

# Adherence to psychiatric medications: Comparing patients with schizophrenia, bipolar disorder and major depression

JUDIT LAZARY<sup>1,2</sup>, LASZLO POGANY<sup>1,2</sup>, CARLOS DE LAS CUEVAS<sup>3</sup>,  
ALEJANDRO G. VILLASANTE-TEZANOS<sup>4</sup> AND JOSE DE LEON<sup>5,6</sup>

<sup>1</sup> National Institute of Mental Health, Neurology and Neurosurgery, Budapest, Hungary

<sup>2</sup> János Szentágothai Doctoral School of Neuroscience, Semmelweis University, Budapest, Hungary

<sup>3</sup> Department of Internal Medicine, Dermatology and Psychiatry and Instituto Universitario de Neurociencia (IUNE), Universidad de La Laguna, Canary Islands, Spain

<sup>4</sup> Department of Preventive Medicine and Population Health, University of Texas Medical Branch, Galveston, TX, USA

<sup>5</sup> Mental Health Research Center at Eastern State Hospital, Lexington, KY, USA

<sup>6</sup> Biomedical Research Centre in Mental Health Net (CIBERSAM), Santiago Apóstol Hospital, University of the Basque Country, Vitoria, Spain

Findings of three articles reporting results in 1372 stabilized outpatients taking 2454 medications in Spain, Argentina, and Venezuela were combined. Prevalence of good adherence was not obviously different across diagnoses: 69.5% (N=212) for schizophrenia, 66.3% (N=142) for bipolar disorder, and 69.8% (N=521) for depression. Besides the focus on stabilized outpatients, other study biases included use of a research sample; limited to oral medications, ignoring long-acting injectable antipsychotics; and lack of data on active substance abuse, clinical severity, and insight. Logistic regression models explored predictors of good vs. poor adherence. The six self-reported variables studied were pharmacophobia, pharmacophilia, high psychological reactance, high internal health locus of control (LOC), high doctor LOC, and skepticism concerning specific medications. ORs were significant in 56% (47/84) of the statistical tests vs. 24% (23/98) of ORs significant in case of 7 demographic/clinical variables ( $p=0.001$ ). At least 2/3 of the ORs for pharmacophobia, pharmacophilia and skepticism were significantly associated with adherence in cases and controls, indicating their independence from diagnoses. In need of replication, three other self-reported measures had differential effects on adherence across diagnoses. High psychological reactance was associated with decreased adherence to antidepressant medications in general, or for patients with mood disorders. High internal LOC as associated with poor adherence may reflect the distrust patients with schizophrenia or severe bipolar disorder have of other people. High doctor LOC was significantly associated with increased adherence only in patients with bipolar disorder, but was significant for all medications, mood stabilizers and antipsychotics, indicating the relevance of the patient-psychiatrist relationship in these patients.

*(Neuropsychopharmacol Hung 2021; 23(4): 363–373)*

**Keywords:** attitude to health; bipolar disorder; depression; medication adherence; health behavior; psychopharmacology; schizophrenia

## INTRODUCTION

This article tries to summarize the prior 4 articles on adherence to medication in this issue (De las Cuevas et al., 2021a; 2021b; 2021c; 2021d) by comparing adherence in schizophrenia, bipolar disorder and major depression using the Sidorkiewicz scale (Sidorkiewicz et al., 2016).

Even though medication is an essential component in the treatment of patients with these severe mental illnesses (schizophrenia, bipolar disorder and major depression) to reduce or eliminate signs and symptoms, to restore the role/function of the individual, and to minimize the risk of relapse/recurrence, poor adherence to prescribed treatments is a global problem of alarming magnitude (Marder, 2003; Weiden et al., 2004; De las Cuevas and de Leon, 2020). Although the rates of non-adherence to psychopharmacological medications differ based on definition and measurement, it has been estimated that between one-third and one-half of psychiatric drugs for long-term diseases are not taken as recommended, 20-30% of patients do not adhere to therapeutic regimens that are curative or relieve symptoms, and 30-40% fail to follow regimens designed to prevent mental health problems (Jónsdóttir et al., 2010; Chapman and Horne, 2013; Semahegn et al., 2020).

## MAJOR PREDICTORS OF ADHERENCE IN SEVERE MENTAL ILLNESSES

The non-adherence of some psychiatric patients to their prescribed treatment is a complex phenomenon determined by different factors. However, there is still considerable ambiguity about the key determinants of non-adherence in psychiatric disorders.

The extent and wide-ranging consequences of inadequate adherence to prescribed medication make research focused on understanding the predictors of non-adherence in all severe mental illnesses important; each of them is essential for designing and evaluating interventions that can improve this health behavior.

### *Effects of clinical/sociodemographic variables on adherence*

Research literature examining demographic, clinical and medication-related factors has supplied inconsistent results that fail to address the complexities

of adherence behavior (Chakrabarti, 2016). Neither demographic nor clinical (illness-related) factors have been successful in predicting nonadherence to prescribed treatment (Scott and Pope, 2002; Byrne et al., 2006; Hung, 2014; Phan, 2016; De las Cuevas et al., 2017; De las Cuevas and de Leon, 2020). These inconsistent results and failure to address the complexities of adherence behavior have motivated a shift to a more patient-centered approach of viewing non-adherence focused on patients' personal beliefs and attitudes as well as their perceptions of the benefits and disadvantages of treatment (De las Cuevas and de Leon, 2017; De las Cuevas et al., 2020).

However, three clinical factors have been considered important for their occasional association with non-adherence (De las Cuevas and de Leon, 2020): concomitant substance use disorder (Rivero-Santana et al., 2013; Czobor et al., 2015; Edgcomb and Zima, 2018), poor insight (Sendt et al., 2015; Czobor et al., 2015; Bitter et al., 2015; Garcia et al., 2016), and severity of disorder (Garcia et al., 2016; Edgcomb and Zima, 2018).

