that were dichotomized into adherence and non-adherence (De las Cuevas et al., 2018b)

Data Analysis

Data management and analyses were carried out using the Statistical Package for the Social Sciences (SPSS) software, 25th version. Table 1 describes all drugs after stratification based on BD and other mental illness. The dependent variable of our study is adherence (yes/no), followed by the dichotomous independent variables and then the continuous variables.

Following a classic textbook (Hosmer & Lemeshow, 2000), we conducted backward stepwise logistic regression models. Table 2 describes the model focused on all medication with its odds ratios (ORs) and 95% confidence intervals (CIs). The ORs from BD and other psychiatric disorders can be compared by their 95% CIs. If they do not overlap, the ORs can be said to be significantly different. This method is very conservative and overlapping 95% CIs can still be significantly different and not provide p values (Streiner, 2016). Thus, logistic regression models with interactions were used to approximate p values of the difference (footnote a of Table 2).

Table 3 focuses on mood stabilizer medications after stratification based on BD and other psychiatric disorders. Table 4 describes the logistic regression models for mood stabilizers.

Table 5 focuses on antipsychotic medications after stratification based on BD and other psychiatric disorders. Table 6 describes the logistic regression models for antipsychotics.

RESULTS

No significant difference in adherence to all medications in the two groups

There were 142 outpatients with BD prescribed 320 psychiatric medications and 1230 other psychiatric outpatients prescribed 2134 medications. Table 1 shows good adherence to all medications in 66.3% of the patients with BD versus 67.2% in the other patients ($p=0.72$, $OR=0.956$, $CI\ 0.746-1.23$).

Significant associations with adherence to all medications common to both groups

Table 2 shows that, after controlling for other variables, five variables were significant in both groups. The OR in high doctor HLOC was 1.87 in BD versus 1.25 in other psychiatric patients (overlapping CIs, $p=0.043$). The OR in high psychological reactance was 0.572 in BD versus 0.798 in other psychiatric patients (overlapping CIs, $p=0.14$). The OR in pharmacophobia was 0.361 in BD versus 0.614 in other psychiatric patients (overlapping CIs, $p=0.002$). The OR for skepticism about a specific medication was 0.300 in BD versus 0.556 in other psychiatric patients (overlapping CIs, $p=0.002$).

Significant association with adherence to all medications specific to patients with BD

Table 2 highlights four ORs for all drugs that were not significant in patients with BD but were significant in psychiatric controls. Two ORs were significant in patients with BD and not in the controls: extreme polypharmacy ($OR=2.487$) and taking the medication for more than 1 year ($OR=0.449$).

The subgroup of prescriptions characterized as extreme polypharmacy in patients with BD was selected. When compared with those without extreme polypharmacy, the patients using extreme polypharmacy showed higher percentages of: 1) adherence, 2) Spanish patients, 3) prescription of

antianxiety medications, 4) pharmacophilia, and 5) high doctor HLOC and lower percentages of 1) antipsychotic prescriptions, and 2) skepticism.

The subgroup of prescriptions characterized by taking that medication for more than 1 year in patients with BD was selected. When compared with those taking a medication for less than 1 year, the patients using prescribed medication for more than 1 year were characterized by higher percentages of: 1) antianxiety agents, 2) Spanish patients, 3) pharmacophilia, and 4) extreme polypharmacy and lower percentages of 1) antipsychotic prescriptions, 2) pharmacophobia and 3) skepticism.

Borderline significant difference but a small OR in adherence to mood stabilizers in both groups

Table 3 illustrates good adherence for 67.3% of the mood stabilizers taken by patients with BD versus 56.2% in the other patients. This bordered on significance ($p=0.051$) due to the large sample size, but the OR was relatively small ($OR=1.64$, $CI\ 0.996-2.70$).

Significant association with adherence to mood stabilizers specific to patients with BD

Table 4, on adherence to mood stabilizers, shows that one OR was not significant in patients with BD, but was significant in the model of psychiatric controls. More importantly, two ORs were included in the BD patients and not in the controls: high doctor HLOC ($OR=2.38$) and skepticism about that mood stabilizer ($OR=0.390$).

No significant difference in adherence to antipsychotic medications in the two groups

Table 5 describes good adherence to antipsychotic medications in 66.0% of the patients with BD versus 69.0% in the other patients ($p=0.56$, $OR=0.871$, $CI\ 0.548-1.39$).

