



ADHERENCE TO TREATMENT AND ANTIPSYCHOTIC LEVELS IN SALIVA IN PATIENTS WITH A FIRST PSYCHOTIC EPISODE

MASTER'S FINAL PROJECT

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ABSTRACT

Introduction. Adherence plays a key role in promptly achieving and maintaining remission in Schizophrenia. Thus, monitoring adherence is of utmost importance to optimize treatments, and evidence suggests that this can be done by measuring salivary levels of antipsychotics, which could have several advantages over the traditional plasma level monitoring.

Aims. We aim to study the relationship between adherence, salivary levels of antipsychotics and clinical outcomes after a first episode psychosis.

Material and methods. This multicentre study includes 223 patients diagnosed of first episode of psychosis (FEP) in remission in the moment of recruitment. We compared salivary levels of antipsychotics, EEAG and PANSS scores in the adherent versus the non-adherent group.

Results. Adherence increased from baseline (49%) to three (52%) and six months (60%). All antipsychotics could be measured in saliva, and there was a positive correlation between saliva and blood levels of Aripiprazole. Adherent patients had a significative decrease in score in PANSS Negative scale ($F = 4.779$, $p = 0.010$) and a tendency to this in PANSS Global scale. PANSS Positive scale and EEAG did not show different outcomes between the two adherence groups.

Conclusions. There is a positive correlation between plasma and salivary levels for Aripiprazole, and such levels are related with dose in adherent patients. Levels of non- adherence are high, almost 50% in first psychotic episode patients., and are associated with higher negative symptoms in follow-up. Further studies should be made to better establish the relationship between salivary and blood levels and between salivary levels and dose

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INTRODUCTION

Psychiatric disorders are a public health challenge, being attributed 14% of the global burden of disease (Semahegn et al., 2018). They affect approximately 450 million people and are the main cause of the years lived with long-term disabilities and dependency (Nicolino, Vedana, Miaso, Cardoso, & Galera, 2011; Semahegn et al., 2018). Depressive disorders (350 million), bipolar disorders (60 million) and schizophrenia (21 million) are the most common psychiatric conditions (World Health Organization, 2016). Schizophrenia is one of the most disabling, affecting 1% of the population, compromising various areas of patient's lives and representing an important burden in social and financial terms, not only for patients but also for caregivers and society (Nicolino et al., 2011).

Prognostic factors in schizophrenia include adequate treatment and adherence, duration of untreated psychosis (DUP), number of relapses and comorbid substance use. Early intervention in these factors is key to the course of illness, making first episode psychosis a question of utmost interest in clinic and research. Symptomatic remission, which criteria were defined by the Remission in Schizophrenia Working Group (Andreasen et al., 2005) is of prognostic value for social functioning and quality of life in schizophrenia. Thus, promptly achieving and maintaining remission is a key factor in reducing the long-term burden of the illness.

Patients with first episode psychosis usually respond well to treatment, but relapse is frequent during the first years, and may be associated with clinical deterioration (Robinson et al., 1999). Literature agrees that in the first year, relapse rates are low, although they rise substantially after two and five-year follow-up. Discontinuation of medication is the most important variable associated with relapse (Koutsouleris et al., 2016).

Achieving therapeutic levels is essential in order to balance effective management of the symptoms with minimal adverse effects, and is determined mainly different factors: dosage, metabolic differences among individuals and mostly, treatment compliance.

According to the WHO, adherence means “a case in which a person’s behaviour in taking medication corresponds with agreed recommendations from health personnel”. Whereas antipsychotic treatment has proven to be effective, maintaining adherence is difficult (Leclerc, Noto, Bressan, & Brietzke, 2015). Nonadherence rates among psychiatric patients are high (Haddad, Brain, & Scott, 2014), approximating 50% a year after a first episode of psychosis (Coldham E. L., Addington J., & Addington D., 2002). Lack of treatment compliance is associated with worse prognosis and greater probability of relapse and rehospitalization (Crespo-Facorro et al., 2011; Nicolino et al., 2011; Robinson et al., 1999).

