

Poor Adherence to Oral Psychiatric Medication in Adults with Schizophrenia May Be Influenced by Pharmacophobia, High Internal Health Locus of Control and Treatment Duration

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Objective: This study in Spain, Argentina, and Venezuela included 212 schizophrenia outpatients prescribed 387 psychiatric medications and 1,160 other psychiatric outpatients prescribed 2,067 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: 1) clinical variables, 2) subscales from the Patient Health Beliefs Questionnaire on Psychiatric Treatment (presence/absence of pharmacophobia and pharmacophilia and high/low psychological reactance, internal health locus of control [HLOC] and doctor's HLOC) and 3) presence/absence of skepticism toward each medication measured by the Beliefs about Medicines Questionnaire (BMQ). **Results:** ORs significant in both groups were: 1) pharmacophobia (OR=0.389 in schizophrenia, OR=0.591 in other patients and not significantly different) and 2) pharmacophilia (respectively OR=2.18, OR=1.59 and significantly higher in schizophrenia: $p=0.012$). Prescribing the medication for >1 year increased adherence in schizophrenia (OR=1.92) while decreasing it in others (OR=0.687). Four ORs were significant in the schizophrenia group but not in the controls: treatment for >1 year (OR=0.161), high internal LOC (OR=0.389), extreme polypharmacy (OR=1.92) and the country of Spain (OR=0.575). Regarding antipsychotics, the study included 204 schizophrenia patients prescribed 240 antipsychotic medications and 301 other patients prescribed 315 antipsychotic drugs. Three ORs were significant for antipsychotic adherence in the schizophrenia group: pharmacophobia (OR=0.324), treatment for >1 year (OR=0.362), and skepticism about specific antipsychotics (OR=0.535). **Conclusions:** Future adherence studies for antipsychotic/all medications should further explore the specificity/commonality of these dimensions in schizophrenia versus other psychiatric patients.

(Neuropsychopharmacol Hung 2021; 23(4): 388–404)

Keywords: attitude to health, medication adherence, health behavior, psychiatry, psychopharmacology schizophrenia

INTRODUCTION

Schizophrenia affects more than 20 million people worldwide with a lifelong chronic, severe, and disabling disorder, often requiring long-term antipsychotic treatment (GBD, 2018). This treatment substantially reduces the risk of relapse (Leucht et al., 2010), but during its course, >50% of patients may exhibit inadequate medication adherence (Semahegn et al., 2020). This leads to poorer outcomes including increased psychotic relapses, hospital admission, suicide attempts and overall mortality (Lindström et al., 2012; Morken et al., 2008; Tiihonen et al., 2011).

Medication adherence: psychological aspects

Box 1 describes 1) our PubMed search, which identified 236 articles on psychological aspects of medication adherence in schizophrenia, and 2) a summary of the 15 most relevant review articles.

The literature agrees that medication adherence is a complex phenomenon conditioned by multiple factors of diverse nature (World Health Organization, 2003). Nevertheless, it is a human behavior modulated by subjective components and should primarily be understood, addressed and investigated based on this dimension. The Health Belief Model (HBM) is very popular in health psychology journals. This model emphasizes the central role of the patient's subjective beliefs, understanding of illness, and treatment options in determining adherence to prescribed medications (Rosenstock, 1974; Sulat et al., 2018). Not unexpectedly, a patient's beliefs and attitudes toward treatment also influence medication adherence in psychiatric patients (De las Cuevas & de Leon, 2017; de Leon & De las Cuevas, 2017).

Medication adherence in schizophrenia: psychological aspects

Methodological challenges greatly complicate the research of medication adherence in schizophrenia including: 1) the fact that adherence is a dynamic process that could change over time; 2) adherence is not an all-or-nothing phenomenon and can vary from one medication to another; 3) the excessive focus on the sociodemographic and clinical variables, 4) neglecting or underestimating the self-reported dimensions; and 5) the lack of psychiatric controls in the published studies.

As the social and environmental contexts of patients suffering schizophrenia may change over time, their experiences with and perceptions of their illness and prescribed medications may also change, modifying previous beliefs about illness and medications and, therefore, their adherence to prescribed treatments (Levanthal et al., 2003; Unni et al., 2016).

In spite of limited supporting evidence (Ballon et al., 2013), polypharmacy in schizophrenia is increasingly common (De las Cuevas & Sanz, 2004). Measurement of treatment adherence during polypharmacy is a really complex task as patients could adhere differently to the various drugs prescribed, making it essential to assess adherence to each individual drug, which was not possible until the introduction of the Sidorkiewicz Adherence Tool (Sidorkiewicz et al., 2016) which has been used in psychiatry (De las Cuevas & de Leon, 2019a; De las Cuevas et al., 2018a; 2018b; 2020).

In some studies, clinical characteristics of psychiatric patients can be statistically associated with adherence to prescribed medications, but no combination of these variables is accurate enough to allow psychiatrists to predict adherence. The idea that sociodemographic or clinical variables are the sole determinants of adherence is discredited by evidence that most of these variables are stable or change little over time while adherence in the same patient may vary widely over time (Horne, 1997; Levanthal et al., 2003).

The HBM literature has not received enough attention in psychiatric journals and in our experience practicing psychiatrists are not familiar with these psychological dimensions and the scales used to measure them. To simplify, we call these dimensions self-reported dimensions and categorize them based on whether they focus on drugs or personality style.

