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METABOLIC ALTERATIONS ASSOCIATED WITH FIRST AND SECOND GENERATION ANTIPSYCHOTICS: AN TWENTY-YEARS OPEN STUDY

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SUMMARY

Introdution: *The initial enthusiasm for atypical antipsychotics, with a lower incidence of extra pyramidal symptoms, was tempered by the association with metabolic disorders. The presence of metabolic alterations significantly influences morbidity and patients' quality life. We performed this open-study to determine the relationship between antipsychotic efficacy and side effects, especially the impact of various antipsychotics on metabolic parameters after 20-year treatment with atypical (SGA) and typical antipsychotics (FGA).*

Method: *62 psychiatric schizophrenic inpatients treated with typical (haloperidol) and atypical (clozapine, risperidone, olanzapine, quetiapine, aripiprazole) antipsychotics were studied over 20 years. Some biological parameters such as blood arterial pressure, lipidic and glucidic profile, liver enzymes, complete blood count, electrocardiogram and body weight (and body mass index) were collected.*

Results*: The results have demonstrated a not homogeneous statistically significant variation of the lipidic and glicidic profile but we have also found a reduction of the recorded values at endpoint vs baseline in aripiprazole and haloperidol groups vs clozapine, olanzapine, and quetiapine groups.*

Conclusions: *We want to point out that to endpoint of the period of observation (20 years) the patients with typical antipsychotics haloperidol reported satisfactory and a better glycemic and lipidic profiles than previous pharmacological treatments with antipsychotics of second generation. Optimal monitoring should include assessments of fasting glucose, lipids, cholesterol, and blood pressure.*

Key words: *metabolic syndrome - first generation antipsychotics - second generation antipsychotics*

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INTRODUCTION

Antipsychotic agents are mainly used for prevention or treatment of schizophrenia and serious psychotic diseases. Antipsychotics of first (FGA) and second generation (SGA) are broad-spectrum neurotherapeutic agents capable of attenuating numerous symptoms. Over the past decade, atypical (or second-generation) antipsychotics have been increasingly used in the treatment of schizophrenia in preference to conventional (first-generation) drugs (Crossley 2010). The second-generation antipsychotics are promoted as offering several therapeutic advantages when compared with the older first-generation agents (e.g., enhanced efficacy for neurocognitive deficits, reduced propensity for neurological adverse events) (McIntyre et al. 2007). For this reason, although the antipsychotics have improved the prospects of many patients with schizophrenia and are widely used, their effectiveness remains limited (Miron 2014). The initial enthusiasm for atypical antipsychotics, with a lower incidence of extra pyramidal symptoms, was tempered by the association with metabolic disorders. The use of antipsychotics is hindered by the frequent occurrence of metabolic side effects, resulting in worsened quality of life and greater mortality as a result of cardiovascular and cerebrovascular disorders in schizophrenia patients than the comparable general population (Yogaratnam 2013). Second generation antipsychotics are associated to increased risk factors for metabolic syndrome (Ravindranath 2012) comprising obesity, dyslipidaemia, glucose intolerance, insulin resistance (or hyperinsulinaemia), hypertension and weight gain in the majority of patients on antipsychotic medication (Vancampfort 2013). Some of these patients have been shown to develop metabolic alteration, with a reduced life expectancy by 20% compared to the general population (Liese 1998, Newman 1991).

Genetic factors leading to insulin resistance (Newcomer 2007) can also contribute to the patients' predisposition to metabolic disorder, and currently there is debate as to whether these disorders are part of the disease process itself through increase of stress factors and inflammatory responses (Cheng 2014). Up to 50% of patients with schizophrenia may develop metabolic syndrome (McEvoy 2005). It remains possible that all factors in some way contribute to the predisposition of metabolic syndrome in these patients, however, antipsychotic drugs are thought to be the main causal factor in the development of metabolic syndrome. Weight gain is the most recognized metabolic effect, although this varies significantly among atypical antipsychotics: clozapine and olanzapine had the highest risk, quetiapine and risperidone moderate risk, aripiprazole, amisulpride and ziprasidone the lowest risk, with a negative impact on the adherence to treatment and the quality of life (Monteleone 2009, Boyer 2014).

