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► **To cite this version:**

Manuel Dias Alves, Jean Arthur Micoulaud-Franchi, Nicolas Simon, Jean Vion-Dury. EEG MODIFICATIONS ASSOCIATED WITH ATYPICAL STRICT ANTIPSYCHOTIC MONOTHERAPIES. Journal of Clinical Psychopharmacology, 2018, 38 (6), pp.555-562. hal-01847854

HAL Id: hal-01847854

<https://hal.science/hal-01847854>

Submitted on 24 Jul 2018

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EEG MODIFICATIONS ASSOCIATED WITH ATYPICAL STRICT ANTIPSYCHOTIC MONOTHERAPIES

Manuel Dias Alves^{1,2} MD MSc, Jean Arthur Micoulaud-Franchi^{3,4} MD PhD, Nicolas Simon^{5,6} MD PhD, Jean Vion-Dury^{1,2} MD PhD

¹ Aix Marseille Univ., FRE CNRS 2006, PRISM « Perception, Représentations, Image, Sound, Music », 13009 Marseille, France.

² Unité de Neurophysiologie, Psychophysiologie et Neurophénoménologie, Pôle Universitaire de Psychiatrie, CHU Ste Marguerite, 13009 Marseille.

³ Service d'Explorations Fonctionnelles du Système Nerveux, Clinique du Sommeil, CHU de Bordeaux, Place Amélie Raba-Léon, 33076 Bordeaux, France

⁴ Univ. Bordeaux, SANPSY, USR 3413, F-33000 Bordeaux, France & CNRS, SANPSY, USR 3413, F-33000 Bordeaux, France

⁵ Aix Marseille Univ, UMR 912 INSERM, IRD, SESSTIM, Marseille, France.

⁶ APHM, Hôpital Sainte marguerite, Service de Pharmacologie Clinique, CAP-TV, 13274, Marseille, France

Keywords: EEG, ELECTROENCEPHALOGRAM, ATYPICAL ANTIPSYCHOTIC, EEG ABNORMALITIES, NEUROLEPTICS.

Word count Text (excluding references, figures and tables): 3653

Corresponding author: manuel.diasalves@gmail.com

Conflicts of interest and Financial disclosures:

The authors declare no conflicts of interest.

Acknowledgments:

We thank our colleagues of Sainte-Marguerite Hospital of Marseille for referring patients. We thank EEG technicians: Adeline Suray and Christelle Berthet of the neurophysiology unit of the psychiatry department of Sainte-Marguerite Hospital. We thank Margaret Frame for her careful reading of the manuscript.

ABSTRACT :

BACKGROUND: Antipsychotics produce EEG modifications and increase the risk of epileptic seizure. These modifications remain sparsely studied specifically for atypical antipsychotics. In this context, our study focuses on EEG modifications associated with atypical strict antipsychotic monotherapies.

METHODS: EEG recordings of 84 psychiatric patients treated with atypical antipsychotics in strict monotherapy (clozapine: n=22, aripiprazole: n=22, olanzapine: n=17, risperidone: n=9, quetiapine: n=8, risperidone long-acting injection: n=4, and paliperidone long-acting injection: n=2) were analyzed. The modifications were ranked according to both slowing and excitability scores.

RESULTS: EEG modifications (in 51 subjects, 60.71%) were graded according to 4 stages combining general slowing and sharp slow waves and/or epileptiform activities. The presence of sharp or epileptiform activities was significantly greater for clozapine (90,9%) compared to other second-generation antipsychotics (aripiprazole: 50%, olanzapine: 58,8%, quetiapine: 37,5%, risperidone: 44,4%). Age, duration of disease progression and diagnosis were not associated as risk factors. EEG modifications were associated with lower doses for treatment with quetiapine but not for specific antipsychotics. EEG modifications and severe excitability were associated with higher chlorpromazine equivalent doses.

CONCLUSIONS: Atypical antipsychotics (clozapine, aripiprazole, quetiapine, olanzapine, risperidone) induce EEG modifications and these are significantly greater for clozapine and appear dependent on chlorpromazine equivalent dose. No encephalopathy was observed in these antipsychotic monotherapies, whatever dose.

The effects of psychotropic substances on electroencephalogram (EEG) were reported shortly after its discovery in 1929¹. Hans Berger described in 1933 the EEG changes induced by barbiturates, morphine and scopolamine². The first studies reporting anomalies induced by antipsychotics appeared at the end of the 1960s with studies on phenothiazine³⁻⁵. Dasberg and Robinson distinguished modifications associated with the toxic effects of drugs and abnormalities secondary to preexisting cerebral abnormalities⁵. Phenothiazine-type antipsychotics induce a slight slowing, amplitude increase, synchronization and anterior spreading of the alpha-activity⁶. Dasberg explains that the effects on the EEG of antipsychotics indicate changes in the cerebral environment that lead to a reorganization of behavior⁷.

