Supplementary Material

A clinimetric approach for improving the measurement of pharmacophobia with replication in two other samples

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Supplementary Introduction

The concept of pharmacophobia

Etymology indicates that the word "pharmacophobia" comes from the Greek roots "φάρμακον (phármakon)", which means drug or medicine, and "φόβος (phóbos)", which means fear. Consequently, pharmacophobia is the fear of taking drugs or medicines [4]. Based on this definition, we can assume that it could be categorized as a specific type of phobia. However, in the strictest sense, the current meaning of the concept does not conform to the diagnostic criteria of a phobic anxiety disorder and seems, instead, to have a new meaning, the type that emerges when a psychiatric idea enters everyday language and deviates from its original medical sense. The diagnosis of phobia involves the presence of an intense fear that interferes with the patient's everyday life. Pharmacophobia is a troubling attitude, but there is no evidence that it is in a meaningful sense phobia. Pharmacophobia is probably rooted in a simple aversion, not fear, and does not affect the patient's daily functioning.

The first appearance in the scientific literature of the term "pharmacophobia" was in an article published in 1973 in the *British Medical Journal* [S1] relative to doctors' attitudes toward the use of amphotericin and the possibly hazardous effects of this drug on patients with kidney disease, resulting in death from progressive infection by an amphotericin-sensitive fungus. This article was the subject of a letter to the editor in the same journal in 1974 [S2]. It was necessary to wait until 1986 for the publication of an article in German in which the term pharmacophobia was used for the first time in reference to patients; it mentioned the possible fear of a pregnant epileptic patient toward her antiepileptic drugs and the role of this fear in medication compliance [S3]. In 2001, the first article in English was published in which pharmacophobia referred to patients; the term was used when idiopathic anaphylaxis led to the development of a phobia to preexisting medications and avoidance of them despite adverse health consequences [S4].

In 2005, the Drug Attitude Inventory (DAI), which had 30 items in the original version, was used for the first time [S5] to classify the studied patients (in this case patients suffering from schizophrenia and schizoaffective psychoses) as "pharmacophobic" or "pharmacophilic". Since then, with the exception of an editorial related to the limited existing evidence of pharmacophobia and pharmacophilia in terms of analgesic use [S6], the rest of the scientific literature has focused on the role played by pharmacophobia in the adherence of the psychiatric patient to his/her prescribed treatment [1, 4, 5, 8, S7-S8].

The DAI

The original DAI (DAI-30) [3] consisted of 30 true/false questions about the various aspects of patients' perceptions and experiences of treatment, but a short version consisting of 10 items (DAI-10) has also been validated [S9]. Nielsen et al. [S10] compared the DAI-30 and the DAI-10 and reported that the long and short versions of the inventory were homogenous (r = 0.82 and 0.72, respectively), highly correlated (0.92), and had good test-retest reliability (0.79). Concerning the construct validity of the 30-item version, factor analyses revealed seven factors that were responsible for 59% [S11] and 63% of the total variance [S12]. The short version of the inventory, the DAI-10, only has one study on its factorial structure, carried out using a modified version that replaced the original dichotomy response format with a 4-point Likert scale [S13], which suggested a 2-factor orthogonal structure reflecting desired effects of the medication and adverse drug reactions (ADRs), or what psychiatric textbooks call side effects.

Pharmacophobia and poor adherence

Poor adherence to prescribed treatment is to be expected in 30-60% of psychiatric patients, irrespective of their disorder or the psychiatric drug used [S14-S18]. Although adherence to treatment is a multidimensional problem [S19], the scientific literature is increasingly showing that patients' attitudes toward their medications play a relevant role in their adherence to their prescribed drug treatment [1, 5, S8, S20-S24]. Using the Health Belief Model [1], we have developed a model of poor adherence that includes 4 major psychological dimensions: (1) patients' attitudes toward prescribed drug treatment in

general, which can be manifested as pharmacophobia, defined as not liking to take any medication; (2) the balance between the necessity of taking medication versus the concerns derived from ADRs; (3) the balance between internal and external health control beliefs; and (4) psychological reactance.

