

Poor Adherence to Oral Psychiatric Medication in Adults with Depression: Psychological Reactance May Have Specific Effects in Depression

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Objective: Medication adherence in psychiatric disorders, including depression, may be influenced by 6 self-reported dimensions: 1) high/low doctor health locus of control (HLOC), 2) high/low internal HLOC, 3) high/low psychological reactance, 4) pharmacophilia, 5) pharmacophobia, and 6) skepticism about a specific medication. This study in Spain, Argentina, and Venezuela included 521 outpatients with depression prescribed 920 psychiatric medications and 851 other psychiatric outpatients prescribed 1534 medications. **Methods:** Logistic regression models were completed in patients with depression and psychiatric controls. The dependent variable was adherence for each psychiatric medication (Sidorkiewicz Adherence Tool). The models provided adjusted odds ratios (ORs) of dichotomous independent variables: clinical variables, and 6 self-reported dimensions. **Results:** ORs significant in both diagnostic groups were: 1) pharmacophobia (OR=0.500 in depression, OR=0.599 in other patients), 2) pharmacophilia (respectively OR=1.51, OR=1.65), 3) treatment for 1 year (respectively OR=0.731, OR=0.608), 4) geriatric age (respectively OR=2.28, OR=3.02), and 5) skepticism about a specific medication (respectively OR=0.443, OR=0.569). Two ORs were significant in the depression group, but not in the controls: the country of Spain (OR=0.744), and high psychological reactance (OR=0.685). The study included 470 depression patients prescribed 510 antidepressants and 348 other patients prescribed 370 antidepressants. One OR was significant for antidepressant adherence in both groups: high psychological reactance (respectively OR=0.597, OR=0.561). **Conclusions:** All clinical studies using self-report include biases but the most important is lack of access to patients not coming for treatment. Future studies should further explore the specificity/commonality of these dimensions, particularly psychological reactance, in depression versus other psychiatric disorders.

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INTRODUCTION

In a recent review on depression in adult patients, Maj et al. (2020) focused on personalized depression treatment. This excellent encyclopedic review brought this topic up to date and highlighted important unmet needs. Attitude toward medication, which we believe is crucial in adherence, was briefly mentioned.

In the 1960s some psychiatric researchers focused on the patient's attitude toward medications and medication adherence (De las Cuevas C & de Leon J, 2017). Then, for many years, the subject of medication adherence received little attention in psychiatry (Blackwell, 1976), although health psychology journals have focused on this area. The Health Belief Model (HBM) was developed to explain and predict health-related behaviors; it emphasizes the central role of a patient's subjective beliefs, understanding of illness, and treatment options in determining adherence to prescribed medications (Rosenstock, 1974; Sulat et al., 2018). Not unexpectedly, patients' beliefs and attitudes towards their treatment also influence medication adherence in psychiatric patients (de Leon & De las Cuevas, 2017; De las Cuevas & de Leon, 2020).

The HBM literature has not received enough attention in psychiatric journals. To simplify, we call these dimensions *self-reported dimensions* and divide them into those focused on personality styles or on medications (De las Cuevas & de Leon, 2020). Personality-style dimensions, obtained by self-report, include psychological reactance and those included under Health Locus of Control (HLOC). Psychological reactance (Rosenberg & Siegel, 2017) is an emotional reaction toward rules perceived as a threat and is typically measured with the Hong Psychological Reactance Scale (Hong & Faedda, 1996).

HLOC reflects patients' beliefs about who or what is responsible for the management of their disorder, in this case a psychiatric disorder, influencing their health behaviors and consequently their mental health outcomes (Wallston, 1989; Wallston & Wallston, 1982). The MHLC-C is an 18-item general purpose, condition-specific locus of control self-report scale that can easily be adapted for use with any medical or health-related condition to assess individuals' beliefs about what influences their health (Wallston et al., 1994). In psychiatric patients, the HLOC's two dimensions are important, the patient (internal) HLOC and the doctor HLOC (De las Cuevas et al., 2016).

The Drug Attitude Inventory (DAI-10) is a questionnaire that reports attitude toward all

medications (Hogan et al., 1996). The original DAI-10 included 10 questions, each with true/false answers pertaining to various aspects of the patient's perceptions and experiences of psychiatric treatment. A clinimetric version of the DAI led us to include 8 items grouped into two subscales: 1) positive versus negative aspects of medications; and 2) pharmacophobia, or fear of the use of pharmacological treatments versus pharmacophilia, a positive attitude toward using or taking medications (De las Cuevas & de Leon, 2019a; 2019b).

Therefore, medication adherence during any psychiatric disorder, including depression, may be influenced by 5 self-reported dimensions: high/low psychological reactance, high/low doctor HLOC and high/low internal HLOC, pharmacophobia and pharmacophilia. To complete the 4 original scales that refer to the patient (Hong Psychological Reactance Scale, Multidimensional HLOC and DAI-10), requires 1-1.5 hours of the patient's time. Therefore, we developed the Patient Health Beliefs Questionnaire on Psychiatric Treatment which requires 15 minutes for completion and includes major items from the 4 scales. The items are classified in 5 subscales: 1) psychological reactance, 2) internal HLOC, 3) doctor HLOC, 4) positive aspects of medication, and 5) negative aspects of medication (De las Cuevas & de Leon, 2019b). It has recently been translated into other languages (Pogany et al., 2020; 2021).