EEG modifications are common in patients with psychiatric disorders⁸. These modifications are also reported in approximately 20-40% of patients with mood disorders and 20-60% of patients with schizophrenia⁸. A high percentage of patients with schizophrenia display EEG modifications with generalized slow activity, dysrhythmia, spikes and spike-wave complexes⁹. Nevertheless, in their retrospective review of EEG request, O'Sullivan et al. assume that the majority of EEG modifications from psychiatric sources can be explained by psychotropic medications¹⁰. In these conditions, the EEG cannot be used for diagnosis of the mental diseases. However EEG can aid in determining whether patients suffering from mental disorders are taking the drugs prescribed, or whether the dosages administered is producing central nervous system side effects or toxicity¹¹.

Treatment with antipsychotics induces EEG modifications¹². Mainly, a general slowing of the background activity, an increase in paroxysmal theta or delta activity and development of epileptiform discharges have been frequently reported in the literature¹³. Despite the introduction of various new molecules into the last thirty years, few studies have focused on EEG modifications induced by one or more atypical antipsychotics except for clozapine with its seizure risk¹². However, paroxysmal EEG activity or slowing EEG was also suggested in addition of the therapeutical effect of other antipsychotics^{5,14}. Some authors have suggested that EEG modifications related to clozapine are associated with a good therapeutic response¹⁵⁻¹⁷.

Most authors use the term "abnormalities" to qualify these EEG modifications¹⁸. In medicine, the term "normal" is used to discern healthy from ill¹⁹. If EEG modifications are associated with the therapeutic effect, the term « EEG abnormalities » appears to be inappropriate in this case, because the word « abnormalities » suggests a deleterious effect¹⁸. Several authors support this concept^{18,20}. Our study is descriptive and for this reason, we will use the descriptive term of « EEG modifications » and not « EEG abnormalities ». Indeed the design of our study was not developed to determine if the EEG modifications described is related to a side effect.

Centorrino et al. demonstrated that EEG modifications appeared to be more severe with second-generation than with first-generation antipsychotics with a particularly high risk of modifications with clozapine (47.1%) and olanzapine (38.5%), a moderate risk for typical antipsychotics (14.5%) and risperidone (28%). In their study, severe modifications (spike discharges or spike-and-wave activity) was observed for clozapine (5.9%) and olanzapine (7.7%) and risperidone (4.0%), but not for haloperidol²¹. The risk factors facilitating significant EEG modifications were the presence of hypertension, the use of an atypical antipsychotic, the diagnosis of bipolarity and older age. Benzodiazepine co-treatment was considered as protective factor²¹.

A study by Pillmann et al. about EEG analysis of 43 olanzapine-treated patients, showed an increase of diffuse slowdown (48.8%), intermittent slowing (34.9%) and epileptiform activity in some patients (9,3%)²². Another study on 54 patients treated with olanzapine demonstrated a significant EEG slowing, sharp waves and paroxysmal slow wave bursts respectively in 70,4%, 22,2% and 14,8% of treated patients. Co-treatment with another antipsychotic would increase EEG modifications while co-treatment with benzodiazepines would decrease modifications²³.

Another study evaluated EEG in 81 patients receiving monotherapy with quetiapine, olanzapine, and haloperidol. One patient in the quetiapine group (5%), 13 patients receiving olanzapine (35%), 5 patients treated with haloperidol (22,8%) presented EEG modifications. Epileptiform activities was observed only in four patients (10,8%) of the olanzapine group¹³.

In summary, the prevalence of EEG modifications appears to differ according to antipsychotic type. Prevalence of EEG modifications in people taking clozapine varies from 25% to 53% according to studies²⁴. Quetiapine appears to induce less EEG modifications^{13,21,25}. However, the number of EEG studies of atypical antipsychotics is reduced.

In this context, we conducted a comprehensive retrospective analysis of EEG recordings on patients with mental disorders and treated with atypical antipsychotic agents in strict monotherapy. We assumed that modifications might depend on the dose and type of antipsychotic. We considered combinations of EEG results with selected clinical and treatment factors. We hypothesized that severe EEG modifications would be associated primarily with clozapine and with a dose-dependent effect.

METHODS:

A data bank of 5217 EEG medical reports recorded from psychiatric patients admitted to the Sainte-Marguerite Psychiatric Hospital in Marseille between January 2012 and December 2016 was used. In this hospital, EEGs were systematically performed for initial assessment or when clinical signs

suggested another pathology or poor treatment tolerance.

From this data bank, we extracted EEG of patients with a strict antipsychotic monotherapy (without any associated psychotropic molecule, including anticonvulsant, lithium, benzodiazepines or antidepressant). The exclusion criteria were age <18 years, epilepsy, brain tumor, stroke, traumatic brain injury without complete clinical recovery, multiple sclerosis, positive HIV test, previous drug overdose leading to coma, presence of known previous EEG abnormalities, treatment with electroconvulsive-therapy (ECT) in the previous 4 months of the EEG recording.