Clinimetrics

In his book *Clinimetrics* [7], Feinstein developed a comprehensive model of how to improve the measurement of clinical phenomena that is particularly relevant for psychiatry [S25-S27], a medical discipline in which subjective judgments by the patient and the physician are particularly important. It is not easy to briefly summarize the rich network of concepts provided by Feinstein in his clinimetrics, but one of his major emphases is that it is very important for clinical measures to be consistently reproduced in different clinical environments (Feinstein called it "hardness") [S28]. In that sense, it is important to incorporate clinimetric principles when developing psychometric instruments [S29, S30]. According to Tomba and Bech [S27], clinimetric principles are important when considering the macro-analysis level of developing rating scales, while at the micro-analysis level psychometric validation may be important, too.

Clinimetric problems of pharmacophobia after considering skepticism

Our research team has used the DAI-10 extensively, and as with other researchers [6], we have always believed that despite its great usefulness there was room for improvement, even without modifying its original questions, but by improving and simplifying the scoring procedures.

In a transcultural study of pharmacophobia in psychiatric patients [8], using the balance between the necessity of taking a medication versus the concerns derived from its ADRs, we identified patients who were skeptical about a specific medication in that the patient thought the specific medication was both unnecessary and potentially unsafe. Pharmacophobia refers to an attitude toward medications in general while skepticism refers to a specific medication. Pharmacophobia was measured by the DAI-10 while skepticism about a specific medication was defined using the Beliefs about Medicines

Questionnaire - Specific Scale (BMQ-Specific) [S31, S32] when a patient had high concern about adverse reactions and low belief in the necessity of taking that medication [8].

This is why we have recently begun studying patient attitudes toward each psychiatric medication and toward all psychiatric medications [S33] by using the new tool developed by Sidorkiewicz [6], which allows assessing adherence for each psychiatric medication individually, as well as all psychiatric medications as a group that the patient is taking. In our multicenter study in three Spanish-speaking countries, we focused on the balance between pharmacophobia and skepticism as predictors of poor adherence to all psychiatric medications [8]. We found that, regarding pharmacophobia, patients recruited at a Venezuelan site behaved very similarly to those from our Spanish site; in fact, the prevalence of pharmacophobia was in the same order of magnitude, with a prevalence of 35% (203/588) at the Spanish site and 23% (45/195) at the Venezuelan site. More importantly, the highest rate of non-adherence to specific medications at the Spanish site was 56% (81/588) of those who were pharmacophobic and skeptical; the highest rate of non-adherence at the Venezuelan site was 56% (53/195) of those who were pharmacophobic. On the other hand, at the third site in Argentina, we found that pharmacophobia as we have traditionally defined it, using the traditional DAI-10 scoring system, had a very low prevalence, 9% (46/508). With such an extremely low prevalence of pharmacophobia at the Argentinian site, it was not surprising that skepticism was the most important predictor of poor adherence, with the highest level of non-adherence at 60% (128/508) who self-reported being skeptical about a specific medication.

Supplementary Methods and Materials

Study design and participants

This cross-sectional, cross-cultural pharmacopsychology study has been described previously [8]. It was completed at outpatient psychiatric services in the Canary Islands (Spain), Mendoza (Argentina) and Mérida (Venezuela) according to good clinical practice for biomedical studies with the corresponding ethics committees approving the study protocol; patient informed consent was received. The inclusion

criteria for the psychiatric outpatients were as follows: (1) 18 years or older, (2) able to read and understand Spanish, (3) diagnosed with a psychiatric disorder; (4) treated with at least 1 psychiatric drug, and (5) participating voluntarily. Inclusion was validated after the patient signed the written informed consent. Each participant filled out a brief socio-demographic survey and the rest of the questionnaires. The main clinical diagnosis was taken from the patient's clinical chart. No reward for participation was offered.