Significant associations with adherence to antipsychotic medications common to both groups

Table 6 illustrates that, after controlling for other variables, one variable was significant in both groups with no significant differences in the ORs. The OR for pharmacophobia was 0.193 in BD versus 0.427 in other psychiatric patients (overlapping CIs and $p=0.001$).

Significant association with adherence to antipsychotic medications, but with opposite direction in BP vs. other psychiatric patients

Table 6 shows that, after controlling for other variables, the OR for pharmacophilia was 0.059 in BD versus 1.80 in other psychiatric patients.

Significant association with adherence to antipsychotics specific to patients with BD

Table 6, on adherence to antipsychotics, describes one OR that was not significant in patients in the BD group, but was significant in the model of psychiatric controls. There were 4 ORs only significant in BD patients: high doctor HLOC (OR=5.00), Spain (OR=5.33), high internal HLOC (OR=0.119) and skepticism about a specific antipsychotic medication (OR=0.053).

DISCUSSION

This is the first study in patients with BD simultaneously exploring the relevance of skepticism, pharmacophobia, pharmacophilia, psychological reactance, doctor and internal HLOC on adherence after controlling for clinical variables, particularly treatment duration. The use of other psychiatric patients as controls helps the researchers gauge what may or may not be specific to BD.

The study of the impact of these attitudinal predictors of poor adherence to prescribed treatment is pertinent since these variables have the potential to be modified, unlike most sociodemographic and clinical variables. Overall, our results confirmed the evidence that beliefs and attitudes are relevant factors in predicting treatment adherence in BD.

Medication adherence is similar in patients with BD and other psychiatric patients

In this sample, medication adherence may be slightly better in patients with BD as the main diagnosis than in other psychiatric patients. Adherence in patients with BD was not significantly different than in other mental disorders for all medications and for antipsychotic medications. Adherence to mood stabilizers was borderline significant ($p=0.051$), but the OR was relatively small (OR=1.64) and may not be significant in future studies of similar design unless they have similar large sample sizes.

High doctor HLOC may be more specific for adherence in patients with BD

In all medications, the OR for high doctor HLOC was significantly stronger in patients with BD (OR=1.87) versus other psychiatric patients (OR=1.25). Moreover, the OR was only significant in BD for mood stabilizers (OR=2.38) and for antipsychotic medication (OR=5.0). All of these ORs are adjusted by other variables that had a significant effect on adherence in the logistic regression models. As no prior study of the effect of HLOC on adherence in BD patients has controlled for other self-reported dimensions, there are no similar studies for comparison. As a matter of fact, a prior study (Sajatovic et al., 2009; Chang et al., 2015) on medication adherence exploring HLOC in BD patients featured important differences in design, including: 1) lack of control for other self-report dimensions, 2) global measurement of adherence without specifying individual medications, and 3) continuous measure of HLOC. Using this alternative design, Sajatovich et al. (2009) found that higher external HLOC led to a positive attitude toward medications. In a study on physical health, Buhagiar et al. (2011) found that patients with BD (and those with schizophrenia spectrum disorders) are significantly more likely to have a HLOC determined by powerful others. Although they do not study adherence and focus on physical health, they proposed that health professionals are in good position to exert a high level of influence on people with severe mental illness in regard to their physical health.

Pharmacophobia and skepticism may have effects on adherence in all psychiatric patients

Pharmacophobia was significant in some analyses. In all meds and in antipsychotic medications, pharmacophobia had significant ORs in both groups, but was significantly stronger in BD. In the smaller sample of mood stabilizers, it was not significant in any group.

Skepticism about some specific medication was significant in both groups for all meds but it was significantly stronger in BD. Regarding antipsychotic medication, skepticism was only significant in BD. In the smaller sample of mood stabilizers, it was not significant in either of the two groups.

Effect of other self-descriptive dimensions on adherence in patients with BD

The association with adherence was less consistent for other self-descriptive dimensions. High psychological reactance had a significant association with adherence in both groups but only in the large sample of all medications. Pharmacophilia was associated with increased antipsychotic adherence in other psychiatric patients, but it unexpectedly decreased antipsychotic adherence in BD patients. High internal control only became significant in decreasing adherence in the model of antipsychotics in BD patients.

