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METABOLIC ALTERATIONS AND DRUG INTERACTIONS: THE ROLE OF THE ASSOCIATION BETWEEN ANTIPSYCHOTICS / MOOD STABILIZERS AND COGNITIVE DEFICITS

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SUMMARY

Alterations in the metabolic profile are one of the main consequences of the use of drug therapies in psychiatric patients. In particular, dysfunction of the metabolic profile (lipid and glycidic) is very frequent in patients taking antipsychotics, especially second-generation ones, and antidepressants. Similar alterations, albeit, to a lesser extent, were highlighted with the use of mood stabilizers. There are some clinical conditions in which clinicians add antipsychotics and mood stabilizers. Our study analyzed this interaction in 116 inpatients. Data showed an overall increase in metabolic parameters in all patients analyzed. However, no statistically significant differences were found in some subgroups of patients. The correlation between metabolic alterations and cognitive dysfunctions in these patients was also analyzed (not statistically significant).

Key words: *metabolic deficits - cognitive deficits – antipsychotics – antidepressants - mood stabilizers*

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INTRODUCTION

Metabolic disorders have been highlighted in psychiatric patients suffering from mood disorders and anxiety disorders (Hung et al. 2014). The simultaneous presence of various alterations of the metabolic profile associated with other alterations has allowed to define the so-called metabolic syndrome. The components of this syndrome include dyslipidemia, hypertension, changes in the glucose profile, obesity. However, alterations of these components are already present in many psychiatric patients regardless of the intake of drug therapies (Corell et al. 2008). Because of the high prevalence of metabolic dysfunctions in patients with primary psychosis, these patients are exposed to a high risk of mortality and morbidity. This is due to the higher incidence of developing diabetes mellitus type 2 and cardiovascular disease (Reininghaus et al. 2022, Abosi et al. 2018). Several international guidelines help clinicians to monitor drug side effects. Among these guidelines the most used are American Diabetic Association and American Psychiatric Association (ADA-APA 2004) for monitoring the metabolic consequences of second-generation antipsychotics. Metabolic deficits are present in a high percentage of patients with bipolar disorder (8-56% of patients (Babić et al. 2010)). A study conducted by the group of Bai et al. (2016) found that 29.4% of patients with bipolar disorder presented a metabolic syndrome. The authors believed that "*the frequent cooccurrence of bipolar disorder and MetS may be characterized by the common genetic links, interconnected pathophysiologies, and interacting biological networks with structural and functional abnormalities in multiple cortical and subcortical brain regions subservient to cognitive and affective processing*". The same study found an increase in metabolic alterations in patients who took mood stabilizers and antipsychotics in combination (36.3% in antipsychotics plus mood stabilizers vs 36% atypical antipsychotics alone (36.0%) vs 10.5% mood stabilizers alone). These data were substantially different from other studies showing a higher prevalence in the combined antipsychotic (AA) group (48.1%) according to ATP III criteria (Cerit et al. 2010).

Furthermore, the primary psychoses (Maj et al. 2021) are associated with the worsening of cognitive functions not only during acute episodes but also during interepisodic periods. Several cognitive domains are involved. Attention, executive function, working memory are the most involved domains. These alterations create a worsening of the quality of life of these patients with repercussions on psychosocial and occupational functions.

Recent studies have highlighted the interaction between metabolic dysfunction and deficits in some cognitive areas (Dalkner et al. 2021). Individuals with bipolar disorder and metabolic alterations had a worsening of executive functions compared to patients without alterations. In the other cognitive domains such as attention / processing speed and verbal learning / memory, no significant interactions were found. Individuals with bipolar depression (BD) and metabolic syndrome (MetS) had impaired executive function in comparison to patients without MetS as well as health control with and without MetS. For attention/processing speed and verbal learning/memory, no significant interactions of MetS and BD were found (Dalknet et al. 2021). The explanation for this higher prevalence is a poor diet,

cigarette smoking, lack of exercise, stress, and abnormalities in the hypothalamic-pituitary-adrenal axis. The side effects of drug therapies aggravate these conditions.

A review by Sneller et al. (2021) found a close association between SGAs (Second Generation Antipsychotics) and increased risk of MetS. The results showed some clinical factors, gender, higher age, concomitant use of mood stabilizers, higher baseline and current BMI, earlier SGA exposure, higher dose, longer duration of treatment and tobacco to be significantly associated with MetS. Patients with primary psychosis present overweight and obesity. These metabolic alterations are both intrinsic to the disease but are also associated with the use of antipsychotic therapies and / mood stabilizers (Reininghaus et al. 2022). Individuals with BD, for example, show a worsening in some cognitive domains, such as attention and concentration that are negatively correlated with weight gain. Central obesity appears to be affecting overall cognitive functioning.

