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Influence of an inconsistent appearance of antipsychotics on drug adherence in patients with schizophrenia

Unax Lertxundi, PhD[a,*], Rafael Hernandez, MD[a], Beatriz Corcóstegui, PhD[b], Olatz Ibarra, PhD[c], Gorka Mentxaka[d], Juan Medrano, MD[e]

Abstract

In this study, we aimed to determine whether an inconsistent appearance of antipsychotic drugs dispensed was associated with poorer adherence in patients with schizophrenia.

To conduct this study, we linked information from different administrative healthcare databases from the Basque Country. Patients with a medication possession ratio (<80%) were considered to be nonadherent.

More than a quarter of the study population (26.9%, 1294/4810) was nonadherent to antipsychotics. Different brands of the same antipsychotic were dispensed to 8.5% of the patients. Inconsistent appearance was not associated with nonadherence to antipsychotics. Lower adherence to antipsychotics was associated with several other factors: age ≥65 or <30 years, prescription of typical antipsychotics or of long-acting injectable compounds, and nonadherence to antihypertensive and lipid-lowering drugs.

Contrary to our expectations, we did not find a significant association between inconsistent appearance of prescribed antipsychotics and poorer adherence. The percentage of patients who were dispensed different brands of the same antipsychotics was also lower than expected.

Abbreviations: ICD-10 = International Classification of Diseases, 10th version, MPR = medication possession ratio.

Keywords: adherence, antipsychotic, inconsistent appearance, schizophrenia

1. Introduction

Nonadherence to antipsychotic drugs has been linked to longer duration of inpatient treatment and poorer symptomatic outcome in patients suffering from schizophrenia. In some studies, it has even been identified as the strongest predictor of relapse in patients with a first episode of psychosis.[1,2]

In schizophrenia, nonadherence has been related to a wide range of factors: disease-related factors (lack of insight, cognitive impairment), patient-related factors (sex, age, substance abuse, marital status), environmental factors (relationship with physician), and treatment-related factors, among others.[3] Notably, considering that the main factor involved in the stability and improvement of patients with schizophrenia is adherence to

antipsychotic treatment, it is easy to deduce that any treatment-related factor affecting adherence can have a profound impact on the course of the disease. Specifically, relevant variables are: the type of antipsychotic drug (typical vs. atypical, adverse effect profile, and long-acting injectable antipsychotics), the total number of drugs prescribed and, critically, the appearance of the different brands dispensed to a given patient could be yet another perceived reason to stop taking their medication. This population may indeed be more susceptible to such cosmetic or other visible changes.

Monitoring pharmacy data may be one of the few practical methods for assessing adherence in large patient populations. In this sense, the medication possession ratio (MPR) has already been related to higher admission risk in this patient population.[4]

[a] Pharmacy Service, Araba Psychiatric Hospital, Internal Medicine Service, Araba Mental Health Network, Vitoria-Gasteiz, Alava, [b] Pharmacy Service, Bermeo Psychiatric Hospital, Bizkaia Mental Health Network, Bermeo, [c] Pharmacy Service, Uribe Kosta Integrated Healthcare Organization, Goieta Kalea, Urduliz, Bizkaia, [d] Informatics service, Central Informatics Department, Osakidetza, Vitoria, Araba, [e] Psychiatry Service, Bizkaia Mental Health Network, Portugalete, Bizkaia, Spain.

* Correspondence: Unax Lertxundi, Pharmacy Service, Araba Psychiatric Hospital, Araba Mental Health Network, C/Alava 43, 01006 Vitoria-Gasteiz, Alava, Spain (e-mail: Unax.lertxundietxebarria@osakidetza.net).

