THE TIME COURSE OF SECOND GENERATION ANTIPSYCHOTIC METABOLIC SIDE EFFECTS: RESULTS FROM A ONE-YEAR PROSPECTIVE EVALUATION IN A COMMUNITY MENTAL HEALTH SERVICE

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Abstract

Object: Although many data have been accumulated on the metabolic side effects of SGAs (Second Generation Antipsychotics) during the last few years, some important questions remain unanswered. Most published studies have a retrospective design and derive from pre-existing data bases lacking important clinical information and it is not clearly defined when and how the metabolic side effects arise. Moreover most of these studies are sponsored by pharmacological industries and may reflect a conflict of interests. Our study is a one of the few prospective studies carried out in the real practice world. It is aimed to evaluate the time course of metabolic disorders during the first 12 months of treatment.

Method: This study is a one-year prospective non-controlled evaluation in a community mental health service. All patients starting a new SGA treatment (clozapine, olanzapine, risperidone or quetiapine) were enrolled. Planned assessments included fasting glucose, cholesterol, triglycerides and BMI (baseline and 4th, 24th, 48th week).

Results: Thirty-nine outpatients provided complete blood samples. At the 24th week we observed an increase in mean BMI and a tendency for cholesterol to increase; at the 48th week we observed only an increase in mean BMI. No further metabolic worsening was observed after the first 6 months of treatment. All new cases of metabolic disorders occurred during the first 6 months of treatment.

Conclusions: Our study highlights that weight gain and metabolic disorders begin to appear right from the first month of treatment and reach a peak at 6 months. Our results suggest that clinical attention right from the first month of SGA treatment could be possible an early detection of metabolic side effects and thus early monitoring could prevent the clinical consequence of metabolic disorders. Therefore, weight, glycaemia and lipaemia should be monitored routinely in clinical practice right from the first months of antipsychotic treatment.

Key Words: Metabolic Side Effects – Second Generation Antipsychotics (SGA) – Clozapine – Olanzapine – Risperidone – Quetiapine – Fasting Glucose – Cholesterol – Triglycerides – BMI – Weight – Glycaemia – Lipaemia

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Introduction

Obesity and metabolic disorders due to Second Generation Antipsychotics (SGA) are a serious and widespread health problem (Basu and Meltzer 2006, Lamberti et al. 2006, Murashita et al. 2007, Peuskens et al. 2007). These drugs are the first line treatment (Davis et al. 2003, Lehman et al 2004, Davis and Chen 2005, Murashita et al. 2007) for schizophrenia and related psychotic disorders. In addition, there is a trend towards an increase in the prevalence of obesity, diabetes mellitus and metabolic disorders in the general population (Ford et al. 2002, Ford et al. 2004), at present representing one of the leading causes of cardiovascular disease (Fontaine et al. 2001).

Many data have been accumulated on the metabolic side effects of SGAs during the last few years, but some important questions remain unanswered. Most published studies have a retrospective design and derive from pre-existing data bases lacking important clinical information (Caro et al. 2002, Gianfrancesco et al. 2002, Koro et al. 2002, Koro et al. 2002, Meyer 2002, Sernyak et al. 2002, Wirshing et al. 2002, Cunningham et al. 2003, Fuller et al. 2003, Citrome et al. 2004, Ascher-Svanum et al. 2005, Megna et al. 2006); it is not clearly defined when and how the metabolic side effects arise. Moreover, possible differences in how SGA metabolic side effects are induced is a much debated question: clozapine and olanzapine have been implicated more frequently than

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risperidone, while a lower number of studies are available for quetiapine. Finally, most of these studies are sponsored by pharmacological industries and may reflect a conflict of interests. The present one-year prospective non-controlled study aimed to evaluate the time course of metabolic disorders due to SGAs by examining the modification of metabolic status in outpatients with mental disorders treated with SGAs in everyday clinical practice.