The DAI-10 scale

The standard DAI-10 phrasing in the Spanish validated version [S33] was used with a modified response format in which patients were asked to rate, on a six-point Likert response format, the degree to which they agreed or disagreed with each statement. The following scoring was used: 1 = strongly disagree, 2 = moderately disagree, 3 = slightly disagree, 4 = slightly agree, 5 = moderately agree, and 6 = strongly agree.

The Sidorkiewicz Adherence Tool

The Sidorkiewicz Adherence Tool is the only scale that allows one to independently measure adherence in each drug. In the adaptation of the Spanish version, we found that dichotomized scoring had reasonable predictive power [S34]. This instrument contains five questions with two or three possible answers, illustrated with practical examples and pictographs, to help patients recognize various medication-taking behaviors for each drug taken, allowing clinicians to identify how patients routinely manage polypsychopharmacy. The original levels of adherence supplied by the tool were dichotomized into "adherent" [which included previous high (1), good (2), and moderate (3) levels] versus "non-adherent" [which included previous poor (4), very poor (5), and discontinuation (6) levels].

Lack of concordance in adherence when taking multiple medications and generalized poor adherence

We refer to patients who were consistent in either high adherence or low adherence across multiple medications as concordant patients. Discordant patients report high adherence for some medications and low adherence for others.

Statistical methods

The data was analyzed using the Statistical Package for Social Sciences (SPSS) software version 21 for Macintosh [S35]; calculations for significance were two-tailed.

The clinimetric plan for developing a clinimetric definition of pharmacophobia

When developing scales, psychometricians [S36] focus on psychometric principles such as internal consistency, an index of whether a scale is measuring only one unique concept. When constructing a composite clinimetric index, Feinstein [6] proposed a sequence of conceptual steps that may be needed. Based on these concepts, we developed a "clinimetric plan" with steps for developing a modified scoring system of the DAI-10 that could be a better measure of pharmacophobia in various clinical environments. This plan started with the DAI-10 from a macroanalysis [S27]; we made decisions based on clinical judgment (first step) and subsequently used psychometric techniques to perform a microanalysis (second and third steps). That led to a second macroanalysis to purify the definition of pharmacophobia using clinimetric concepts (fourth and fifth steps) and to the final test regarding better predictive power of the new clinimetric definition of pharmacophobia (sixth step). A good proof of the success of this new definition of pharmacophobia would be consistent ability to reproduce it, particularly in a clinical environment where the traditional definition of pharmacophobia did not work well, namely, the Argentinian site [8].

First step: elimination of two confusing items from the DAI-10. Although the original DAI-10 dichotomized format requires respondents to endorse one of two opposites, our clinical experience with the scale led us to modify the response format, allowing more precisely characterized attitudes toward medication to be measured using a range of responses that reflect attitude intensity and polarity [S37]. A

cursory reading of the items included in the inventory shows that five of them are positively phrased and refer to desired effects of drug treatment, mainly symptom reduction (Items 1, 4, 7, 9 and 10), while three of them are negatively phrased and refer to ADRs (Items 2, 5 and 8). On the other hand, the two remaining items appear to refer to other dimensions, since Item 6 (I take medication only when I feel ill) is conceptually ambiguous and Item 3 (I take medications of my own free choice) refers to the perceived control over one's drug treatment. According to our previous experience with this instrument, we proceeded to remove from our analyses Items 3 and 6 of the inventory.

Second step: An exploratory factor analysis of the eight remaining items will rate two factors (liking and disliking medications) in the three sample groups. An exploratory factor analysis with orthogonal varimax rotation was planned for the eight selected items of the DAI-10 across the three sample groups with the idea of demonstrating a two-factor solution: "liking medications" (possibly including Items 1, 4 , 7, 9 and 10) as the positive factor and "disliking medications" (possibly including Items 2, 5 and 8) as the negative factor. The varimax rotation was selected because it simplifies the interpretation of the factors [S35]. The varimax rotation provides orthogonal factors which are not correlated. The items with the highest scores for each of the factors would be used to develop subscales by adding them (this ignores the weight of the items that comprise the factor). The relationship between these subscales would be explored with a linear correlation since, although the factors are not correlated, the subscales can be correlated.