In the Basque Country (Spain), different brands of the same drug (same active ingredient, same dose, and same pharmaceutical formulation) may be dispensed to a patient by pharmacists without considering the physical attributes of the product and/or its packaging (color, size, shape, etc.). In relation to this, several studies have shown that changes in the appearance of a pharmaceutical drug (lack of a consistent appearance) can lead to poorer adherence in the context of various diseases.[5] Indeed, several groups have called for the implementation of measures that guarantee that a consistent appearance is maintained when drugs are prescribed in the pharmacy.[6] In the context of schizophrenia, there has been little research into the influence of drugs having an inconsistent appearance on adherence rates. One of the few studies in this field, carried out in Catalonia, Spain, found that olanzapine capsules were associated with better adherence rates than olanzapine tablets. The authors hypothesized that this was because only one brand of capsules is available in Spain. Therefore, the pharmacist could only dispense 1 drug brand and therefore the appearance did not change throughout the entire study period. This study represents a call for increased awareness of the possibility of previously unrecognized adherence barriers.

In this study, we aimed to determine whether an inconsistent appearance of antipsychotic drugs dispensed was associated with poorer adherence.

2. Methods

2.1. Data source and study population

To conduct this study, we linked information from different administrative healthcare databases (e-Osabide and PRESBIDE) using encrypted unique identifiers. These databases contain information concerning the health and prescriptions of patients in the Basque Country, an autonomous region in northern Spain, with a population of 2,171,886 people,[7] in which mental health care is provided by Osakidetza, the region's public health service. A unique patient identifier (called the CIC number) is used across the entire region allowing linkage between data from different databases.

To identify our cohort of patients with schizophrenia, we initially obtained data on all patients with an International Classification of Diseases, 10th version (ICD-10) diagnostic code of schizophrenia (F20*) who were treated in any community mental health clinic in the Basque Country between June 2, 2016 and June 2, 2017. Since 2011, all public community mental health clinics use share a single IT platform (e-Osabide), which contains information about diagnostics. Then, we applied 3 exclusion criteria. First, we excluded patients admitted to any hospital (psychiatric or not) for any reason during the study period, in order to avoid the potential effects of acute events and lower insight on adherence. Moreover, while in hospital, patients are not prescribed drugs through PRESBIDE. PRESBIDE, the prescription software tool in the Basque Country, that includes all outpatient prescription medications funded by the region's drug benefit plan, gathers the list of pharmacological treatments of history every patient. In addition, it provides information about drug dispensations by pharmacies. In Spain, antipsychotic drugs are almost totally funded by the government, patients paying a maximum of around €5 per prescription. Second, all patients who did not receive an antipsychotic prescription during the study period were also excluded, as our main aim was to measure adherence to antipsychotic drugs. Antipsychotics where defined as drugs with anatomical therapeutic chemical code N05A* excluding lithium.[8]

Lastly, we excluded patients discharged from the community mental health clinic during the study period due to incomplete data to appropriately estimate MPR.

2.2. Clinical and demographic data

Data were recorded on: age, sex, comorbid substance use disorders (defined as any ICD-10 disorder from F10 through F19), and the total number of drugs. With regard to antipsychotic treatment, the following data were obtained: individual antipsychotic, type of drug (typical vs. atypical) and route of administration (long-acting injectable vs. oral). For this classification, the following drugs were considered "typical" antipsychotics: haloperidol, pimozide, perphenazine (for which there were supply problems during the study period), chlorpromazine, levomepromazine, zuchlopentixole, and clothiapine. On the other hand, olanzapine, clozapine, risperidone, sertindole, paliperidone, amisulpride, asenapine, quetiapine, ziprasidone, and aripiprazole were considered "atypical" antipsychotics.

Information was also recorded concerning prescriptions of the most relevant drugs for "somatic" health problems, that is, antidiabetic, antihypertensive and lipid-lowering agents.

2.3. Measure of adherence: medication possession ratio

The MPR was used as an indirect measure of adherence both to antipsychotics and somatic drugs (listed above). MPR expresses the percentage of time a patient has access to their medication, considering the number of days of drug supply received by a given patient and the refill interval. In our case, we chose a maximum study period of 8 months, ending on June 2, 2017. The calculation of MPR is set out in more detail as supplementary data in Fig. S1, http://links.lww.com/MD/C592. In order to measure adherence, we only included in our analysis active treatments for which patients had long-term prescriptions, that is, those which could be dispensed to the outpatient in the pharmacy at any moment during the study period.