Method

Data were collected over 2 years (2003-2004) at a Community Mental Health Centre (CMHC) in Bologna (Italy). The subjects for the present study were outpatients who started a new course of treatment with an SGA during the index period. No exclusion criterion was applied being this a naturalistic and prospective study; thus patients with every kind of psychosis were included. None of the patients included had organic psychosis or substance dependence, as those patients are referred to specific units. The study design did not affect clinical routine: the choice of the antipsychotic and the dosage were entirely decided by the treating psychiatrists. Informed consent was obtained from eligible patients. This study was performed with the approval of the Bologna University Ethics Committee, in compliance with the Helsinki Declaration.

A baseline assessment was performed before taking the drug, then three subsequent evaluations were performed at the 4th, 24th and 48th week. Clinical records were used for psychiatric diagnoses according to DSM IV (APA 1994) criteria. Patients' socio-demographic, clinical (family history of physical disease) and treatment (current antipsychotic and doses, kind of previous antipsychotic treatment and kind of other psychotropic drugs with potential metabolic side effects) information was collected using an *ad hoc* schedule. Fasting plasma glucose, triglycerides and cholesterol levels were determined by enzymatic procedures applying the Roche/Hitachi Modular D-P automated chemistry analyzer and using the standard analytical system packs Glucose/God-pap, Cholesterol/CHOD cod-pap and Triglycerides/GPO-pap. Patients'weight and the computed BMI were also measured.

Statistical Analysis

We used analysis of variance (ANOVA) with repeated measures to examine the differences between baseline, 4 weeks, 24 weeks and 48 weeks in BMI, glucose, cholesterol and triglyceride levels. Patients who were treated with hypoglycaemic agents (n=3) were excluded from the glucose analysis. One outlier patient with triglycerides levels exceeding 2sd was excluded from the triglycerides analysis. The alpha level was considered significant when below 0.0125 (Bonferroni corrected: 0.05/4 laboratory indexes). Then we performed post-hoc analysis to show differences between baseline and 4 to 48 weeks of treatment.

The relationship between changes in metabolic parameters, BMI, and the sociodemographic (sex and age), clinical (psychiatric diagnosis, diabetes and dyslipidemia familiarity, metabolic abnormality at baseline, type of previous antipsychotic treatment, type of co-therapy with metabolic side effects) and treatment (type of SGA) variables were investigated by analysis of covariance (ANCOVA). When we used an analysis of covariance (ANCOVA) including as covariates kind of SGA, previous antipsychotic treatment, or co-therapy with other psychoactive drugs, we covaried with type of medication (dummy variable) and not with total doses. Finally we evaluated the bivariate correlations between metabolic parameters and SGA doses with Pearson correlation analysis.

The transitions from normal to abnormal BMI and metabolic parameters were evaluated by the chi-square analysis and Fisher exact test. Abnormal metabolic levels and BMI were defined in our study on the basis of the National Cholesterol Education Program (McIntyre et al. 2003) and Word Health Organisation (Alberti et al. 1998) criteria as follows: 1) BMI was defined as abnormal when between 25 and 29.9 for overweight (equal to or greater than 30 for obesity); 2) abnormal blood glucose level was when equal to or greater than 110 mg/dl (equal to or greater than 126 mg/dl for diabetes); 3) the blood cholesterol level was defined as abnormal when equal to or greater than 200 mg/dl; 4) and blood triglyceride levels when equal to or greater than 150 mg/dl. For categorical analysis the power of our sample to detect differences between the two groups was calculated considering an alpha value of 1.25%. For t-tests, we calculated a power of 0.80 to detect a medium-large effect size (d=0.59) (Cohen 1988).

For all the analyses we used Statistica for Windows (Statsoft, Kernel Release 5.5).

Results

Sample and Attrition

Fifty-seven patients started a new SGA treatment in the index period; All patients were evaluated at baseline, but only 39 (68.4%) underwent the complete assessment at the 4th ,24th, and 48th week. However patients with complete assessment could not have all the measurements of the metabolic variables and weight. Among the 18 patients who were not included in the study group, 5 missed blood testing and 13 were no longer in treatment with the SGA prescribed at baseline: 5 for clinical improvement, 5 for side effects (three cases of hyperprolactinaemia and two of weight increase) and 3 for lack of efficacy. Overall the patients who were not evaluated at 6 and 12 months did not differ from the study sample as to baseline socio-demographic, clinical and treatment features.