### *Our research has focused on self-reported dimensions*

Our adherence studies have focused on self-reported measures that according to our review of the literature may be better predictors of adherence than demographic and clinical variables (De las Cuevas & de Leon et al., 2020). Thus, we have expanded our methodology by developing short tools to assess adherence (De las Cuevas et al., 2021d). The development of the Patient's Health Belief Questionnaire on Psychiatric Treatment (De las Cuevas & de Leon, 2019) and its translation to Hungarian (Pogany et al., 2021) has allowed inpatient studies (Pogany & Lazary, 2021).

The Patient Health Beliefs Questionnaire on Psychiatric Treatment which provides 5 self-reported personality dimensions: negative aspects of medication (pharmacophobia), positive aspects of medication (pharmacophilia), high/low psychological reactance, high/low doctor health locus of control (HLOC) and high/low internal HLOC. Based on the Beliefs about Medicines Questionnaire we have developed a measure of skepticism for each specific medication. Skepticism is defined as a patient's high concern about adverse reaction to an individual medication and a low belief in its necessity (De las Cuevas et al., 2018d).

### ***Lack of studies focusing on diagnosis and medication class***

As far as we know there are no published studies comparing adherence in schizophrenia, bipolar disorder, and depression. Thus, we designed a study in Spain, Argentina, and Venezuela (De las Cuevas et al., 2021a; 2021b; 2021c). In this large study in 3 countries including 1372 stabilized outpatients taking 2454 medications, we did not find relevant differences in adherence since good adherence was present in 69.5% (212 patients) with schizophrenia, 66.3% (142 patients) with bipolar disorder, and 69.8% (521 patients) with depression (De las Cuevas et al., 2021a; 2021b; 2021c). This study also for the first time explored differences on predictors of adherence across medication classes such as antipsychotics, mood stabilizers, and antidepressants.

### **THE EFFECTS OF BIASES IN OUR STUDY IN 3 COUNTRIES**

This large outpatient study in Spain, Argentina, and Venezuela is not free of biases (De las Cuevas et al., 2021a; 2021b; 2021c). It is not easy to construct a research study on adherence that can accurately represent the real world of adherence out in the community, as some patients may not come for psychiatric treatment and therefore never get close to entering any research study. We have focused on stabilized outpatients. Other biases in this study include research (vs. clinical) samples, the focus on oral medications ignoring long-acting injectable (LAI) antipsychotics, the lack of data on active substance abuse, clinical severity, or insight.

### ***Outpatient focus***

Community psychiatry assumes that people with psychiatric disorders can be most effectively helped when they live with their families and friends and are supported by the society in which they live. However, there are situations in which a person with a psychiatric disorder must be admitted to a psychiatric ward, they include: imminent risk of danger to self or others as a result of a behavioral health condition; disturbance of mood, thought or behavior which renders the person acutely incapable of developmentally appropriate self-care or self-regulation; disturbance of mood, thought or behavior that requires an assessment or medication trial that

cannot be safely or adequately implemented in a less restrictive setting; or level of functioning that does not meet the above criteria, but the person cannot return to his or her residence due to risk of harm to self or others due to a treatable behavioral health disorder, or there is a likelihood of imminent behavioral decompensation. At present, there is still little information in the literature concerning adherence to psychiatric inpatient treatment among patients with psychiatric disorders (Timlin et al., 2013), probably as a consequence of the close supervision of patients when taking medication in these medical devices and the fact that a considerable number of patients cannot refuse due to their altered mental state. But the situation changes once the patient's symptoms improve and he/she is discharged. From this moment on, (i.e., during outpatient care), it is the patient who decides if he wants to and should continue with the prescribed treatment, making the assessment of adherence essential.

The fact that all of our adherence studies in the past have focused on more or less stabilized psychiatric outpatients living in the community where they are cared for entails some biases that deserve to be discussed. The flaws of the sample selection process (sample selection bias) lead to situations where some groups or individuals in the population are less likely to be included in our samples in Spain, Argentina, and Venezuela.

Spain has a National Healthcare System that guarantees universal coverage and free healthcare access to all Spanish nationals, regardless of economic situation. In this way, the Spanish sample may be much more representative since it represents a catchment area from Spain's free universal health system. In Venezuela and Argentina, the healthcare models are highly fragmented with health coverage distributed among the public and private sectors with unequal access, so our samples did not include patients with underprivileged socioeconomic status.

In our Spanish sample from the Canary Islands, the lack of long-term psychiatric hospitals in the Canary Islands may have improved representativeness; the most severe patients could be included if they came for treatment with oral medications and signed the consent form. No data exists in the Canary Islands that establishes how many schizophrenia patients do not come for treatment, but a national cohort in Finland indicated that on average up to 30% of schizophrenia treatment years may not include antipsychotic treatment (Taipale et al., 2018).

### ***Biases of a research sample***

Since all of our research patients studied exercise control over the decision to participate in the study to a certain extent (i.e., the participants may decide whether to participate in the research or not), the selected sample does not represent the entire population of psychiatric patients.

The samples studied come from three different health-care systems among the three countries. Spain, Argentina, and Venezuela that have very different mental health systems that allow varying degrees of access and availability of psychotropic medicines. Although in Spain, mental health care satisfactorily responds to the needs of the population through community mental health services integrated into the National Health Service, which is publicly financed and provides universal health care free of charge at the point of use. In Argentina and Venezuela, psychiatric hospitals continue to be the core of mental health care; outpatient care is still limited and psychotropic medications are only partially available.

### ***Lack of data on lai antipsychotics***

In patients with chronic schizophrenia, bipolar and schizoaffective disorders, for example, LAI antipsychotics are typically used to maintain treatment adherence but they remain underutilized in clinical practice (Correll et al., 2016). Regulation varies throughout the world; in some countries LAIs are sometimes started as a compulsory treatment for inpatients, but their continuation needs patient approval once his/her mental state allows him/her to participate in the shared decision-making process (Haddad et al., 2014). If, as a result of adequate prescription, the patient improves, it is possible that he/she will gain insight and continue treatment of his/her own accord. In the medium or long term, this therapeutic approach will only improve adherence if the patient agrees to use the treatment.