Patients were considered to be nonadherent when their MPR for any drug was <80%. Taking medication as prescribed 75% to 80% of the time has been generally considered an acceptable level of adherence.[4,9]

2.4. Inconsistent appearance of dispensed antipsychotics

We measured the number of different brands of each antipsychotic dispensed to patients during the study period. We also calculated the percentage of patients affected by brand changes overall and for each individual antipsychotic.

2.5. Ethical approval

The Clinical Research Ethics Committee of the Basque Country approved this study. It was not considered necessary to obtain informed consent since patient anonymity was preserved during collection and analysis of clinical and demographic data, and the study did not alter routine clinical practice in any way.

2.6. Statistical analysis

Descriptive statistics were calculated to analyze characteristics of the study population and to estimate prevalence rates. For categorical variables, a chi-squared test was used to determine whether the nonadherence rate differed significantly between groups.

Subsequently, a stepwise logistic regression model was applied to investigate whether inconsistent appearance was independently associated with nonadherence to antipsychotics. To adjust for potential confounders, the following variables were included in the model: age, sex, comorbid substance use disorders, total number of dispensed drugs, type of antipsychotic (typical vs. atypical), and route of administration (long-acting injectable vs. oral). Nonadherence to antidiabetic, antihypertensive, and lipid-lowering agents was also considered as a potential confounder. Results were considered to be statistically significant if $P < .05$.

Statistical analyses were performed using SPSS software (SPSS Statistics for Windows, Version 23.0. IBM Corp., Armonk, NY).

3. Results

After applying all inclusion and exclusion criteria, we obtained a sample of 4810 patients with a diagnosis of schizophrenia who were treated during the study period (Fig. 1). Their mean age was 50 years and 64.2% of patients were male.

Table 1 summarizes some other clinical and demographic data of the study population. Only 7% of the population had comorbid substance use disorders. With regard to somatic drugs, 11% of the patients were on antidiabetics, 15% on antihypertensives, and 17.3% were on lipid-lowering drugs.

More than 40% of the patients received more than 1 antipsychotic during the study period. Olanzapine, which was prescribed to 1374 patients, was the most frequently dispensed antipsychotic, followed by paliperidone (1083), aripiprazole (820), clozapine (807), and risperidone (724) (Table 2).

3.1. Adherence

More than a quarter of the study population (26.9%, 1294/4810) was nonadherent (MPR < 80%) to antipsychotics during the study period. The rates of nonadherence to somatic drugs were lower (19.2% for antidiabetics, 17.7% for antihypertensives, and 21.5% for lipid-lowering drugs).