Treatment characteristics and medication adherence in patients with BD

Regarding adherence to all drugs, taking a medication for more than 1 year (OR=0.449) and extreme polypharmacy (OR=2.487) were only significant in patients with BD and not in the controls. The decrease in adherence to a specific medication in BD patients after 1 year of treatment probably reflects the difficulty that BD patients experience in being adherent for the long term. It was unexpected that extreme polypharmacy (≥ 4 medications) increases adherence since in the whole sample in Spain extreme polypharmacy appears to be a factor contributing to poor adherence (De las Cuevas et al., 2020). The analysis of this BD subsample who were prescribed extreme polypharmacy suggests that increased adherence may be a sign of agreement with their doctors about the need to treat psychiatric comorbidity, particularly anxiety. As a matter of fact, Vázquez et al. (2014) proposed that anxiety symptoms and syndromes co-occur commonly in patients with bipolar disorder, but “co-morbid” phenomena may be part of the BD phenotype rather than separate illnesses.

Limitations

The Spanish sample may be much more representative since it represents a catchment area from Spain's free universal health system, while in Venezuela

and Argentina the healthcare models are highly fragmented with health coverage distributed among the public and private sectors and with unequal access.

Any study using self-reported adherence in clinical samples is hampered by its nature. The most non-adherent patients are the ones who have not come for treatment. Moreover, any patient not willing to sign a consent form was not included in this sample of patients taking medications.

This is a multicenter study with no external support, where the use of objective measures such as blood levels or pill counts (Sajatovic et al., 2015; Whalley Buono et al., 2017) was not possible. We used self-report measures to study 80 different pharmacological compounds in 3 different countries, as self-report was the only possible efficient way to study medication adherence of so many individual medications (Stirratt et al., 2015; De las Cuevas & de Leon, 2020).

Our study used no measures of insight into disease and only included relatively stable outpatients. In the article describing the validation of our scale, the Patient's Health Belief Questionnaire on Psychiatric Treatment, we stressed the need to improve it by adding a short cross-sectional measure of insight (De las Cuevas & de Leon, 2019a). This addition will not measure past or future changes in insight. During acute exacerbations patients may have decreasing insight and may not cooperate with studies of adherence and self-reported dimensions.

CONCLUSION

Future studies of adherence to all medications and to specific medications including mood stabilizers (Bauer et al., 2019) need to further explore which of these dimensions are specific to BD and which are common to all psychiatric disorders. If our results are replicated in another sample of patients with BD, it may be important to develop personalized interventions to increase medication adherence in patients with BD that are focused on improving communication between patients and their psychiatrists.

Table 1. All psychiatric medications: Comparing dependent and independent variables in bipolar disorder and other MDs^a

Variable (range)	Bipolar Disorder: 142 patients with 320 medications ^c	Other MD ^b :1230 patients with 2134 medications ^d
Dependent Variable		
Adherence ^e		
Yes	66.3% (212/320)	67.2% (1435/2134)
No	33.7% (108/320)	32.8% (699/2134)
Dichotomous Independent Variables		
Female gender	57.7% (82/142)	58.0% (714/1230)
Geriatric age	9.9% (14/142)	8.1% (100/1230)
University education	51.4% (73/142)	32.0% (394/1230)
Spain	28.2% (40/142)	44.6% (549/1230)
Treatment >1 year	93.7% (133/142)	66.7% (820/1230)
Extreme polypharmacy (≥4 medications)	12.7% (18/142)	5.5% (68/1230)
Medication > 1 year	72.5% (232/320)	54.7% (1168/2134)
Pharmacophobia	31.0% (44/142)	28.5% (350/1230)
Pharmacophilia	28.2% (40/142)	31.9% (292/1230)
Skeptical about specific medication	20.3% (65/320)	29.8% (636/2134)
High psychological reactance	50.7% (72/142)	46.7% (574/1230)
High internal HLOC	50.7% (72/142)	48.9% (601/1230)
High doctor HLOC	46.5% (66/142)	42.3% (520/1230)
Continuous Independent Variables^f (mean±SD)		
Age (years) (≥18)	46.1±13.9 (N=142)	43.8±14.3 (N=1230)
Number of medications (1-6)	2.25±1.2 (N=142)	1.73±0.9 (N=1230)
Duration of medication (months)	58.8±57.6 (N=320)	40.1±56.9 (N=2134)
Positive aspects of medication (5-30)	23.4±5.3 (N=142)	22.5±5.1 (N=1230)
Negative aspects of medication (3-18)	9.3±3.9 (N=142)	9.1±3.8 (N=1230)
Necessity (1-5)	3.70±0.96 (N=320)	3.47±0.95 (N=2134)
Concern (1-5)	2.77±1.1 (N=320)	3.00±1.0 (N=2134)
Psychological reactance (3-18)	12.7±4.2 (N=142)	12.3±4.4 (N=1230)
Internal HLOC (3-18)	13.6±3.6 (N=142)	13.6±3.7 (N=1230)
Doctor HLOC (3-18)	15.6±3.1 (N=142)	15.4±3.0 (N=1230)

Abbreviations: health locus of control, HLOC; mental disorders, MDs; standard deviation, SD.