Third step: the subscales derived from the factors should have better internal consistency (after correcting for the number of items) than the original scale in the three samples. Psychometricians focus on the internal consistency of the scale using the traditional Cronbach's α [S38], but frequently do not acknowledge that α is heavily influenced by the number of items on the scales; scales with many items tend to have high α. A neglected issue is that Cronbach was aware of this limitation of α, and provided a

method of correction with an index that Cronbach called r_{ij} [S38]. Thus, it was proposed that the new subscale should produce greater values of r_{ij} than the original scales in the three clinical samples.

Fourth step: identifying clinimetric pharmacophobic patients (high in disliking and low in liking medications). Following our experience with skepticism, [8], we considered using the positive and negative aspects of liking or disliking psychiatric medication as independent underlying dimensions of the instrument in order to obtain more precise distinctions between patients' attitudinal positions. According to the median score on the liking subscale, patients were classified as low or high on liking medications. Similarly, according to the median score on the disliking subscale, patients were classified as low or high on disliking medications. Then patients were grouped into four "attitudinal groups": (1) clinimetric pharmacophilic: those with a high score in liking medication and a low score in disliking medication, (2) indecisive: those with high scores in both liking medication and disliking medication, (3) unconcerned: those with low scores in both liking medication and disliking medication, and (4) clinimetric pharmacophobic: those with a low score in liking medication and a high score in disliking medication. These clinimetric pharmacophilic patients with a high score in liking medication and a low score in disliking medication may be different from the pharmacophobic patients identified by the unidimensional DAI-10.

Fifth step: clinimetric identification of patients with consistent non-adherence after eliminating patients with inconsistencies in adherence. At this level of the analysis, only patients showing concordant adherence in all their medications were included. Concordant patients are those who were consistent in high adherence or low adherence. Discordant patients report high adherence for some medications and low adherence for others; they were excluded from the sixth step.

Sixth step: the clinimetric pharmacophobia definition should have better ability in the three samples than the old pharmacophobia definition to predict genuine non-adherence according to significance and effect size. Although most psychiatric articles focus on finding significant results, there is general agreement

among statisticians that effect size may be much more relevant in the clinical world than significance [S39]. One can get significant results by increasing the sample size to thousands of patients but, on the other hand, a highly significant effect with limited effect size may be irrelevant in the clinical environment, where the findings need to survive the inherent "noise" and variability of the clinical environment. Feinstein [S28] emphasized "as essential requirements the fundamental attribute of 'hard' data is consistency. When attempts are made to repeat an observation, either by the same or by another observer, the results should agree."

We have previously used the Sidorkiewicz tool [6] to classify patients in dichotomous fashion, either with or without poor adherence in these 3 samples [8]. Thus, we can estimate significance and effect size based on the traditional definition of pharmacophobia by using the 10-item scale (present vs. absent) to predict poor adherence (present vs. absent) in the 3 samples and compare it with the newer measure of clinimetric pharmacophobia (present vs. absent). This means comparing them by using cross-tabulations for each site. There is general agreement in the literature that significance in cross-tabulation is calculated by a chi-square (χ^2) test. Therefore, the new version should provide greater significance in results for the 3 sites. On the other hand, the literature provides several measures of effect size for cross-tabulations [S40-S43]. There is general agreement that odds ratios (ORs) and the phi coefficient are good measures of effect size in cross-tabulations. In a 2 x 2 table, another measure of effect size, the Cramer V, provides the same values as the phi coefficient so it is not described. The χ^2 value is also a measure of effect size, but it is influenced by sample size [S40]. In this case, the two cross-tabulations have the same sample size and can be compared by using the χ^2 value; moreover, a formula has been developed to test whether the difference between the two χ^2 values is significant or not [S42]. In this case, we will test whether the χ^2 value of the new clinimetric pharmacophobia measure is significantly better in predicting poor adherence than the older version for the three sites.