Adherence is a complex behaviour and non-adherence to medication is multifactorial (Hartung et al., 2017). Some studies highlight the necessity of differentiating between intentionally non-compliant patients and those who cannot properly comply due to difficulties understanding and remembering the prescription, as its causes and kind of intervention needed may differ for each group.

Factors associated with intentional non-compliance included younger age, substance abuse, forensic history, lower functioning level, positive symptoms, longer duration of untreated psychosis, lack of insight, self-stigmatization, side effects, dissatisfaction with information received, and negative beliefs and attitudes towards the illness and medication (Barbeito et al., 2014; Feldhaus et al., 2018; García et al., 2016; Leclerc et al., 2015; Nicolino et al., 2011), the latter being the most significant ones in predicting non-adherence (Hickling, Kouvaras, Nterian, & Perez-Iglesias, 2018). This agrees with the Health Belief Model, which poses that patients are more likely to adhere to the medication if they believe the benefits will outweigh the costs (Becker, 1974).

There is evidence that compliance of some psychiatric treatments can be monitored through salivary measures. For instance, salivary and blood correlations have been observed for chlorpromazine, clozapine, diazepam, lithium and valproate (Jain et al., 2011; May, Van Putten, Jenden, & Cho, 1978; Murru et al., 2017; Yamazumi & Miura, 1981). However, salivary medication and biomarker measurements are often overlooked in medicine; issues like oral contamination, restriction to selective drugs in unionized form and pH influenced-fluctuations have contributed to this. On the other hand, the use of saliva in measuring drug concentrations has several advantages: easy and faster sampling, better acceptance from the patients as it poses no risks or pain, more convenient for health professionals... all of which allows for more frequent monitoring; besides, salivary measurements may be better for highly protein-bound drugs, as they represent only the unbound fraction, contrary to plasma levels that measure both the bound and unbound fractions (May, Van Putten, Jenden, & Cho, 1978).

HYPOTHESIS AND OBJECTIVES

HYPOTHESIS:

Antipsychotics can be measured in saliva.

Adherence to antipsychotic medication can partially predict the outcome after a first episode of psychosis.

OBJECTIVES:

Main objective:

To determine if antipsychotics can be measured in saliva

Secondary objectives:

1. To describe the sociodemographic aspects of patients with first episode psychosis
2. To study the relationship between salivary and plasma levels of antipsychotics
3. To study the relationship between adherence and salivary levels of antipsychotics
4. To establish a relationship between salivary levels of antipsychotics and psychotic symptoms
5. To establish a relationship between adherence and functionality

MATERIAL AND METHODS

Data for this study was taken from the multicentric longitudinal cohort study “Clinical applicability of a predictive model of relapse in first episodes of schizophrenia – Estudio de aplicabilidad clínica de un modelo predictivo de recaídas en primeros episodios de esquizofrenia”, in which Dr. Gonzalez-Pinto is the coordinator of the adherence package. The database consisted in 223 patients (148 men and 64 women, age range 19-40 years), recruited from different hospitals participating in the multicentre study, with diagnosis of first episode of psychosis (FEP) in remission in the moment of recruitment, divided in adherent and non-adherent to medication.

Inclusion criteria in the original study included:

1. Age between 16 and 40
2. Meet diagnostic criteria for first episode of psychosis
3. Meet Standardized Remission Criteria in schizophrenia (Andreasen et al., 2005)
4. Not having suffered from a relapse since debut of illness
5. Speak Spanish fluently
6. Having signed the Informed Consent.

Exclusion criteria for the original study were:

1. Traumatic brain injury accompanied by loss of consciousness
2. Intellectual disability, understood not only as CI under 70, but also by developmental difficulties
3. Somatic pathology that may have mental repercussions.