Among patients who started a new SGA treatment in the index period, thirty patients were previously in therapy with First Generation Antipsychotic (FGA) or SGA and required a treatment change (because inefficacy of therapy or side effects), while nine patients were drug-free (table 2).

Demographic and Basic Descriptive Data

Table 1 shows the clinical and demographic features of the study sample at baseline: the mean cholesterol level was borderline (threshold 200 mg/dl). The mean BMI level was over the overweight threshold but did not pass the obesity threshold. The mean level of triglycerides and glucose were within the normal range; however 2 patients had diabetes (glycaemia >126 mg/dl).

The correlations with clinical and socio-demographic features were investigated. Patients with a family history of diabetes had significantly higher mean BMI and higher prevalence of obesity (BMI e" 30) than patients without one (mean BMI: 31.2±4.7 vs 25.5±3.9 - F=9.4, df 1(30), p=0.002; obesity: 12.9% vs 7.8%, chi sq.=6.2, df=1, p=0.013).

Treatment distribution and mean drug doses

Seventeen patients received quetiapine, thirteen olanzapine, five risperidone and four clozapine (table 2). The large majority of patients treated with quetiapine had previously been treated with SGA (n=11, 64% chi-sq. 18,2, df 1, p<0.0001), two treated with olanzapine and none treated with risperidone. Obviously, all patients on clozapine had in the past received other antipsychotic treatment. Twelve patients were treated with co-therapy since the baseline (8 with SSRI antidepressants and 4 with mood stabilizers); after the first month of treatments two more patients had a co-therapy with SSRI, while only 11 patients took adjunctive co-therapy after the sixth and twelve months of SGA treatment (table 2).

At the 24th week, the mean drug doses were 500.0±182.6 mg/die in the clozapine group, 2.8±1.3 mg/die in the risperidone group, 9.0±6.3 mg/die in the olanzapine group and 367.6±289.8 in the quetiapine group. Two patients (one with quetiapine and one with clozapine) were treated with oral hypoglycaemic agents as from baseline, one patient (on olanzapine) after one month, and one patient (on olanzapine) after six months. Three patients treated with clozapine were obese at baseline. No other clinical differences among the treatment groups were observed.

Change Over Time and Incidence of obesity and metabolic disorders

Table 3 displays descriptive data for mean changes in BMI, glucose, cholesterol and triglycerides at the 4th, 24th and 48th week compared to baseline. Overall it has been possible to compare with ANOVA analysis 25 patients on BMI change, 23 on glucose change, 33 on cholesterol and 26 patients on triglycerides. Mean BMI significantly increased during the study period , markedly during the first 6 months. A trend towards an increase in cholesterol mean levels was observed during the first 6 months, but the cholesterol mean level decreased during the last six months. Triglycerides and glucose mean levels remained substantially stable over time.

Figure 1 describes the prevalence of overweight, obesity, hyperglycaemia, diabetes, hypercholeste-

Table 1. *Socio-demographic and clinical features at the baseline*

Male	22 (56%)
Age	49.0±7.3
Psychiatric Diagnosis	
Schizophrenia and other Psychotic Disorders	21 (54%)
Mood Disorders	15 (38%)
Psychosis NOS	3 (8%)
Family History of	
Diabetes	10 (26%)
Dyslipidemia	11 (28%)
Mean metabolic parameters values	
BMI	27.2±4.3
Glycaemia[1] (mg/dl)	91.0±17.3
Cholesterolaemia (mg/dl)	203.6±37.5
Trigliceridaemia [2] (mg/dl)	132.2±58.3
Percentage of metabolic disorders	
Overweight	13 (33%)
Obesity	9 (23%)
Hyperglycaemia	3 (8%)
Diabetes	2 (5%)
Hypercholesterolaemia	17 (44%)
Hypertriglyceridaemia	11 (28%)

[1]Mean calculated without the glycaemia level of two patients treated with hypoglycaemic agents
[2] Mean calculated without the triglyceride level of one outlying patient