The data collected in the medical records included sex, age, medical history, presence of psychiatric or neurological comorbidities, duration of disease, type of antipsychotic and daily dose administration prior to EEG registration. Long-acting antipsychotic injection doses were converted to an oral dose according to their oral dose equivalents. The doses of antipsychotic drugs (mg/day) were converted to chlorpromazine equivalents (mg/day) according to the equivalences established by Woods and al.²⁶.

Atypical antipsychotic agents were also divided into oral immediate-acting drugs (92.86% [n=78]) and long-acting injection drugs (7.14% [n=6]). Seven treatment groups were formed with 7 individual antipsychotic agents, including 2 treatment groups by long-acting injection antipsychotic.

EEG recording

The EEG recordings were performed according to the recommendations of the American Society for Electroencephalography, with a standard placement of 10 electrodes on 20 electrodes²⁷ on an EB-Neuro Galiléo system (Fiorenza, Italy) using 26 cup electrodes located according to the international 10–20 system: Fp1/p2, F7/8, F3/4, Fz, FC3/4, FCz, C3/4, T3/4, Cz, CP3/4, CPz, P3/4, T5/6, Pz, O1/2, and Oz. The reference electrode was positioned on the nose, and the ground was on an Fpz electrode. Electrode impedance was maintained below 5 k Ω . Data were digitalized continuously at 1024 Hz, with a 12-bit resolution. A low pass filter was set at 100 Hz prior to the digitalization.

The EEG was recorded during the waking state, 3 minutes of hyperventilation and intermittent photic stimulation for all patients. EEGs were recorded in the morning between 9 am and 12 pm, after breakfast. EEGs were recorded for at least 20 min. During the recording, the participant was monitored visually and by EEG for signs of drowsiness or sleep, which if happen, lead the technician neurophysiologist to speak and arouse him briefly and report this on the medical report. Two experienced and certified neurophysiologists interpreted all EEGs independently and one blind evaluator blinded to medication, dosage and diagnosis of patients. In case of disagreement, the records

were re-evaluated and discussed to reach consensus.

We assumed that these modifications could be distinguished into 2 categories of severity score: « slowing » and « neuronal excitability ». This classification is inspired by the classification of Micoulaud-Franchi et al.²⁸ about EEG effects of psychotropic drugs, itself adapted from this of Centorrino et al.²¹. This adaptation was done in order to classify the effects of psychotropic drugs in a wider range to include iatrogenic encephalopathies and to better guide the clinician about the therapeutic strategy. EEG modifications are classified as follows (Table 1). Concerning EEG activity slowing: 1 = no slowdown (predominant alpha rhythm), 2 = predominant theta rhythm, 3 = predominant theta rhythm with delta bursts, 4 = predominant delta rhythm. Concerning neuronal excitability: A = no signs of neuronal abnormal excitability, B = paroxysmal activities (sharp slow waves) occurring only during EEG activation (hyperventilation and/or intermittent photic stimulation), C = spontaneous paroxysmal activities during the whole recording, D = paroxysmal epileptiform discharges. An EEG without anomalies is ranked 1A. One EEG recording suggesting an encephalopathy is ranked 4C or 4D. We did not report drowsiness during any EEG recordings. Examples of these EEG modifications are presented Figure 1A and Figure 1B.

Statistical methods

Chi-square and Fisher's exact test (when appropriate) were used for comparisons of excitability score. Comparisons of the mean daily dose of oral antipsychotics according to the molecules with the EEG modifications (presence or not, score = C or not) were tested by Student-t test after verification if the data displayed a normal distribution. Means are indicated as averages and standard deviations (SD, standard deviation). The clinical factors were organized by categories to allow the use of contingency tables (chi-square) to test associations with EEG modifications (presence or not). Results with $p \geq 0.05$ were considered statistically insignificant. The ANOVA test was used to compare the equivalent dose of chlorpromazine, the excitability and the type of drug. The analyzes were carried out on the data analysis program R (R Development Core Team. *R: A language and environment for statistical computing* R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Eighty-four patients treated with atypical antipsychotics in strict monotherapy were included in this retrospective study. Patients received clozapine (n=22), aripiprazole (n=22), olanzapine (n=17), risperidone (n=9), quetiapine (n=8), risperidone long-acting injection (n=4), and paliperidone long-acting injection (n=2) (Figure 2). Among the subjects selected, 19.05% (n=16) were from full-time hospitalization and 80.95% (n=68) from day-hospitalization. Their mean age was 34.24 years (SD: 12.09, range 18 to 74) and 70.24% (n=59) were men. Psychiatric diagnoses (based on the DSM-IV criteria) included schizophrenia (69.05% [n=58]), schizoaffective disorder (11.9% [n=10]), bipolar disorder (11.9% [n=10]), major depressive episode (2.38% [n=2]) and a non-diagnostic category (4.76% [n=4]).

EEG modifications (score \neq 1A) were observed in 60,71% of the patients enrolled in the study (n=51) (Table 2).