Besides these self-reported dimensions referring to personality, 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. The necessity-concern framework can be summarized as skepticism by combining the necessity and concern scores. A patient who is skeptical about a specific medication indicates that both high concern about adverse reactions and low belief in their necessity are present (De las Cuevas et al., 2018a; De las Cuevas et al., 2021).

Major depressive disorders are commonly occurring disorders affecting more than 264 million people around the world; they are associated with a wide range of indicators of impairment and secondary morbidity, representing the leading cause of disability worldwide and acting as a major contributor to the overall global burden of disease (GBD 2018; Kessler & Bromet, 2013). Although studies have proven that short-term psychotherapies are equally as efficacious as antidepressant medications in treating depression (Mynors-Wallis et al., 2000; Ward et al,

Box 1. Reviews of psychology of medication adherence in depression

PubMed search of reviews of adherence in depression (10/29/2021)
"Medication Adherence/psychology"[Mesh] AND "depressive disorder" revealed 149 articles, of which 22 were systematic reviews or reviews. Of these 22 review articles, we eliminated 17: 11 focusing on adherence toward medical medications, 3 on treatment-resistant depression, 1 on adherence in psychopharmacology in general and 2 focus on the effects of sexual adverse drug reactions, which left 5 articles that are briefly reviewed below.
Marrero et al. (2020)
<ul style="list-style-type: none"> • Medication adherence in psychiatric patients was associated with health beliefs and psychological variables, such as self-efficacy and locus of control. • Family support was also positively related to medication adherence. • The authors concluded that medication adherence requires a consideration of multicausality, which depends on sociodemographic, clinical, and psychological factors.
Acharya & Agius M (2018)
<ul style="list-style-type: none"> • This review proposes that depression may contribute to poor adherence.
Hung (2014)
<ul style="list-style-type: none"> • Better adherence to and persistence in antidepressant treatment was associated with old age. • Poorer adherence to and persistence in antidepressant treatment was associated with minority groups, immigrants, a low income and no health insurance. • Better adherence to and persistence in antidepressant treatment was associated with positive attitudes toward depression and antidepressants, as well as previous experiences and vicarious experiences of depression and antidepressant treatment. • Poorer adherence to and persistence in antidepressant treatment was associated with adverse effects, pregnancy, dissatisfaction with treatment, poor relationship of patients with healthcare professionals and lack of information.
Pompili et al. (2013)
<ul style="list-style-type: none"> • The authors identified several predictors of nonadherence among patients with mood disorders including younger age (below 40 years old), comorbidity with substance use and personality disorders, patients' beliefs, poor insight, illness severity, treatment-related side effects, specific features of the disease and a poor therapeutic alliance.
Rizvi & Kennedy (2011)
<ul style="list-style-type: none"> • The discovery of new antidepressants with fewer adverse drug reactions may lead to better adherence.

2000), the prevalent treatment is antidepressants since psychotherapy is not always available and prescribing medication fits more easily into routine clinical practice. Although antidepressants have been criticized for their limited efficacy (Moncrieff & Kirsch, 2005), these medications will only help patients with depression if they adhere to them properly, and the fact is that it is estimated that approximately 50 percent of psychiatric patients and 50 percent of primary care patients prematurely discontinue antidepressant therapy (Sansone & Sansone, 2012).

Box 1 describes our PubMed search, which identified 149 articles on psychological aspects of medication adherence in depression, and briefly summarizes 5 relevant review articles.

Box 2 describes our systematic PubMed searches on adherence and depression, which led to 18 articles using any of these psychological scales: the Hong Psychological Reactance Scale in 2 articles, HLOC in 1 article, DAI in 7 articles, and BMQ in 8 articles. Of these 18 articles, only 3 combined 2 of these scales and they were by our group (De las Cuevas et al., 2013; 2014a; 2014b); 2 used some kind of controls to compare with the patients with major depression (Kamaradova et al., 2016; Tay, 2007).

We 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, included lower numbers (De las Cuevas et al., 2018a; 2019) and did not single out the diagnosis of depression.

In these new analyses, we divided the sample in two, based on depression or another psychiatric diagnosis; the goal was to explore which self-reported psychological dimensions and clinical variables are specifically associated with adherence in depression versus those variables that also influenced adherence in other mental disorders.