Data available included socio-demographic, clinical and biological variables. Socio-demographic variables included age, gender, education, socioeconomic status. Clinical variables included

psychotic symptoms, functionality and relapses. Socio-demographic and clinical data were gathered in semi-structured interviews conducted by mental health professionals, in which the following questionnaires were administered.

Adherence was measured using the Morisky-Green test, an autoaplicated questionnaire validated for the assessment of compliance to treatment (Culig & Leppée, 2014; Morisky, Green, & Levine, 1986). Spanish version was validated by Val Jimenez et al. (Val Jiménez, et al., , 1992). Measures were gathered at baseline and three and six months after recruitment. Global adherence was evaluated considering the three measures, being adherent when obtaining positive adherence in two or more out of three visits.

Functionality was assessed with the Spanish version of the GAF – Global Assessment of Functionality scale, the EEAG – Escala de Evaluación de la Actividad Global (Jones, Thornicroft, Coffey, & Dunn, 1995). Assessment was made at baseline and at three and six month follow-up.

Psychotic symptoms were assessed at baseline and three and six month follow-up, using the PANSS – Positive And Negative Syndrome Scale (Kay, Fiszbein, & Opler, 1987), Spanish version by Peralta and Cuesta (Peralta & Cuesta, 1994).

Biological parameters consisted in saliva samples collected in order to determine saliva levels of the following antipsychotics: risperidone, paliperidone, olanzapine, quetiapine and aripiprazole. Sampling was conducted at baseline, and three and six months after remission. Samples were collected without stimulation, using tubes specially adapted for saliva (Salivette o SARSTEDT®, nº REF51.1534.001). The tubes were kept at – 20°C until analysis. Saliva was extracted by centrifugation at 2500 g for 10 minutes and analysed with liquid chromatography-tandem mass spectrometry, only in those cases in which three samples for the same patient were collected.

Data analysis was carried with the programme SPSS Statistics for Windows, version 23, and the level of significant was set at $p < 0.05$. For the sociodemographic variables, comparisons between the adherence groups were made using bivariate analyses. T-Student tests for independent samples were used for continuous variables and contingency tables for categorical variables.

The association between salivary levels and the dose of antipsychotics was evaluated with Pearson correlations. The relation between adherence and the salivary levels of antipsychotics as well as the association between the salivary levels and the clinical symptoms were analysed following a two-step procedure:

1. First, we performed a multiple linear regression including in the models all the potential confounders. Only those significant variables or those that produced a significant change in the coefficient of the independent variable were included in the final model. Finally, the interaction terms were evaluated.
2. Once the final model was performed, we included the dose of the antipsychotic as confounding variable in order to evaluate its mediation effect.

ETHICAL ASPECTS:

The original project from which this study feeds was granted approval by the Ethical Committees (CEIC) of the respective hospitals taking part in it. All patients included in the study gave written informed consent.

RESULTS

		Total sample (n=143)	Non-adherent (n=73)	Adherent (n=70)	Statistic
Gender	Male	97 (67.8%)	52 (71.2%)	45 (64.3%)	X ² = 0.790, p=0.374
	Female	46 (32.2%)	21 (28.8%)	25 (35.7%)	
Age		26.40 (6.24)	26.51 (6.16)	26.29 (6.36)	t= 0.211, p= 0.833
SE level	Low	35 (26.7%)	18 (26.1%)	17 (27.4%)	X ² = 0.866, p= 0.649
	Medium	58 (44.3%)	33 (47.8%)	25 (40.3%)	
	High	38 (29.0%)	18 (26.1%)	20 (32.3%)	
Education level	No studies	12 (8.5%)	7 (9.6%)	5 (7.2%)	X ² = 3.502, p= 0.320
	Basic	36 (25.4%)	22 (30.1%)	14 (20.3%)	
	Secondary	61 (43.0%)	31 (42.5%)	30 (43.5%)	
	University	33 (23.2%)	13 (17.8%)	20 (29%)	
Cannabis use		82 (57.3%)	46 (63%)	36 (51.4%)	X ² = 1.961, p= 0.161
Drug	ARI	50 (37.9%)	26 (38.8%)	24 (36.9%)	X ² = 0.050, p= 0.824 X ² = 0.501, p= 0.479 X ² = 0.266, p= 0.606 X ² = 0.730, p= 0.393 X ² = 0.014, p= 0.906
	CLO	10 (7.6%)	4 (6.0%)	6 (9.2%)	
	OLA	28 (21.2%)	13 (19.4%)	15 (23.1%)	
	PAL	33 (25.2%)	19 (28.4%)	14 (21.9%)	
	RIS	22 (16.8%)	11 (16.4%)	11 (17.2%)	