We performed this open-study to determine the relationship between antipsychotic efficacy and side effects, especially the impact of various antipsychotics on metabolic parameters after 20-year treatment with atypical (SGA) and typical antipsychotics (FGA). The aims has been to identify advantages and disadvantages of GAs in terms of quality of life, costs and benefits of therapy with antipsychotics.

METHODS

Sixty-two psychiatric inpatients diagnosed with schizophrenia or schizoaffective disorder (DSM-IV-TR diagnosis), and treated with typical (haloperidol) and atypical (clozapine, risperidone, olanzapine, quetiapine, aripiprazole) antipsychotics were studied over 20 years. We retrospectively evaluated also data collected during the period of observation in a routine clinical setting. Some biological parameters such as blood arterial pressure, lipidic and glucidic profile, liver enzymes, complete blood count, electrocardiogram and body weight (and body mass index) were collected.

Data were extrapolated at baseline (T0) and after 1 (T1), 5 (T2), 10 (T3), 15 (T4) and 20 (T5) years during every clinical control visit in relation to antipsychotic therapy. The rating scales administered were the following: Clinical Global Impression-Improvement (CGI-I) (Guy 1976); Positive and Negative Syndrome Scale (PANSS) (Kay 1989); Brief Psychiatric Rating Scale (BPRS) (Overall 1962), Quality of Life Index (QLi) (Ferrans 1985). Partial data were obtained with the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984) and the Scale for Assessment of Negative Symptoms (SANS) (Andreasen 1983).

Statistical analysis

t tests for continuous variables and $\chi 2$ tests for proportion was used for analysis. Data were analyzed using 2-tailed tests of significance with 95% confidence intervals. p value of <0.05 delineates: significant difference in switching group of patients.

Limits and criticism

We have used only patients' data who continued to take the same antipsychotic therapy for all the duration of the observation period. Some patients have used other drugs which are not antipsychotics in combination. Patients who have shown significant changes in biological parameters were subjected to specific treatment programs (pharmacological, dietary restrictions, improvement in lifestyle). Because of organizational and helpfulness problems the data concerning measurement of the waist circumference are incomplete and restricted to a limited number of patients.

RESULTS

The results have demonstrated a not homogeneous statistically significant variation of the lipidic and glicidic profile but we have also found a reduction of the recorded values at endpoint vs baseline in aripiprazole and haloperidol groups. Clozapine and olanzapine treatment are associated with an increased risk of diabetes mellitus and dyslipidaemia, during the 20-year follow-up. Analyzing some results we can demonstrate that the mean values of total cholesterol and triglyceride are higher particularly in clozapine and olanzapine groups. The glycemic values are not statistically different in quetiapine, aripiprazole, and haloperidol groups. No significant statistical variations were observed in complete blood count, electrocardiogram, liver enzymes, blood pressure and body weight. The efficacy therapeutic data were presented in our previous works (EPA 2014, ECNP 2013).

In Table 1 epidemiological data are shown; while in Figure 2 Lipid and Glicid parameter results are highlighted.