METHODS

Study design and participants

The ethics committee of the Canary Islands Health Service approved this study, and all the participating patients provided written informed consent approved by the corresponding institutional review boards. This 2017 cross-sectional cross-cultural psychopharmacology study included outpatient

Box 2. PubMed search (10/29/2021) to identify articles on self-reported dimensions, depression and adherence

The search using "Psychological Reactance" AND depression AND adherence provided 1 article (De las Cuevas et al., 2014a) and another article was identified using the old word "compliance" (Jaeger, 2015).
The search using "Health locus of control" AND depression AND adherence OR compliance) provided 18 articles, but only one relevant for major depression (De las Cuevas et al., 2014a).
The search using "Drug Attitude Inventory" AND depression AND adherence provided 22 articles, but only 7 relevant for major depression (De las Cuevas et al, 2013; 2014b; Kamardova et al., 2016; Murata et al., 2012; Serrano et al., 2014; Sedláčková et al., 2015; Tay, 2007).
The search using ("Beliefs about Medicine Questionnaire" OR "Beliefs about Medicines Questionnaire") AND depression AND adherence provided 36 articles, of which 8 were relevant for major depression (Al Jumah et al., 2014; Brown et al., 2005; Chawa et al., 2020; De las Cuevas et al., 2013; 2014b; Hunot et al., 2007; López-Torres et al., 2013; Zapata et al., 2017).

psychiatric patients 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. Clinical diagnoses were made based on the International Classification of Diseases, 11th revision. The patient filled out the questionnaires for each drug used; then the research team entered the records in the database, categorizing the drugs by class. After consecutive recruitment in each center we obtained a final sample of 1372 psychiatric outpatients using 2454 psychotropic drugs.

Scales

The Patient Health Beliefs Questionnaire on Psychiatric Treatment has 17 items rated on a 6-point Likert scale (from 1, totally disagree, to 6, totally agree). There are 5 subscales. Four subscales have 3 items: psychological reactance, internal HLOC, doctor’s HLOC and negative aspects of medications. One subscale has 5 items: positive aspects of medications. Psychological reactance, internal HLOC and doctor’s HLOC were split at the median rating for each country to generate high and low score groups (Table 1, footnotes f to h). Positive and negative aspects of medication were split at the median (Table 1, footnote i). Then pharmacophobia was defined as having high negative and low positive scores and pharmacophilia as having low negative and high positive scores.

The BMQ-Specific measures the necessity beliefs and concerns beliefs about the potential negative effects of taking medicines. It includes 10 items on two subscales, each with five items assessing patients’ beliefs about the medication they were prescribed for a specific illness in terms of necessity and concern about taking it. The degree of agreement with each

statement is indicated on a five-point Likert scale, ranging from 1 (strongly disagree) to 5 (strongly agree). By using median split and subgrouping, each drug in each patient was characterized by the presence or absence of skepticism (low necessity, high concern) (Table 1, footnote j).

Polypharmacy is increasingly common in psychiatric patients. In this situation, measurement of treatment adherence is a really complex task because patients with depression could adhere differently to each drug prescribed. This makes 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). It is comprised of 5 questions leading to 6 levels of adherence that were dichotomized into adherence and non-adherence. In this sample, adherence to every prescribed psychiatric drug was assessed using the Spanish validated version of the Sidorkiewicz Adherence Tool (De las Cuevas et al., 2018b).

Data Analysis

Data management and analyses were carried out using the Statistical Package for the Social Sciences (SPSS) software, 25th version. All p values were two-tailed. Table 1 describes all drugs after stratification based on depression and other psychiatric disorders. First comes the dependent variable of our study, adherence (yes/no), then the dichotomous independent variables and then the continuous variables.

Following a classic textbook (Hosmer & Lemeshow, 2000), we conducted backward stepwise logistic regression models. Table 2 describes the models focused on all medication with its odds ratios (ORs) and 95% confidence intervals (CIs). There is one model for patients with depression and another for those with other psychiatric disorders. The ORs from depression and the psychiatric controls can be

Table 1. All psychiatric medications: Dependent and independent variables in depression and other mental disorders^a

Variable (range)	Depression 521 patients with 920 meds ^c	Other Mental Disorders ^b 851 patients with 1534 meds ^d
Dependent Variables		
Adherence ^e Yes	69.8% (642/920)	65.5% (1005/1534)
No	30.2% (278/920)	34.5% (529/1534)
Dichotomous Independent Variables		
Female gender	67.6% (352/521)	52.2% (444/851)
Geriatric age	11.5% (60/521)	6.3% (54/851)
University education	32.8% (171/521)	34.8% (296/851)
Spain	43.0% (224/521)	42.8% (364/851)
Treatment >1 year	65.1% (339/521)	72.2% (614/851)
Extreme polypharmacy	6.1% (32/521)	6.3% (54/851)
Medication > 1 year	55.0% (506/920)	58.3% (894/1534)
High psychological reactance ^f	50.3% (262/521)	45.1% (384/851)
High internal health locus of control ^g	50.9% (265/521)	47.9% (408/851)
High doctor health locus of control ^h	45.1% (235/521)	41.2% (351/851)
Pharmacophobia ⁱ	23.6% (123/521)	31.8% (271/851)
Pharmacophilia ⁱ	39.3% (205/521)	26.7% (227/851)
Skeptical about a specific medication ^j	30.5% (281/920)	27.4% (420/1534)
Continuous Independent Variables^k		
Age (years) (≥18)	46.8±14.7 (N=521)	42.3±13.8 (N=851)
Number of medications (1-6)	1.8±0.9 (N=521)	1.8±1.0 (N=851)
Duration of medication (months)	32.3±42.8 (N=920)	48-7±63.7 (N=1534)
Psychological reactance (3-18)	13.1±4.2 (N=521)	11.8±4.3 (N=851)
Internal health locus of control (3-18)	13.6±3.6 (N=521)	13.5±3.7 (N=851)
Doctor health locus of control (3-18)	15.7±2.7 (N=521)	15.2±3.1 (N=851)
Positive aspects of medication (5-30)	22.8±4.6 (N=521)	22.5±5.5 (N=851)
Negative aspects of medication (3-18)	8.6±3.5 (N=521)	9.4±4.0 (N=851)
Necessity (1-5)	3.5±0.9 (N=920)	3.5±1.0 (N=1534)
Concern (1-5)	3.1±0.9 (N=920)	2.9±1.0 (N=1534)