Despite their potential to positively impact adherence, prescription rates vary considerably among service providers, and often fall below 20% nationally (Jaeger & Rossler, 2010). In our healthcare environment in Spain, Argentina and Venezuela, these drugs are usually reserved for more difficult-to-treat psychiatric patients (more severe disease, poorer global functioning, and less insight into the illness) and those least likely to adhere to oral therapy (Llorca et al., 2018). The number of patients willing

to take LAI in Spanish, Argentina or Venezuelan samples is, unfortunately, very small. There are no outpatient commitments in these countries to force medications and oral medications are preferred by patients over LAI antipsychotics. Thus, there was no attempt to study adherence to LAI antipsychotics, but the key aspect of adherence for LAI antipsychotics is showing up for the injection. In our samples of 212 patients with schizophrenia, there were 4.2 % (9/212) taking at least one other oral medication, but no oral antipsychotics. We have no data in how many of them were taking LAI antipsychotics or how many of the 203 patients with schizophrenia taking at least one oral antipsychotic were also taking a LAI antipsychotic.

### ***Lack of data on active substance abuse***

Comorbidity between substance use disorders and psychiatric disorders varies enormously from country to country and from culture to culture, but it appears reasonable that in those countries with substantial prevalence, active substance abuse is an important factor independent of lack of adherence in psychiatric patients (De las Cuevas and de Leon, 2020).

Our adherence studies of outpatients in Spain, Argentina, and Venezuela (De las Cuevas et al., 2021a; 2021b; 2021c) are not likely to include patients with significant active substance abuse since the studied patients were relatively stable, coming to outpatient treatment and willing to sign a written consent form.

As described, in Argentina and Venezuela outpatient care is still limited, psychotropic medications are only partially available, and the included patients were not likely to have clinically relevant substance abuse. In Spain dual disorders (coexistence of an addictive disorder and another mental health disorder) are an important challenge in mental health that in some countries, such as Spain, are currently attended by insufficient specific health care resources other than the mental health network belonging to the National Health Service (Szerman et al., 2014). Although not studied in our sample from the Canary Islands, we believe that outpatients are similar to published Spanish samples (Gurpegui et al., 2004; Arias et al., 2013; Al-Halabí et al., 2016). As with these other studied Spanish samples, our outpatients, particularly those with schizophrenia, tend to consume high amounts of coffee and tobacco. To a lesser extent, they occasionally take some alcohol or cannabis derivatives but no other street drugs (Gurpegui et al., 2004; Arias et al., 2013; Al-Halabí et al., 2016).

**Table 1.** Comparison of odds ratios (ORs) in cases vs. controls<sup>a</sup> in depression, bipolar disorder and schizophrenia: significant<sup>b</sup> self-reported dimensions

	Pharmacophobia	Pharmacophilia	High Psychological Reactance	High Internal LOC	High Doctor LOC	Skepticism
<b>Depression</b>						
All drugs	<i>0.500 vs 0.599</i>	1.51 vs 1.65	0.685 vs NS	NS vs 0.607	NS vs 1.68	<i>0.443 vs 0.569</i>
Antidepressants	<i>0.312 vs NS</i>	NS vs 2.847	0.597 vs 0.561		NS vs 1.80	<i>0.450 vs NS</i>
<b>Bipolar</b>						
All drugs	<i>0.361 vs 0.614</i>	NS vs 1.84	0.572 vs 0.798	NS vs 0.731	1.87 vs 1.25	<i>0.300 vs 0.566</i>
Mood stabilizers		NS vs 3.22			2.38 vs NS	<i>0.390 vs NS</i>
Antipsychotics	<i>0.19 vs 0.427</i>	<i>0.059 vs 1.80</i>		0.119 vs NS	5.00 vs NS	<i>0.053 vs NS</i>
<b>Schizophrenia</b>						
All drugs	<i>0.389 vs 0.591</i>	2.18 vs 1.59	NS vs 0.721	<i>0.389 vs NS</i>	NS vs 1.28	NS vs 0.550
Antipsychotics	<i>0.324 vs 0.237</i>		NS vs 0.237	NS vs 0.626		<i>0.535 vs NS</i>

<sup>a</sup> In the three analyses of all drugs, the number of cases vs. controls was 1) 521 patients with major depression taking 920 medications vs. 851 controls taking 1534 medications; 2) 142 patients with bipolar disorder taking 320 medications vs. 1230 controls taking 2134 medications; and 3) 212 patients with schizophrenia taking 387 medications vs. 1160 controls taking 2067 medications. In the analysis of antidepressants, the number of cases vs. controls was 470 patients with major depression taking 510 antidepressants vs. 348 controls taking 370 antidepressants. In the analysis of mood stabilizers, the number of cases vs. controls was 104 patients with bipolar disorder taking 122 mood stabilizers vs. 136 controls taking 140 mood stabilizers. In the two analyses of antipsychotics, the number of cases vs. controls was: 1) 87 patients with bipolar disorder taking 97 antipsychotics vs. 417 controls taking 458 antipsychotics, and 2) 204 patients with schizophrenia taking 240 antipsychotics vs. 301 controls taking 315 antipsychotics.