Excitability and slowing score

Epileptiform modifications (score B and C) were associated with clozapine in 20 patients (90,9% of the patients of the clozapine group), with olanzapine in 10 patients (58,8% of the olanzapine group), with aripiprazole in 11 patients (50%), with quetiapine in 3 patients (37,5%) and with risperidone in 4 patients (44,4%), for oral molecules. Slight EEG slowing modifications (score = 2) were found in 1 patient with olanzapine (5,88% of the olanzapine group), in 4 patients with clozapine (18,2%), and severe (score = 3) for only 1 patient with clozapine (4,55%). No patients with encephalopathy (scores 4C or 4D) have been found.

Unlike typical epileptic abnormalities, the sharp slow waves and other epileptiform activities display a particular pattern different from the sharp slow waves observed in vascular insufficiency, for example: their locations vary during the recording, they can appear anywhere in cortex, they are frequently asynchronous. They do not indicate a focus and they create the impression of “blinking cortex”²⁰.

We found no correlation between the presence or severity of EEG modifications and clinical outcomes collected by consulting medical records. The following factors were not associated with EEG modifications: duration of disease > 5 years ($\chi^2 = 0.0051$, $df = 1$, $p = 0.94$), age > 40 years ($\chi^2 = 0.094$, $df = 1$, $p = 0.76$), diagnosis of schizophrenia ($\chi^2 = 1.21$, $df = 1$, $p = 0.27$).

Type of molecule

The distribution of excitability score according to molecules is clearly different. Clozapine induces many excitability modifications (score C is predominant) since paliperidone long-acting injection does not modify EEG. The occurrence of epileptiform activities was significantly higher for the group of patients receiving clozapine compared to that receiving aripiprazole ($\chi^2 = 9.35$, $df = 1$, $p = 0.007$), olanzapine ($p = 0.026$, Fisher's exact test), quetiapine ($p = 0.007$, Fisher's exact test), risperidone ($p = 0.012$, Fisher's exact test). No difference concerning the presence of epileptiform activities between other groups of molecules was found. Only clozapine and olanzapine induce EEG slowing in 6 patients.

Daily dose of antipsychotic

Since the dates of antipsychotic injections were not known, we chose not to include them in the dose comparisons in order to avoid « end-of-dose » effects. The results of comparing the mean daily doses of oral antipsychotics according to the presence of EEG or absence of EEG modifications and according to the presence of a C score or not are presented in Table 3.

No significant differences were found for the mean daily doses (in mg per day) of antipsychotic drugs between patients without EEG modifications and those with EEG modifications (aripiprazole: $t = 0.34$, $df = 20$, $p = 0.73$; olanzapine: $t = 0.29$, $df = 15$, $p = 0.77$; clozapine: $t = -0.49$, $df = 20$, $p = 0.66$; risperidone: $t = 0.45$, $df = 7$, $p = 0.67$; quetiapine: $t = 2.23$, $df = 6$, $p = 0.067$) (Table 3).

The mean daily dose of antipsychotics was not different according to molecule between patients with severe excitability score (score = C) or not (score = A, B) for aripiprazole ($t = -1.74$, $df = 20$, $p = 0.09$) for olanzapine ($t = 0.53$, $df = 15$, $p = 0.59$), for clozapine ($t = -1.16$, $df = 20$, $p = 0.25$), for risperidone ($t = 0.54$, $df = 7$, $p = 0.60$) and for quetiapine ($t = 1.35$, $df = 6$, $p = 0.22$) (Table 4).

Chlorpromazine equivalent doses of antipsychotic

The daily doses of oral antipsychotics in chlorpromazine equivalents were different between clozapine and aripiprazole ($t = 7.018$, $df = 42$, $p < 0.001$), clozapine and olanzapine ($t = -5.95$, $df = 37$, $p < 0.001$), clozapine and risperidone ($t = -5.75$, $df = 29$, $p < 0.001$). Daily doses of chlorpromazine

equivalents were different between patients with severe modifications (score = C) versus patients without severe modifications (score = A, B) ($t = -2.80$, $df = 76$, $p = 0.006$) (Table 5). No relationship was found between excitability score, type of drugs and dose (chlorpromazine equivalent) ($F = 1,29$, $p = 0,26$) (Figure 3). Nevertheless, score C was more frequently observed with high doses of chlorpromazine equivalent (> 500 mg/d).

DISCUSSION:

Excitability and slowing score

In this study, EEG data were examined from 84 patients treated with strict monotherapy of clozapine, olanzapine, quetiapine, aripiprazole, risperidone, long-acting risperidone and long-acting paliperidone. The modifications related to neuronal excitability (sharp slow waves and/or epileptiform activities) and induced by these different molecules are more frequent than in some other studies^{21,22}. Precisely, the modifications related to neuronal excitability in this study consist of slow angular activities, sometimes slow spikes, whose characteristic is to be of variable and transient localization. Unlike typical epileptic abnormalities, these iatrogenic modifications display an asynchronous pattern giving an impression of “blinking” cortex. This first result might be explained by the absence of benzodiazepines associated with antipsychotic treatment. It has been assumed that co-treatment with benzodiazepines may decrease the presence of EEG anomalies induced by antipsychotics^{21,23}. Compared to the study conducted by Centorrino et al.²¹, we found a relationship between the equivalent dose of chlorpromazine and EEG modifications (Table 3) probably for the same reason. Nevertheless, we can hypothesize that clozapine is probably responsible for this dose effect as shown in Figure 3, since clozapine treatments display the higher doses of equivalent dose of chlorpromazine.