According to Nunnally and Berstain [S36], predictive validity is "using an instrument to estimate some criterion behavior that is external to the measuring instrument itself". In that sense, with this sixth step we are trying to establish that clinimetric pharmacophobia has better predictive validity than the old definition of pharmacophobia.

Supplementary results

Descriptive analyses

From April 2017 to January 2018, 1320 consecutive psychiatric outpatients were recruited from mental health outpatient services at the Spanish, Argentinian and Venezuelan sites. Supplementary Table S1 shows their socio-demographic and clinical variables according to site, as well as from the combined sample, which had a mean age of 44.1 years; approximately 58% were women, 44% completed secondary school, and 32% had a university degree. The most important main diagnoses were schizophrenia, 18%; bipolar disorder, 11%; depressive disorders, 41%; anxiety disorders, 24%; and personality disorders, 6%. Patients took a mean of 1.8±0.8 psychoactive medications; the most important classes were antidepressants in 37% of patients, antianxiety benzodiazepines in 28%, antipsychotics in 22%, and mood stabilizers in 13%. The mean number of different psychoactive drugs prescribed per patient was 1.8. According to the Sidorkiewicz adherence tool, global self-reported adherence indicated that almost a third of the patients self-reported non-adherence to their prescribed psychotropic treatment.

Second step of the clinimetric plan: two-factor solution in exploratory factor analysis of 8 DAI items

Supplementary Table S2 illustrates that, as predicted, the Spanish sample provided a two-factor solution, which explained 49% of the total variance. As expected, Items 1, 4, 7, 9 and 10 comprise the larger factor, "liking" medications, referring to the positive aspects of medication, whereas Items 2, 4 and 8 comprise the second factor, disliking medications, referring to the negative aspects of medication. A small negative linear correlation was registered between the two subscales calculated by adding the items with the highest loading of each factor ($r= -0.188$, $p<0.001$). The Venezuelan sample provided the same

two factors with very similar weight for the items. The Argentinian sample provided two similar factors, but it was complicated by items being moved to the opposite factor with a negative weight.

Third step of the clinimetric plan: better internal consistency (after correcting for number of items) of the new subscales when compared to the original scale at each site

The two-factor solution from the Spanish sample, well-replicated in the Venezuelan sample, provided a subscale for liking medication which included Items 1, 4, 7, 9 and 10 with a weight of 1 per item, and a subscale for disliking medication, which included Items 2, 4, and 8 with weight of 1 per item. These subscales had reasonable internal consistency even in the Argentinian site, which provided a slightly different factor analysis. When the Cronbach's α of the original 10-item scale was corrected by the number of items, the r_{ij} was very low and ranged in 3 samples from 0.10 to 0.17 (Supplementary Table S3). The first subscale of liking medication had more reasonable values, ranging from 0.29 to 0.36; the second subscale ranged from 0.19 to 0.34.

Fourth step of the clinimetric plan: identifying consistent pharmacophobic patients

Using the median score for each sample (23 in the Spanish sample, 23 in the Argentinian and 25 in the Venezuelan) on the "liking medication" subscale and the median score (10 in the Spanish sample, 8 in the Argentinian and 9 in the Venezuelan) on the "disliking medication" subscale, patients were classified into four "attitudinal groups" (Supplement) with a prevalence of clinimetric pharmacophobia of 28% (165/588) at the Spanish, 29% (147/508) at the Argentinian, and 27% (60/224) at the Venezuelan sites. Supplementary Table S4 explains how the new clinimetric definition appears more precise, since some indecisive and unconcerned patient attitudes contaminated the old definition of pharmacophobia and some pharmacophilic patients appeared pharmacophobic in the more sophisticated clinimetric definition of pharmacophobia, which is consistent in producing low scores in liking medications and high scores in disliking medications.