<sup>b</sup> Only ORs with  $p < 0.05$  are included. When the other pair (cases or control) was non-significant, they are described as NS. When both ORs in cases and controls were not significant, no values are presented. *The use of italics reflects extremely significant ( $p \leq 0.001$ ) ORs.*

### **Lack of data on clinical severity**

Increased illness severity has sometimes been reported as a factor decreasing treatment adherence in schizophrenic, bipolar, and depressive patients (Rivero-Santana et al., 2013; García et al., 2016), no systematic review that compared adherence across different levels of severity in these severe mental disorders is available. Our studies including >1000 patients in 3 countries was not supported by any grant funding so it was not possible to add labor-intensive assessments such as clinical scales of severity of psychiatric symptoms. Anyway, a cross-section of the current symptoms may not reflect the long-term longitudinal severity of the illness. When we tried to develop a measure of long-term severity for stabilized outpatients with schizophrenia in Spain, we found that a cross-sectional assessment of psychiatric symptoms was not particularly helpful since they were relatively low; thus, we had to develop a measure of severity based on what was a high number of hospitalizations in that catchment area that did not have long-term psychiatric hospitals (Aguilar et al., 2005). If one agrees that a high number of hospitalizations is a good measure of severity in a catchment area the problem is that this measure of illness severity is highly dependent on long-term adherence and it is possible that it may not be completely independent of

the current self-reported adherence. One suspects that current self-reported adherence may vary according to stage of illness and the presence or absence of recent hospitalizations, but also may have some influence on the long-term outcome of the illness.

### **Lack of data on insight**

Insight and medication adherence used to be highly correlated (bidirectional association) in patients with severe psychiatric disorders, with both co-varying during the course of the disorder and improvements in one are accompanied by improvements in the other (Novick et al., 2015; García-Cabeza et al., 2018). However, many issues remain unanswered concerning insight's role in adherence, partly due to the inconsistent definitions of the concept but also due to contradictory results about the impact of insight on patient outcomes (Charkraborty & Basu, 2010). Recent studies have recognized that insight does not predict outcomes, changes over time, and is dependent on the trajectory of the individual's illness and the social and cultural context arguing that "insight" is an explanatory model and a coping strategy (Jacob, 2020).

Thus, the concept of insight has evolved from an all or none phenomenon unitary construct to a multidimensional, continuous and modifiable construct with different facets and degrees (Baier,

**Table 2.** Comparison of cases vs. controls in depression, bipolar disorder and schizophrenia: clinical and demographic variables

	Geriatric Age	Treatment > 1 year	Specific medication > 1 year	Extreme polypharmacy (≥ 4 medications)	Spain	University education	Female gender
<b>Depression</b>							
All drugs	2.28 vs 3.02	0.731 vs 0.608			0.744 vs NS		
Antidepressants		NS vs 0.518			0.597 vs 1.65	NS vs 0.606	
<b>Bipolar</b>							
All drugs	NS vs 2.81	0.639 vs NS		2.49 vs NS			
Mood stabilizers							
Antipsychotics	NS vs 3.29				5.33 vs NS		
<b>Schizophrenia</b>							
All drugs	NS vs 2.48	0.161 vs NS	1.92 vs 0.687	1.92 vs NS	0.575 vs NS		NS vs 1.27
Antipsychotics	NS vs 4.34	0.362 vs NS					

2010). At present, in the context of severe psychiatric disorders, insight is considered a multi-dimensional and complex construct that reflects a patient's recognition of having a mental illness and awareness that treatment could be beneficial (Cleary et al., 2014).

This study in Spain, Argentina, and Venezuela did not include any measure of insight. Since impaired insight into psychiatric illness has been recognized as one of the principal drivers of medication nonadherence (Kim et al., 2020), we added an insight subscale to our questionnaire called the Patient's Health Belief Questionnaire on Psychiatric Treatment (De las Cuevas & de Leon, 2019). We hope that this may increase its validity as adherence tool in future studies. Although Lincoln et al. (2007) have suggested that a one-item measure could be sufficient for a screening of insight in severe psychiatric disorders, we preferred to include three distinct, yet somewhat overlapping, self-reported items that assess the patient's understanding of his or her mental illness, the need for treatment, and the need to see a psychiatrist, that will allow us to learn more about specific aspects of insight and their clinical relevance.

## ADHERENCE IN SCHIZOPHRENIA, BIPOLAR DISORDER, AND DEPRESSION

### *Self-reported dimensions better predictors than clinical measures*

In a prior review we have argued that self-reported dimensions may be more relevant than clinical and demographic factors in predicting lack of adherence (De las Cuevas and de Leon, 2020). Logistic regression models in 3 case groups (schizophrenia, bipolar

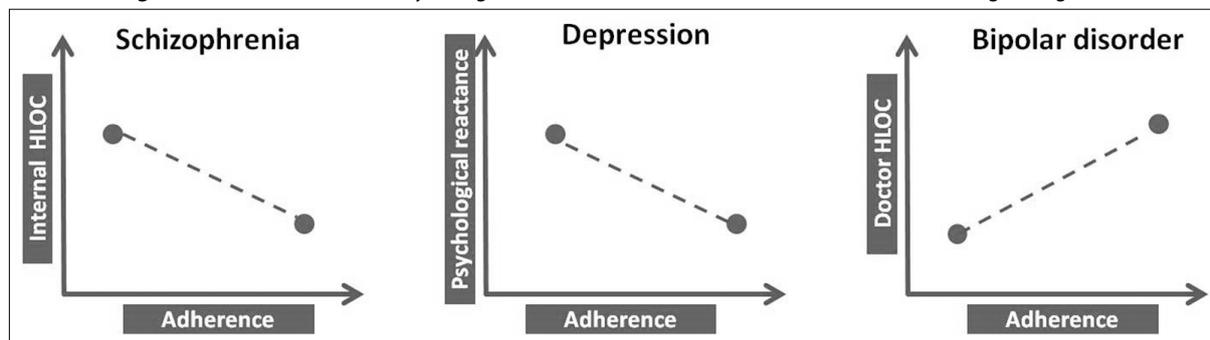
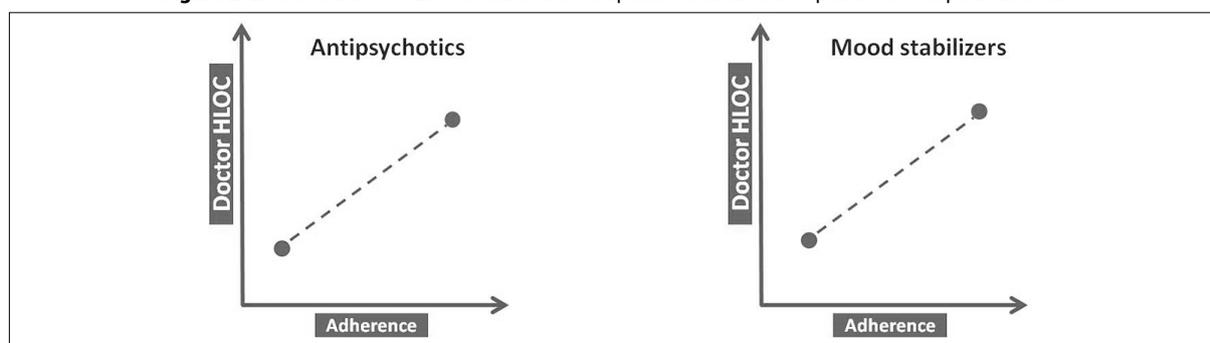
disorder and major depression) and controls were used to study predictors of good vs. poor adherence. To clarify, when a disorder is presented as cases (e.g., schizophrenia), the others (e.g., bipolar disorder, depression and other heterogenous patients) were considered controls.