Clozapine and olanzapine were the antipsychotics associated with higher adherence rates, while fluphenazine, clothiapine,
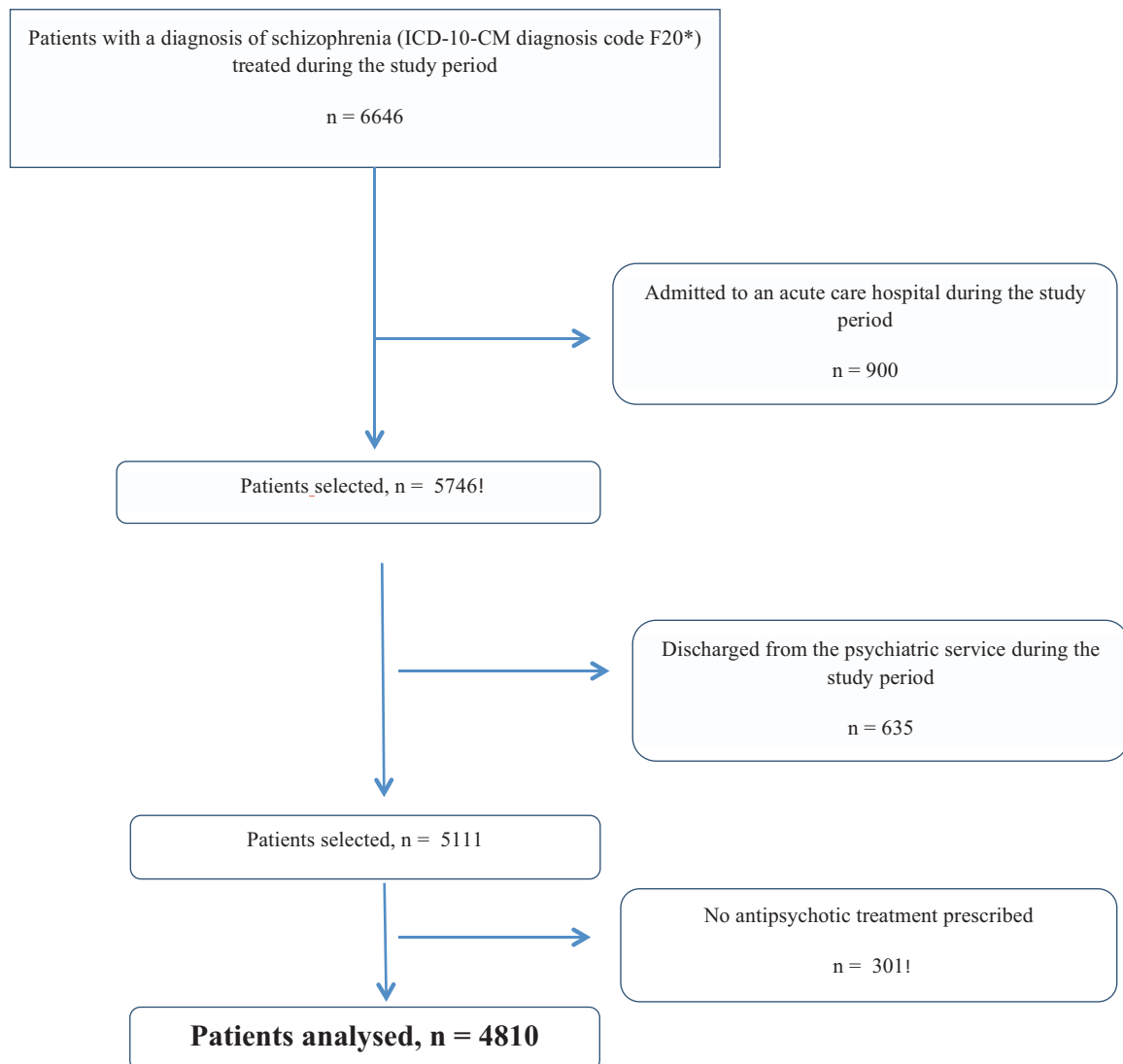

Figure 1. A significant wall thickening in gastric antrum, localized dent wall and partial gastric mucosa missing were noted; there was an increased density of perigastric fatty tissue, a measure of 52 mm*40 mm cloudy high density shadow noted in the middle, small lymph node seen around that area.

Table 1

Clinical and demographic data of the study population (n = 4810).

Age, mean ± SD (range), n (%)	50.01 ± 12.4 (15–99)
	<19 years: 9 (0.2)
	19–30 years: 233 (4.8)
	31–50 years: 2331 (48.5)
	51–65 years: 1712 (35.6)
	>65 years: 525 (10.9)
Sex male, n (%)	3089 (64.2)
Patients with substance abuse disorders, n (%)	336 (7.0)
Number of different dispensed drugs, mean ± SD; range	4.3 ± 2.8 (1–20)
Patients dispensed a long acting intramuscular antipsychotic, n (%)	1197 (24.9)
Patients dispensed >1 different antipsychotic during the study period, n (%)	1936 (40.2)
Nonadherent, n (%)	693 (35.7)
Patients prescribed antidiabetic drugs (A10B), n (%)	540 (11.2)
Nonadherent, n (%)	104 (19.2)
Patients prescribed antihypertensive drugs, n (%)	720 (15.0)
Nonadherent, n (%)	128 (17.7)
Patients prescribed lipid-lowering drugs (C10), n (%)	832 (17.3)
Nonadherent, n (%)	179 (21.5)
Patients nonadherent to antipsychotic drugs, n (%)	1294 (26.9)
Patients who experienced a lack of consistent appearance in antipsychotics dispensed, n (%)	409 (8.5)
Mean number of different drug brands dispensed, mean ± SD (range)	1.73 ± 0.06 (1–10)