The purpose of our study was to evaluate the alterations in the metabolic profile in a group of patients with primary psychosis from the association of antipsychotics with mood stabilizers. The possible interference of cognitive deficits on metabolic alterations in the same group of patients was also analyzed.

METHOD

One hundred sixteen [total 116 (mean age: 49.19 years, ± SD 13.06 yrs), 44 men (mean age: 47.77 years, ± SD 13.83 yrs), 72 females (mean age: 50.04 years ± SD 12.61 yrs) inpatients of the Psychiatric Rehabilitation Center "Villa dei Pini" located in Avellino, Italy, affected by Primary Psychosis (Maj et al. 2021) were recruited in our study. All inpatients met the diagnostic criteria of the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders - APA, 2014) for schizophrenia, schizoaffective disorder, bipolar disorder (type I and II), and borderline personality disorders. The main inclusion criteria were the following: age range between 18 and 65; therapeutic compliance, simultaneous intake of mood stabilizers and antipsychotics for ≥ 6 months.

The main exclusion criteria were the following: double diagnosis for Addiction Disorders, uncertainty of therapeutic continuity and poor adherence to therapy.

Initially, 387 subjects who met the inclusion criteria according to the DSM-5 for Primary Psychosis were recruited for the study. Initial screening resulted in the selection of 116 inpatients with study inclusion characteristics representing 29.97% of the total number of patients initially involved in the study.

All patients were recorded at baseline (T0) and after 6 months (T1) the following epidemiological and anamnestic data: age; sex, marital status, levels of education (years), profession, use and / or abuse of drugs and / or alcohol, smoking (see Table 1).

Table 1. Epidemiological data

	N	Mean	±SD
Age (yrs)			
Total	116	49.19	13.06
Female	44	47.77	13.83
Male	72	50.04	12.61
Diagnosis			
BD	25	49.04	13.74
BP	16	47.94	12.85
MDD	18	46.47	9.95
S	57	44.94	16.37
Educ lev (yrs)	116	12.47	5.96
		Number	%
Marital status			
married		34	29.31
single		68	58.62
widower		14	12.07
Addiction			
smoking		67	57.75
alcohol		14	12.07
other		5	4.31

Legend: BD: Bipolar disorder; BPD: Borderline Personality Disorder; MDD: Major Depressive Disorder; S: Schizophrenia

Sensitive data have been subject to remodeling for the statistical survey in the subsequent times of administration of the scales, as indicated below.

The following biological parameters were recorded for all patients at the start of the study and subsequently within the time frame established by the project itself: blood pressure, heart rate, weight, height; BMI (Body Mass Index), lipid and glucose metabolic profile (cholesterolemia, triglyceridemia).

At the beginning of the observation period indicated as baseline or T0 and subsequently after 6 months (T1), the following assessment scales were administered to all patients at the same time as the recording of biological parameters:

- Global Assessment of Functioning Scale (GAF) (Endicott et al. 1976). It was used to evaluate psychological, social, and occupational functioning on a hypothetical mental health continuum.
- Brief Psychiatric Rating Scale (BPRS) (Overall 1988) for psychopathological assessment.
- Epitrack® cognitive tool was used to evaluate changes in the cognitive profile. It's a quick and easy-to-use assessment tool that is designed for identifying and tracking drug side effects in epilepsy patients. Our study is an innovative condition for the use of this tool in patients suffering from cognitive spectrum disorder (Lutz et al. 2005, Franza et al. 2016).

Pharmacological treatment: all patients took mood stabilizers (lithium, carbamazepine, lamotrigine, valproic acid) and a second-generation antipsychotics (SGAs) (aripiprazole, risperidone, olanzapine, quetiapine, paliperidone).

Table 2. Glycemic and Cholesterolemia data (T0 vs T1)

	Glyc T0		Glyc T1		N pairs	Mean difference	SE of diff.	Eta squared	T-score	P	Difference T0 vs T1
	mean	± SD	mean	± SD							
Total	96.802	±19.921	105.017	±22.703	116	-8.216	2.106	0.116	3.901	0.000	+
BD	94.120	±13.827	107.360	±20.748	25	-13.240	3.797	0.327	3.487	0.002	+
BPD	93.438	±14.877	99.375	±21.878	16	-5.938	4.103	0.116	1.447	0.168	-
MDD	98.278	±20.531	108.556	±21.437	18	-10.278	4.219	0.248	2.436	0.026	+
S	98.456	±23.149	104.456	±24.297	57	-6.000	3.537	0.048	1.696	0.095	-
	Cholest T0		Choles T1								
Total	178.913	±40.903	179.974	±51.615	116	-1.061	4.517	0.000	0.235	0.815	-
BD	176.840	±46.806	195.400	±54.223	25	-18.560	8.449	0.162	2.197	0.038	+
BPD	173.188	±23.080	175.438	±44.955	16	-2.250	12.666	0.002	0.178	0.861	-
MDD	195.722	±49.720	184.444	±45.916	18	11.278	11.430	0.051	0.987	0.338	-
S	176.071	±38.603	172.946	±53.527	56	3.125	6.614	0.004	0.472	0.638	-