^a No attempt was made to compare statistical significance between the two groups (bipolar disorder vs. other MD), which would have provided multiple significance tests and risk of false positives by chance. Moreover, the article's goal is not that these variables are significant in these two groups, but these dichotomous variables are significantly associated with adherence and the associations with adherence between the two groups are significantly different.

^b Diagnoses were schizophrenia 17.2% (212/1230), depressive disorders 42.4% (521/1230), anxiety disorders 25.2% (319/1230), personality disorders 5.4% (67/1239), substance abuse 1.8% (22/1230), and other psychiatric disorders 8.0% (98/1230).

^c The psychiatric drugs were antipsychotics 30.3% (97/320), mood stabilizers 38.1% (122/320), antidepressants 11.6% (37/320), antianxiety and non-benzodiazepine Z hypnotics, 19.4% (62/320), and others 0.6% (2/320).

^d The psychiatric drugs were antipsychotics 21.5% (458/2134), mood stabilizers 6.6% (140/2134), antidepressants 39.5% (843/2134), antianxiety and non-benzodiazepine Z hypnotics 31.1% (663/2134), and others 1.0% (21/2134).

^e The mean±SD score using the Sidorkiewicz Adherence Tool was 2.76±1.98 in 142 bipolar patients vs. 2.57±1.97 in 1230 patients with other mental disorders.

^f In prior articles using logistic regression models, we have been reviewed by statistically-oriented reviewers who remind us that continuous independent variables have more statistical power than dichotomous independent variables. We agree with that statement but for clinical reasons we only included in Table 2 the logistic regression model with dichotomous independent variables. The logistic regression model with continuous independent variables is available upon request to the authors. It was not included because clinicians have difficulty managing the raw scores from all this psychological data and, more importantly, because these self-reported scales vary from country to country (e.g., a score of 4 may not mean the same in each country). Dichotomization by median score helps to correct for this difference.

Table 2. All psychiatric medications: logistic regression model (adherence yes/no as dependent variable)

Variable	Bipolar Disorder OR (95% CI)	Other MD OR (95% CI)	Comparison ^a
Dichotomous Model^b			
High doctor HLOC	1.87 (1.06-3.29) P=.030	1.25 (1.01-1.55) P=.038	P=0.043 ^c Overlapping CI Stronger in bipolar disorder
High psychological reactance	0.572 (0.331-0.989) P=.046	0.798 (.657-.969) P=.023	P=0.14 ^c Overlapping CI
Pharmacophobia	0.361 (.198-.656) P=.001	0.614 (.489-.770) P<.001	P=0.002 ^c Overlapping CI Stronger in bipolar disorder
Skepticism about specific med	0.300 (.155-.528) P<.001	0.556 (.449-.689) P<.001	P=0.002 ^c Overlapping CI Stronger in bipolar disorder
Medication > 1 year	0.449 (.239-.846) P=.013	NS	NS in other mental disorders
Extreme polypharmacy	2.49 (1.27-4.87) P=.008	NS	NS in other mental disorders
Geriatric age	NS	2.81 (1.768-4.450) P<.001	NS in bipolar disorder
Treatment > 1 year	NS	0.639 (.514-.795) P<.001	NS in bipolar disorder
High internal control	NS	0.731 (.600-.880) P=.002	NS in bipolar disorder
Pharmacophilia	NS	1.839 (1.43-2.37) P<.001	NS in bipolar disorder

Abbreviations: CI, confidence interval; HLOC, health locus of control; MDs, mental disorders; NS, not significant; OR, odds ratio; SPSS, Statistical Package for the Social Sciences.

^a ORs can be compared by their 95% CIs. If they do not overlap, the ORs can be said to be significantly different. Logistic regression models were fitted, including adherence as the dependent variable and the significant independent variables. Different models were fitted adding the variable bipolar disorder and an interaction term with each one of other independent variables. When the logistic regression model provided a significant p value for the interaction between bipolar disorder and the other independent variables, this helped support the conclusion that the ORs of the bipolar disorder sample and the other sample were significantly different.

^b Both models fit well, as measured by the Hosmer and Lemeshow test. For the bipolar model $\chi^2=5.930$, $df=8$, $p=.665$ and for the other MD model $\chi^2=8.974$, $df=8$, $p=.345$. The default in SPSS entry 0.05 and removal 0.10 was modified to entry 0.05 and removal 0.05.