The self-reported dimensions that focus on drugs may focus on specific drugs or drugs in general. The Beliefs about Medicines Questionnaire (Horne et al., 1999) focuses on each medication and measures perception of necessity and concerns that the patient has regarding that specific medication. It can be used to define the concept of skepticism, which is high concern about adverse reactions and low belief in the necessity of a medication (De las Cuevas et al., 2018).

The Drug Attitude Inventory (DAI-10) is a questionnaire that reports one's attitude toward medications, in general (Hogan et al., 1983). It can be used to define the concepts of pharmacophobia, or fear of the use of pharmacological treatments and pharmacophilia, or a positive attitude toward using or trying medications (De las Cuevas & de Leon, 2019a; 2019b).

Box 1. Reviews of the psychology of medication adherence in schizophrenia

Expert guidelines in schizophrenia
Expert guidelines for schizophrenia treatment (Dixon et al., 2010; NICE, 2014) describe the impact of poor adherence in schizophrenia and guidelines on treatment-resistant schizophrenia (Howes, et al., 2017; Kane et al., 2019) insist on ruling out non-adherence before diagnosing treatment-resistance. Velligan et al. (2009) in a guideline on adherence in SPMI commented on an article on patient attitudes in patients with bipolar disorder (Clatworthy et al. 2009).
PubMed search of reviews (2021-10-17)
The search "Medication Adherence/psychology"[Mesh] AND "schizophrenia"[Title] produced 236 articles, of which 30 were reviews. Of these 30 articles, we eliminated 13 articles (6 not in English, 2 on non-psychiatric medications, the 2 guidelines included above, 1 on bipolar disorder, 1 on a clinical trial and 1 editorial repeating the message of the review). We read in detail 2 which had an unusual focus on boredom and physical attractiveness and are not summarized below. This left the following 15 summarized articles:
Bright (2017)
He focused on difficulties in measuring adherence. In our experience this problem is common to all psychiatric patients.
Altamura et al., (2012); Citrome (2012); Correll (2014); Goff et al. (2010) Morrissette & Stahl (2012)
These five reviews mainly focused on the utility of LAI formulations for improving long-term adherence.
Fleischhacker (2002)
He indicated that the treatment outcome is better for younger patients in a first psychotic episode than it is for patients who are more chronically ill, although young patients are much more sensitive to adherence problems than older patients.
Franz et al. (2012)
They reported that therapeutic decisions are influenced by patients' and physicians' characteristics.
Hegedüs and Kozel (2014)
Adherence therapy does not improve adherence in comparison to treatment as usual or a control intervention.
Kikkert and Dekker (2017)
Despite being intensively studied, we have little understanding of underlying mechanisms leading to nonadherence.
Llorca (2008)
He proposed that partial adherence with antipsychotic medication is a significant barrier to achieving optimal outcomes in schizophrenia and that the problem increases with the duration of treatment and is difficult to monitor.
Sendt et al. (2015)
They reported that despite greater methodological rigor in determining studies to include in their systematic review, guiding clinicians in this vital area is difficult and most of the studies discussed contained small sample sizes.
Tham et al. (2016)
They stated that greater insight and less severe psychotic symptoms are associated with increased adherence in general. There is no discussion of the phases of the illness and the differences between in- and outpatients.
Wade et al. (2017)
Reasons for non-adherence included: 1) lack of medication efficacy, 2) lack of compatibility with personal medication or religious beliefs, 3) side effects, 4) influential relationships, and 5) stigma and economic difficulties.
Weiden (2016)
He stressed that patients with schizophrenia frequently do not disclose to their treating physicians that they are not adherent, so their physicians think they are treatment-resistant, when almost half of them are actually nonadherent.

LAI: long-acting antipsychotic; SPMI: serious and persistent mental illness.

Dimensions of personality style obtained by self-report include psychological reactance and those included under Health Locus of Control (HLOC), which refers to who is responsible for the management of a disorder. Two HLOC dimensions, the patient (internal) and the doctor, are important in psychiatric patients (Wallston, 1989; Wallston & Wallston, 1982). Psychological reactance can be defined as an emotional reaction toward rules perceived as a threat and is measured with the Hong Psychological Reactance Scale (Hong & Faedda, 1996; Rosenberg & Siegel, 2017).

In summary, medication adherence in schizophrenia may be influenced by 6 self-reported dimensions: skepticism, pharmacophobia, pharmacophilia, high/low psychological reactance, high/low doctor HLOC and high/low internal HLOC. Each drug is rated by each patient using the BMQ and this generates a score on the level of skepticism regarding each medication. To complete the other four scales that refer to the patient, the DAI-10, Hong Psychological Reactance Scale and Multidimensional HLOC, requires 1-1.5 hours. The Patient Health Beliefs Questionnaire on Psychiatric Treatment includes the major items

Box 2. Systematic PubMed searches of self-reported dimension, adherence and schizophrenia (2021-10-17)