Fifth step of the clinimetric plan: identifying patients with consistently poor adherence

The number of patients with concordant adherence was 482 (82% of 582) patients at the Spanish site, 372 (73% of 508) at the Argentinian site and 181 (82% of 224) at the Venezuelan site. In these patients with concordant adherence, the percentage with consistently poor adherence was 30% (147/482) at the Spanish site, 24% (88/372) at the Argentinian site and 35% (64/181) at the Venezuelan site. It makes clinical sense only to consider patients with consistently poor or high adherence for the sixth step.

The sixth step of the clinimetric plan is described in the main text

Supplementary Discussion

When compared with the old definition of pharmacophobia (from the DAI-10) in our Spanish sample, the 6-step clinimetric plan provided a clinimetric definition that had better internal consistency adjusted by number of items in the new subscales and better prediction of non-adherence. As a matter of fact, the prediction of poor adherence was significantly better ($p=0.025$) and the effect size measures were higher. More surprising was the Argentinian sample in which the old definition of pharmacophobia had performed poorly in prior analyses [8]; the new definition's subscales showed better internal consistency adjusted by number of items than the DAI-10, along with remarkably better predictive ability for non-adherence. When compared with the old definition, the prediction of non-adherence was significantly better ($p = <0.001$) and the effect size measures were higher with a phi coefficient of 0.471 and an OR = 8.43.

The clinimetric definition had no such consistent results in the Venezuelan sample. It had better internal consistency adjusted by number of items, but there was no significant difference in predicting non-adherence, although values tended to be higher using the old definition.

Limitations

We cannot rule out, as a first limitation, that the much smaller sample size of the Venezuelan sample may have contributed to the inconsistent results. Although the 6 steps of our clinimetric plan were developed a priori after discussion by the first and last authors, we cannot find any similar plan previously

published, to which we could compare our outcomes. The results appear reasonable, although not perfect, to us but we cannot deny that in the Venezuelan sample the clinimetric definition did not behave as predicted, since it showed no significantly better prediction than the old definition.

A second limitation is that these samples do not represent all types of psychiatric patients. Although the sample studied includes a considerable number of psychiatric outpatients with different psychiatric diagnoses, they all come from three mental health outpatient sites and include patients with relatively chronic and stable courses of illness. For these reasons, our findings may not be generalizable to other patient populations, such as acute psychiatric patients or hospitalized patients. Moreover, the study relied on self-report measures which carry a potential risk of misstatement or response bias.

A third limitation is that research on the concept of pharmacophobia is in its infancy. Many published psychiatric studies include small samples with no attempt at replication, while this study included >1000 patients from 3 different sites in 3 different countries, so the reader may be surprised by our comment that this new clinimetric definition needs to be tested in multiple other large samples and countries using the DAI-10 in versions other than Spanish.

A fourth limitation is that clinical pharmacopsychology is in its infancy and needs to include not only psychometric approaches but also clinimetric approaches that reflect the complexity of psychological dimensions in the clinical environment. Despite the clinical utility previously demonstrated by the DAI-10 [S10, S44], the evaluation of the potentially complex interplay of positive and negative aspects toward psychiatric medication has been limited until now because the DAI-10 defined patients' attitudes toward psychiatric medication as a unidimensional continuum. Our results highlight the relevance of integrating a two-dimensional view of liking and disliking psychiatric drug treatment with some patients being consistent by scoring low in liking medications and high in disliking, our clinimetric pharmacophobic patient; others showed consistency by scoring high in liking medications and low in disliking medications, our clinimetric pharmacophilic patient. Still others gave a mixed response, depending upon how the

questions were presented; we labeled them indecisive or unconcerned. As a matter of fact, the literature on attitudes demonstrates that positive and negative attitudes can co-occur in the same patient [S45, S46]. A further reminder of the complexity of attitudes toward psychiatric medications is that pharmacophobia is an attitude toward psychiatric medications in general. However, a patient can believe that he/she does not specifically need a specific medication and may be specifically concerned about some of its specific ADRs; this is not pharmacophobia. Rather, we have termed it skepticism about a specific medication [8].