^c Significance was tested by a logistic regression model where adherence was the dependent variable and other variables and an interaction term with bipolar disorder and the variable represented in each row are the predictors.

Table 3. Mood stabilizer medications: Comparing dependent and independent variables in bipolar disorders and other MDs

Variable	Bipolar Disorder 104 patients with 122 mood stabilizers	Other MD ^a 136 patients with 140 mood stabilizers
Dependent Variables		
Adherence ^d Yes	64.8% (79/122)	52.9% (74/140)
Adherence ^d No	35.2% (43/122)	47.1% (66/140)
Dichotomous Independent Variables		
Female gender	64.4% (67/104)	50.7% (69/136)
Geriatric age	8.7% (9/104)	2.9% (4/136)
University education	51.9% (54/104)	36.0% (49/136)
Spain	30.8% (32/104)	41.9% (57/136)
Treatment >1 year	94.2% (98/104)	81.6% (111/136)
Extreme polypharmacy (≥4 medications)	82.7% (86/104)	24.3% (33/136)
Mood stabilizer polypharmacy	16.3% (17/104)	2.9% (4/136)
Medication > 1 year	77.0% (94/122)	69.3% (97/140)
Pharmacophobia	30.8% (32/104)	32.4% (44/136)
Pharmacophilia	28.8% (30/104)	26.5% (36/136)
Skeptical about specific medication	23.0% (28/122)	27.1% (38/140)
High psychological reactance	50% (52/104)	55.9% (76/136)
High internal HLOC	49.0% (51/104)	50.0% (68/136)
High doctor HLOC	47.1% (49/104)	35.3% (48/136)
Continuous Independent Variables (mean±SD)		
Age (years) (≥18)	46.0±14.2 (N=104)	41.5±13.8 (N=136)
Number of medications (1-6)	2.5±1.2 (N=104)	2.6±1.3 (N=136)
Number of mood stabilizers (1-3)	1.2±0.4 (N=104)	1.0±0.1 (N=136)
Duration of medication (months)	61.6±56.9 (N=122)	52.5±57.2 (N=140)
Positive aspects of medication (5-30)	23.4±5.1 (N=104)	22.9±4.4 (N=136)
Negative aspects of medication (3-18)	9.1±3.7 (N=104)	9.6±3.5 (N=136)
Necessity (1-5)	3.8±0.9 (N=122)	3.6±0.9 (N=140)
Concern (1-5)	2.9±1.0 (N=122)	2.9±1.0 (N=140)
Psychological reactance (3-18)	12.7±4.4 (N=104)	12.8±4.3 (N=136)
Internal HLOC (3-18)	13.4±3.7 (N=104)	13.8±3.5 (N=136)
Doctor HLOC (3-18)	15.8±2.7 (N=104)	15.1±3.1 (N=136)

Abbreviations: health locus of control, HLOC; mental disorders, MDs; standard deviation, SD.

^a Diagnoses were schizophrenia 24.3% (33/136), bipolar disorders 33.1% (45/136), anxiety disorders 11.0% (15/136), personality disorders 14.7% (20/136), substance abuse 4.4% (6/136), and other psychiatric disorders 12.5% (17/136).

^b The mean ±SD score in the Sidorkiewicz Adherence Tool was 2.87±2.0 in bipolar disorder vs. 2.98±1.8 in other mental disorders.

Table 4. Mood stabilizer medications: logistic regression model (adherence yes/no as the dependent variable)

Variable	Bipolar Disorder OR (95% CI)	Other MD OR (95% CI)	Comparison
Dichotomous Model^a			
High Doctor HLOC	2.38 (1.80-5.24) P=.031	NS	NS in other MD
Skepticism about specific medication	0.390 (.158-.963) P=.041	NS	NS in other MD
Pharmacophilia	NS	3.217 (1.413-7.324) P=.005	NS in bipolar disorder

CI, confidence interval; HLOC, health locus of control; NS, not significant; OR, odds ratio; SPSS, Statistical Package for the Social Sciences.

^a Both models fit well as measured by the Hosmer and Lemeshow test. For the bipolar disorder model $\chi^2=0.00$, $df=0$, $p=$ and for the other MD model $\chi^2=3.836$, $df=2$, $p=.147$. All procedures were the same for all medications except that the mood stabilizer sample had a smaller sample size, so we decided to keep the SPSS default: entry 0.05 and removal 0.05.

Table 5. Antipsychotic medications: Comparing dependent and independent variables in bipolar disorders and other MDs.