SD = standard deviation.

levomepromazine, haloperidol, and quetiapine were associated with lower adherence rates. No other antipsychotics were significantly correlated with adherence in the univariate analysis.

3.2. Inconsistent appearance of dispensed antipsychotics

Different brands of the same antipsychotic were dispensed to 8.5% of the patients (409/4810), and the mean number of brands dispensed per patient was 1.73. Brand changes were most frequent for quetiapine, followed by ziprasidone and olanzapine See supplementary data, Fig. S2, http://links.lww.com/MD/C592.

3.3. Association between inconsistent appearance and nonadherence to antipsychotics

Inconsistent appearance was not associated with nonadherence to antipsychotics. On the other hand, as shown in Table 3, lower

adherence to antipsychotics was associated with several other factors: age ≥65 or <30 years, prescription of typical antipsychotics or of long-acting injectable compounds, and nonadherence to antihypertensive and lipid-lowering drugs. Notably, substance use disorders were not associated with poorer adherence. Lastly, adherence did not differ between the sexes.

4. Discussion

As far as we are aware, our study is the first to systematically measure lack of adherence to prescribed antipsychotics in relation to changes in the physical attributes of the drugs in a large population of patients with schizophrenia. Contrary to our expectations, we did not find a significant association between inconsistent appearance of prescribed antipsychotics and poorer adherence. The percentage of patients who were dispensed different brands of the same antipsychotics was also lower than expected, with only 8.5% of the patients experiencing a change of brand. Interestingly, different brands were dispensed to almost a quarter of patients on quetiapine.

Although male patients have shown better medication adherence in some research,[1] no such association between sex and adherence was found in our cohort. On the other hand, in line with other studies,[10,11] we found poorer adherence in both the youngest (<30 years) and the oldest (≥65 years) patients. Although elderly patients would be expected a priori to be more vulnerable to any impact of changes in drug appearance on adherence (due to cognitive and/or visual impairment, for example), no definitive conclusions could be drawn due to the small size of the corresponding subgroup (only 15 elderly patients having been dispensed multibrand antipsychotics).

The percentage of patients who were prescribed more than 1 antipsychotic during the study period was relatively high, around 40%, a figure comparable to that we found previously in hospitalized patients.[12] Antipsychotic polypharmacy could increase the likelihood of adverse effects, thus causing a poorer adherence. Further, it could also be argued that more severe patients, who are found to have a lower adherence to treatment, are more often treated with more than 1 drug. The same can be said about the association found between prescription of long-acting injectable antipsychotic and lower adherence rates.

The rates of nonadherence to lipid-lowering drugs, antihypertensives, and antidiabetics were lower than that found for antipsychotics. This finding could have several explanations. It might be that these types of drugs are better tolerated by patients than antipsychotics. On the other hand, it could also be that

Table 2

Association of antipsychotics with nonadherence.