Table 1 shows that in this group of studies in schizophrenia, bipolar disorder, and depression, the 6 self-reported variables (pharmacophobia, pharmacophilia, high psychological reactance, high internal LOC, high doctor LOC and skepticism) had significant ( $p < 0.05$ ) odds ratios (ORs) associated with adherence in 56% (47/84) of the statistical tests conducted. Table 2 illustrates that the ORs of the 7 demographic or clinical variables studied were significant in 24% (23/98) of the statistical tests conducted. When these two prevalences were compared, the 56% was significantly higher than the 24% in a 2-sided Fisher exact test ( $p = 0.001$ ). This indicates that in these samples, the self-reported measures as a group were significantly better predictors of adherence than demographic and clinical variables.

If we focus on the presence of very highly significant ORs ( $p \leq 0.001$ ) associated with adherence, it is highly unlikely that these ORs with very low  $p$  values are significant due to the multiple significance tests performed. The prevalences were 32% (27/84) in the self-reported measures vs. 7% (7/98). This difference was also significant ( $p < 0.001$ ).

### *Self-reported measures may have differential effects according to diagnosis*

Table 1 shows that in our studies in schizophrenia, bipolar disorder, and depression, three self-reported

**Figure 1.** Effects of HLOCs and Psychological reactance on Adherence to all medications, according to diagnosis**Figure 2.** Effects of Doctor HLOC on adherence to specific medications in patient with bipolar disorder

measures were significant ( $p < 0.05$ ) in most of the statistical tests for adherence ORs including both cases and controls. The ORs for pharmacophobia were significant in 79% (11/14) of the statistical tests conducted, skepticism in 57% (8/14), and pharmacophilia in 64% (9/14). Thus, this suggests to us that for the most part these three variables may be important determinants in most patients with severe mental illnesses, independent of their clinical diagnoses.

In need of replication in future samples, it is possible that 3 other self-reported measures may have differential effects on adherence across diagnoses. High psychological reactance was significantly associated with decreased adherence in patients with depression for all medications and antidepressants. It was significant for antidepressants in patients who had other diagnoses besides major depression and for all medications in patients with bipolar disorder. Thus, this may suggest that it is possible that high psychological reactance may be associated with decreased adherence for antidepressant medications

in general or be more relevant for patients with mood disorders (Figure 1).

High internal LOC was significantly associated with decreased adherence to all medications only in one group of cases, patients with schizophrenia (Figure 1). Interestingly, this variable was also significant for antipsychotics in patients with bipolar disorder, despite the small sample of 87 patients taking 97 antipsychotics (Figure 2). These are probably the most severe and most prone to psychosis of the 142 patients with bipolar disorder. Thus, high internal HLOC as a predictor of poor adherence may reflect the distrust patients with schizophrenia (De las Cuevas et al., 2021c) or severe bipolar disorder have of other people regarding control of their mental illness.

High doctor LOC was significantly associated with increased adherence only in one group of cases, the bipolar patients and, interestingly, it was significant for all medications, mood stabilizers and antipsychotics (Figure 2). This would suggest that the patient-psychiatrist relationship may be particularly relevant for adherence in patients with bipolar disorder.

## CONCLUSIONS

In this large study in 3 countries including 1372 stabilized outpatients taking 2454 medications, we did not find relevant differences in adherence since good adherence was present in 69.5% (212 patients) with schizophrenia, 66.3% (142 patients) with bipolar disorder, and 69.8% (521 patients) with depression (De las Cuevas et al., 2021a; 2021b; 2021c). This study also, for the first time, explored differences in predictors of adherence across medication classes such as antipsychotics, mood stabilizers and antidepressants. Besides the circumscription to stabilized outpatients, other biases in this study include use of research samples; focus on oral medications, while ignoring LAI antipsychotics; and the lack of data on active substance abuse, clinical severity, and insight.

In spite of these limitations, this group of studies in schizophrenia, bipolar disorder, and depression found that the 6 self-reported variables (pharmacophobia, pharmacophilia, high psychological reactance, high internal LOC, high doctor LOC and skepticism about specific medications) had significant ORs in 57% (48/84) of the statistical tests versus 23% (23/98) of the ORs of the 7 demographic or clinical variables. This was statistically significant, indicating that in these samples, the self-reported measures as a group were significantly better predictors of adherence than the studied demographic and clinical variables.

The ORs pharmacophobia, pharmacophilia and skepticism were significantly associated with adherence in at least 2/3 of the statistical tests conducted. Thus, this suggests to us that, for the most part these three variables may be important determinants of adherence in most patients with severe mental illnesses, independent of their clinical diagnoses.