Variable	Bipolar Disorders 87 patients with 97 antipsychotics	Other MD ^a 417 patients with 458 antipsychotics
Dependent Variables		
Adherence ^d Yes	66.0% (64/97)	69.0% (316/458)
No	34.0% (33/97)	31.0% (142/458)
Dichotomous Independent Variables		
Female gender	54.0% (47/87)	46.5% (194/417)
Geriatric age	9.2% (8/87)	7.7% (32/417)
University education	49.4% (43/87)	26.6% (110/417)
Spain	23.0% (20/87)	38.4% (160/417)
Treatment >1 year	93.1% (81/87)	77.0% (321/417)
Extreme polypharmacy (≥ 4 medications)	18.4% (16/87)	11.3% (47/417)
Antipsychotic polypharmacy	11.5% (10/87)	9.4% (39/417)
Medication > 1 year	60.8% (59/97)	56.8% (260/458)
Pharmacophobia	32.2% (28/87)	31.7% (132/417)
Pharmacophilia	31.0% (27/87)	28.3% (118/417)
Skeptical about specific medication	17.5% (17/97)	25.8% (1187/458)
High psychological reactance	49.4% (43/87)	38.4% (160/417)
High internal HLOC	50.6% (44/87)	49.2% (205/417)
High doctor HLOC	47.1% (41/87)	44.6% (186/417)
Continuous Independent Variables (mean\pmSD)		
Age (years) (≥ 18)	46.8 \pm 13.9 (N=87)	43.1 \pm 14.0 (N=417)
Number of medications (1-6)	2.6 \pm 1.3 (N=87)	2.1 \pm 1.1 (N=417)
Number of antipsychotics (1-3)	1.1 \pm 0.3 (N=87)	1.1 \pm 0.3 (N=417)
Duration of medication (months)	45.3 \pm 48.5 (N=97)	48.8 \pm 66.8 (N=458)
Positive aspects of medication (5-30)	23.8 \pm 5.6 (N=87)	23.0 \pm 5.3 (N=417)
Negative aspects of medication (3-18)	9.3 \pm 4.0 (N=87)	9.6 \pm 4.0 (N=417)
Necessity (1-5)	3.7 \pm 0.9 (N=97)	3.6 \pm 0.9 (N=458)
Concern (1-5)	2.7 \pm 1.1 (N=97)	2.9 \pm 1.1 (N=458)
Psychological reactance (3-18)	12.5 \pm 4.2 (N=87)	11.4 \pm 4.5 (N=417)
Internal HLOC (3-18)	13.6 \pm 3.8 (N=87)	13.6 \pm 3.7 (N=417)
Doctor HLOC (3-18)	15.3 \pm 3.6 (N=87)	15.4 \pm 3.1 (N=417)

Abbreviations: health locus of control, HLOC; mental disorders, MDs; standard deviation, SD.

^a Diagnoses were schizophrenia 48.7% (203/417), depressive disorders 20.4% (85/417), anxiety disorders 9.8% (41/417), personality disorders 7.9% (33/417), substance abuse 1.7% (7/417), and other psychiatric disorders 11.5% (48/417).

^b The mean \pm SD score in the Sidorkiewicz Adherence Tool was 2.78 \pm 1.9 in bipolar disorders vs. 2.90 \pm 1.1 in other MDs.

Table 6. Antipsychotic medications: logistic regression model (adherence yes/no as dependent variable)

Variable	Bipolar Disorder OR (95% CI)	Other MD OR (95% CI)	Comparison
Dichotomous Model^a			
Pharmacophobia	0.193 (.039-.959) P=.044	0.427 (.268-.682) P<.001	P=0.001 ^b Overlapping CI Stronger in bipolar disorder
Pharmacophilia	0.059 (.013-.276) P<.001	1.801 (1.060-3.121) P=.036	ORs had opposite direction Not overlapping CI
Spain	5.33 (1.03-27.68) P=.046	NS	NS in other MD
High Doctor HLOC	5.00 (1.31-18.13) P=.019	NS	NS in other MD
High Internal HLOC	0.119 (.029-.485) P=.003	NS	NS in other MD
Skepticism about a specific med	0.053 (.009-.389) P=.001	NS	NS in other MD
Geriatric age	NS	3.292 (1.118-9.699) P=.031	NS in bipolar disorder

CI, confidence interval; HLOC, health locus of control; NS, not significant; OR, odds ratio; SPSS, Statistical Package for the Social Sciences.