The search 'Beliefs about Medicines Questionnaire AND schizophrenia [Title] AND adherence' provided 12 articles, of which 10 did not include the questionnaire, leaving only 2 articles with the questionnaire (Samalin et al., 2016; Kretchy et al., 2021)
The search "'Drug Attitude Inventory" AND schizophrenia [Title] and adherence' provided 46 articles (Misdrahi et al., 2002; Jeste et al., 2003; Freudenreich et al., 2004; Murawiec, 2005; Kim et al., 2006; Voruganti et al., 2006; Ikebuchi et al., 2008; Mohamed et al., 2009; Rossi et al., 2009; Stolovy et al., 2009; Dassa et al., 2010; Gaebel et al., 2010; Meier et al., 2010; Kikkert et al., 2011; Louzã et al., 2011; Medina et al., 2012; Nielsen et al., 2012; Yang et al., 2012; Brain et al., 2013; Nitzan et al., 2013; Yalcin-Siedentopf et al., 2014; Kane et al., 2015; Lee et al., 2015; Mauri et al., 2015; Nakhli et al., 2015; Yilmaz & Okanlı, 2015; Dahan et al., 2016; Matsuda et al., 2016; Wang et al., 2016; Widschwendter et al., 2016;2018; Caqueo-Úrizar et al., 2017;2020;2021; Hori et al., 2017; Iasevoli et al., 2017; Yanagida et al., 2017; Campbell et al., 2018; Xu et al., 2018; Ben Thabet et al., 2019; Endriyani et al., 2019; Kassem et al., 2019; Kondrátová et al., 2019; Bartoli et al., 2020; Nagai et al., 2020; Lim et al., 2021).
The search "'Psychological Reactance" AND schizophrenia [Title] AND adherence' provided no articles but using the old term "compliance": we found one article (Moore et al., 2000).
The search "'Health locus of control" AND schizophrenia [Title] AND adherence' provided 2 articles (Combes & Feral, 2011; Jaeger et al., 2014).

from these four scales and has five subscales: 1) positive aspects of medication, 2) negative aspects of medication, 3) psychological reactance, 4) internal HLOC, and 5) doctor HLOC (De las Cuevas & de Leon, 2019a). It has recently been translated into other languages (Pogany et al., 2021).

Systematic review in schizophrenia of self-reported scales for medication adherence

Box 2 describes our systematic PubMed search on adherence and schizophrenia, leading to 51 articles using these four psychological scales (BMQ: 2 articles, DAI: 46 articles, Hong Psychological Reactance Scale: 1 article, and HLOC: 2 articles). None of these 51 articles combined more than one of these scales at the same time, and only two (Iasevoli et al., 2017; Medina et al., 2012) used other psychiatric controls to explore what is specific to adherence in schizophrenia.

Box 1 summarizes expert guidelines for treatment in schizophrenia. These guidelines describe the impact of poor adherence in schizophrenia; they insist on ruling out non-adherence before diagnosing treatment resistance. An expert consensus guideline on adherence in serious and persistent mental illness dedicated a short paragraph to patient attitudes (Velligan et al., 2019).

We have conducted an ethnopsychopharmacology study in psychiatric outpatients in Spain, Argentina, and Venezuela including 1,372 patients using 2,454 psychiatric drugs. Prior analyses focused on the sample in general and included lower numbers (De las Cuevas et al., 2018a; 2019; 2021). In this new analysis, we divided the sample into two groups, schizophrenia and other patients, to explore which self-reported psychological dimension and clinical

variables are specifically associated with adherence in schizophrenia or are common in other psychiatric disorders.

METHODS

Study design and participants

This 2017 cross-sectional cross-cultural psychopharmacology study included outpatient psychiatric patients recruited after signing a consent form in 3 centers in the Canary Islands (Spain), Mendoza (Argentina) and Mérida (Venezuela). The inclusion criteria for the psychiatric outpatients were as follows: (1) age 18 or older, (2) literate in Spanish, (3) diagnosed with a psychiatric disorder; (4) treated with at least 1 psychiatric drug, and (5) participating voluntarily.

After consecutive recruitment in each center we had a final sample of 1372 psychiatric outpatients using 2454 psychotropic drugs. Clinical diagnoses were made according to the International Classification of Diseases, 10th revision. The patients completed the scales for the medications used and then the research team entered the records in the database and categorized the medications by class (De las Cuevas et al., 2018a; 2019).

Scales

The BMQ-Specific measures patient beliefs regarding the necessity of taking medicines and concerns about the potential negative effects of taking medicines. Each patient's attitude toward each drug used was marked by the presence or absence of skepticism (low necessity, high concern).

Table 1. All psychiatric medications: comparing dependent and independent variables in schizophrenia and other MDs

Variable (range)	Schizophrenia 212 patients taking 387 psychiatric meds ^b	Other MDs ^a 1160 patients taking 2067 psychiatric meds ^c
Dependent Variables		
Adherence ^d Yes	69.5% (269/387)	66.7% (1378/2067)
No	30.5% (118/387)	33.3% (689/2067)
Dichotomous Independent Variables^e		
Female gender	30.7% (65/212)	63.0% (731/1160)
Geriatric age	3.8% (8/212)	7.8% (91/1160)
University education	18.9% (40/212)	36.8% (427/1160)
Spain	63.2% (134/212)	39.1% (454/1160)
Treatment > 1 year	91.5% (194/212)	65.4% (759/1160)
Extreme polypharmacy	10.8% (23/212)	5.4% (63/1160)
Medication > 1 year	77.8% (301/387)	53.2% (1100/2067)
Pharmacophobia	28.8% (61/212)	28.7% (313/1160)
Pharmacophilia	29.7% (63/212)	31.8% (369/1160)
Skeptical about specific medication	18.9% (73/387)	30.4% (628/2067)
High psychological reactance	31.6% (67/212)	49.9% (579/1160)
High internal health locus of control	51.9% (110/212)	48.5% (563/1160)
High doctor health locus of control	49.5% (105/212)	41.5% (481/1160)
Continuous Independent Variables^f		
Age (years) (≥18)	41.2±12.0 (N=212)	44.5±14.6 (N=1160)
Number of medications (1-6)	1.8±1.2 (N=212)	1.8±0.9 (N=1160)
Duration of medication (months)	73.7±78.3 (N=387)	36.7±50.4 (N=2067)
Positive aspects of medication (5-30)	23.4±5.5 (N=212)	22.4±5.1 (N=1160)
Negative aspects of medication (3-18)	9.6±4.1 (N=212)	9.0±3.7 (N=1160)
Necessity (1-5)	3.8±1.0 (N=387)	3.4±0.9 (N=2067)
Concern (1-5)	2.6±1.1 (N=387)	3.0±1.0 (N=2067)
Psychological reactance (3-18)	9.4±3.9 (N=212)	12.8±4.2 (N=1160)
Internal LOC (3-18)	13.7±3.8 (N=212)	13.5±3.6 (N=1160)
Doctor LOC (3-18)	15.3±3.4 (N=212)	15.4±2.9 (N=1160)