In need of replication in future samples, our study suggested the possibility that 3 other self-reported measures may have differential effects on adherence across diagnoses. High psychological reactance may be associated with decreased adherence for antidepressant medications in general or be more relevant for patients with mood disorders. High internal LOC as a predictor of poor adherence may reflect the distrust patients with schizophrenia or severe bipolar disorder have of other people regarding control of their mental illness. High doctor LOC was significantly associated with increased adherence only in the patients with bipolar disorder, but significantly associated for all medications, mood stabilizers and

antipsychotics. This would suggest that the patient-psychiatrist relationship may be particularly relevant for adherence in patients with bipolar disorder.

---

**ACKNOWLEDGMENTS:** The authors thank Lorraine Maw, M.A., at the Mental Health Research Center at Eastern State Hospital, for editorial assistance.

---

## DECLARATION OF COMPETING INTEREST :

The authors have declared that there are no conflicts of interest in relation to the subject of this study. All the authors contributed to and have approved the final manuscript. No commercial organizations had any role in writing this paper for publication. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

---

## CORRESPONDING AUTHOR: Judit Lazary

Országos Mentális, Ideggyógyászati és Idegsebészeti Intézet  
H-1135 Budapest, Lehel u. 59.  
E-mail: lazaryjudit@gmail.com

---

## REFERENCES

1. Aguilar, M.C., Gurpegui, M., Diaz, F.J., & de Leon, J. (2005). Nicotine dependence and symptoms in schizophrenia: naturalistic study of complex interactions. *Br J Psychiatry*, 186, 215-21. doi: 10.1192/bjp.186.3.215
2. Al-Halabi, S., Fernández-Artamendi, S., Díaz-Mesa, E.M., García-Álvarez, L., Flórez, G., Martínez-Santamaría, E., et al. (2016). Tobacco and cognitive performance in schizophrenia patients: the design of the COGNICO study. *Adicciones*, 29, 6-12. doi: 10.20882/adicciones.724
3. Arias, E., Szerman, N., Vega, P., Mesias, B., Basurte, I., Morant, C., et al. (2013). Abuse or dependence on cannabis and other psychiatric disorders. Madrid study on dual pathology prevalence. *Actas Esp Psiquiatr*, 41, 122-129.
4. Baier, M. (2010). Insight in schizophrenia: a review. *Curr Psychiatry Rep*, 12, 356-361. doi: 10.1007/s11920-010-0125-7
5. Bitter, I., Fehér, L., Tényi, T., & Czobor P. (2015). Treatment adherence and insight in schizophrenia. *Psychiatr Hung*, 30(1), 18-26.
6. Byrne, N., Regan, C., & Livingston, G. (2006). Adherence to treatment in mood disorders. *Curr Opin Psychiatry*, 19(1), 44-49. doi: 10.1097/01.yco.0000191501.54034.7c
7. Chakrabarti, S. (2016). Treatment-adherence in bipolar disorder: A patient-centred approach. *World J Psychiatry*, 6(4), 399-409. doi: 10.5498/wjp.v6.i4.399
8. Chapman, S.C., & Horne, R. (2013). Medication nonadherence and psychiatry. *Curr Opin Psychiatry*, 26(5), 446-452. doi: 10.1097/YCO.0b013e3283642da4
9. Charkraborty, K., & Basu, D. (2010). Insight in schizophrenia- a comprehensive update. *German J Psychiatry* 13, 17-30.