Legend: BD: Bipolar disorder; BPD: Borderline Personality Disorder; MDD: Major Depressive Disorder; S: Schizophrenia

Table 3. Triglyceridemia and BMI data (T0 vs T1)

	Triglyc T0		Triglyc T1		N pairs	Mean difference	SE of diff.	Eta Squared	T-score	P	Difference T0 vs T1
	mean	± SD	mean	± SD							
Total	135.687	±72.191	141.652	±72.658	116	-5.965	6.816	0.007	0.875	0.383	
BD	154.720	±81.627	158.920	±73.410	25	-4.200	12.426	0.005	0.338	0.738	-
BPD	143.813	±100.482	150.438	±63.396	16	-6.625	23.148	0.005	0.286	0.779	-
MDD	121.889	±48.756	153.833	±76.892	18	-31.944	16.540	0.172	1.931	0.070	-
S	114.250	±49.620	152.161	±79.718	56	-37.911	7.958	0.288	4.764	0.000	+
	BMI T0		BMI T1								
Total	27.490	±5.397	28.206	±6.052	116	-0.716	0.234	0.075	3.057	0.003	+
BD	29.948	±6.025	31.190	±7.362	25	-1.242	0.510	0.192	2.435	0.023	+
BPD	29.276	±4.040	28.893	±4.309	16	0.383	0.716	0.018	0.534	0.601	-
MDD	25.153	±2.778	26.401	±3.800	18	-1.248	0.450	0.299	2.773	0.013	+
S	26.633	±5.611	27.257	±6.047	56	-0.624	0.335	0.058	1.861	0.068	-

Legend: BD: Bipolar disorder; BPD: Borderline Personality Disorder; MDD: Major Depressive Disorder; S: Schizophrenia

All the relevant data were analysed using EZAnalyze Version 3.0, Microsoft Excel Add-ln (Suffolk University in Boston, Massachusetts, USA). Paired-samples t-test used for analysing data (age, gender, scales, etc.). Test: $p<0.05$ was taken as statistically significant.

RESULTS

The data obtained were analyzed as a comparison between the means of the total scores of each metabolic subgroup identified in our research (glycemia, cholesterolemia, triglyceridemia, BMI) in T0 and T1. Furthermore, we have analyzed differences for each metabolic subgroup and patient disorders between T0 or T1 (see table 2).

The data obtained from the glycidic profile showed a statistically significant difference in the whole group of patients with an increase in the mean overall score (T0 vs T = 1-8.216; T-Score: 3.901; p: 0.000). This score indicates an overall increase in blood glucose values. Analysis of the data in each group of disorders revealed statistically significant differences in patients with bipolar disorder (T0 vs T1 = Mean Difference: -13.240; T-Score: 3.487; p:0.002) and major depressive disorder ((T0 vs T1 = Mean Difference -10.278; T-Score: 2.426; p: 0.026).

Non-statistically significant differences were observed in borderline personality disorder and schizophrenia subgroups.

Data analysis if T0 vs T1 for plasma cholesterol levels indicated an overall statistically insignificant difference (T0 vs T1= Mean Difference: 1.061; T-Score: 0.235; p: 0.815). Non-statistically significant differences

Table 4. Percentage of obesity in inpatients group T0 vs T1

	T0		T1	
	N	%	N	%
Total	38	32.76	47	40.52
BD	13	40.33	14	54.17
BPD	6	37.50	7	43.75
MD	6	16.66	7	38.89
S	13	23.21	19	33.93

Legend: BD: Bipolar disorder; BPD: Borderline Personality Disorder; MDD: Major Depressive Disorder; S: Schizophrenia

Table 5. Psychopathological and cognitive assessment scales T0 vs T1

	Mean	± SD	Mean	± SD	N pairs	Mean difference	SE of diff.	Eta squared	T-score	P	Difference T0 vs T1
Epitrack	21.926	8.140	22.832	7.089	95	-0.905	0.798	0.013	1.134	0.259	-
BPRS	52.026	10.302	50.791	9.379	115	1.235	0.903	0.016	1.368	0.174	-
GAF	47.139	9.899	47.852	11.393	115	-0.713	0.824	0.006	0.865	0.389	-

were found in all patient subgroups except bipolar disorder (T0 vs T1 = Mean Difference: 8.449; T-Score: 2.197; p: 0.038). Although there are variations in the mean total score (T0 vs T1 = 135.687 vs 141.652), the triglyceric plasma value scores did not show statistically significant differences (T0 vs T1 = Mean Difference: 5.965; T-Score: 0.875; p: 0.383). Similar scores were observed in all patient subgroups (see tables 2 and 3).