MD, mental disorders; SPSS, Statistical Package for the Social Sciences.

^a Diagnoses were bipolar disorders 12.2% (142/1160), depressive disorders 44.9% (521/1160), anxiety disorders 26.7% (310/1160), personality disorders 5.8% (67/1160), substance abuse 1.9% (22/1160), and other psychiatric disorders 8.4% (98/1160).

^b Psychiatric medications were antipsychotics 62.3% (241/387), mood stabilizers 8.8% (34/387), antidepressants 8.5% (33/387), antianxiety and non-benzodiazepine Z hypnotics, 17.3% (67/387), anticholinergics 1.6% (6/387), and others 1.6% (6/387).

^c Psychiatric medications were antipsychotics 15.2% (315/2067), mood stabilizers 11.1% (230/2067), antidepressants 41.0% (847/2067), antianxiety and non-benzodiazepine Z hypnotics 31.8% (658/2067), anticholinergics 0.1% (3/2067), and others 0.7% (14/2067).

^d The mean±SD score in the Sidorkiewicz Adherence Tool was 2.55±1.92 in 212 schizophrenia patients vs. 2.63±1.87 in 1160 patients with other mental disorders.

^e Data management and analyses were carried out using the SPSS software 25th version. No attempt was made to compare statistical significance, which would have provided multiple significance tests and risk of false positives by chance. This article's goal is not that these variables are significantly associated in these two groups, but that they are significantly associated with adherence and these associations are significantly different between the two groups.

^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 by asking the authors. It was not included because clinicians have difficulty managing raw scores of all of these psychological scores and, more importantly, because these self-reported scales vary from country to country (e.g., a score of 4 may not mean the same thing in each country). Dichotomization by median score helps correct for this difference.

The Patient Health Beliefs Questionnaire on Psychiatric Treatment has 17 items and five subscales referring to the patient: positive aspects of medications, negative aspects of medications, psychological reactance, internal HLOC and doctor's HLOC.

Every prescribed psychiatric drug was dichotomized into adherence and non-adherence by the Spanish validated version (De las Cuevas et al., 2018b) of the Sidorkiewicz Adherence Tool.

Data Analysis

Table 1 has two columns (left: all drugs prescribed in patients with schizophrenia and right: all drugs prescribed in patients with other mental disorders) and three rows [first: the dependent variable of our study, adherence (yes/no)]; second: the dichotomous independent variables; and third: the continuous independent variables).

Following a classic textbook (Hosmer & Lemeshow, 2000), we conducted backward stepwise logistic regression models. Table 2 is focused on all medications. It describes the adjusted odds ratios (ORs) and 95% confidence intervals (CIs). The adjusted ORs from schizophrenia and the other sample can be compared by the overlap of their 95% CIs, but this is a conservative method (Streiner, 2016) which provided no p values. Thus, logistic regression models with interactions were used to approximate p values of the difference (footnote a of Table 2).

Table 3 focuses on antipsychotic medications after stratification of schizophrenia and other mental disorders. Table 4 describes the logistic regression models for antipsychotic medications.

RESULTS

Adherence to all medications

No significant difference in adherence to all medications in 2 groups

Table 1 describes good adherence for 69.5% of the drugs taken by schizophrenia patients versus 66.7% for the drugs taken by the other patients ($p=0.28$, $OR=1.14$, $CI\ 0.091-1.44$).

Significant association with adherence to all medications common to 2 groups

Table 2 shows that, after controlling for other variables, pharmacophobia is a powerful predictor in both groups with an $OR=0.389$ in schizophrenia and an $OR=0.591$ in other psychiatric patients, which was not significantly different (overlapping CIs and $p=0.33$). The schizophrenia $OR=2.18$ of pharmacophilia appears to be significantly higher ($p=0.012$) than the $OR=1.59$ in other psychiatric patients.

Significant association with adherence to all medications in opposite direction

Prescribing a medication for more than 1 year increased adherence in schizophrenia $OR=1.92$ while decreasing adherence in other psychiatric illnesses ($OR=0.687$). The subgroup of drugs prescribed for more than 1 year in schizophrenia patients was selected. They tend to be characterized by a) high percentages of: 1) extreme polypharmacy, 2) prescription of medications that are not antipsychotics, and 3) pharmacophilia, with b) lower percentages of 1) pharmacophobia, and 2) skepticism. The logistic regression model in this subgroup provides similar variables, which increased adherence in the whole schizophrenia group (Spain, pharmacophobia, high internal control and extreme polypharmacy), but had an unexpected significant $OR=1.862$ for high doctor HLOC. This subgroup of medications (many besides antipsychotics) appears to have been prescribed for more than 1 year, apparently involving some agreement with the psychiatrist.

