Pharmacological and non-pharmacological correlates of acute akathisia in first-episode psychosis

(Trabajo de fin de Máster)

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Approval from the tutor

To whom it may concern,

This letter provides confirmation that Dr. Jorge Gómez-Arnau Ramírez was a visiting scientific in Professor Benedicto Crespo Facorro laboratory PAFIP (Programa Asistencial a las Fases Iniciales de Psicosis, University Hospital Marqués de Valdecilla, Cantabria University, Santander, Spain). Over this time, he gained experience in neuroscience research, and advanced statistical modelling in the study of psychiatric disorders. Dr. Gómez-Arnau performed an exciting project about the akatisia phenomena in fisrt episode treatment. This work has been summarized in his Master Project. In summary, he was a valuable asset to the lab.

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1. ABSTRACT

Introduction: Acute akathisia is a complex syndrome, secondary to the use of drugs, with a prevalence close to 25% with the use of first-generation antipsychotics (FGA). Akathisia is often difficult for patients to tolerate and may worsen psychosis course. Although some authors have described risk factors for acute akathisia, most evidence originates from chronic samples. The aim of this study is to examine risk factors for the development of acute akathisia in a sample of first-episode of psychosis (FEP) patients. *Methods*: 505 FEP patients were examined for the presence of akathisia during the six first weeks of antipsychotic treatment. Barnes akathisia scale (BAS) was used for this purpose. Patients were assessed for socio-demographic, clinical and analytic data. Information on pharmacological treatments was also collected. Univariate analyses were performed to identify plausible predictors of akathisia. A logistic regression model was conducted. *Results*: There were no significant differences between akathisic and non akathisic patients in terms of demographic, clinical and analytical variables. Haloperidol treated patients developed more akathisia. As for second-generation antipsychotics (SGA), akathisia was significantly more frequent with the use of aripiprazole and risperidone. *Discussion/conclusions*: Previous findings, which linked akathisia and drug abuse or iron deficiency, could not be replicated. Differences between individual antipsychotics in terms of akathisia

risk are discussed. There is a need of further studies on this topic, in early psychotic samples.

2. KEY WORDS

Akathisia; Schizophrenia; First-episode; Antipsychotics.

3. INTRODUCTION

Akathisia characterizes by an inability to stay still together with a subjective feeling of inner restlessness. It is a complex syndrome, with different possible underlying causes and several phenomenological subtypes [1, 2]. It is accepted, however, that in most cases akathisia is secondary to the use of drugs, especially neuroleptics [3]. Acute akathisia appears in the first six weeks after the introduction of a new treatment or a change in dose, while tardive akathisia occurs more than three months after initiation of treatment [3, 4]. Most patients will develop acute akathisia in the first two weeks of treatment [5]. The prevalence of akathisia in patients treated with neuroleptics is highly variable across different studies, although a rate of 25% with first-generation antipsychotics (FGA) seems reasonable [3]. With regard to second-generation antipsychotics (SGA), a recent study, carried out in routine clinical practice, reported a

prevalence of 18.5% [6]. Other authors have reported higher rates [7]. The prevalence of tardive akathisia is probably lower [8].

The clinical relevance of akathisia arises from the fact that it may be particularly difficult for patients to tolerate. The presence of akathisia has been linked to higher levels of anxiety [1], discomfort and dysphoria, and may worsen the course of psychosis [9]. In addition, some authors have suggested that akathisia is related to the presence of higher rates of suicidality in psychotic patients following the introduction of treatment [10, 11]. Akathisia is one of the major side effects of antipsychotic medication that associates with lack of adherence to treatment [12, 13]. Ultimately, akathisia is a syndrome with a significant subjective component, which is often accompanied by intense affects, and could lead to decompensation in different areas [14]. Hence, the ability to predict its occurrence could be of particular clinical interest.