Table 1

As showed in **Table 1**, no significative differences were observed between the adherence groups.

Adherence increased from baseline (49% = 70/143) to three months (52% = 59/114), and remained stable at six months (60% = 58/96).

All antipsychotics could be measured in saliva, with levels varying as shown in **Table 2**.

	Visits		
	Baseline	3 months	6 months
<i>Aripiprazole</i>	11.89 (69.72)	2.92 (11.49)	2.41 (5.68)
<i>Clozapine</i>	21.44 (46.08)	37.80 (48.93)	14.63 (28.66)
<i>Olanzapine</i>	27.67 (89.31)	9.94 (17.09)	7.11 (8.91)
<i>Risperidone</i>	3.69 (7.78)	0.64 (0.72)	0.39 (0.48)
<i>Paliperidone</i>	11.91 (11.78)	10.61 (13.00)	8.98 (11.04)

Table 2

Relationship between salivary and plasma levels of antipsychotics

We found a positive correlation between saliva and blood levels of Aripiprazole at three ($r=0.580$, $p=0.001$) and six months ($r=0.506$, $p=0.027$). Although we did not reach significance for the rest of the data analysed, we see a tendency to positive association.

Relationship between dose and salivary levels of antipsychotics:

No relationship between dose and saliva levels was found in the non-adherent group for any of the medications studied.

In the adherent group, we found a significative relationship at baseline between dose and saliva levels of Aripiprazole ($r=0.743$, $p<0.001$). We did not find significative relationship between dose and saliva levels of Olanzapine, Clozapine, Risperidone and Paliperidone.

Relationship between global adherence and clinical outcome:

Global adherence was achieved when being adherent in at least two out of three visits (baseline, 3 months and 6 months). Patients who were globally adherent obtained better

outcomes in the PANSS Negative scale, with a significant decrease in the score ($F = 4.779$, $p = 0.010$) when compared with the non-adherent group (*Table 3, Figure 1*); a tendency to this was also observed in the PANSS Global scale (*Table 4, Figure 2*), though results did not reach statistical significance ($F = 3.326$, $p = 0.072$). PANSS Positive scale and EEAG did not show different outcomes in the adherent group in comparison to the non-adherent group, as in shown in *Table 5*.

<i>PANSS Negative</i>	Adherent	Non-adherent
<i>Baseline</i>	15.00 (0.79)	13.29 (0.85)
<i>3 months</i>	13.45 (0.71)	13.33 (0.77)
<i>6 months</i>	12.25 (0.73)	13.14 (0.79)