Significant association with adherence to all medications specific to the schizophrenia group

Table 2 illustrates that four ORs for all medications were not significant in schizophrenia but were significant in psychiatric controls. Four ORs were significant in schizophrenia and not in the controls: treatment for > 1 year ($OR=0.161$), high internal control ($OR=0.389$), extreme polypharmacy ($OR=1.92$) and the country of Spain ($OR=0.575$).

There was a relatively high reported adherence of 80% in schizophrenia patients who were in their first year of treatment, but this data referred only to a small sample of 30 medications. Interestingly, in almost all cases of non-adherence the patient reported being skeptical about that specific drug and/or was pharmacophobic.

In those schizophrenia patients with high internal HLOC, adherence was somewhat lower at 64.0% and males were overrepresented (79.2%). The logistic regression model indicated that treatment duration > 1 year had an extremely powerful effect in decreasing adherence ($OR=0.080$, $CI\ .016\ to\ 0.393$).

The group with excessive polypharmacy appears to represent a subgroup within those classified as being prescribed a medication for > 1 year and taking medications besides antipsychotics. They are characterized by high frequencies of pharmacophilia and doctor LOC, and low frequencies of pharmacophobia and skepticism. When high internal LOC was present, it had an extremely negative effect on adherence.

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

Variable	Schizophrenia OR (95% CI)	Other MDs OR (95% CI)	Comparison ^a
Dichotomous Model^b			
Pharmacophobia	0.389 (.223-.678) P=.001	0.591 (.470-.744) P<.001	P=0.33 ^d Overlapping CI
Pharmacophilia	2.18 (1.18-4.06) P=.013	1.59 (1.24-2.05) P=.001	P=0.012 ^d Overlapping CI Stronger in schizophrenia
Medication >1 year	1.92 (1.03-3.57) P=.040	0.687 (.564-.838) P<.001	Different direction ^c Not overlapping CI
Treatment >1 year	0.161 (.053-.495) P=.001	NS	NS in other MDs
High internal HLOC	0.389 (.223-.678) P=.001	NS	NS in other MDs
Extreme polypharmacy	1.92 (1.03-3.57) P=.040	NS	NS in other MDs
Spain	0.575 (.334-.987) P=.045	NS	NS in other MDs
Female gender	NS	1.27 (1.04-1.56) P=.018	NS in schizophrenia
Geriatric age	NS	2.48 (1.63-3.77) P<.001	NS in schizophrenia
High doctor HLOC	NS	1.28 (1.04-1.59) P=.023	NS in schizophrenia
High psychological reactance	NS	0.721 (.593-.876) P=.001	NS in schizophrenia
Skeptical about specific med	NS	0.550 (.444-.680) P<.001	NS in schizophrenia

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

^a The adjusted ORs from schizophrenia and the other sample 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; overlapping 95% CIs can still be significantly different (Streiner, 2016) using a statistical test. Logistic regression models were fitted including adherence as the dependent variable and the significant independent variables. Different models were fitted adding the variable schizophrenia and an interaction term with each one of the other independent variables and countries. When the logistic regression model provided a significant p value for the interaction between schizophrenia country and the other independent variables, this helped support the conclusion that the ORs of schizophrenia and the other sample were significantly different.

^b Both models fit well as measured by the Hosmer and Lemeshow test. For the schizophrenia model $\chi^2=9.566$, $df=8$, $p=.297$, and for the other SMI model $\chi^2=1.680$, $df=8$, $p=.989$. The default in SPSS entry 0.05 and removal 0.10 was modified to entry 0.05 and removal 0.05.

^c In schizophrenia, this variable increases adherence, while in other MDs, this variable decreases adherence.

^d Significance was tested by a logistic regression model where adherence was the dependent variable and schizophrenia, along with other variables and an interaction term with schizophrenia, and the variable represented in each row are the predictors. We classified the OR as stronger in schizophrenia when the OR >1 was significantly higher in schizophrenia or the OR <1 was significantly lower in schizophrenia.

In the Spanish schizophrenia group: 1) adherence was 65.9%, somewhat lower, 2) extreme polypharmacy was much more frequent, and 3) treatment lasted for > 1 year. These had very significant effects on decreasing adherence.

Adherence to antipsychotic medications

No significant difference in adherence to antipsychotic medications

Table 3 describes good adherence in 72.1% of the antipsychotic drugs taken by schizophrenia patients versus 65.7% in the patients with other mental disorders ($p=0.31$; OR=1.15, CI, 0.879-1.51).

Significant association with adherence to antipsychotic medications common to 2 groups

Table 4 shows that, after controlling for other variables, pharmacophobia was a powerful predictor in both groups with an OR=0.324 in schizophrenia and an OR=0.237 in other disorders, but the ORs were not significantly different.

Significant association with adherence to antipsychotic medications specific to the schizophrenia group

Table 4 indicates that three ORs were not significant in the schizophrenia group but were significant among the psychiatric controls. More importantly, two ORs were included in the schizophrenia group and not in the controls: treatment for > 1 year (OR=0.362) and skepticism about that particular antipsychotic drug (OR=0.535). Antipsychotic adherence diminished from 78.9% (15/19) in the small group of patients with antipsychotic prescriptions treated for < 1 year to 71.5% (158/221) for > 1 year. Similar to non-adherence to all drugs, non-adherence to antipsychotic prescriptions during the first year was associated with pharmacophobia and/or skepticism.