Whether there are clinical or demographic factors that may predispose to the development of acute akathisia remains an unsolved question. While classical studies indicate that neither age nor gender significantly influence on the incidence of akathisia [3, 8], there seems to be evidence of a weak association between the development of akathisia and a prior presence of substance abuse, especially cocaine [15]. Some authors have studied the relationship between akathisia and a measurable deficit in body iron stores, with unequal findings [16-18]. The available data regarding the association of

akathisia with other factors, such as cognitive dysfunction [19], duration of illness [20], or acculturation [21] are inconclusive. As for the risk of akathisia with specific antipsychotics, meta-analytic evidence suggests that SGA are somewhat more benign than FGA [22, 23], whereas differences between individual SGA seem to be less clear, partly because of the paucity of head-to-head studies [7, 24, 25].

Thus far, studies on risk factors for the development of akathisia have generally been conducted on chronic or even institutionalized patients, often transversally and with no relation to acute psychosis treatment. By contrast, studies on first episodes of psychosis (FEP) are performed on patients subjected to less confounding factors, whether derived from chronicity at itself, or from the prescription of antipsychotic polytherapy or concomitant medication [26].

The aim of this study is to examine pharmacological and non-pharmacological risk factors for the development of acute akathisia in a sample of FEP patients. As a main hypothesis, akathisic patients will more often present substance abuse and will have lower levels of serum iron, thus replicating the most consistent findings in chronic patient studies. Furthermore, the use of haloperidol will lead to a greater a risk of akathisia than that of SGA.

4. METHODS

4.1. STUDY SETTING

Data for the present research were obtained from a large epidemiological cohort as part of a longitudinal intervention program on FEP (PAFIP) conducted at the University Hospital "Marqués de Valdecilla" in Cantabria, Spain, which main procedures have already been described elsewhere [27]. The program was approved by the local institutional review board. Patients and their families provided informed consent prior to inclusion.

4.2. SUBJECTS

From February 2001 to August 2015, patients referred to the psychiatric unit were included in PAFIP on the basis of the following criteria: 1) age between 15 and 60; 2) residency in the catchment area; 3) experiencing their first episode of psychosis; 4) no prior treatment with antipsychotic medication or, if previously treated, a total time of adequate antipsychotic treatment shorter than six weeks; 5) DSM-IV criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder or psychotic disorder not otherwise specified. Patients were excluded if they met any of the following criteria: 1) DSM-IV criteria for drug

dependence; 2) DSM-IV criteria for mental retardation; 3) history of neurological disorder or brain injury. The diagnoses were confirmed by an experienced psychiatrist, applying the Structured Clinical Interview for DSM-IV (SCID-I), six months after the baseline visit.

4.3. STUDY DESIGN

The original design was that of a prospective, randomized, flexible-dose and open-label study. Participants were randomly assigned to treatment. At intake, all patients were considered as antipsychotic naïve. Patients who were taking antipsychotics at intake underwent a 5-day washout period before starting treatment. Dose ranges were as follows: haloperidol 3-9 mg/day; risperidone 3-6 mg/day; olanzapine 5-20 mg/day; quetiapine 100-600 mg/day; ziprasidone 40-160 mg/day and aripiprazole 5-30 mg/day. Study protocol allowed the use of anticholinergic agents (biperiden), benzodiacepines and antidepressants for clinical reasons. Anticholinergic medication was never used prophylactically.

4.4. ASSESSMENTS

For the purpose of the present investigation, only the first six weeks after treatment initiation were considered, since this is the critical period for the onset of acute akathisia [3].

The presence of akathisia was determined by a score ≥ 2 on the global item of the Barnes Akathisia Scale (BAS), at anytime within the first six weeks. The use of this sole item for diagnostic purposes has proven good inter-rate validity as well as adequate reliability when compared to neurophysiological complementary tests [28, 29].

At baseline, sociodemographic and clinical information was obtained from patients and their relatives, including age, gender, marital status (single vs. cohabiting), employment status (employed vs. unemployed), need of hospitalization, duration of untreated illness (DUI), duration of untreated psychosis (DUP) and use of substances of abuse. General psychopathology at entry was assessed with the Brief Psychiatric Rating Scale (BPRS) [30], whereas positive and negative dimensions of psychosis were measured with the Scale for the Assessment of Positive Symptoms (SAPS) [31] and the Scale for the Assessment of Negative Symptoms (SANS) [32]. Simpson-Angus Scale (SAS) was used for assessing extrapyramidal symptoms (EPS) at admission.