10. Cleary, S.D., Bhatti, S., Broussard, B., Cristofaro, S.L., Wan, C.R., & Compton, M.T. (2014). Measuring insight through patient self-report: an in-depth analysis of the factor structure of the Birchwood Insight Scale. *Psychiatry Res*, 216, 263-268. doi: 10.1016/j.psychres.2014.01.043
11. Correll, C.U., Citrome, L., Haddad, P.M., Lauriello, J., Olfson, M., et al. (2016). The use of long-acting injectable antipsychotics in schizophrenia: evaluating the evidence. *J Clin Psychiatry*, 77(suppl 3), 1-24. doi: 10.4088/JCP.15032su1
12. Czobor, P., Van Dorn, R.A., Citrome, L., Kahn, R.S., Fleischhacker, W.W., & Volavka, J. (2015). Treatment adherence in schizophrenia: a patient-level meta-analysis of combined CATIE and EUFEST studies. *Eur Neuropsychopharmacol*, 25(8), 1158-1166. doi: 10.1016/j.euroneuro.2015.04.003
13. De las Cuevas, C., Baptista, T., Motuca, M., Villasante-Tezanos, A.G., et al. (2021c). Poor adherence to oral psychiatric medication in adults with schizophrenia may be influenced by pharmacophobia, high internal health locus of control and treatment duration. *Neuropsychopharmacol Hung*, in press
14. De las Cuevas, C., Betancort, M., & de Leon, J. (2020). The necessity-concern framework in the assessment of treatment adherence of psychiatric patients and the role of polypharmacy in a Spanish sample. *Hum Psychopharmacol*, 35, e2721. doi: 10.1002/hup.2721.
15. De las Cuevas, C., & de Leon, J. (2017). Reviving research on medication attitudes for improving pharmacotherapy: focusing on adherence. *Psychother Psychosom*, 86, 73-79. doi: 110.1159/000450830
16. De las Cuevas, C., & de Leon, J. (2019). Development and validation of the Patient's Health Belief Questionnaire on Psychiatric Treatment. *Patient Prefer Adherence*, 13, 527-536. doi: 10.2147/PPA.S201144
17. De las Cuevas, C., & de Leon, J. (2020). Self-report for measuring and predicting medication adherence: experts' experience on predicting adherence in stable psychiatric outpatients and on pharmacokinetics. *Patient Prefer Adherence*, 14, 1823-1842. doi: 10.2147/PPA.S242693
18. De las Cuevas, C., de Leon, J., Peñate, W., & Betancort, M. (2017). Factors influencing adherence to psychopharmacological medications in psychiatric patients: a structural equation modeling approach. *Patient Prefer Adherence*, 11, 681-690. doi: 10.2147/PPA.S133513
19. De las Cuevas, C., Pogany, L., Lazary, J., & de Leon J. (2021d) Practical approach to measuring and predicting medication adherence by outpatient's self-report after more than 10 years of research. *Neuropsychopharmacol Hung*, in press
20. De las Cuevas, C., Motuca, M., Baptista, T., & de Leon, J. (2018). Skepticism and pharmacophobia toward medication may negatively impact adherence to psychiatric medications: a comparison among outpatient samples recruited in Spain, Argentina, and Venezuela. *Patient Prefer Adherence*, 12, 301-310. doi: 10.2147/PPA.S158443
21. De las Cuevas, C., Motuca, M., Baptista, T., Villasante-Tezanos, A.G., & de Leon, J. (2019). Ethnopsychopharmacology study of patients' beliefs regarding concerns about and necessity of taking psychiatric medications. *Hum Psychopharmacol*, 34, e2688. doi: 10/1002/hup.2688
22. De las Cuevas, C., Motuca, M., Baptista, T., Villasante-Tezanos, A.G., et al. (2021a). Poor adherence to oral psychiatric medication in adults with depression: psychological reactance may have specific effects in depression. *Neuropsychopharmacol Hung*, in press
23. De las Cuevas, C., Villasante-Tezanos, A.G., Motuca, M., & de Leon, J. (2021e) Effect of necessity-concern framework and polypharmacy on treatment adherence in psychiatric patients. Comparing an Argentinian with a Spanish sample. *Hum Psychopharmacol*, 36, e2776. doi: 10.1002/hup.2776
24. De las Cuevas, C., Villasante-Tezanos, A.G., Motuca, M., Baptista, T., Lazary, J., & de Leon J. (2021b). Poor adherence to oral psychiatric medication in adults with bipolar disorder: the psychiatrist may have more influence than in other severe mental illnesses. *Neuropsychopharmacol Hung*, in press
25. Edgcomb, J.B., & Zima, B. (2018). Medication adherence among children and adolescents with severe mental illness: a systematic review and meta-analysis. *J Child Adolesc Psychopharmacol*, 28(8), 508-520. doi: 10.1089/cap.2018.0040.
26. García S, Martínez-Cengotitabengoa M, López-Zurbano S, Zorrilla I, López P, et al. (2016). Adherence to antipsychotic medication in bipolar disorder and schizophrenic patients: a systematic review. *J Clin Psychopharmacol*, 36(4), 355-371. doi: 10.1097/JCP.0000000000000523
27. Garcia-Cabeza, I., Díaz-Caneja, C.M., Ovejero, M., & de Portugal, E. (2018). Adherence, insight and disability in paranoid schizophrenia. *Psychiatry Res*, 270, 274-280. doi: 10.1016/j.psychres.2018.09.021
28. Gurpegui, M., Aguilar, M.C., Martínez-Ortega, J.M., Diaz, F.J., & de Leon, J. (2004). Caffeine intake in outpatients with schizophrenia. *Schizophr Bull*, 30(4), 935-945. doi: 10.1093/oxfordjournals.schbul.a007143
29. Haddad, P.M., Brain, C., & Scott, J. (2014). Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies. *Patient Relat Outcome Meas*, 5, 43-62. doi: 10.2147/PROM.S42735
30. Hung, C.I. (2014). Factors predicting adherence to antidepressant treatment. *Curr Opin Psychiatry*, 27(5), 344-349. doi: 10.1097/YCO.0000000000000086
31. Jacob, K.S. (2020). Insight in psychosis: A critical review of the contemporary confusion. *Asian J Psychiatr*, 48, 101921. doi: 10.1016/j.ajp.2019.101921
32. Jaeger, M. & Rossler, W. (2010). Attitudes towards long-acting depot antipsychotics: a survey of patients, relatives and psychiatrists. *Psychiatry Res*, 175(1-2), 58-62. doi: 10.1016/j.psychres.2008.11.003
33. Jónsdóttir, H., Opjordsmoen, S., Birkenaes, A.B., Engh, J.A., Ringen, P.A., Vaskinn, A., et al. (2010). Medication adherence in outpatients with severe mental disorders: relation between self-reports and serum level. *J Clin Psychopharmacol*, 30(2), 169-175. doi: 10.1097/JCP.0b013e3181d2191e
34. Kim, J., Ozzoude, M., Nakajima, S., Shah, P., Caravaggio, F., Iwata, Y., et al. (2020). Insight and medication adherence in schizophrenia: An analysis of the CATIE trial. *Neuropharmacology*, 168, 107634. doi: 10.1016/j.neuropharm.2019.05.011
35. Lincoln, T.M., Lullmann, E., & Rief, W. (2007). Correlates and long-term consequences of poor insight in patients with schizophrenia: a systematic review. *Schizophr Bull*, 33, 1324-1342. doi: 10.1093/schbul/sbm002
36. Llorca, P.M., Bobes, J., Fleischhacker, W.W., Heres, S., Moore, N., Bent-Ennakhil, N, et al. (2018). Baseline results from the European non-interventional Antipsychotic Long acting injection in schizophrenia (ALTO) study. *Eur Psychiatry*, 52, 85-94. doi: 10.1016/j.eurpsy.2018.04.004
37. Marder, S.R. (2003). Overview of partial compliance. *J Clin Psychiatry*, 2003, 64 Suppl 16, 3-9.