There were only 47 antipsychotic prescriptions associated with skepticism and they were also associated with high frequency of pharmacophobia and of psychological reactance and very low frequency of pharmacophilia and high doctor LOC. Therefore, it is not surprising the self-reported adherence was 57.4% (20/47), the lowest in any schizophrenia subsample.

DISCUSSION

This is the first study simultaneously exploring the relevance of skepticism, pharmacophobia, pharmacophilia, psychological reactance, doctor and internal HLOC on adherence after controlling for clinical variables, particularly treatment duration. Use of psychiatric controls helped to distinguish what may or may not be specific to schizophrenia.

Pharmacophobia and pharmacophilia

In this sample, attitude toward medication in general appears to be the most important and consistent factor influencing adherence across all analyses and subsamples. Adherence was decreased by pharmacophobia and increased by pharmacophilia and these effects tend to be stronger in schizophrenia but happened in other mental disorders.

This is not a completely new finding. In a systematic review of the literature on schizophrenia which comments on the HBM, Lacro et al. (2002) found, in 8/10 studies with the DAI, negative attitude toward medication was associated with non-adherence. In the expert panel review, Velligan et al. (2009) listed negative attitudes towards medications in general as potential contributors to poor adherence in schizophrenia and bipolar disorder. Our study contribution included elaborate and precise definitions of pharmacophobia and pharmacophilia, which remain strongly and consistently significantly associated with adherence after controlling for multiple confounders. This association was not specific to schizophrenia

Skepticism (low necessity and high concern) about a specific medication

In the analysis of adherence to all medications, skepticism was significant in patients with other mental illness with an OR=0.550 even after controlling for pharmacophobia and pharmacophilia. It did not reach significance in the schizophrenia group, where pharmacophobia and pharmacophilia may be more important. There was some weaker evidence that in some subgroups of schizophrenia prescriptions (such as antipsychotic prescription during the first year), skepticism may be important in adherence. This was a small set of antipsychotic prescriptions confounded by high levels of other negative factors, such as high

Table 3. AP medications: comparing dependent and independent variables in schizophrenia vs. other MDs

Variable	Schizophrenia 204 patients taking 240 APs	Other MDs ^a 301 patients taking 315 APs
Dependent Variables		
Adherence ^b Yes	72.1% (173/240)	65.7% (207/315)
No	27.9% (67/240)	34.3% (108/315)
Dichotomous Independent Variables		
Female gender	29.4% (60/204)	60.1% (181/315)
Geriatric age	3.9% (8/204)	9.0% (27/301)
University education	18.1% (37/204)	38.9% (117/301)
Spain	27.9% (57/204)	39.5% (119/301)
Treatment > 1 year	92.2% (188/204)	71.4% (215/301)
Extreme polypharmacy	10.8% (22/204)	13.6% (41/301)
AP polypharmacy	16.7% (34/204)	4.7% (14/301)
Medication > 1 year	75.4% (181/240)	43.8% (138/315)
Pharmacophobia	28.9% (59/204)	33.6% (101/301)
Pharmacophilia	29.9% (61/204)	27.9% (84/301)
Skeptical about specific medication	19.5% (47/240)	27.9% (88/315)
High psychological reactance	30.4% (62/204)	46.8% (141/301)
High internal HLOC	52.0% (106/204)	47.8% (144/301)
High doctor HLOC	49.0% (100/204)	42.2% (127/301)
Continuous Independent Variables		
Age (years) (≥18)	41.3±11.9 (N=204)	45.4±15.2 (N=301)
Number of medications (1-6)	1.8±1.2 (N=204)	2.4±1.1 (N=301)
Number of antipsychotics (1-3)	1.18±0.4 (N=204)	1.05±0.2 (N=301)
Duration of medication (months)	71.5±79.6 (N=204)	30.6±41.3 (N=301)
Positive aspects of medication (5-30)	23.4±5.6 (N=204)	23.0±5.2 (N=301)
Negative aspects of medication (3-18)	9.6±4.1 (N=204)	9.5±4.0 (N=301)
Necessity (1-5)	3.8±1.0 (N=240)	3.5±0.9 (N=315)
Concern (1-5)	2.6±1.1 (N=240)	3.1±1.0 (N=315)
Psychological reactance (3-18)	9.3±3.8 (N=204)	13.0±4.3 (N=301)
Internal HLOC (3-18)	13.8±3.8 (N=204)	13.5±3.7 (N=301)
Doctor HLOC (3-18)	15.3±3.3 (N=204)	15.4±3.1 (N=301)

AP, antipsychotic; HLOC, health locus of control; MD, mental disorders.

^a Diagnoses were bipolar disorders 28.9% (87/301), depressive disorders 28.2% (85/301), anxiety disorders 13.6% (41/301), personality disorders 11.0% (33/301), substance abuse 2.3% (7/301), and other psychiatric disorders 15.9% (48/301).

^b The mean±SD score using the Sidorkiewicz Adherence Tool was 2.4±1.9 in schizophrenia vs. 2.6±1.9 in other mental disorders.

frequency of pharmacophobia and psychological reactance, and low levels of pharmacophilia and high doctor HLOC. Therefore, it is not surprising that skepticism rarely was significant by itself in the schizophrenia analyses. It appears to act as the last drop in a full glass.

Only 2 prior studies were identified in our BMQ search for adherence in schizophrenia (Box 2) and only one of them studied skepticism. This French study (Samalin et al., 2016), which measured adherence to drugs in general and did not include a measure of pharmacophobia, was probably actually a study of what we call pharmacophobia, a negative attitude to all medications.