Fasting venous blood samples were collected at baseline, and were analyzed for glycemia, serum iron and copper, vitamin B12 and folic acid by automated methods.

Data on medication use was recorded at baseline except for anticholinergics, which use was registered for the six-week overall period. Chlorpromazine equivalent dose (CPZeq) was calculated for antipsychotic drugs using the minimum effective dose method [33].

4.5. STATISTICAL ANALYSIS

All data were tested for normality and equality of variances using Shapiro-Wilk and Levene tests, respectively. Univariate analyses were performed to identify plausible demographic, clinical and treatment-related predictors of acute akathisia. Chi-square, t-tests and Mann-Whitney U tests were used when appropriate. A post-hoc pairwise comparison on akathisia rates was established between groups of antipsychotic drugs, performing repeated Z-tests with a Bonferroni correction for multiple comparisons. Additionally, a logistic regression model was carried out with akathisia as a dependent variable. The variables introduced as predictors were those with a significance level of 10% in the univariate analysis, as well as age and CPZEq. Backward stepwise procedure was chosen to fit the model.

IBM SPSS 22.0 was used for statistical analyses. Performed statistical tests were two-tailed and significance level was set at 95%.

5. RESULTS

5.1. SAMPLE CHARACTERISTICS

542 patients were included in PAFIP from February 2001 to August 2015. Of these, 37 subjects were excluded from the final analysis since they did not have any post-baseline akathisia measure. Therefore, the final sample consisted of 505 subjects. Mean age at intake was 30.0 years (*SD=9.6*) and 56.6% were male. 68.9% of the patients required hospitalization during the first episode of their illness. Mean DUP was 12.8 months (*SD=28.9*) and mean DUI was 22.3 months (*SD=37.9*).

5.2. PREVALENCE OF AKATHISIA

Signs of akathisia were detected in 117 patients (23.2%) within the first six weeks, after randomization; whereas a single patient (0.2%) was diagnosed with akathisia at baseline.

5.3. DIFFERENCES IN SOCIODEMOGRAPHIC AND CLINICAL VARIABLES

As depicted in table 1, there were no significant differences between akathisic and non-akathisic patients, in terms of

demographic, clinical or analytical variables. Akathisic patients showed a subtle trend toward a lower use of substances of abuse, particularly cannabis and alcohol.

5.4. DIFFERENCES IN TREATMENT-RELATED VARIABLES

146 patients were initially randomized to aripiprazole, 129 to risperidone, 59 to quetiapine, 58 to ziprasidone, 57 to olanzapine and 56 to haloperidol. The incidence of akathisia was significantly associated with the antipsychotic drug at baseline ($X^2=57.60$; $p<0.001$). Prescription rates of benzodiazepines and antidepressants, and antipsychotic doses at baseline were equivalent between the two groups (table 2).

5.5. COMPARISON BETWEEN ANTIPSYCHOTIC GROUPS

As shown in table 3, haloperidol-randomized patients developed more akathisia (55.4%) and required anticholinergic agents more often. A p-value <0.004 was set for pairwise comparisons following a Bonferroni correction. Repeated Z-tests revealed that akathisia rate was significantly higher in the haloperidol group than in the remaining groups (*Haloperidol vs Aripiprazol, Z=4.257, p<0.001; Haloperidol vs Olanzapine, Z=5.805, p<0.001; Haloperidol vs Quetiapine, Z=6.158, p<0.001; Haloperidol vs Risperidone, Z=3.682, p<0.001; Haloperidol*