Clinical relevance of our results in pharmacophobia if validated in further samples

If our results are validated by future studies which verify that pharmacophobia and pharmacophilia are not a unidimensional continuum, this fact may have important practical implications for adherence to prescribed treatment. Psychiatric patients' attitudes toward psychiatric drug treatment seem to represent a final common pathway toward medication adherence [S47]. The fact that more positive psychiatric patient attitudes toward drug treatment are associated with better medication adherence is of great interest since it may be possible to intervene to change attitudes [S48]. Those psychiatric patients who are unconcerned about their psychiatric treatment might benefit from education about the course of their psychiatric disorder, the evolution of symptoms, the time necessary to wait for certain psychoactive drugs to work, the relevance of maintenance treatment when necessary, and the existing relationship between poor therapeutic adherence and the risk of relapse and/or recurrence of the psychiatric disorder. In contrast, indecisive psychiatric patients may benefit from the identification and correction of any misunderstanding they have about their drug treatments, putting in their proper place the possible ADRs and addressing any doubt or concern of the patient about them. Finally, clinimetric pharmacophobic psychiatric patients may benefit from exploration of their level of awareness of their disease, their history of previous insufficient or excessive treatments, as well as their cultural beliefs about medication and any existing barrier in their care setting [S49].

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Supplementary Table S1. Socio-demographic and clinical characteristics of the samples studied

	Total N=1320	Spain N=588	Argentina N=508	Venezuela N=224	p
AGE mean	44.1±14.3	45.7±13.1	42.2±15.5	43.9±13.8	<0.001[a]
18-34 years	31% (409)	24% (141)	40% (203)	29% (65)	
35-50 years	34% (449)	39% (229)	28% (142)	35% (78)	
51-65 years	28% (370)	30% (178)	24% (122)	31% (70)	
>65 years	7% (92)	7% (40)	8% (41)	5% (11)	
SEX					<0.001[b]
male	42% (554)	47% (278)	34% (171)	47% (105)	
female	58% (766)	53% (310)	66% (337)	53% (119)	
EDUCATION LEVEL					<0.001[b]
can read and write	1% (18)	3% (16)	0% (0)	1% (2)	
primary school	23% (295)	27% (160)	19% (97)	17% (38)	
secondary school	44% (580)	44% (258)	48% (246)	34% (76)	
college/university	32% (426)	26% (154)	33% (165)	48% (108)	
MAIN DIAGNOSIS					<0.001[b]
schizophrenia	16% (210)	23% (134)	4% (21)	25% (55)	
bipolar disorder	11% (138)	7% (40)	10% (42)	21% (46)	
depressive disorder	39% (509)	38% (224)	53% (267)	8% (18)	
anxiety disorder	22% (289)	29% (169)	17% (84)	17% (36)	
personality disorder	5% (65)	3% (16)	8% (42)	4% (7)	
other diagnoses	8% (109)	1% (5)	8% (42)	27% (62)	
NUMBER OF DRUGS mean	1.8±0.8	1.9±1.1	1.7±0.8	1.6±0.8	
monotherapy	49% (645)	49% (288)	46% (234)	55% (123)	<0.001[b]
polytherapy	51% (675)	51% (300)	54% (274)	45% (101)	
DRUG CLASS					<0.001[b]
antipsychotics	22% (290)	19% (112)	18% (91)	46% (103)	
mood stabilizers	13% (172)	11% (65)	14% (71)	13% (29)	
antidepressants	37% (488)	35% (206)	49% (249)	12% (27)	
antianxiety	28% (370)	35% (206)	19% (97)	29% (65)	
DAI-10 mean	3.6±3.8	2.5±4.0	4.7±3.0	3.7±3.8	
pharmacophobic (-10 to 0)	23% (302)	35% (203)	9% (46)	24% (53)	<0.001[b]
pharmacophilic (>0 to 10)	77% (1018)	65% (385)	91% (462)	76% (171)	
ADHERENCE					0.293[b]
yes	68% (898)	68% (400)	70% (354)	64% (154)	
no	32% (422)	32% (188)	30% (154)	36% (70)	

DAI-10: Drug Attitude Inventory with 10 items.