Internal HLOC and doctor HLOC

High internal HLOC was associated with a significant OR (0.389) after controlling for confounders for all medication in schizophrenia patients but did not reach significance for antipsychotic medications in schizophrenia patients.

In the other psychiatric patients, high doctor HLOC had a significant OR (OR=1.28), suggesting that psychiatrists might have some positive effects on adherence in them. Only in a subsample of schizophrenia patients was high doctor HLOC significant in those taking multiple medications for comorbidities during periods > 1 year. It is possible

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

Variable	Schizophrenia OR (95% CI)	Other MDs OR (95% CI)	Comparison
Dichotomous Model^a			
Pharmacophobia	0.324 (.170-.621) P=.001	0.237 (.141-.400) P<.001	P=0.075 ^b Overlapping CI
Treatment >1 year	0.362 (.108-1.211) P=.099	NS	NS in other MDs
Skepticism about specific medications	0.535 (.261-1.097) P<.088	NS	NS in other MDs
High health locus of internal control	NS	0.626 (.372-1.051) P=.077	NS in schizophrenia
Geriatric age	NS	4.34 (1.39-13.51) P=.011	NS in schizophrenia
High psychological reactance	NS	0.237 (.141-.400) P<.001	NS in schizophrenia

CI, confidence interval; MD, mental disorders; 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 schizophrenia model $\chi^2=0.775$, $df=3$, $p=.855$, and for the other MD model $\chi^2=5.730$, $df=6$, $p=.454$. All procedures were the same for each medication, except that because antipsychotics had a smaller sample size, we decided to keep the SPSS default: entry 0.05 and removal 0.10.

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

that this may reflect the use of some medication on which both a schizophrenia patient and psychiatrist can agree.

Our study cannot be compared with two prior HLOC studies in schizophrenia (Box 2) which used a correlational design. In a systematic review of medication adherence in general, Náfrádi et al. (2017) reported that doctor HLOC and high internal HLOC were consistently found to promote medication adherence. In our schizophrenia patients, high internal control acted in the opposite way, at least regarding adherence to all medications in general. Thus, high internal HLOC may reflect their distrust of other people regarding control of their mental illness.

Psychological reactance

In our schizophrenia patients, psychological reactance had no role after controlling for attitude toward medication or toward HLOC. The only prior published study of psychological reactance in schizophrenia did not control for those variables (Box 2).

The 1-year barrier to medication adherence

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial provided very sobering results; after 1.5 years, 74% of the patients were no longer on the antipsychotic with which they started the trial (Lieberman et al., 2005). Thus, it should not have been surprising that > 1 year of treatment would decrease adherence in our naturalistic sample.

Concerning adherence to all drugs, the OR for treatment > 1 year was 0.161 and for pharmacophobia was 0.389 (Table 2). Regarding adherence to antipsychotic drugs, the respective ORs were 0.362 and 0.324 (Table 4). These similar values suggest that 1 year of treatment may be just as great a barrier to adherence as pharmacophobia.

Studies of adherence in first psychotic episodes listed the following as predictors of non-adherence in the first years: 1) negative attitude toward medications, 2) hostility and uncooperativeness, 3) lack of insight, and 4) substance abuse (de Haan et al., 2007; Kamali et al., 2006; Mutsatsa et al., 2003; Quach et al., 2009).

Spanish sample and representativeness

Spain has a National Healthcare System that guarantees universal coverage and free healthcare access to all Spanish nationals, regardless of economic situation. 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. This probably explains why self-reported adherence to all drugs in Spain was somewhat lower at 65.9% in all drugs; 68.1% (143/210) for all antipsychotics and 70.4% (107/152) in patients taking only one antipsychotic.

Any study using self-report of adherence in clinical samples is “doomed” from the start. The most non-adherent schizophrenia patients from this catchment area are the ones who have not come for treatment for years. Second, any patient who is not willing to sign a consent form was not included in this sample of patients taking oral medications. Third, those schizophrenia patients with active substance use, a major reason for non-adherence (Quach et al., 2009) are sent to another center for substance abuse treatment; when the abuse is in remission, this Spanish community mental health center becomes the only treatment provider. Fourth, there was no attempt to measure adherence to long-acting injectable (LAI) antipsychotics since that approach is fundamentally different than for oral medications. The key aspect to adherence for LAI antipsychotics is showing up for the injection. The number of patients willing to take LAI in our Spanish center is, unfortunately, very small. There are no outpatient commitments in Spain to force medications and as oral medications are offered for free and all treatments are free, most schizophrenia patients prefer oral to LAI antipsychotics. 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 establish 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). In our sample, there were 4.7% of schizophrenia patients (10/212) taking at least one other oral medication, but no antipsychotics.

Personalizing adherence in schizophrenia versus other mental illnesses

In a recent systematic review, Velligan et al. (2017) wrote, “A key reason directly associated with intentional nonadherence was a negative attitude toward medication, a mediator of effects of insight and therapeutic alliance.” In our sample, pharmacophobia was an important predictor of lack of adherence but was not specific to schizophrenia. Skepticism was much more relevant in other psychiatric patients although it may be relevant for some schizophrenia patients as an additive factor. The therapeutic alliance, indirectly measured by doctor HLOC, appears to have some positive effects on non-schizophrenia patients, but schizophrenia patients appear to be mainly driven by their internal HLOC, which had negative effects on medication adherence.

This cross-sectional study had no cross-sectional measure of insight, but it is reasonable that the 1-year barrier is probably explained by a lack of trust after 1 year of medication in general (or antipsychotics in particular). Even without measuring insight, our results on the differential and independent effects of pharmacophobia, internal control and the 1-year barrier provide a glimpse of what personalized interventions for adherence (Velligan et al., 2008) in this sample may look like and how self-report measures can help improve adherence (Stirrat et al., 2015).