vs Ziprasidone, Z=4.027, p<0.001). Aripiprazole (24.0%) and risperidone (27.1%) use significantly associated with greater akathisia than quetiapine (3.4%) and olanzapine (5.3%) prescription (*Aripirazole vs Olanzapine, Z=3.071, p=0.002; Aripiprazole vs Quetiapine, Z=3.469, p<0.001; Risperidone vs Olanzapine, Z=3.410; p<0.001; Risperidone vs Quetiapine, Z=3.799, p<0.001*). There were no significant differences between ziprasidone (19.0%) and the other SGA (*Ziprasidone vs Aripiprazole, Z=-0.772, p=0.44; Ziprasidone vs Olanzapine, Z=2.247, p=0.02; Ziprasidone vs Quetiapine, Z=2.680, p=0.007; Ziprasidone vs Risperidone, Z=-1.199, p=0.23*), as well as between aripiprazole and risperidone (*Z=0.600, p=0.55*) and between olanzapine and quetiapine (*Z=0.497, p=0.62*).

5.6. PREDICTIVE MODEL

The variables entered into the logistic regression were: antipsychotic drug at baseline, cannabis use, cocaine use, alcohol use, age and CPZEq. The regression analysis was performed for 499 subjects whose data for the six variables were available. The model was statistically significant (χ^2*=64.961; p<0.001*) and accounted for 18.5% of the variance (*Nagelkerke* R^2*=0.185*). Use of cannabis (*OR=0.611; p=0.037*) and antipsychotic drug (*p<0.001*) were significant predictors of akathisia after exclusion of redundant variables. Overall, the model correctly predicted 78.0% of patients,

with high specificity (96.6%) but an unacceptably low sensitivity (15.7%).

6. DISCUSSION

To our knowledge, the present study is a pioneer in exploring potential risk factors for the development of akathisia in a large, real-world, FEP sample. Thus, although it was not possible to provide a consistent predictive model for the development of acute akathisia, some interesting insights, especially concerning the use of antipsychotic drugs, can be drawn.

Baseline demographic and clinical features were very similar in both akathisic and non-akathisic patients. This could suggest that both groups belong to the same population, at least in psychopathological terms. The presence of akathisia at baseline was anecdotal in both groups (0.2%). To some extent, this would confirm the nature of akathisia as a treatment-derived syndrome, in contrast to other motor symptoms which have been described in drug-naïve patients, and have been linked to the pathophysiology of schizophrenia [34, 35].

We failed to replicate previous findings that linked an increase in akathisia with the use of substances of abuse, either cocaine [36, 37], alcohol [20], or cannabis [38], and suggested the presence of a striatal dopaminergic downregulation in those patients [36]. In the present

study, the relationship was even slightly opposite. These differences should be interpreted cautiously since, both in our study and in previous works, effect sizes were small. Moreover, previous findings were mainly extracted from samples of chronic patients with longer illness evolutions, thus not entirely comparable to FEP patients. The hypothesis that states that low serum iron levels predispose the development of akathisia could not be supported. This theory, which originates from a possible pathophysiological analogy between akathisia and restless leg syndrome, could not be confirmed by other authors [9, 17, 18]. Although here too the favorable evidence originates from chronic patient samples, it would have been interesting to have a measure of ferritin, which may be a better representation of body iron deposits [16]. Additional laboratory parameters, which relate to the occurrence of neurological disorders, such as serum copper, vitamin B12 or folic acid, were not altered in akathisic patients.

Akathisic patients did not take higher antipsychotic doses at baseline. While some classical studies reported a dose-dependent link between akathisia and use of FGA [1, 17], other authors have argued that this relationship might not be so simple, but depends on factors such as the particular antipsychotic type or dosage increases over time [5]. The use of benzodiazepines or antidepressants at baseline had no influence on akathisia rate. Antidepressant prescription was nonetheless very limited, so that the conclusions must be cautious.

As expected, a higher incidence of akathisia was identified with haloperidol. Its use implied an elevated attributable risk of 28.3% over the next drug (risperidone). These findings are consistent with those reported in a recent study, performed in a clinical-routine comprehensive sample, which showed that SGA use entailed a lower risk of akathisia compared with FGA [6]. In clinical trials conducted on FEP samples, haloperidol provoked significantly more akathisia than risperidone [39], olanzapine [40], or quetiapine [41]. The risk of akathisia in FEP patients seems to be generally higher with the use of FGA than with SGA [22, 23]. Some authors have suggested that the differences between SGA and FGA on akathisia rates may result from a use of markedly high doses of haloperidol in regular clinical practice [42]. However, interestingly, in our study, the initial mean dose of haloperidol was relatively low when compared with that of SGA.