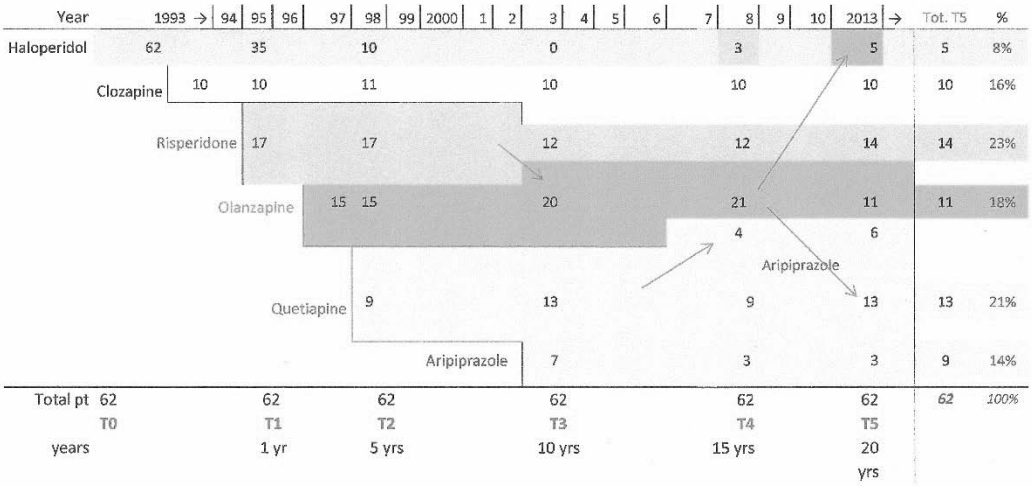
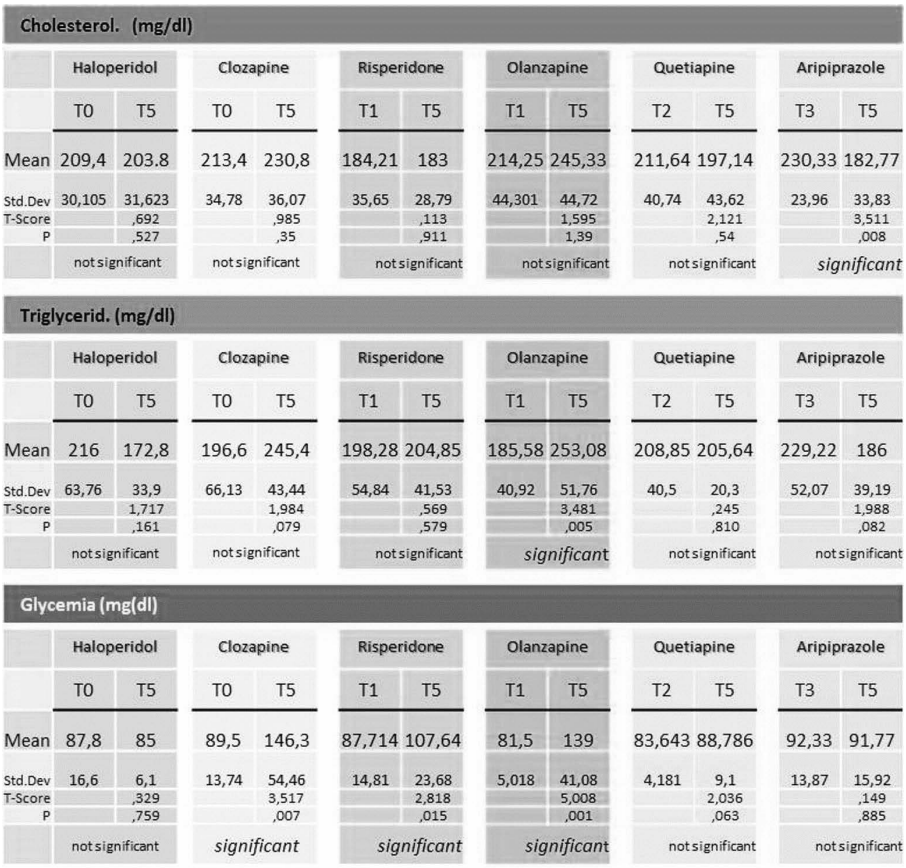


Figure1. Timetable: switching antipsychotics 62 schizophrenic patients from 1993 to 2013



Cholesterol. (mg/dl)

	Haloperidol		Clozapine		Risperidone		Olanzapine		Quetiapine		Aripiprazole	
	T0	T5	T0	T5	T1	T5	T1	T5	T2	T5	T3	T5
Mean	209,4	203.8	213,4	230,8	184,21	183	214,25	245,33	211,64	197,14	230,33	182,77
Std.Dev	30,105	31,623	34,78	36,07	35,65	28,79	44,301	44,72	40,74	43,62	23,96	33,83
T-Score		,692		,985		,113		1,595		2,121		3,511
P		,527		,35		,911		1,39		,54		,008
	not significant		not significant		not significant		not significant		not significant		*significant*	