An EEG slowing was observed in 6 patients (7.14%) only. In psychiatric patients, diffuse slowing accounts for 40% of all electroencephalographic modifications and is therefore the most frequent modification detected in EEG²⁹. The diffuse slowing of the EEG activity is often attributed to the effects of psychotropic medications³⁰ and compared to the effect of electroconvulsive therapy¹⁸, but can also be considered as the presence of an encephalopathic process³¹. Dasberg and Robinson have suggested that a diffuse or paroxysmal EEG slowdown under antipsychotic therapy might be indicative of better clinical response³. On the contrary, Boutros found a longer duration of hospitalization and an increased number of drugs and dosages in the patient group exhibiting an EEG slowdown. He suggested that this slowdown could be a reflection of the increased disease severity³². In our study, the use of monotherapies might explain the low number of patients with EEG slowing (n=6).

We have proposed a more detailed classification concerning the iatrogenic induced EEG modifications. In the present study, the EEG slowing is infrequent. This part of our classification of anomalies would be more relevant in the study of association of psychotropic drugs on more severe

pathologies and longer duration of evolution. In addition, we have observed that our classification is also more adapted to the encephalopathies and their outcome.

Type of molecule

It is known that the risk of convulsive seizures induced by antipsychotics is higher for clozapine than for risperidone and aripiprazole³³. EEG monitoring is suggested when the daily dose is 20 mg for olanzapine³⁴ and 400 mg for clozapine³⁴. Itil and Soldatos advise to repeat a neurophysiological examination and to review the history of the disease in search of seizure symptoms if epileptiform abnormalities on the EEG with a first-generation antipsychotic treatment were found¹⁴. As clozapine, olanzapine may induce EEG modifications such as slow waves, sharp waves and paroxysmal slow-wave discharges^{22,23,34}, but its convulsive risk is considered to be low²³. Our results on olanzapine effects are consistent with these studies. Only one previous study was interested in the prevalence of EEG modifications associated with aripiprazole³⁵. The prevalence was 5,9% and the modifications were not severe. We found severe EEG modifications in 27% of our subjects with aripiprazole but our classification is different. This result is to be compared with the higher risk of convulsive seizures induced by clozapine than risperidone and aripiprazole³³. EEG modifications induced by quetiapine are uncommon^{13,21,25} but we found EEG modifications associated with low daily doses of quetiapine. We have found no EEG modifications in relation to the daily doses of clozapine as compared to other studies³⁶⁻³⁸. These modifications have been described in relation to the plasma doses of clozapine³⁹⁻⁴¹. We were unable to compare plasma clozapine levels due to lack of data. Taking these results altogether it is difficult to predict the risk of convulsive seizures using EEG, more so if we postulate that excitability modifications are related to the therapeutic effect.

Although the number of patients was low, we found EEG modifications with patients treated with risperidone long acting injection. We did not find any studies on the prevalence of EEG changes and atypical antipsychotics long-acting injection. Studies on samples of larger subjects would be useful for studying the presence of EEG modifications on this type of treatment and more broadly on long-action atypical antipsychotics.

EEG modifications and clinical response

Only a few studies have focused on the link between EEG changes and clinical improvement. These studies focused on clozapine. Authors reported that EEG modifications under clozapine treatment appeared to be associated with good clinical response¹⁵⁻¹⁷. In clozapine monotherapy, the presence of paroxysmal EEG activities is known to be correlated with clinical efficacy, particularly in depressive symptoms¹⁵. This observation refers to “forced normalization” in epileptic patients, i.e. the emergence of psychotic symptoms when the reduction of paroxysmal activities by anti-convulsant therapy occurs in epileptic patients⁴². On the contrary, epileptic modifications seem to protect against psychosis. The induced paroxysmal activities could therefore be considered as the therapeutic effect and not only as a side effect. According to this hypothesis, it is possible that the therapeutic effect of clozapine and other antipsychotics is related to increase the excitability in subcortical or cortical zones of the brain⁴³. Some authors suggested a “reversal normalization” effect, with a possible phenomenon of “psychobiological compensation”²⁰. In agreement with this hypothesis, it has been reported that the addition of anticonvulsant may reduce the effect of clozapine^{44,45}, although Varma et al. suggest the use of prophylactic valproate when the clozapine plasma level exceeds 500 µg/l if the EEG shows clear epileptiform discharges²⁴.