Large multisite clinical trials did not reveal significant differences in akathisia rates between different SGA, either in chronic [7] or in FEP populations [43]. Moreover, the relative scarcity of head-to-head studies [25] and the absence of specific measures of akathisia in some clinical trials [44], result in a quite unsolid evidence on the issue. In the present study, however, we found a fairly clear gradation between different SGA, both in the incidence of akathisia as in the need for adjuvant anticholinergic medication. Whereas risperidone and aripiprazole were associated with an increased risk of acute akathisia, this risk seems to be very low for olanzapine and

quetiapine. Meanwhile, ziprasidone would be positioned in an intermediate risk zone. With respect to risperidone, high rates of akathisia with its use, already described by other authors, are consistent with a high D2 blockade and with what is known about the pathophysiology of akathisia [45, 46]. The explanation is less obvious for the high incidence of akathisia with the use of aripiprazole, which in some works is close to that of FGA [47]. It has been suggested that, while other more sedating antipsychotics tend to mask signs of akathisia, this would not happen with the use of aripiprazole, as it seldom causes notable sedation [48]. Eventually, while the risk of akathisia using ziprasidone is placed in an undetermined area, though still closer to FGA for some authors [43]; our results support that olanzapine and quetiapine entail a very low risk, probably similar to placebo [25].

This study has several important limitations that should be taken into account. First, the original study design was that of three prospective and separate clinical trials conducted at different times. Despite a high homogeneity between the three study protocols, the fact of combining their results into a single case-control study could reduce the level of evidence of the findings. Second, as a practical, real-world trial, neither patients nor evaluators were blinded to the treatments. This could have biased measuring study outcomes, particularly akathisia rates. Nevertheless, as a non-industry-funded study, the risk for systematic biased measuring is limited. Third,

although the study sample was considerably large, available information for some variables (e. g., serum iron) was limited to far fewer participants. Besides, the exclusion of heaviest drug users (those with dependence criteria) from the study could have an impact on the final findings. And last, the incidence of akathisia may have been underrated. Some patients might have experienced symptoms that went unnoticed, between evaluations. Also, the use of anticholinergic correctors could have masked some of the akathisia incidence. However, as their prophylactic prescription was not permitted, the use of anticholinergics should rather be considered as a clinician-dependent consequence of akathisia.

7. CONCLUSIONS

In a large sample of FEP patients, haloperidol use was associated with a higher incidence of acute akathisia. Among SGA, risk of akathisia was greater with risperidone and aripiprazole and almost anecdotal with quetiapine and olanzapine. As regards potential clinical and demographic correlates of akathisia, we were unable to fit a consistent predictive model. For a better understanding of the development of akathisia with acute antipsychotic treatment, there is a need of further studies on early psychosis, which would save methodological difficulties.

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9. TABLES

Table 1.