Figure 1. *Prevalence of metabolic disorders at baseline, 1, 6 and 12 months*

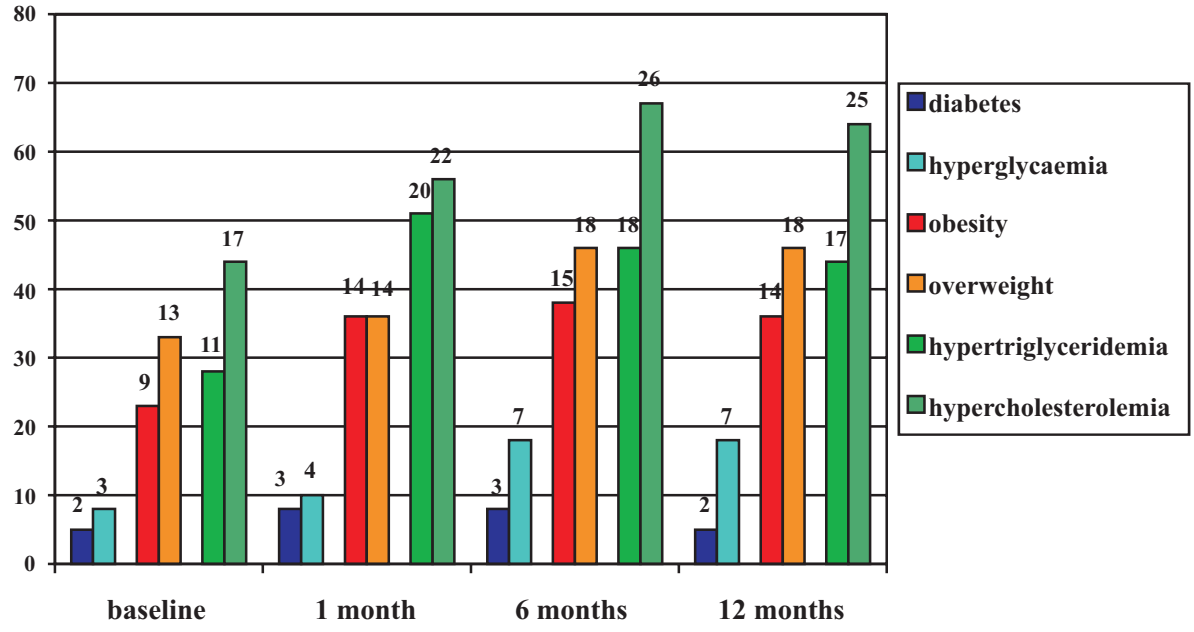

Table 2. *Treatments*

	Clozapine (n=4)	Risperidone (n=5)	Olanzapine (n=13)	Quetiapine (n=17)	SGA (n=39)
Treatments Doses (mg)					
Baseline	375.0±253.3	3.4 ±2.7	10.6 ±6.3	153.0±138.6	
1 month	512.5±143.6	3.6 ±2.7	11.0 ±8.9	264.8±181.6	
6 month	500.0±182.6	2.8 ±1.3	9.0 ±6.3	367.6±289.8	
Past treatments					
Drug naïve	-	2 (40%)	5 (39%)	2 (12%)	9 (23%)
FGA	1 (25%)	3 (60%)	6 (46%)	4 (23%)	14 (36%)
SGA	3 (75%)	-	2 (15%)	11 (64%) *	16 (41%)
Cotherapy with metabolic side effects					
Baseline	1 (25%)	2 (40%)	4 (31%)	5 (29%)	12 (31%)
1 month	1 (25%)	2 (40%)	6 (46%)	5 (29%)	14 (36%)
6 months	1 (25%)	2 (40%)	3 (27%)	5 (29%)	11 (28%)
12 months	1 (25%)	2 (40%)	3 (27%)	5 (29%)	11 (28%)

*chi-sq. 18,2, df 1, p<0.0001, quetiapine vs all others

rolaemia and hypertriglyceridaemia at one, six and twelve months of study. We noticed that the higher incidence of new cases of obesity and metabolic disorders was reached at 6 months; during the subsequent 6 months several cases recovered. One patient developed *ex novo* diabetes from the first month of treatment with olanzapine (reaching the 126 mg/dl glucose level threshold in two consecutive fasting blood tests). This patient was treated with oral hypoglycaemic agent and recovered after the first 6 months of SGA. None of the sociodemographic, clinical and treatment variables were found to affect the time course of weight and metabolic parameters during the study period. In particular, we did not find any correlations between SGA doses and time course of metabolic side effects.