[a]t-student

[b]Chi-square

Supplementary Table S2. Principal component analysis of the 8 selected items from the DAI-10[a]

	FACTOR 1 Positive aspects of medication			FACTOR 2 Negative aspects of medication		
	Spain	Venezuela	Argentina	Spain	Venezuela	Argentina
EIGENVALUES[b]	2.37	2.51	3.09	1.48	1.63	1.91
ITEMS						
1. For me, the good things about medication outweigh the bad	**0.645**	**0.729**	**0.541**	-0.126	0.010	0.460
2. I feel strange, ‘‘doped up’’, on medication	-0.012	0.060	-0.079	**0.815**	**0.814**	**-0.812**
4. Medications make me feel more relaxed	**0.642**	**0.619**	**0.645**	0.100	-0.054	0.237
5. Medication makes me feel tired and sluggish	0.048	-0.091	-0.107	**0.825**	**0.855**	**-0.831**
7. I feel more normal on medication	**0.722**	**0.780**	**0.658**	-0.069	-0.178	0.401
8. It is unnatural for my mind and body to be controlled by medications	-0.300	-0.135	**-0.658**	**0.462**	**0.538**	0.245
9. My thoughts are clearer on medication	**0.668**	**0.633**	**0.684**	-0.172	-0.114	0.174
10. Taking medication will prevent me from having a breakdown	**0.556**	**0.655**	**0.466**	-0.033	0.010	0.368

[a]In this exploratory factor analysis, the extraction method was principal component analysis and the rotation method was varimax with Kaiser normalization. The rotation converged in 3 iterations. The Kaiser Melkin-Olkin (KMO) measure of sampling adequacy was 0.705 in the Spanish analysis, 0.705 in the Venezuelan analysis and 0.804 in the Argentinian analysis. Bartlett's Test of Sphericity was χ^2=614.6, df=28 p<0.001 in the Spanish analysis, χ^2=316.3, df=28, p<0.001 in the Venezuelan sample and χ^2=897.1, df=28, p<0.001 in the Argentinian sample.
[b]Two criteria were used to select the number of factors, an eigenvalue > 1 and the scree test. Both criteria agreed that we should obtain two factors in each of the 3 analyses based on country.
The weight shown in **bold** indicates the highest weight of the item in Factor 1 or 2.

Supplementary Table S3. Comparisons of internal consistency

	Spain	Venezuela	Argentina
	Cronbach α[a]		
DAI-10 (10 items)	0.50	0.52	0.67
New clinimetric scales			
Liking medication (5 items)	0.67	0.72	0.74
Disliking medication (3 items)	0.52	0.61	0.44
	rij[b]		
DAI-10 (10 items)	0.10	0.10	0.17
New clinimetric scales			
Liking medication (5 items)	0.29	0.33	0.36
Disliking medication (3 items)	0.26	0.34	0.19

DAI-10: Drug Attitude Inventory with 10 items.

[a]Cronbach α is influenced by the number of items.

[b]$r_{ij} = \alpha/n + (1-n)\ \alpha$ (n= number of items). This coefficient is not influenced by the number of items, as it is corrected for the number of items.

Table S4. New clinimetric definitions versus old classification of pharmacophobia and pharmacophilia

	Spanish		Argentinian		Venezuelan	
	Old Pharmaco-		Old Pharmaco-		Old Pharmaco-	
	phobia	philia	phobia	philia	phobia	philia
Clinimetric definitions						
Pharmacophobic	77%(127/165)	23% (38/165)	25% (37/147)	75% (110/147)	65% (39/60)	35% (21/60)
Indecisive	20% (18/91)	80% (73/91)	10% (3/31)	90% (28/31)	9% (4/47)	91% (43/47)
Unconcerned	33% (57/171)	67% (114/171)	5% (6/126)	95% (120/126)	17% (10/60)	83% (50/60)
Pharmacophilic	<1% (1/161)	99% (160/161)	0% (0/204)	100% (204/204)	0% (0/57)	100% (57/57)