Demographic and clinical characteristics of akathisic and non-akathisic patients

	Entire sample N = 505	**Akathisic** n = 117	**Non-akathisic** n = 388	
	n (%)	*n (%)*	*n (%)*	*Statistics*
Sex (male) (n=505)	290 (57.4)	67 (57.3)	223 (57.5)	X^2=0.00; p=0.968
Unemployed (n=500)	218 (43.6)	53 (45.3)	165 (43.1)	X^2=0.18; p=0.672
Single (n=501)	371 (74.1)	88 (75.2)	283 (73.7)	X^2=0.11; p=0.743
Hospitalization (n=504)	349 (69.2)	83 (71.6)	266 (68.6)	X^2=0.38; p=0.540
Smoking (n=504)	286 (56.7)	59 (50.4)	227 (58.7)	X^2=2.48; p=0.115
Alcohol (n=501)	260 (51.9)	52 (44.8)	208 (54.0)	X^2=3.02; p=0.082
Cannabis (n=505)	220 (43.6)	42 (35.9)	178 (45.9)	X^2=3.64; p=0.056
Cocaine (n=504)	96 (19.0)	16 (13.8)	80 (20.6)	X^2=2.70; p=0.100
Stimulants (n=504)	43 (8.5)	10 (8.6)	33 (8.5)	X^2=0.00; p=0.969
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	*Statistics*
Age, years (n=505)	30.0 (9.6)	29.7 (10.4)	30.1 (9.4)	u=21354; p=0.332
DUI, months (n=472)	22.3 (37.9)	24.5 (40.9)	21.7 (36.9)	u=19452; p=0.642
DUP, months (n=493)	12.9 (28.9)	16.0 (35.7)	12.0 (26.5)	u=21038; p=0.745
SAPS (n=504)	13.8 (4.4)	13.6 (4.5)	13.9 (4.4)	u=21466; p=0.393
SANS (n=502)	6.5 (6.1)	6.3 (5.8)	6.5 (6.1)	u=21932; p=0.814
BPRS (n=502)	63.1 (13.8)	62.4 (13.1)	63.4 (14.0)	F=1.50; p=0.461
SAS (n=505)	0.51 (1.2)	0.68 (1.7)	0.46 (1.0)	u=22192; p=0.636
Glycemia, mg/dl (n=489)	86.7 (15.9)	86.3 (11.0)	86.8 (17.2)	u=21068; p=0.670
Seric Fe, mEq/l (n=139)	96.5 (51.5)	101.4 (66.2)	94.2 (43.0)	F=2.09; p=0.445
Seric Cu, mEq/l (n=139)	100.4 (27.5)	99.0 (24.5)	101.0 (28.8)	F=0.01; p=0.700
Folate, µg/dl (n=178)	7.8 (4.5)	7.3 (3.2)	7.9 (4.7)	u=1928; p=0.843
B12, µg/dl (n=181)	456.8 (347.2)	401.9 (138.1)	466.4 (371.5)	u=1892; p=0.458

Table 2.

Treatment-related characteristics of akathisic and non-akathisic patients

	Entire sample N = 505	**Akathisic** n = 117	**Non-akathisic** n = 388	
	n (%)	*n (%)*	*n (%)*	*Statistics*
Antipsychotic at baseline (n=505)				
Aripiprazole	146 (28.9)	35 (29.9)	111 (28.6)	X^2=57.60; p<0.001
Haloperidol	56 (11.1)	31 (26.5)	25 (6.4)	
Olanzapine	57 (11.3)	3 (2.6)	54 (13.9)	
Quetiapine	59 (11.7)	2 (1.7)	57 (14.7)	
Risperidone	129 (25.5)	35 (29.9)	94 (24.2)	
Ziprasidone	58 (11.5)	11 (9.4)	47 (12.1)	
Antidepressants at baseline (n=503)	8 (1.6)	2 (1.7)	6 (1.6)	X^2=0.01; p=0.907
Benzodiacepines at baseline (n=502)	304 (60.6)	71 (60.7)	233 (60.5)	X^2=0.00; p=0.975
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*
CPZEq at baseline	265.3 (88.9)	258.2 (83.2)	267.5 (90.6)	F=0.38; p=0.301

Table 3.

Akathisia rate, Biperiden use and CPZEq by treatment group

	Aripiprazole n=146	**Haloperidol** n=56	**Olanzapine** n=57	**Quetiapine** n=59	**Risperidone** n=129	**Ziprasidone** n=58
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Akathisia	35 (24.0)	31 (55.4)	3 (5.3)	2 (3.4)	35 (27.1)	11 (19.0)
Use of Biperiden	29 (19.9)	42 (75.0)	2 (3.5)	2 (3.4)	30 (23.3)	10 (17.2)
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*
CPZEq at baseline	223.5 (59.1)	259.5 (87.8)	324.5 (87.2)	249.1 (113.4)	295.9 (89.6)	267.2 (68.1)