Table 3

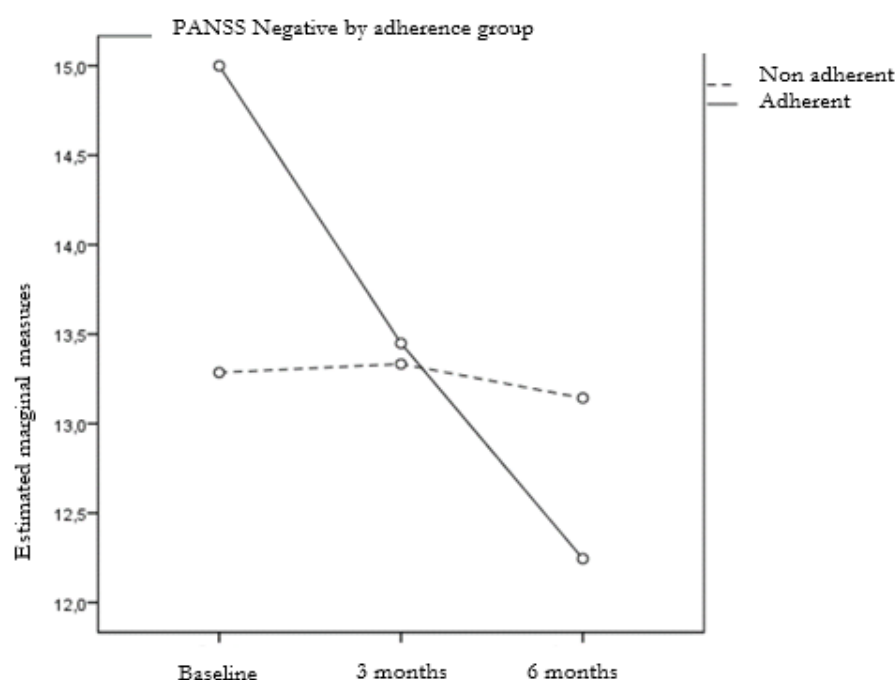


Figure 1

<i>PANSS Global</i>	Adherent	Non-adherent
<i>Baseline</i>	49.00 (1.93)	48.02 (2.09)
<i>3 months</i>	45.39 (1.84)	47.45 (1.99)
<i>6 months</i>	43.43 (2.06)	46.45 (2.23)

Table 4

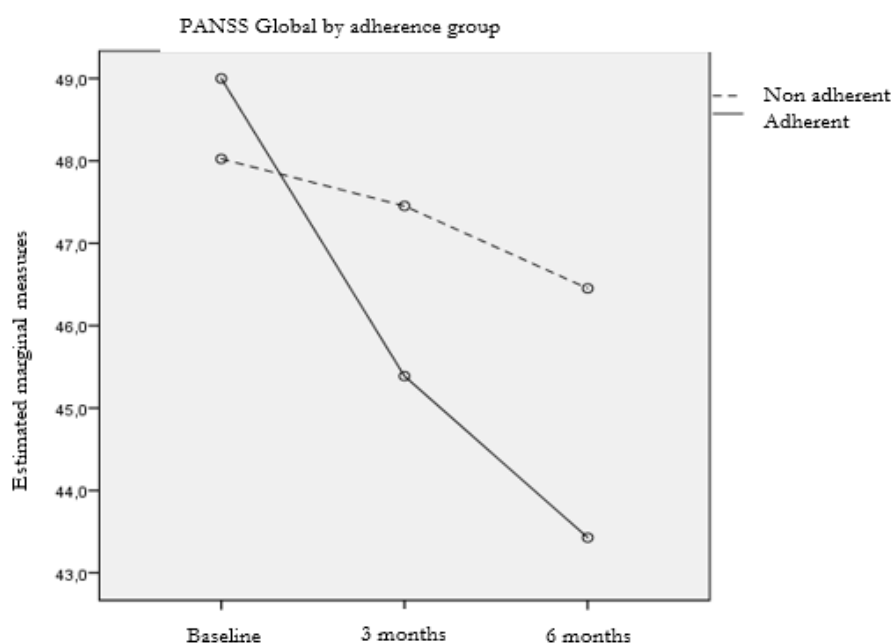


Figure 2.