Limitations

The prior sections describe the practical limitations in studying the most non-adherent patients who may not be using the Spanish free health system and may have no access to our recruitment centers in Argentina and Venezuela. This study has all the limitations of self-report measures but included 80 different pharmacological compounds in 3 different countries; therefore, self-report was the only possible efficient way to study medication adherence (Stirrat et al., 2015). In a multicenter study with no external support, the use of objective measures such as blood levels (Velligan et al., 2020) was not possible. Finally, insight was not measured but we suspect that what we call the 1-year barrier reflects changes in insight over time. Nevertheless, in the validation article for our scale (De las Cuevas & de Leon, 2019a), we stressed the need to improve it by adding a short cross-sectional measure of insight. This addition cannot measure past or future changes in insight.

CONCLUSION

This study in schizophrenia and psychiatric controls explored the relevance of skepticism, pharmacophobia, pharmacophilia, psychological reactance, doctor and internal HLOC on adherence after controlling for clinical variables, particularly treatment duration. Pharmacophobia and pharmacophilia were strongly associated with adherence in all patients. Treatment for >1 year and high internal HLOC decreased adherence to all drugs only in the schizophrenia sample. Pharmacophobia, treatment for >1 year and skepticism decreased adherence to antipsychotics in the schizophrenia sample. Future studies on adherence to all medications and to antipsychotic medications need to further explore which of these dimensions are specific to schizophrenia and which are common to all psychiatric patients.

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

CONFLICTS OF INTEREST: The authors have declared that there are no conflicts of interest in relation to the subject of this study. No commercial organizations had any role in writing this paper for publication.

FUNDING SOURCES: None

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A farmakofóbia, a belső egészségkontrollhely és a kezelés időtartama befolyásolhatja a szkizofrén betegek adherenciáját

Célkitűzés: A vizsgálatban 212, szkizofrénia miatt Spanyolországban, Argentínában és Venezuelában ambuláns pszichiátriai kezelés alatt álló beteg vett részt, akik együttesen 387 pszichiátriai gyógyszert szedtek. Emellett a vizsgálatba 1160 olyan beteget is bevontunk, akik egyéb pszichiátriai betegség miatt álltak ambuláns kezelés alatt, ennek a betegcsoportnak a tagjai összesen 2067 pszichiátriai gyógyszert szedtek. **Módszer:** Logisztikus regressziós modellel vizsgáltuk a Sidorkiewicz skálával (Sidorkiewicz Adherence Tool) meghatározott adherenciát mint függő változót az egyes gyógyszerek esetében. Regressziós modellel meghatároztuk a dichotom független változók korrigált esélyhányadosát (OR): 1.) klinikai változók, 2.) a PHBQPT alszámai (a farmakofóbia és farmakofília megléte/hiánya, alacsony/magas pszichológiai reaktancia, belső egészségkontrollhely (Internal HLOC), és az orvos egészségkontrollhely (Doctor HLOC) alszámai pontszámai és 3.) a Beliefs About Medicines Questionnaire (BMQ) segítségével megítélt, az egyes gyógyszerekre vonatkozó szkepticizmus megléte/hiánya változók esetében. **Eredmények:** Mindkét betegcsoportban szignifikáns volt az esélyhányados (OR): 1.) farmakofóbia (OR=0,389 a szkizofrén csoportban, OR=0,591 a más pszichiátriai betegség miatt kezelt betegek csoportjában) és 2.) farmakofília (a szkizofrén csoportban OR=2,18, a más betegségek miatt kezelt csoportjában OR=1,59; a szkizofrén csoportban az érték szignifikánsan magasabb volt, $p=0,012$). Az egy évnél hosszabb ideje tartó kezelés esetén a szkizofrén betegek csoportjában javult az adherencia (OR=1,92), az egyéb pszichiátriai betegségek miatt kezelt betegek csoportjában pedig romlott (OR=0,687). Négy esélyhányados (OR) csak a szkizofrén csoportban volt szignifikáns, a más betegség miatt kezelt betegekben nem: az egy évnél hosszabb kezelési időtartam (OR=0,161), magas belső HLOC pontszám (OR=0,389), extrém mértékű polipragmázia (OR=1,92), és a spanyolországi lakhely (OR=0,575). A vizsgálatban résztvevő 204 szkizofrén beteg együttesen 240 antipszichotikumot szedett, a nem szkizofrénia miatt kezelt csoportban pedig 301 beteg számára írtak fel összesen 315 antipszichotikumot. Három esélyhányados (OR) bizonyult szignifikánsnak az antipszichotikumokra vonatkozó adherenciát illetően a szkizofrén csoportban: a farmakofóbia (OR=0,324), az egy évnél hosszabb ideje tartó gyógyszeres kezelés (OR=0,362), és az antipszichotikumokkal kapcsolatos szkepticizmus (OR=0,535). **Következtetés:** Az antipszichotikumokra és más hatóanyagokra vonatkozó adherencia további vizsgálata szükséges annak érdekében, hogy az ezt befolyásoló tényezők közötti hasonlóságok és különbségek azonosíthatók legyenek a szkizofrénia és a más pszichiátriai betegségek miatt kezelt páciensek esetében.

Kulcsszavak: egészséghez való viszonyulás, adherencia, egészségmagatartás, pszichiátria, pszichofarmakológia, szkizofrénia