^a No attempt was made to compare statistical significance, which would have provided multiple significance tests and risk of false positives by chance. Moreover, the goal of the article was not to test whether or not the differences in these variables are significantly between these two groups, but whether or not they are significantly associated with adherence and whether or not these associations are significantly different between the two groups.

^b Diagnoses were schizophrenia 24.9% (212/851), bipolar disorders 16.7% (142/851), anxiety disorders 36.4% (310/851), personality disorders 7.9% (67/851), substance abuse 2.6% (22/851), and other psychiatric disorders 11.5% (98/851).

^c The psychiatric drugs were antipsychotics 9.5% (87/920), mood stabilizers 5.0% (46/920), antidepressants 55.4% (510/920), antianxiety and non-benzodiazepine Z hypnotics, 29.6% (272/920), and others 0.5% (5/920).

^d The psychiatric drugs were antipsychotics 30.5% (468/1534), mood stabilizers 14.1% (216/1534), antidepressants 24.1% (370/1534), antianxiety and non-benzodiazepine Z hypnotics 29.5% (453/1534), anticholinergics 0.7% (10/1534), and others 1.1% (17/1534).

^e The mean ±SD score in the Sidorkiewicz Adherence Tool was 2.46±1.9 in 521 depressive patients vs. 2.71±1.9 in 851 patients with other mental disorders.

^f Median in Spain: 9; Argentina: 16; Venezuela:12.

^g Median in Spain: 14; Argentina: 14; Venezuela:14

^h Median in Spain: 17; Argentina: 16; Venezuela:17.

ⁱ Median of positive aspects of medication in Spain: 23; Argentina: 22; Venezuela: 26. Median of negative aspects of medications: Spain: 10; Argentina: 9; Venezuela: 9.

^j Median of necessity: Spain: 3.8; Argentina: 3.8; and Venezuela: 3.6. Median of concern: Spain: 2.6; Argentina: 3.6; and Venezuela: 2.6. By splitting at the median, the necessity and concerns subscales generated four attitudinal groups with clinical significance: accepting (high necessity, low concern), ambivalent (high necessity, high concern), indifferent (low necessity, low concern), and skeptical (low necessity, high concern). Then the attitude to each drug was dichotomized based on presence or absence of skepticism.

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

compared by their 95% CIs. If they do not overlap, the ORs can be said to be significantly different. This method is very conservative and overlapping 95% CIs can still be significantly different (Streiner, 2016) and not provide 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 antidepressant medications after stratification by depression and other mental disorders. Table 4 describes the logistic regression models for antidepressant drugs.

RESULTS

Adherence in depression and other psychiatric disorders

Significantly increased adherence to all medications in depression but with small ORs

Table 1 shows good adherence in 69.8% of the drugs taken by depression patients versus 65.5% in the other patients. This was significant due to the large sample size ($p=0.023$), but the OR was small (OR=1.22, CI 1.02-1.45).

Significant increased adherence in antidepressants but with small ORs

Table 3 displays good adherence in 75.1% of the antidepressant medications taken by depression patients versus 65.9% in the other patients. This was significant ($p=0.003$) due to the large sample size, but the OR was relatively small (OR=1.56, CI 1.16-2.09).

Variables associated with adherence to all medications

Significant associations with adherence to all medications common to 2 groups

Table 2 illustrates that, after controlling for other variables, five variables were significant in both groups with no significant differences in the ORs. The OR in pharmacophobia was 0.500 in depression versus 0.599 in other psychiatric patients (overlapping CIs and $p=0.96$). The OR in pharmacophilia was 1.51 in depression versus 1.65 in other psychiatric patients (overlapping CIs and $p=0.55$). The OR for treatment for 1 year was 0.731 in depression versus 0.608 in other patients (overlapping CIs and $p=0.27$). The OR in geriatric age was 2.28 in depression versus 3.02 in other

psychiatric patients (overlapping CIs and $p=0.61$). The OR for skepticism about a specific medication was 0.443 in depression versus 0.569 in other psychiatric patients (overlapping CIs and $p=0.66$).

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

Table 2 describes two ORs for all drugs that were not significant in depression but were significant in psychiatric controls. Two ORs were significant in depression, but not in the controls: the country of Spain (OR=0.744) and high psychological reactance (OR=0.685).

In the Spanish group with depression, the logistic regression model indicated neither pharmacophobia nor pharmacophilia had significant effects. On the other hand, skepticism and high psychological reactance decreased adherence while female gender and geriatric age increased adherence.

In those patients with depression and high psychological reactance, adherence was somewhat lower at 64.2% and the logistic regression model indicated pharmacophobia and skepticism decreased adherence while geriatric age, high level of education and high internal control increased adherence.