<i>PANSS Positive</i>	Adherent	Non adherent
<i>Baseline</i>	9.30 (3.12)	9.31 (2.77)
<i>3 months</i>	8.64 (2.48)	9.31 (3.01)
<i>6 months</i>	8.65 (3.12)	9.17 (3.04)
EEAG	Adherent	Non adherent
<i>Baseline</i>	68.02 (13.92)	68.40 (13.10)
<i>3 months</i>	72.35 (13.41)	70.58 (11.65)
<i>6 months</i>	75.56 (11.77)	73.10 (11.53)

Table 5

Salivary antipsychotic levels and symptoms

At baseline, higher levels of Aripiprazole were associated with higher scores in the PANSS Global scale ($b = 0.052$, $p = 0.023$); the results did not vary when introducing dose as a confounding variable. At three months, higher Aripiprazole levels were associated with higher scores in the PANSS Positive scale ($b = 0.012$, $p = 0.008$); once again, results did not vary when introducing dose as a confounding variable.

At baseline, higher Clozapine levels, were associated with lower scores in the PANSS Negative scale ($b = -0.081$, $p = 0.024$) and in the PANSS Global scale ($b = -0.220$, $p = 0.011$). We obtained similar results at three months, both in the PANSS Negative scale ($b = -0.109$, $p = 0.014$) and in the PANSS Global scale ($b = -0.300$, $p < 0.001$), and at six months in the PANSS Negative scale ($b = -0.175$, $p = 0.021$). We found no variation in results in none of the visits (baseline, and three and six months) when including dose as a confounding variable.

Regarding the EEAG scale, although there was no relation neither at baseline nor at 3 months, at 6 months there was a significant mediation of the Clozapine dose in the relationship between the salivary levels of Clozapine and the scores of the EEAG scale; at first the relation between salivary levels and the EEAG scale was not significant ($b = 0.134$, $p = 0.465$), but when including dose as covariable, both the dose and the relation between salivary levels and EEAG became significant (dose: $b = -0.195$, $p = 0.035$; CLOSA: $b = 0.678$, $p = 0.028$).

DISCUSSION

All antipsychotic and their metabolites could be measured in saliva. This is a relevant finding, as saliva levels can be a tool to check compliance, in order to take the correct decisions in clinical settings. In fact it is not unusual to increase the dose of antipsychotics in order to improve symptoms, when the problem is lack of adherence and it would probably be a better approach to give information about efficacy and prognosis. In addition, we found a positive correlation between plasma and salivary levels for Aripiprazole. This finding poses special importance, as there are no previous studies about the relationship between aripiprazole in plasma and saliva. Previous studies found correlations between plasma and salivary levels for Chlorpromazine, Clozapine, Diazepam, Lithium and Valproate (Jain et al., 2011; May et al., 1978; Murru et al., 2017; Yamazumi & Miura, 1981). Our findings about Risperidone and Olanzapine, go in line with these results. The lack of correlation between plasma and salivary levels in our study for Clozapine and Paliperidone could be explained by the shortage of subjects with available data in this pharmacologic group. This differences in results between pharmacologic groups could also be explained by the fact that high protein-binding antipsychotics, such as Aripiprazole, could be easier to determine in saliva than others. In fact, it interesting to point out that we found a relationship between aripiprazole dose and saliva levels.

Saliva offers some advantages over plasma, its sampling being simple, stress-free, non-invasive and more convenient than blood testing for health care provider and patient, allowing multiple collections in a day at any place; it is also able to measure the “unbound” biologically active or free hormone levels. Disadvantages to consider would be the possible interference with substances such as food and beverages and contamination of the oral mucosa, so restrictions regarding eating, drinking, teeth brushing may be required or at least evaluated in subsequent studies.

Levels of adherence in our patients are similar to those found in other studies, being adherent about half of the sample studied. Adherence increased slightly during the first year of follow up. Other investigators found high levels of non-adherence to medication (Haddad et al., 2014), approximating 50% a year after a first episode of psychosis (Coldham E. L. et al., 2002). Lack of treatment compliance is associated with worse prognosis and greater probability of relapse and rehospitalization (Crespo-Facorro et al., 2011; Nicolino et al., 2011; Robinson et al., 1999).