38. Novick, D., Montgomery, W., Treuer, T., Aguado, J., Kraemer, S., & Haro JM. (2015). Relationship of insight with medication adherence and the impact on outcomes in patients with schizophrenia and bipolar disorder: results from a 1-year European outpatient observational study. *BMC Psychiatry*, 15, 189. doi: 10.1186/s12888-015-0560-4
39. Phan, S.V. (2016). Medication adherence in patients with schizophrenia. *Int J Psychiatry Med*, 51(2), 211-219. doi: 10.1177/0091217416636601
40. Pogany L, De las Cuevas C, & Lazary J. (2021). Validation and analysis of the Patient's Health Belief Questionnaire on Psychiatric Treatment in a sample of Hungarian psychiatric patients. *Neuropsychopharmacol Hung*, 23, 221-231.
41. Pogany L, Lazary J. Health Control Beliefs and Attitude Toward Treatment in Psychiatric and Non-Psychiatric Clinical Samples. *Front Psychiatry*. 2021 Apr 29;12:537309. PMID: 34025463; PMCID: PMC8132472. doi: 10.3389/fpsy.2021.537309
42. Rivero-Santana, A., Perestelo-Perez, L., Pérez-Ramos, J., Serrano-Aguilar, P., & De las Cuevas, C. (2013). Sociodemographic and clinical predictors of compliance with antidepressants for depressive disorders: systematic review of observational studies. *Patient Prefer Adherence*, 7, 151-169. doi: 10.2147/PPA.S39382
43. Scott, J., & Pope, M. (2002). Nonadherence with mood stabilizers: prevalence and predictors. *J Clin Psychiatry*, 63(5), 384-390. doi: 10.4088/jcp.v63n0502
44. Semahegn, A., Torpey, K., Manu, A., Assefa, N., Tesfaye, G., & Ankomah A. (2020) Psychotropic medication non-adherence and its associated factors among patients with major psychiatric disorders: a systematic review and meta-analysis. *Syst Rev*, 9(1):17. doi: 10.1186/s13643-020-1274-3
45. Sendt, K.V., Tracy, D.K., & Bhattacharyya, S. (2015). A systematic review of factors influencing adherence to antipsychotic medication in schizophrenia-spectrum disorders. *Psychiatry Res*, 30, 225(1-2), 14-30. doi: 10.1016/j.psychres.2014.11.002
46. Sidorkiewicz, S., Tran, V.T., Cousyn, C., Perrodeau, E., & Ravaud, P. (2016). Development and validation of an instrument to assess treatment adherence for each individual drug taken by a patient. *BMJ Open*, 6, e010510. doi: 10.1136/bmjopen-2015-010510
47. Szerman, N., Vega, P., Grau-López, L., Barral, C., Basurte-Villamor, I., Mesias B, et al. (2014). Dual diagnosis resource needs in Spain: a national survey of professionals. *J Dual Diagn*, 10(2), 84-90. doi: 10.1080/15504263.2014.906195
48. Taipale, H., Mittendorfer-Rutz, E., Alexanderson, K., Majak, M., Mehtälä, J., Hoti, F, et al. (2018). Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia. *Schizophr Res*, 197, 274-280. doi:10.1016/j.schres.2017.12.010
49. Timlin, U., Riala, K., & Kyngäs H. (2013). Adherence to treatment among adolescents in a psychiatric ward. *J Clin Nurs*, 22(9-10), 1332-1342. doi: 10.1111/jocn.12024
50. Weiden, P.J., Kozma, C., Grogg, A., & Locklear, J. (2004). Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. *Psychiatr Serv*, 55(8), 886-891. doi: 10.1176/appi.ps.55.8.886

## Pszichotróp gyógyszer-adherencia: szkizofréniával, bipoláris zavarral és major depresszióval élő páciensek összehasonlítása

A tanulmányban 1372, stabil pszichés állapotú, ambuláns pszichiátriai kezelés alatt álló spanyol, argentin és venezuelai beteg adatait mutatjuk be, három különböző vizsgálat eredményeit összesítve. A megfelelő adherencia előfordulása tekintetében nem találtunk releváns különbséget az egyes diagnosztikus kategóriák között: szkizofrénia esetében ez a betegek 69,5% (n=212), bipoláris affektív zavar esetében 66,3% (n=142), depresszió miatt kezelt betegeknél pedig 69,8% (n=521) volt. Az eredményeket a klinikai vizsgálati körülményeken kívül potenciálisan az is torzíthatja, hogy a vizsgálatokba kizárólag stabil pszichés állapotú betegek kerültek bevonásra, akik per os gyógyszeres kezelésben részesültek, hosszúhatású antipszichotikus injekciós kezelés alatt álló beteg nem vett részt a vizsgálatban, továbbá a szerhasználattal, a betegség súlyosságával és a betegségtudat meglétével kapcsolatos adatok is hiányoztak. Logisztikus regressziós modellekkel vizsgáltuk a megfelelő, valamint a hiányos adherencia prediktorait. A vizsgált hat változó a farmakofóbia, farmakofília, magas pszichológiai reaktancia, magas belső egészségkontrollhit, magas orvos egészségkontrollhely pontszám és az egyes gyógyszerekkel kapcsolatos szkepticizmus volt. Az esélyhányados (OR) a statisztikai tesztek 56%-a (47/84) esetében volt szignifikáns, a hét demográfiai/klinikai változó esetében ez 24% (23/98) volt. A farmakofóbiára, farmakofíliára és szkepticizmusra vonatkozó esélyhányadosok (OR) legalább 2/3-a szignifikáns összefüggést mutatott az adherencia mértékével a betegek és kontrollszemélyek esetében, a diagnózistól függetlenül. További három tényezőnek volt kimutatható befolyása az adherencia mértékére. A magas pszichológiai reaktanciához hiányos adherencia társult az antidepresszívummal kezelt betegek esetében. A magas belső egészségkontrollhely-pontszámhoz társuló hiányos adherencia a szkizofrénia vagy súlyos bipoláris affektív zavar miatt kezelés alatt álló betegek esetében a páciensek más személyekkel szembeni bizalmatlanságát tükrözheti. A magas orvos egészségkontrollhely alszála pontszám és a megfelelő adherencia között csak bipoláris betegek esetében sikerült szignifikáns összefüggést találni, de ebben a populációban ez az összefüggés valamennyi alkalmazott gyógyszercsoport esetében kimutatható volt, ami az orvos-beteg kapcsolat jelentőségére hívja fel a figyelmet.

**Kulcsszavak:** egészségi állapottal szembeni viszonyulás, bipoláris affektív zavar, depresszió, adherencia, egészségmagatartás, pszichofarmakológia, szkizofrénia