Variables associated with adherence to antidepressant medications

Significant association with adherence to antidepressant medications common to 2 groups

Table 4 shows that, after controlling for other variables, high psychological reactance was a predictor in both groups with an OR=0.597 in depression and an OR=0.561 in other patients, but the ORs were not significantly different.

Significant association with adherence to antidepressant medications, but in opposite direction

After controlling for other variables, the country of Spain variable decreased adherence in depression, OR=0.597, while it increased adherence in other psychiatric patients (OR=1.646). We selected this subgroup of antidepressant prescriptions in Spain for depression. They tend to be characterized by high percentages of females (62%). In the logistic regression model in this subgroup three variables decreased adherence: high psychological reactance,

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

Variable	Depression OR (95% CI)	Other Mental Disorders OR (95% CI)	Comparison ^a
Dichotomous Model^b			
Pharmacophobia	0.500 (.348-.721) P<.001	0.599 (.461-.777) P<.001	P=0.96 ^c Overlapping CI
Pharmacophilia	1.51 (1.04-2.19) P=.030	1.65 (1.22-2.23) P=.001	P=0.55 ^c Overlapping CI
Treatment >1 year	0.731 (.52-1.24) P=.069	0.608 (.460-.802) P<.001	P=0.27 ^c Overlapping CI
High internal health locus of control	NS	0.607 (0.483-0.762) P<.001	NS in depression
Spain	0.744 (0.546-0.1015) P=.062	NS	NS in other mental disorders
Geriatric age	2.28 (1.30-3.98) P=.004	3.02 (1.65-5.55) P<.001	P=0.61 ^c Overlapping CI
High doctor health locus of control	NS	1.68 (1.31-2.16) P<.001	NS in depression
High psychological reactance	0.685 (0.506-0.928) P=.015	NS	NS in other mental disorders
Skeptical about a specific medication	0.443 (.320-.614) P<.001	0.569 (.440-.735) P<.001	P=0.66 ^c Overlapping CI

CI = confidence interval; NS = not significant; OR = odds ratio; SPSS = Statistical Package for the Social Sciences.

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

^b Both models had good fitness as measured by the Hosmer and Lemeshow test. For the depression model $\chi^2=11.538$, $df=8$, $p=.173$ and for the other mental disorder model $\chi^2=7.041$, $df=8$, $p=.532$. The default in SPSS, entry 0.05 and removal 0.10, was modified to entry 0.05 and removal 0.05.

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

antidepressant polypharmacy and skepticism about the particular antidepressant drug.

Significant association with adherence to antidepressant medications specific to the group with depression

Table 4 describes three ORs as not significant in the group with depression, but they were significant in the model for psychiatric controls. More importantly, two ORs were included in the group with depression and not in the controls: pharmacophobia (OR=0.312) and skepticism about the particular antidepressant drug (OR=0.450).

Antidepressant adherence diminished to 52.9% (119/225) in the group of patients with depression and pharmacophobia who were prescribed antidepressants. This is the lowest adherence we found in any depression subgroup in these analyses. The logistic regression model indicated that high psychological reactance, taking the antidepressant for more than 1 year, and skepticism significantly decreased adherence, while being from Spain increased adherence.

Antidepressant adherence diminished to 58.2% (145/249) in the group taking antidepressant prescriptions and associated with skepticism. The logistic regression model indicated high psychological

Table 3. Antidepressant medications: Dependent and independent variables in depression and other mental disorders

Variable (range)	Depression 470 patients with 510 antidepressants	Other Mental Disorders ^a 348 patients with 370 antidepressants
Dependent Variables		
Adherence ^b Yes	75.1% (383/510)	65.9% (244/370)
No	24.9% (127/510)	34.1% (126/370)
Dichotomous Independent Variables		
Female gender	68.7% (323/470)	56.3% (196/348)
Geriatric age	11.7% (55/470)	4.6% (16/348)
University education	33.0% (155/470)	38.8% (135/348)
Spain	42.8% (201/470)	39.4% (137/348)
Treatment >1 year	64.0% (301/470)	65.8% (229/348)
Extreme polypharmacy	6.6% (31/470)	9.2% (32/348)
Antidepressant polypharmacy	8.3% (39/470)	6.3% (22/348)
Medication > 1 year	51.2% (261/510)	48.1% (178/370)
High psychological reactance	50.4% (237/470)	49.4% (172/348)
High internal health locus of control	51.3% (241/470)	45.1% (157/348)
High doctor health locus of control	44.9% (211/470)	35.1% (122/348)
Pharmacophobia	22.1% (104/470)	29.6% (103/348)
Pharmacophilia	40.6% (191/470)	31.0% (108/348)
Skeptical about a specific medication	29.6% (151/510)	26.5% (98/370)
Continuous Independent Variables		
Age (years) (≥18)	46.6±13.7 (N=470)	41.5±13.6 (N=348)
Number of medications (1-6)	1.8±0.9 (N=470)	2.1±1.1 (N=348)
Number of antidepressants (1-3)	1.1±0.3 (N=470)	1.1±0.2 (N=348)
Duration of medication (months)	26.7±34.5 (N=510)	32.6±49.0 (N=370)
Psychological reactance (3-18)	13.3±4.2 (N=470)	12.9±4.1 (N=348)
Internal health locus of control (3-18)	13.7±3.6 (N=470)	13.6±3.4 (N=348)
Doctor health locus of control (3-18)	15.7±2.6 (N=470)	15.2±2.7 (N=348)
Positive aspects of medication (5-30)	22.9±4.4 (N=470)	22.4±4.8 (N=348)
Negative aspects of medication (3-18)	8.5±3.4 (N=470)	8.9±3.7 (N=348)
Necessity (1-5)	3.5±0.8 (N=510)	3.41±0.9 (N=370)
Concern (1-5)	3.0±0.9 (N=510)	3.0±0.9 (N=370)