^a Both models fit well as measured by the Hosmer and Lemeshow test. For the bipolar disorder model $\chi^2=12.670$, $df=7$, $p=.081$ and for the other MD model $\chi^2=0.582$, $df=3$, $p=.901$. All procedures were the same for all medications except that antidepressants had a lower sample size, so we decided to keep the SPSS default: entry 0.05 and removal 0.05.

^b Significance was tested by a logistic regression model where adherence was the dependent variable and other variables and an interaction term with bipolar disorder and the variable represented in each row are the predictors.

Box 1. Reviews of the psychology of medication adherence in bipolar disorder

PubMed search (2021/10/16) of article reviews
"Medication Adherence/psychology"[Mesh] AND "bipolar disorder" [Mesh]" produced 92 articles, of which 15 were reviews. These 15 reviews are briefly reviewed below.
Boyce et al. (2018)
The long-acting injectable formulations may be better for non-adherent patients or those with unstable illness.
Hartung et al. (2017)
There was insufficient evidence on interventions for improving medication adherence in bipolar disorder.
Mago et al. (2014)
Adverse effects (including weight gain, perceived cognitive impairment, tremors, and sedation) are an important reason for nonadherence to mood stabilizers in bipolar disorder.
Crowe et al. (2012)
They reviewed the studies of psychosocial interventions to improve medication adherence in bipolar disorders. None of the factors studied distinguished the effective and non-effective interventions. The factors studied were: 1) the characteristics of the interventions, 2) clinical characteristics of the groups and 3) methodological factors.
Malhi et al. (2012)
Lithium therapy: 1) is a safe and effective agent, 2) should be used as first-line whenever indicated, and 3) can be improved by a better understanding of its science and by a strategic management of its plasma levels.
Laakso (2012)
The article proposes that psychiatric nurses by using Motivational Interviewing may improve medication adherence.
Látalová (2012)
Better insight is associated with better medication adherence. Impaired insight is associated with: 1) impairments of executive functions and memory, 2) higher severity of psychotic symptoms, 3) illness episode versus remission, 4) mixed versus pure manic episodes, 5) bipolar II versus bipolar I patients, 5) pure mania versus bipolar or unipolar depression. Psychosocial treatments can improve insight and outcomes.
Vega et al. (2011)
This article focused on clinical differences between men and women with bipolar disorder and analyzed differences in medication adherence. Women had greater adherence than men but also were less prone to present with manic episodes, have less comorbid drug abuse and later onset. In women, earlier onset and being single increased non-adherence.
Macneil et al. (2011)
They propose that evidence supporting the effectiveness of psychological interventions is growing. These interventions need to be modified for young people who are early in the course of the disorder.
Maurel et al. (2010)
Psychosocial interventions are reviewed; consideration is given that they may enhance medication adherence and prevent relapses. Each intervention may have different advantages. They reviewed: 1) psychoeducation, 2) cognitive and behavioral therapy, 3) behavioral family therapy, 4) interpersonal therapy and 5) and social rhythm therapy.
Velligan et al. (2010)
This review does not focus on bipolar disorder. A panel of experts reviewed the methodological challenges to study adherence research in psychiatric patients.
Berk et al. (2010)
They stressed the relevance of a person-centered approach for improving adherence which requires considering the risk factors and barriers for non-adherence. They recommend psycho-education for improving medication adherence.
Velligan et al. (2009)
The experts agreed that non-adherence is common in bipolar disorder (and schizophrenia). Factors associated with non-adherence in bipolar disorder (and schizophrenia) include: 1) poor insight and lack of illness awareness, 2) distress associated with specific side effects (particularly weight gain) or a general fear of side effects, 3) inadequate efficacy with persistent symptoms, and 4) believing medications are no longer needed. Persistent grandiosity and manic symptoms may be the most important symptomatic contributors to non-adherence in patients with bipolar disorder.
Miklowitz & Scott (2009)
Psychosocial treatments in bipolar disorder are cost-effective. Increasing medication adherence may be among the mediating mechanisms.
Davies et al. (2008)
This is a case study of the collaborative practice model to the long-term care of individuals with bipolar disorder. Key elements in the model are joint patient-provider treatment planning and decision making.