Triglycerid. (mg/dl)

	Haloperidol		Clozapine		Risperidone		Olanzapine		Quetiapine		Aripiprazole	
	T0	T5	T0	T5	T1	T5	T1	T5	T2	T5	T3	T5
Mean	216	172,8	196,6	245,4	198,28	204,85	185,58	253,08	208,85	205,64	229,22	186
Std.Dev	63,76	33,9	66,13	43,44	54,84	41,53	40,92	51,76	40,5	20,3	52,07	39,19
T-Score		1,717		1,984		,569		3,481		,245		1,988
P		,161		,079		,579		,005		,810		,082
	not significant		not significant		not significant		*significant*		not significant		not significant	

Glycemia (mg(dl)

	Haloperidol		Clozapine		Risperidone		Olanzapine		Quetiapine		Aripiprazole	
	T0	T5	T0	T5	T1	T5	T1	T5	T2	T5	T3	T5
Mean	87,8	85	89,5	146,3	87,714	107,64	81,5	139	83,643	88,786	92,33	91,77
Std.Dev	16,6	6,1	13,74	54,46	14,81	23,68	5,018	41,08	4,181	9,1	13,87	15,92
T-Score		,329		3,517		2,818		5,008		2,036		,149
P		,759		,007		,015		,001		,063		,885
	not significant		*significant*		*significant*		*significant*		not significant		not significant	

Figure 2. Lipid and Glicid parameter results

Table 1. Baseline Epidemiological data (T0 - 1993)

	Number of patients		mean age	SD ±	%
Baseline	62	Total	34.84	10.05	
	20	Female	34.15	8.16	32.3
	42	Male	34.70	11.60	67.7

Overweight and obesity

The criteria for defining metabolic syndrome include those formulated by the National Cholesterol Education Program (the Adult Treatment Panel III (ATP-III) and adapted ATP-III (ATP-III-A) criteria (Grundy 2005)) and the criteria of the International Diabetes Federation (IDF) (Alberti 2006). Current definitions for metabolic syndrome aim for ease of use in clinical settings, and they have similar diagnostic thresholds. However, the role of abdominal obesity is central to the IDF definition, providing ethnicity-specific thresholds for waist circumference (Alberti 2009).

Using WHO criteria for overweight and obesity of a BMI of 25-29.9 kg/m2 and a BMI of 30 kg/m2 and over, 52,3% of subjects were found to be overweight and 13.5% subjects to be obese. This finding is a 2-fold higher prevalence of obesity compared to the general population. Data have shown also the higher incidence of overweight patients in the treatment group with olanzapine and clozapine and a lower incidence in the group theated with haloperidol and aripiprazole.

CONCLUSIONS

The results confirm studies on efficacy and effectiveness of both SGAs and FGAs, and their influence on metabolic profile and other biological parameters. Our data has demonstrated a strong link between patients who are mentally ill and metabolic alterations. This study has highlighted the main concerns that predispose these patients to metabolic alterations with antipsychotic medications, which can increase their health risks of secondary complications such as obesity, dyslipidaemia, glucose intolerance, hypertension and weight gain. Patients treated with medications that have the potential for weight gain and metabolic side effects should have weight and metabolic parameters evaluated even more frequently. The European Psychiatric Association (De Hert 2009) recommends that in patients taking antipsychotics, monitoring should take place at the initial presentation and before the first prescription of any antipsychotic and, for patients with normal baseline tests, measurements should be repeated at 6 weeks and 12 weeks after treatment initiation and at least annually thereafter. Optimal monitoring should also include assessments of fasting glucose, lipids, cholesterol, and blood pressure (Vancampfort 2013).

We want to emphasize that to endpoint of the period of observation (20 years) the patients with typical antipsychotics haloperidol reported satisfactory and better glycemic and lipidic profiles than with previous

pharmacological treatments with antipsychotics of second generation. Despite the limits of the study (small examined sample, absence of controls, contemporaneous consumption of other medicines), these data can represent a "real world " study in patients observed during our daily out-patient practice.

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Conflict of interest: None to declare.

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