Our study shows that other second-generation antipsychotics (including long-acting injectable molecules) also induce EEG modifications. Prospective studies are needed to define the clinical significance of types and levels of EEG modifications induced by atypical antipsychotic. These EEG modifications require exploring their link with the prognosis and clinical response to second-generation antipsychotic therapy.

Limitations and conclusion

The limitations of this study are the following: a) this is a retrospective design using the analysis of EEG coming from a database and medical records. So, in such a design, all the variables cannot be systematically documented; b) a control group of healthy subjects could not be established; c) we were unable to correct the equivalence of chlorpromazine by patient weights due to missing data in the clinical records; d) the clinical significance of EEG modifications was not specified; e) it was not possible to have control groups (healthy subjects, patients with psychiatric disease without treatment) because of the study design; f) for the same reason, it was not possible to know of EEG status of the patients prior to treatment, g) the number of subjects receiving certain antipsychotics was very low. Consequently, prospective studies are needed to define the clinical significance of certain types and

levels of EEG modifications. In spite of these limitations, the strength of the study is the analysis of strict antipsychotic monotherapies on the brain electric activity.

In conclusion, this preliminary study has yielded several interesting results. Clozapine in monotherapy is the molecule that gives the most frequent EEG modifications compared to other atypical antipsychotic. These modifications are rather of the epileptiform type, although an EEG slowing is also observed. Quetiapine appears to induce modifications in low doses. Serious epileptiform modifications are associated with greater equivalent doses of chlorpromazine. Our results reinforce the routine use of electroencephalogram in the monitoring of second-generation antipsychotic treatments and support further work to investigate the relationship between EEG modifications and clinical symptoms.

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SLOWING AND EXCITABILITY CLASSIFICATION			
SLOWING SCORE		EXCITABILITY SCORE	
RANK	DESCRIPTION	RANK	DESCRIPTION
1	Absent (predominant alpha)	A	Absent
2	Theta slowing	B	Sporadic epileptiform discharges or sharp slow waves during hyperventilation or photic stimulation
3	Theta slowing with delta bursts	C	Sporadic epileptiform discharges or sharp slow waves during the whole recording
4	Delta slowing	D	Long lasting epileptiform discharges

TABLE 1: Classification for EEG slowing and excitability (inspired by the classification of Micoulaud-Franchi et al.²⁸)

ANTIPSYCHOTICS	n	AGE		CHLORPROMAZINE EQUIVALENT DOSE (mg/d)		EEG MODIFICATIONS SCORE ≠ 1A	
		MEAN	SD	MEAN	SD	n	%
Immediate, oral							
ARIPIPRAZOLE	22	28.8	7.77	186.4	100.1	11	50
CLOZAPINE	22	39.36	13.25	668.2	344.2	20	90.9
OLANZAPINE	17	33	11.81	230.3	144.5	10	58.8
QUETIAPINE	8	34.13	9.88	425	319	3	37.5
RISPERIDONE	9	33.33	15.16	150	70.7	4	44.4
Long-acting, injection (LI)							
RISPERIDONE LI	4	37.5	16.42	137.5	37.9	3	75
PALIPERIDONE LI	2	45.5	9.19	175	37.4	0	0

TABLE 2: Percentage of EEG modifications (score >1A) according to the antipsychotic treatment in 84 hospitalized psychiatric patients (n = number of patients)

ANTIPSYCHOTIC	EEG MODIFICATIONS			ABSENCE OF EEG MODIFICATIONS			<i>t-test</i>
	n	DOSE MEAN (mg/d)	SD	n	DOSE MEAN (mg/d)	SD	
ARIPIRAZOLE	11	14.55	7.23	11	13.41	8.08	n.s.
OLANZAPINE	10	11.08	7.30	7	12.14	7.69	n.s.
CLOZAPINE	20	347.5	172.04	2	200	141.42	n.s.
RISPERIDONE	4	2.75	1.79	5	3.2	0.96	n.s.
QUETIAPINE	3	116.67	76.38	5	480	268.33	n.s.

(n: number of patients; n.s . not significant; *Differences statistically significant.)

TABLE 3: Comparison of mean daily doses of each oral antipsychotic according to modifications (score >1A) vs no modifications of EEG.

ANTIPSYCHOTIC	SCORE=C			SCORE=A or B			<i>t-test</i>
	n	DOSE MEAN (mg/d)	SD	n	DOSE MEAN (mg/d)	SD	
ARIPIRAZOLE	6	18.33	6.83	16	12.34	7.27	n.s.
OLANZAPINE	6	10.21	6.73	11	12.23	7.73	n.s.
CLOZAPINE	18	344	179,3	4	275	158,1	n.s.
RISPERIDONE	2	2.5	0.71	7	3.14	1.57	n.s.
QUETIAPINE	2	125	106.07	6	416.66	285.77	n.s.

(n: number of patients; n.s . not significant; *Differences statistically significant.)

TABLE 4: Comparison of mean daily doses of oral antipsychotics according to excitability score.