Discussion

The present study on SGA-related weight gain and metabolic disorders is one of the few research projects carried out in an everyday clinical setting and covering the first 12 months of treatment. The few other prospective studies specifically aiming to evaluate SGA

Table 3. *Changes in metabolic mean values after 1, 6 and 12 months*

	Baseline	1 month	6 months	12 months	f	df	p*
BMI**	27.2±4.3	27.9±4.2	29.0±4.7	29.1±4.7	12.1	3(75)	**<0.0001**
Glucose[1]mg/dl	91.0±17.3	88.6±15.2	88.6±12.0	92.0±29.5	0.7	3(69)	0.58
Cholesterolmg/dl	203.6±37.5	212.7±45.7	218.7±43.3	209.5±41.3	2.4	3(99)	0.68
Triglycerides[2]mg/dl	132.2±58.3	161.8±89.8	134.3±72.1	141.7±79.1	1.9	3(78)	0.14

*significance for 0-12 months means comparison
** Post Hoc Analysis :
-baseline vs 6 months: p= 0.000035
-1 month vs 6 months p=0. 012986
-1month vs 12 months p=0.006090
[1] mean calculated without the glycaemia level of two patients treated with hypoglycaemic agents
[2] mean calculated without the triglyceride level of one patient

metabolic side effects have a shorter follow-up period (Eder et al. 2001, Ryan et al. 2004, Chiu et al. 2006, Rettenbacher et al. 2006, Wu et al. 2006, Peuskens et al. 2007). Even if we have a small sample size our findings could add further knowledge to previous data mainly by highlighting the time course of these side effects. Our study highlights that weight gain and metabolic disorders begin to appear right from the first month of treatment and reach a peak at 6 months.

Consistently with the literature (McIntyre et al. 2003, Hummer et al. 1995, Henderson et al. 2000, Ganguli et al. 2001, Atmaca et al. 2003, Garyfallos et al. 2003, Lindenmayer et al. 2003, Howes et al. 2004, Covell et al. 2004, Lieberman et al. 2005, Peuskens et al. 2007), the most pronounced metabolic side effect from SGAs observed in our sample was a significant mean BMI increase, followed by a less prominent increase in the mean cholesterolaemia level. Both the parameters had an increase in the first six months. At the twelfth month there were no further increases: the mean cholesterol proved a little decreased, the mean BMI did not change. The incident cases analysis showed a time course consistent with the mean changes in parameters. The cumulative number of metabolic disorder incident cases is 10 at the first month, 16 at the sixth month and 14 at the twelfth month. The highest number of new pathological cases features was hypercholesterolaemia: one third of the patients developed hypercholesterolaemia during the first six months of treatment. A remarkable number of patients developed overweight and obesity; a lower number developed *ex-novo* hyperglycaemia and hypertriglyceridaemia. Virtually all new cases of metabolic disorders appeared during the first six months of treatment. Thus, we believe that an early and on-going evaluation is of primary importance for a good clinical practice. The rate of obesity and metabolic disorders observed in the current study were higher than the prevalence in the general population as from baseline (Dunstan et al. 2002, Ford 2005, De Hert et al. 2006) and similar to the prevalence found in extensive studies of psychiatric samples (Allison et al. 1999, Coodin 2001, Homel et al. 2002), as we reported in our previous cross-sectional study (Tarricone et al. 2006). The baseline metabolic profile of our sample worsened further during the treatment period. We did not find correlations between sociodemographic, clinical and treatment variables with the time course of metabolic side effects in our study sample. The absence of differences among SGAs in causing metabolic side effects could be due to the smallness of our sample size; furthermore the present study was not designed to detect differences between SGAs, as discussed in the next section on methodological limitations. Though our result should be regarded with caution since the small sample size, our finding are in accordance with those of the other clinical prospective studies which showed the high impact of different SGA on body weight (Hummer et al. 1995, Briffa and Meehan 1998, Henderson et al. 2000, Atmaca et al. 2003, Garyfallos et al. 2003, Lindenmayer et al. 2003, Covell et al. 2004, Lieberman et al. 2005, Peuskens et al. 2007) and with the results of the large Allison metanalysis (Allison et al. 1999). Neither did we find a correlation between SGA doses and the mean metabolic levels and BMI levels, which would accord with the data in the literature (Henderson et al. 2000, Lindenmayer et al. 2003, Basson et al. 2001, Kinon et al. 2001, Reynolds et al. 2003).