Antipsychotics	No. of patients (% nonadherent)	Odds ratio
Associated with better adherence		
Clozapine	807 (20.7%)	0.66 (0.55–0.80); χ^2 = 19, $P < .001$
Olanzapine	1374 (21.9%)	0.69 (0.59–0.80); χ^2 = 24.4, $P < .001$
Associated with poorer adherence		
Fluphenazine*	91 (62.6%)	4.71 (3.07–7.25); χ^2 = 60.2, $P < .001$
Clothiapine	182 (40.6%)	1.91 (1.41–2.59); χ^2 = 18.2, $P < .001$
Levomepromazine	113 (38%)	1.69 (1.15–2.48); χ^2 = 7.32, $P < .001$
Haloperidol	221 (36.6%)	1.61 (1.21–2.13); χ^2 = 11.19, $P = .007$
Quetiapine	495 (33.5%)	1.42 (1.16–1.73); χ^2 = 12.34, $P < .001$

Not statistically significant: Paliperidone (1083; 26.7%), aripiprazole (820; 28%), pimozide (8; 0%), risperidone (724; 26.4%), amisulpride (151; 24.5%), zuchlopentixole (129; 29.4%), ziprasidone (85; 20%), perphenazine (46; 35.5%), asenapine (29; 24.1%), chlorpromazine (8; 25%), sertindole (6; 16.6%).
* Data not reliable due to supply problems during the study period.

Table 3

Association of antipsychotic nonadherence with different variables: logistic regression results.

	Crude odds ratio (95% confidence interval)	Adjusted odds ratio[†,‡] (95% confidence interval)
Lack of a consistent appearance	1.21 (0.97–1.52) NS	1.24 (0.98–1.56) NS
Age >65 or <30 y	1.47 (1.25–1.52)	1.48 (1.25–1.77)[*]
Nonadherence to lipid-lowering drugs	2.2 (1.62–2.99)	2.08 (1.51–2.85)[*]
Nonadherence to antihypertensives	2.5 (1.74–3.58)	2.28 (1.56–3.31)[*]
Intramuscular depot antipsychotics	1.48 (1.28–1.71)	1.46 (1.26–1.70)[*]
Typical antipsychotics	1.49 (1.24–1.80)	1.47 (1.27–1.70)[*]

NS = not significant.

[†] Adjusted for sex, substance abuse disorders, total number of drugs dispensed

[‡] Patients on fluphenazine were excluded from the logistic regression

[*] $P < .0001$.

patients on such drugs are precisely those that are most closely monitored through clinical check-ups and hence represent a patient population with better overall adherence.[13]

The lower adherence to typical antipsychotics, which in our market are mainly single-brand products and consequently consistent in appearance, is a finding that underlines that nonadherence does not seem to be attributable to changes in the physical attributes of a drug.

4.1. Limitations and strengths

A number of key factors should be kept in mind when interpreting our results: First, we did not use a direct measure of adherence, but rather an indirect method, namely, estimation of the MPR. Thus, true adherence to antipsychotics could not be verified in this study. Second, given the study design, we were not able to measure certain factors that have been related to adherence in patients with schizophrenia, including marital and socioeconomic status, adverse effects, and previous treatments. Third, there were serious problems with the supply of long-acting injectable fluphenazine during the study period, it having to be imported from abroad. Drug importation requires specific prescription and dispensation procedures that are not currently included in PRESBIDE. It is therefore likely that we have underestimated adherence to this particular drug, and hence, we excluded it from the logistic regression analysis. Fourth, the impact of antipsychotic polypharmacy and drug switches on nonadherence could not be measured, since we could only detect patients who were dispensed more than 1 antipsychotic during the study period, without considering if all were simultaneously used by the patient.

On the other hand, the design of our study allowed for a complete appraisal of adherence to antipsychotics in our entire region. Further, the exclusion of patients admitted to hospital restricted the study population to clinically stable patients, avoiding the effects of acute events and lower insight on adherence. Finally, the comparison with adherence to drugs for somatic problems allowed us to rule out that nonadherence to antipsychotics was a result of a general lack of self-care.

5. Conclusion

In this study, we did not find a significant association between inconsistent appearance of prescribed antipsychotics and poorer adherence in a large population of patients with schizophrenia. Different brands of the same antipsychotic were dispensed to 8.5% of the patients, a proportion lower than expected. Lower adherence to antipsychotics was associated with several other factors: age ≥65 or <30 years, prescription of typical antipsychotics or of long-acting injectable compounds, and nonadherence to antihypertensive and lipid-lowering drugs.

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