		SCORE=C		SCORE =A or B			
ANTIPSYCHOTIC	n	CHLORPROMAZINE EQUIVALENT DOSE MEAN (mg/d)	SD	n	CHLORPROMAZINE EQUIVALENT DOSE MEAN (mg/d)	SD	<i>t-test</i>
All oral antipsychotics	34	463.97	360.11	44	271.7	244.5	p= 0.0064*

(n: number of patients; n.s . not significant; *Differences statistically significant.)

TABLE 5: Comparison of mean daily doses of oral antipsychotics equivalent chlorpromazine according to excitability score. When all the doses are converted in chlorpromazine equivalent, one can observe that the EEG excitability increase in patients with high doses of Chlorpormazine EQ.

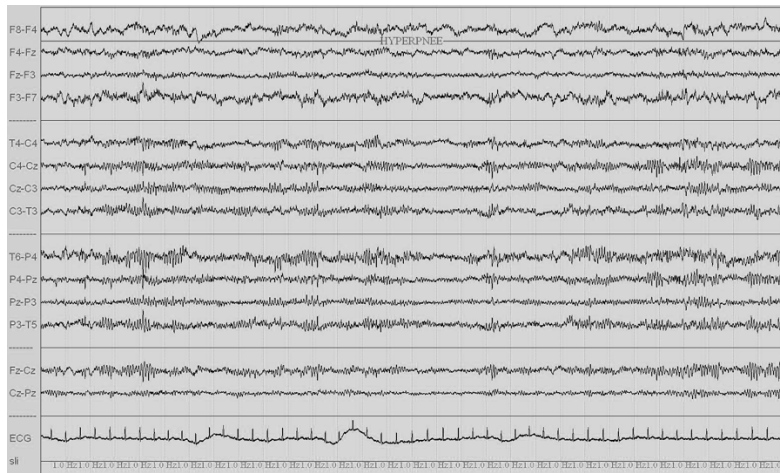


FIGURE 1A: EEG records showing the typical modifications observed in the EEG, for a patient treated by aripiprazole (score 1B).

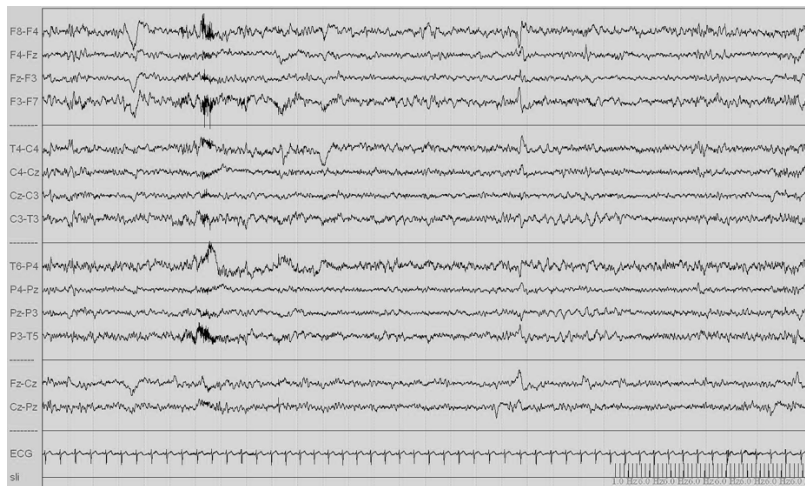


FIGURE 1B: EEG records showing the typical modifications observed in the EEG, for a patient treated by clozapine (score 3C)