Data regarding the differences in changes in total BMI values and for each patient subgroup are shown in Table 4. There was a general increase in the mean total scores and in the bipolar disorder and major depression disorder subgroups. Notably, the total scores showed a statistically significant difference (T0 vs T1 = Mean Difference: 0.716; T-Score: 3.057; p: 0.003).

In lithium/valproate augmentation, significant increases in body weight were observed at 6 months: 4.7±1.9 kg in the lithium/valproate group, and 1.8±0.7 kg in the adjunctive SGAs group; however, this difference was nonsignificant. In the lamotrigine/SGAs study, a slight increase in body weight has been demonstrated after 6 months (0.72±0.98 kg). These results are comparable to those of other studies (Kemp et al. 2013). Table 4 shows the percentages of obesity (total score and score of each subgroup of disorders). The prevalence of total obesity T0 vs T1 was 32.76 vs 40.52%.

The largest percentage differences were observed in bipolar disorder and Major Depressive Disorder (respectively, 40.33% (T0) vs 54.17% (T1) and 16.66% (T0) vs 38.89% (T1).

Table 5 shows the results of the analysis of the scores on the BPRS scales (T0 vs T1 = Mean Difference: 0.905; T-Score: 1.134; p: 20.259), GAF (T0 vs T1 = Mean Difference: 1.235; T-Score: 1.368; p: 0.174), and Epitrack ((T0 vs T1 = Mean Difference: 0.713; T-Score: 0.865; p: 0.389).

The differences in the total scores and each subgroup, while interesting, were not statistically significant. It should be noted that 21 (18.10%) patients had not completed the Epitrack®, indicative of the difficulty of participating in the administration of the test or the refusal. The comparison between differences in the values of the glycidic, lipid and BMI profiles versus the differences in the cognitive profile of the subjects analyzed did not show statistically significant differences.

CONCLUSIONS

The results of our study are comparable to those of other studies. Indeed, the study conducted by Corell et al. (2008) had shown that the percentage of patients treated with SGAs and Mood stabilizers affected by metabolic alterations was between 43.2% and 45.9%.

In our previous work we observed that 52.3% of patients with primary psychosis were overweight and 13.5% were obese. (WHO criteria) (Franza & Cervone 2014). A body weight gain has been associated with poorer outcome in several psychiatric disorders. However, this relationship is unclear (McElroy et al. 2016). Another study (Dalkner et al. 2021) showed a prevalence of metabolic alterations in 30.4% of individuals with BD, mainly in males and smokers. The results of our observational study confirmed previous observations on the role of drug treatment with mood stabilizers in combination with antipsychotics (Kuperberg et al. 2022, Mazereel et al. 2020, Chen et al. 2014, Faghihi et al. 2012). However, the results obtained were not significant in all patient subgroups. An overlap of data was observed in the subgroup of individuals with depression and bipolar disorder. On the other hand, the results obtained with the BMI were statistically significant. All diagnostic groups had statistically significant differences. The need for more in-depth research into the assessment of changes in the cognitive profile and metabolic alterations is fundamental.

The limit must be sought above all in the evaluation tools used. In our study we observed a very high refusal rate from the administration of the cognitive assessment tool. In fact, as already shown in our previous studies (Franza et al. 2018, 2017, 2015) there is a need to use rapid, simple, and patient-pleasing clinical evaluation tools. The aim of our study was to provide an overall picture of the work done in normal clinical activity in a psychiatric rehabilitation center in a group of residential patients.

Given the numerous criticalities and limitations of our study, it would be necessary to further research in this field to identify clinical markers that can identify and direct the patient's overall treatment.

Contribution of individual authors:

Nicoletta Fiorentino: contribution to writing and to bibliographic research.

Annalisa Soddu: contribution to writing.

Barbara Solomita: contribution to writing and to bibliographic research

Giuseppe Rosato: contribution to writing.

Francesco Franza: conception and preparation of the manuscript.

Giuseppe Tavormina: revision of the manuscript.

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