^a Diagnoses were schizophrenia 8.9% (31/348), bipolar disorders 10.3% (36/348), anxiety disorders 52.3% (182/348), personality disorders 12.9% (45/348), substance abuse 2.9% (10/348), and other psychiatric disorders 12.6% (44/348).

^b The mean ±SD score using the Sidorkiewicz Adherence Tool was 2.26±1.7 in depression vs. 2.65±1.8 in the other mental disorders.

reactance was significant and pharmacophobia decreased adherence while pharmacophilia increased adherence.

DISCUSSION

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

The study of the impact of these attitudinal predictors of poor adherence to prescribed treatment

is pertinent since these variables have the potential to be modified, unlike most sociodemographic and clinical variables. Overall, our results confirmed the evidence that beliefs and attitudes are relevant factors in predicting treatment adherence in depressive disorders.

Medication adherence in patients with depression is not worse than in other psychiatric patients

In this sample, the data suggests that medication adherence may be slightly better in patients with depression as the main diagnosis than in other psychiatric patients. Adherence in patients with depression was significantly better (OR=1.22, CI 1.02-1.45) for all medications and for antidepressant medications (OR=1.56, CI 1.16-2.09). These ORs are

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

Variable	Depression OR (95% CI)	Other Mental Disorders OR (95% CI)	Comparison
Dichotomous Model^a			
Spain	0.597 (.387-.921) P=.020	1.646 (1.011-2.679) P=.045	Different direction Not overlapping CI
University education	NS	.606 (.374-.981) P=.042	NS in depression
High doctor health locus of control	NS	1.795 (1.043-3.091) P=.035	NS in depression
High psychological reactance	0.597 (.385-.927) P=.021	0.561 (.352-.895) P=.015	P=0.14 ^b Overlapping CI
Pharmacophilia	NS	2.847 (1.554-5.218) P=.001	NS in depression
Pharmacophobia	.312 (.194-.504) P<.001	NS	NS in other mental disorders
Treatment >1 year	NS	.518 (.323-.831) P=.006	NS in depression
Skeptical about a specific medication	.450 (.284-.713) P=.001	NS	NS in other mental disorders

CI = confidence interval; NS = not significant; OR = odds ratio; SPSS = Statistical Package for the Social Sciences.

^a Both models had good fitness as measured by the Hosmer and Lemeshow test. For the depression model $\chi^2=8.153$, $df=8$, $p=.227$ and for the other MD model $\chi^2=2.513$, $df=8$, $p=.961$. All procedures were the same for all medications except that as antidepressants 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 depression, along with other variables and an interaction term with depression and the variable represented in each row, are the predictors.

relatively small and may not be significant in future studies with similar design unless they have similar large sample sizes. Thus, it may be safer to predict that it is not likely that future studies will find a lower level of adherence in patients with depression as the main diagnosis than in other psychiatric patients.

Psychological reactance may relate more specifically to adherence in patients with depression

The analyses of adherence to all medications (Table 2) indicate that psychological reactance significantly decreased adherence in patients with depression (OR=0.685) while it did not reach significance in psychiatric controls. In the 2 logistic regression models in subsamples of patients with depression, psychological reactance had significant ORs, too. The analyses of adherence to antidepressant medications (Table 4) indicate that psychological reactance significantly decreased adherence in

patients with depression (OR=0.595) and also in controls (OR=0.561). In the 3 logistic regression models of antidepressant medications in subsamples of patients with depression, psychological reactance had significant ORs, too.

These results appear to suggest that high psychological reactance decreased adherence in a consistent way in patients with depression independent of the medication, while in controls it appears to be decreased only toward the relevant antidepressant. This relevance of psychological reactance in adherence is not completely unexpected, since we include it in our scale, but it is somewhat surprising since our prior analyses ignoring medication class indicated that pharmacophobia and skepticism were the major predictors of poor adherence in these samples when psychiatric diagnoses were not considered (De las Cuevas et al., 2018a; 2019). Future studies need to replicate and further explore why psychological reactance may be more relevant for patients with depression than in other psychiatric

patients and perhaps more relevant for patients taking antidepressants independent of the major diagnosis.

Pharmacophobia and pharmacophilia may be common to adherence in all psychiatric patients

As indicated, our prior analyses in this sample (De las Cuevas et al., 2018a) predicted that pharmacophobia decreased adherence while pharmacophilia increased adherence. Table 2 indicates that the effects of pharmacophobia and pharmacophilia on adherence to all psychiatric medications are similar in patients in depression and other psychiatric patients. Adherence to antidepressant medications is limited by the smaller sample size, but Table 4 shows that pharmacophilia was only significant in other psychiatric patients while pharmacophobia was only significant in patients with depression.