Our study did show better results in negative symptoms in adherent patients than in non-adherent patients, which relevance resides in the fact that negative symptoms are common, enduring and debilitating component of the psychopathology of schizophrenia (Stahl & Buckley, 2007). They are associated with higher levels of impairment and poorer outcomes (Vella & Pai, 2015), having greater impact on functioning than positive symptoms (Rabinowitz et al., 2012) and are also more challenging to evaluate objectively (Stahl & Buckley, 2007) to treat, being the effects of current psychopharmacological treatments at best modest (Buckley & Stahl, 2007). These findings could serve as a start point for more studies about the optimization of pharmacological strategies to tackle negative symptoms and their effects in long-term follow-up.

Lack of association with EEAG could be explained by the high functionality levels of our patients, and by shortness of the follow-up (most of the patients in the moment of the analysis hadn't reached one year since recruitment), which could have not been enough time for deficits to appear. Also, lack of association between adherence and positive symptoms is probably due to low positive symptoms in this sample. Both our results and current literature support the importance of adherence to treatment as a prognostic factor in schizophrenia. A metanalysis by García et al. (García et al., 2016) highlights the prognostic relevance of early interventions focused on adherence enhancement. Novick et al (Novick et al., 2010) links non-adherence in schizophrenia to an increased risk of relapse, hospitalization and suicide attempts. Myers et. al (Myers, Bhatti, Broussard, & Compton, 2017) link non-adherence to greater positive symptom

severity and likelihood of continuing drug-use. Regarding the strategies for improving adherence, psychoeducation family interventions and motivational therapy have been associated with an improve in compliance; and long-acting injectable antipsychotics are among pharmacological strategies gaining popularity (Greene et al., 2018; Hartung et al., 2017). Nonetheless medication adherence continues to be one of the main challenges in assessment of first episode psychosis, an idea that is consistent with the results of our study, in which only 49% of the patients were adherent at baseline, a proportion that only increased slightly at three months (52%), and six months (60%), meaning that an important fraction of patients remain undertreated even after months of psychiatric follow-up.

The positive correlation between higher levels of antipsychotics and higher results in PANSS scale could be explained by the fact that prescription is guided by symptoms, so more symptomatic patients would receive higher doses of medication, thus accounting for the higher levels.

LIMITATIONS:

One limitation shared with most longitudinal studies is the loss of subjects, due to the frequency and long-term duration of the project.

Other limitation lies in inter-observer differences in clinical assessment, although we expect these differences to be minor due to the specific training of the mental health professionals and the use of validated tests.

We also need to consider that, as the original project is yet to finish, data available is limited and the preliminary results than can be obtained may not be of statistical or clinical significance. For instance, data about Aripiprazole and Paliperidone include both oral and intramuscular treatments. The sample was too small to do separate analyses, although we cannot exclude significant results with Paliperidone with larger samples of oral or intramuscular treatments.

Considering the use of biological samples, known for their variability, and the shortage of data available, a non-parametric approach could have been more adequate, in spite of this we choose to conduct parametric analysis in order to be less restrictive with the analysis.

Lastly, shortage of data hindered the establishment of a relationship between variables, although been this a preliminary analysis from a larger study, we expect this issue to be solved in future approaches.

CONCLUSIONS

- Antipsychotics can be measured in saliva
- There is a positive correlation between plasma and salivary levels for Aripiprazole.
- Levels of aripiprazole in saliva are related with the dose in adherent patients.
- Levels of non-adherence are high, almost 50% in first psychotic episode patients.
- Adherence is associated with lower negative symptoms in follow-up.
- Further studies should be made to better establish the relationship between salivary and blood levels and between salivary levels and dose.

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