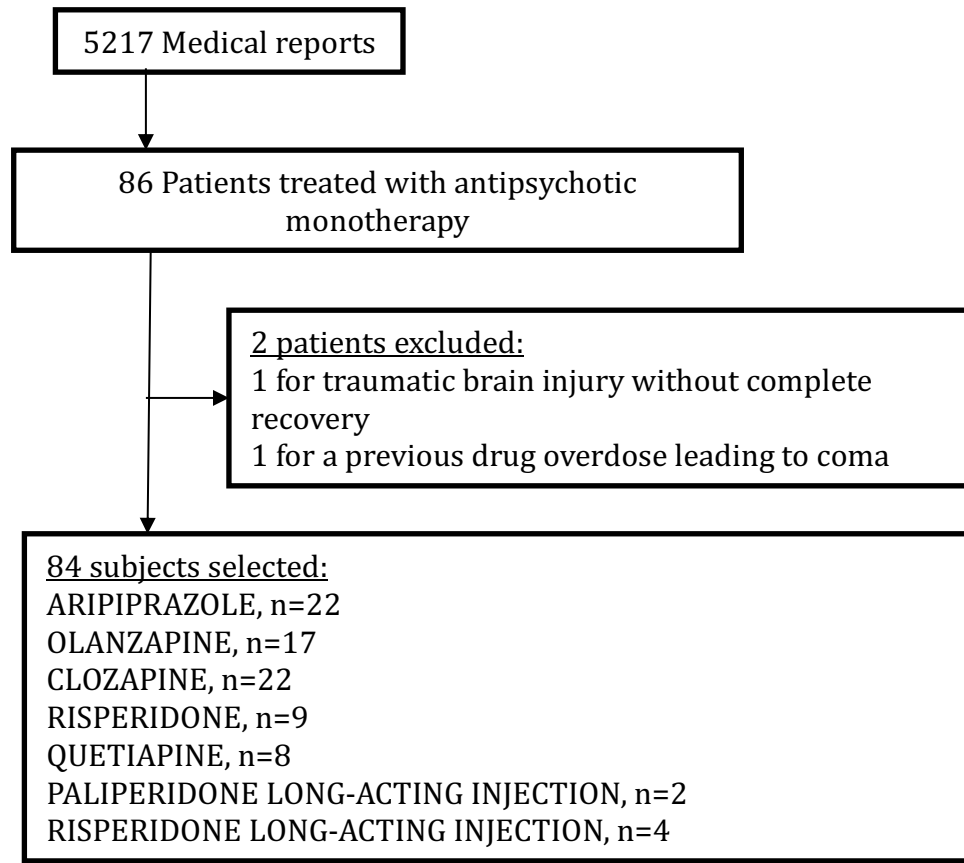


FIGURE 2: Flowchart of the study.

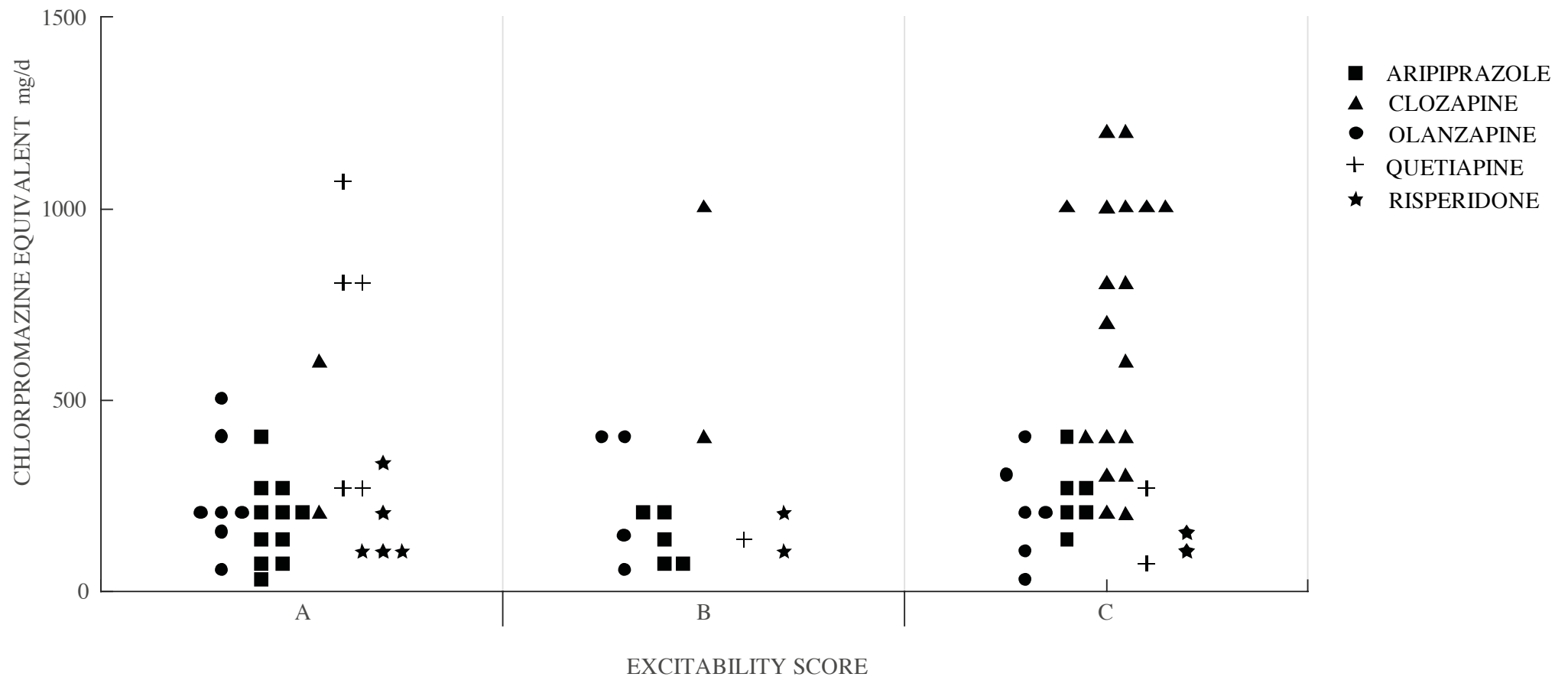


FIGURE 3: EEG Results of Excitability score by type and dose (in chlorpromazine equivalent, in mg/day) of each antipsychotic for 78 patients with oral atypical antipsychotic monotherapy.