Skepticism about a specific medication may decrease adherence in all psychiatric patients

Table 2 indicates that the effects of skepticism about a specific medication on adherence to all psychiatric medications are similar in patients with depression (OR=0.443) and other psychiatric patients (0.569). In the smaller sample of adherence to antidepressant medication, being skeptical may be common to adherence in all psychiatric patients about a specific medication, but was only significant in patients with depression (OR=0.450). In 4/5 of logistic regression models in subsamples of adherence to all medications or antidepressant medications, being skeptical about a specific medication had significant ORs, too.

In summary, being skeptical appears to decrease adherence similarly to pharmacophobia by decreasing adherence consistently in all the psychiatric patients in our study. It is important to emphasize that our models indicate that both pharmacophobia and being skeptical toward a specific drug have independent effects.

Internal HLOC and doctor HLOC may not be relevant in patients with depression

Table 2 indicates that internal HLOC and doctor HLOC had significant effects only in psychiatric controls and not in depression. In the smaller sample circumscribed to antidepressant medication, doctor HLOC was only significant in psychiatric controls. In summary, HLOC appears not to have any relevant effect on patients with depression. To further clarify

this issue, we started with univariate analyses that showed internal HLOC had no significant effects on adherence to all medications. On the other hand, doctor HLOC had a small effect in increasing adherence OR=1.544 (CI 1.158-2.057, p=0.003). This effect became non-significant as soon as any of the 3 medication attitude variables (pharmacophobia, pharmacophilia or skepticism) were added to the univariate model. In summary, patients may listen to their doctors about medication adherence but once they consider their attitude toward medication, the doctor's effect is no longer relevant. Regarding replication in future studies, one can predict that doctor HLOC may have a significant effect on medication adherence in any study not controlling for the patient's attitude toward medications.

It will be interesting to see if future studies with large samples and a similar design verify that doctors may have little or no relevant influence on the decision to adhere to psychiatric medications. We suspect that many psychiatrists may not be happy to see our results about the lack of positive effect of doctors on adherence in patients with depression. Our sample suggests that close to 1/3 of psychiatric medication prescriptions may be a complete waste of time and money. Moreover, we recommend that any psychiatrist considering labeling his/her patient as suffering from treatment-resistant depression should consider the possibility of poor adherence (Fava et al., 2020).

The lack of effect of high internal HLOC on adherence to all medications in depressive patients is surprising since it had an effect on other psychiatric patients after controlling for confounders (OR=0.607, CI 0.483-0.762) and high psychological reactance had significant effects on patients with depression (OR=0.685, CI 0.506-0.928). The unfamiliar reader may think that psychological reactance and high internal control may be similar concepts. In an experimental design comparing measures of psychological reactance and HLOC, Xu (2017) proposed that the connections between both concepts are "crude" and that psychological reactance's main situational effect is completely independent of HLOC or maybe somewhat moderated by different HLOC styles.

The role of Spain in patients with depression

In the analyses of adherence to all psychiatric medications, the sample from Spain had decreased adherence in patients with depression. This could indicate that the Spanish sample may include

more severely ill patients and 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, along with unequal access, so our samples may not include patients with underprivileged socioeconomic status and more disability.

Treatment duration

In the analyses of adherence to all psychiatric medications, being in treatment for more than 1 year decreased adherence in patients with depression (OR=0.731) and also in psychiatric controls (OR=0.608). This may be related to different stages in the treatment of depression and other psychiatric disorders (Cosci & Fava, 2013).

Personalizing adherence in depression versus other mental illnesses

The literature stresses the need for paying attention to self-report in order to develop personalized approaches (Maj et al., 2020). Our prior analyses (De las Cuevas et al., 2018a; 2019), and these current analyses, after stratifying for depression and antidepressant medication, indicated that in this sample, pharmacophobia and being skeptical toward a specific drug decreased adherence in all psychiatric patients. Nevertheless, it is important that other samples of patients with depression and psychiatric controls replicate the finding that high psychological reactance may be a specific factor in decreased adherence in depression. If this replication occurs, it may be important to develop personalized interventions that are focused on psychological reactance in order to gain medication adherence in patients with depression.

Limitations

The first limitation, the lower representativeness of the Argentinian and Venezuelan samples, has been described. More importantly, any study using self-report of adherence in clinical samples is "doomed" from the start. The most non-adherent patients are the ones who have not come for treatment in years. Similarly, any patient not willing to sign a consent form was not included in this sample of patients taking oral medications.

This study used self-report measures for 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; Whalley Buono et al., 2017). In a multicenter study with no external support, the use of objective measures such as blood levels was not possible (De las Cuevas & de Leon, 2020).

Insight was not measured. However, in the article describing the validation of our scale, the Patient's Health Belief Questionnaire on Psychiatric Treatment (De las Cuevas & de Leon, 2019b), we stressed the need to improve it by adding a short cross-sectional measure of insight. This addition will not be able to measure past or future changes in insight. Adherence is a dynamic concept and insight is a dynamic concept (De las Cuevas & de Leon, 2020); thus, cross-sectional designs may have problems capturing their temporal relationship.