Box 2. PubMed search (2021/10/16) of self-reported dimensions, bipolar disorder and adherence

"Health locus of control" AND bipolar disorder AND adherence provided 5 articles. (Darling et al., 2008; Sajatovic et al., 2009a; 2011; Chang et al., 2015; Hatzioannou et al., 2021).
"Psychological Reactance" AND bipolar disorder AND adherence provided 0 articles.
"Drug Attitude Inventory" AND bipolar disorder and adherence provided 9 articles (Pollice et al., 2008; Sajatovic et al., 2009b; Teter et al., 2011; Barraco et al., 2012; Medina et al., 2012; Montes et al., 2013; Rej et al., 2016; Lee et al., 2019; Maurin et al., 2020).
"Beliefs about Medicines Questionnaire" AND bipolar disorder AND adherence provided 2 articles (Jónsdóttir et al., 2009; Klein et al., 2020).

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Gyenge adherencia orális pszichotróp gyógyszerrel kezelt felnőtt bipoláris pácienseknél: a pszichiáterek szerepe jelentősebb, mint más súlyos mentális betegségekben

Célkitűzés: Bipoláris affektív zavar miatt kezelés alatt álló betegek adherenciáját hat, a betegek beszámolója alapján körülhatárolható tényező befolyásolhatja: 1) magas/alacsony pszichológiai reaktancia, 2) magas/alacsony belső egészségkontrollhely pontszám (I-HLOC), 3) magas/alacsony orvos HLOC pontszám, 4) farmakofóbia, 5) farmakofília, 6) szkepticizmus a gyógyszerekkel kapcsolatban. A vizsgálatba 142 ambuláns kezelés alatt álló, bipoláris affektív zavarban szenvedő beteget és 1230 más pszichiátriai betegség miatt ambuláns kezelésre szoruló beteget vontunk be. A bipoláris affektív zavar miatt kezelés alatt álló betegek csoportjában összesen 320 pszichiátriai gyógyszert szedtek, a másik betegcsoportban pedig összesen 2134 pszichiátriai gyógyszert írtak fel a betegeknek. **Módszerek:** A betegek adherenciáját a Sidorkiewicz-féle eszközzel (Sidorkiewicz Adherence Tool) ítéltük meg. Logisztikus regressziós modellel vizsgáltuk az adherenciát mint függő változót valamennyi gyógyszer vonatkozásában. A klinikai változókra és 6 önjellemző dimenzóra vonatkozó esélyhányadosokat a dichotóm változókra korrigálva adtuk meg. **Eredmények:** Az alábbi változók esetében mértünk mindkét csoportban szignifikáns esélyhányados (OR) értéket: 1.) magas orvos HLOC (OR=1,87 bipoláris affektív zavarban, OR=1.25 a többi diagnózis esetében), 2.) magas pszichológiai reaktancia (OR=0,572, OR=0,798), 3.) farmakofóbia (OR=0,361, OR=0,614) és 4.) adott gyógyszerrel kapcsolatos szkepticizmus (OR=0,300, OR=0,556). Két esélyhányados (OR) csak a bipoláris affektív zavarban szenvedő betegek esetében volt szignifikáns: a gyógyszeres kezelés > 1 éves időtartama (OR=0,449), és az extrém mértékű polipragmázia (OR=2,49). A vizsgálatban 104 bipoláris affektív zavarban szenvedő beteg vett részt, akik együttesen 136 hangulatstabilizáló gyógyszert szedtek, valamint 136 egyéb pszichiátriai betegség miatt kezelt beteg, akik számára összesen 140 hangulatstabilizáló szert írtak fel. A hangulatstabilizálóra vonatkozó adherencia tekintetében két esélyhányados (OR) csak bipoláris affektív zavar esetén mutatott szignifikáns összefüggést: a magas orvos HLOC pontszám, és a gyógyszerrel kapcsolatos szkepticizmus (OR=2,38 valamint OR=0,390). A vizsgálatban 87 bipoláris affektív zavarban szenvedő beteg összesen 97 antipszichotikumot, míg 417, egyéb pszichiátriai kórkép miatt kezelt páciens együttesen 458 antipszichotikumot szedett. Az antipszichotikumokra vonatkozó adherencia négy esélyhányados (OR) esetében csak a bipoláris affektív zavar miatt kezelt csoportban volt szignifikáns. **Következtetés:** A következő vizsgálatok célkitűzése az lehet, hogy valamennyi alkalmazott gyógyszerre vonatkozó adherencia esetében feltárja az ezt meghatározó tényezők közötti különbségeket és hasonlóságokat, különösen az orvos HLOC vonatkozásában, összehasonlítva a bipoláris affektív zavar miatt és egyéb pszichiátriai kórkép kapcsán kezelésre szoruló páciensek jellemzőit.

Kulcsszavak: egészséghez való viszonyulás, bipoláris affektív zavar, adherencia, egészségmagatartás, pszichofarmakológia