Limitations

The limitations of our study are inherent in our study design. This is an observational and naturalistic study, carried out to evaluate the metabolic side effects of SGA in a real world outpatients setting.

Patients with differing socio-demographic and clinical features were followed-up. Despite checking for these variables as covariates in the ANCOVA analysis, we cannot rule out that such differences may have been confounding factors influencing our results. On the other hand, our study design allowed us to give a more representative picture of the real clinical setting. Moreover our study is one of the few in this field to have been designed and carried out independently of the drug companies. Limitations of our study include the attrition rate of our study group which resulted in a small sample size. This reduced our power which was

only sufficient to observe medium-large effect sizes, and therefore smaller effects may have been missed by our study. Moreover, although the attrition was governed by clinical factors, it was comparable among the four treatment groups.

The little sample size, the variable dose of the antipsychotic medication in the study period, together with the differing previous treatment histories among treatment groups, make it impossible to clarify whether different SGAs imply a different time course for the metabolic side effects. In particular, we were not able to report the length of time that previous treatments have been administered and the concurrent dosing of adjunctive medication that have been administered during the index period. Moreover, we have not assessment of physical exercise or diet which may have an important influence on metabolic profiles.

Since patients with schizophrenia and patients treated with FGAs are known to be at higher risk of developing obesity and diabetes mellitus than the general population (Drury and Farron-Ridge 1921, Lorenz 1922, Kasanin 1926, Mohan et al. 1999, Dwyer et al. 2001, Bushe and Holt 2004, Kohen 2004, Toalson et al. 2004, De Hert et al. 2006), further research with a control group are needed to define the specific time course of SGA metabolic side effects.

Conclusions

Our results enlightened that metabolic side effects arise since the first months of treatment. Clinical attention right from the first month of SGA treatment could imply a early detection of metabolic side effects; thus, early plasma and weight monitoring could reduce the clinical consequence of metabolic disorders.

Considering the early development of the metabolic side effects, monitoring of weight, fasting plasma glucose levels, fasting cholesterol, and triglycerides should be carried out routinely in clinical practice since the baseline and with particular efforts during the first six month of treatment; after the initial period, evaluations of the metabolic side effects should be obtained periodically. International guidelines agree to evaluate and monitor weight and metabolic side effects more strictly in the first months of treatment with SGA, but they suggest different follow up for each parameters: APA and ADA 2004 recommend to monitor weight quarterly, family history, waist circumference, blood pressure and glycaemia yearly, lipid profile every five years; Lambert and Chapman 2004 recommends to evaluate BMI quarterly, blood pressure, glycaemia and lipid profile every six months; Expert Consensus Meeting (Dublin 2004) suggest monitoring of glycaemia in SGA naïve people every four months and then yearly.

Particular efforts should be devoted to implementing early strategies of counselling on patient lifestyles and behaviour, which could *per se* potentially limit the antipsychotic metabolic side effects (Faulkner et al. 2003, Mauri et al. 2006, Alvarez-Jimenez et al. 2006). Clinical counselling right from the first month of treatment could prevent the metabolic consequence of SGA treatment by increasing patient and carer awareness, adopting primary prevention strategies (diet, exercise...) and early detection of these disorders. Moreover, clinicians should consider that several personal and familial risk factors could enhance the risk of developing metabolic disorders from SGAs.

Thus, as international consensus conferences have recommended (APA and ADA 2004, Expert Consensus Meeting, Dublin 2004, Lambert and Chapman 2004), clinicians should be aware of any personal and family risk factors of obesity and metabolic disorders when treating patients with antipsychotic agents. Further clinical and genetic investigations are required to ensure prompt identification of patients at high vulnerability for SGA metabolic side effect development.

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