Third, in Spain those patients with active substance use, a major reason for non-adherence, are sent to another community center for substance abuse treatment; when the abuse is in remission, this Spanish community mental health center becomes the only treatment provider. In Argentine and Venezuelan samples, active substance abusers are not likely to go for treatment to these treatment centers.

Finally, this study only explored medication adherence and did not ask about interest in psychological treatments. We agree that psychological treatments are very important in depression, but unfortunately, they are not easily available in these 3 recruitment centers, which use medication as the first and most important intervention.

CONCLUSIONS

In spite of its limitations, this is the first adherence study in patients with depression that simultaneously explored multiple attitudes (psychological reactance, doctor and internal HLOC, pharmacophobia, pharmacophilia and skepticism) after controlling for clinical variables and using psychiatric patients as controls. Our results appear to suggest that high psychological reactance decreased adherence in a consistent way in patients with depression independent of the medication, while in controls it appears to be decreased only toward the relevant antidepressant. Other variables consistently influencing depression and psychiatric controls included pharmacophobia, pharmacophilia and skepticism about a specific medication.

Future studies on adherence to all medications and to antidepressant medications need to further explore which of these dimensions are specific to depression and which are common to all psychiatric patients. If our results are replicated in other samples of patients with depression, it may be important to develop personalized interventions to gain medication adherence in patients with depression that are focused on psychological reactance.

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Gyenge adherencia orális pszichotrop szerekkel kezelt felnőtt depressziósoknál: a pszichológiai reaktancia specifikus hatása a depresszióra

Célkitűzések: A depresszió és általában a különböző pszichiátriai betegségek miatt kezelt páciensek adherenciáját hat olyan tényező befolyásolja, melyekről a páciensek által elmondottak alapján tájékozódhatunk: 1.) magas/alacsony doktor egészségkontrollhely (Doctor HLOC), 2.) magas/alacsony belső egészségkontrollhely (Internal HLOC) 3.) magas/alacsony pszichológiai reaktancia, 4.) farmakofília, 5.) farmakofóbia, és 6.) gyógyszerrel kapcsolatos szkepticizmus. A Spanyolországban, Argentínában és Venezuelában végzett vizsgálatba 521 ambuláns pszichiátriai kezelés alatt álló depressziós beteget vontak be, akik számára együttesen 920 pszichiátriai gyógyszert írtak fel. Emellett 851, más pszichiátriai betegség miatt ambuláns kezelés alatt álló páciens is bevontak, akik összesen 1534 gyógyszert szedtek. **Módszerek:** Logisztikus regressziós modellt alkalmaztak a depresszió miatt kezelt betegeknél és az egyéb pszichiátriai kórképek miatt kezelés alatt álló kontrollszemélyeknél. A modellel a dichotóm változókra, a klinikai változókra, és 6 önjellemző dimenzióra korrigált esélyhányadost (OR) adtunk meg. Valamennyi pszichiátriai gyógyszer esetében a függő változó az adherencia mértéke volt, melyet a Sidorkiewicz Adherencia Skálával határoztunk meg. **Eredmények:** A következő tényezők esetében tártunk fel mindkét csoportban szignifikáns esélyhányadost (OR): 1.) farmakofóbia (OR=0,500 a depresszió csoportban, OR=0,599 a többi pszichiátriai betegségben), 2.) farmakofília (OR=1,51 és OR=1,65), 3.) egy évig tartó gyógyszeres kezelés (OR=0,731 és OR=0,608), 4.) idős kor (OR=2,28 és OR=3,02), és 5.) a gyógyszerrel kapcsolatos szkepticizmus (OR=0,443, OR=0,569). Két esélyhányados (OR) kizárólag a depresszió miatt kezelt csoportban bizonyult szignifikánsnak, a kontroll esetében nem: spanyolországi lakhely (OR=0,744), és magas pszichológiai reaktancia (OR=0,685). A vizsgálatba 470 depresszió miatt kezelt beteget vontak be, akik együttesen 510 antidepresszívumot szedtek, emellett 348 más pszichiátriai betegség miatt kezelés alatt álló személy is részt vett a vizsgálatban, akik számára összesen 370 antidepresszívumot írtak fel. Egyetlen esélyhányados (OR) bizonyult szignifikánsnak mindkét csoportban az antidepresszívumokra vonatkozóan, a magas pszichológiai reaktancia (OR=0,597 és OR=0,561). **Következtetés:** Valamennyi olyan klinikai vizsgálatban számítani kell a torzításra, amelyben az adatok a bevont személyek beszámolójából származnak, azonban ennél is fontosabb probléma forrását jelenti az, hogy a vizsgálatokról távol maradó páciensek adatai elvesznek. További vizsgálatok szükségesek ahhoz, hogy az adherenciát befolyásoló tényezők, különösen a pszichológiai reaktancia tekintetében a hasonlóságok és különbségek megállapíthatók legyenek a depressziós és az egyéb pszichiátriai betegség miatt kezelt betegek körében.

Kulcsszavak: egészséghez való viszonyulás, depresszió, adherencia, egészség magatartás, pszichofarmakológia