Development of Metabolic Syndrome in Drug-Naive Adolescents after 12 months Second-Generation Antipsychotic treatment.

Abstract.

Objectives:

Poor physical health and shorter life expectancy often follows from mental illness. If the obesity or metabolic aberration starts in childhood or adolescence, the risk of an adverse outcome is even higher. Second generation antipsychotics (SGAs) are suspected to increase cardiovascular risk, possibly through the development of the metabolic syndrome (MetS).

Methods:

Drug-naïve adolescents were recruited after contact with the Psychosis Team. Changes, relative to baseline, in body mass index (BMI), waist circumference (WC), blood pressure (BP), fasting blood glucose (FBG), and high-density lipoprotein (HDL) cholesterol were determined, with follow-up every third month, or when available in the case files.

Results:

35 SGA-naïve patients aged 7–19 (mean:15.5) years with a diagnosis of psychosis were included. The overall rate of MetS was 0% at baseline and 20% at 12 months. There was a significant increase in BMI (18.4% [$p < 0.001$]), WC (14.3% [$p < 0.001$]), TG (25.2% [$p = 0.039$]), and FBG (3.6% [$p = 0.038$]), while there was a significant decrease in HDL (-11.5% [$p < 0.001$]). No significant change was found for BP. The monthly increase in BMI (0.29 kg/m^2) was approximately 10 times that of the World Health Organization BMI growth charts (0.036 kg/m^2).

Conclusions:

This is, to our knowledge, the first study to include all of the aforementioned aspects in drug-naïve adolescents over a 12 month period. This study found a significant shift of all parameters (except BP) of MetS, and demonstrates a clear progression towards MetS due to SGA-use. These adolescents need proper follow-up, not only monitoring, but also preventive measures that can stagger this development.

Introduction.

The life expectancy of people with severe mental disorders has been shown to be drastically shortened. In a scandinavian study, life expectancy was reduced by approximately 15 years for women, and 20 years for men[1]. Cardiovascular disease and Diabetes Mellitus type 2 (DM 2) appears to be more prevalent than in the mentally healthy population[2].

The use of second generation antipsychotics (SGAs) is steadily increasing, both in Europe and the USA[3]. SGAs have been proven effective for both psychotic disorders, autism spectrum disorders[3], and ADHD[4]. In Denmark, SGA use in 0-17-year olds has increased by more than 150% from 2002-11[5].

SGA use has long been suspected to disturb metabolism. Furthermore, a large weight gain in childhood/adolescence often extends into adulthood[6,7] and may lead to more severe outcomes[8] than if contracted at an early age. Also, adolescents have been found to be more susceptible than adults to the changes in BMI that SGAs inflict, both when compared with non-naïve[9] and naïve adults[10].

All this together points to a lifelong struggle for those adolescents who are treated with SGAs and develop metabolic disturbances as a consequence.

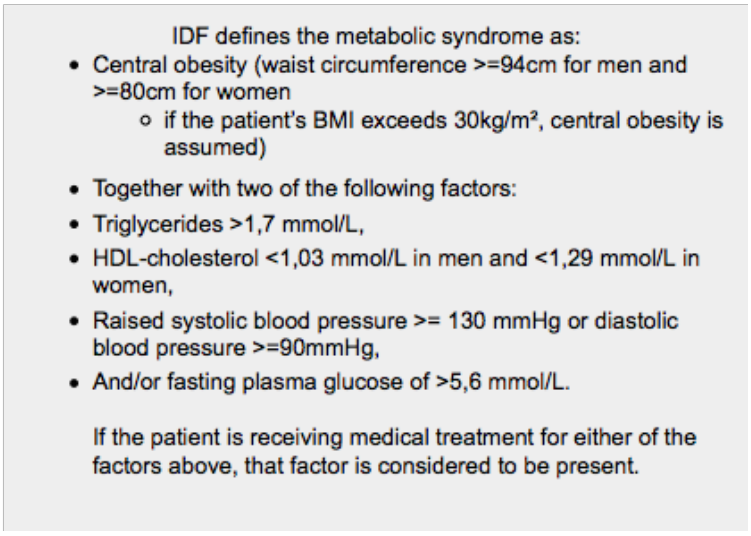

Figure 1. IDF's definition of the metabolic syndrome.

The metabolic syndrome (MetS) is a cluster of risk factors that increases the patients' vulnerability to cardiovascular events and DM 2. This article employs the International Diabetes Federation's definition of the metabolic syndrome[11] (see Figure 1).

SGA use in adults has been shown to affect several aspects of the MetS-definition. It can be rapid, as demonstrated in a study of physically and mentally healthy adults, where olanzapine was administered for 3 days, resulting in HDL-cholesterol decreasing by 10%, and triglycerides increasing by 22%[12].

Furthermore, a comprehensive review found that fasting blood glucose changes in children/adolescents occur early with SGA treatment, and that the prevalence of DM 2 is increased 8 times compared to normal controls, 1.5 times compared to psychiatric controls[13]. This highlights the need for a drug-naïve study gorup.

Hypertension, the final element of MetS, has not been widely studied in children/adolescents. In a naturalistic cohort study, 26% of the adults treated with SGAs suffered from hypertension[14], and illustrates the potential harm that SGAs might do after some years of treatment.

In adults receiving SGAs, MetS was present in 32.5%[15]. For adolescents, one of only few studies on MetS in this population found a prevalence of 19% in SGA-treated children[16].

This article aims to demonstrate weight gain and metabolic side-effects in drug-naïve adolescents over the first 12 months of SGA-treatment. This is done in a naturalistic setting, describing all features of the MetS as well as the syndrome as a whole.

Methods and Materials.

Design

12 month follow-up cohort study, based on clinical records.

Material

All patients referred to the Early Intervention Team at the Unit for Child- and adolescent psychiatry in Odense, Denmark, in 2011-14 (Figure 2).
Inclusion criteria: <20 years of age at initiation of SGAs, a diagnosis of psychosis, and SGA-treated for ≥12 months.
Exclusion criteria: IQ <70, diagnosis within the autism spectrum, somatic illness affecting metabolism, not drug-naïve at baseline, or declined to participate.

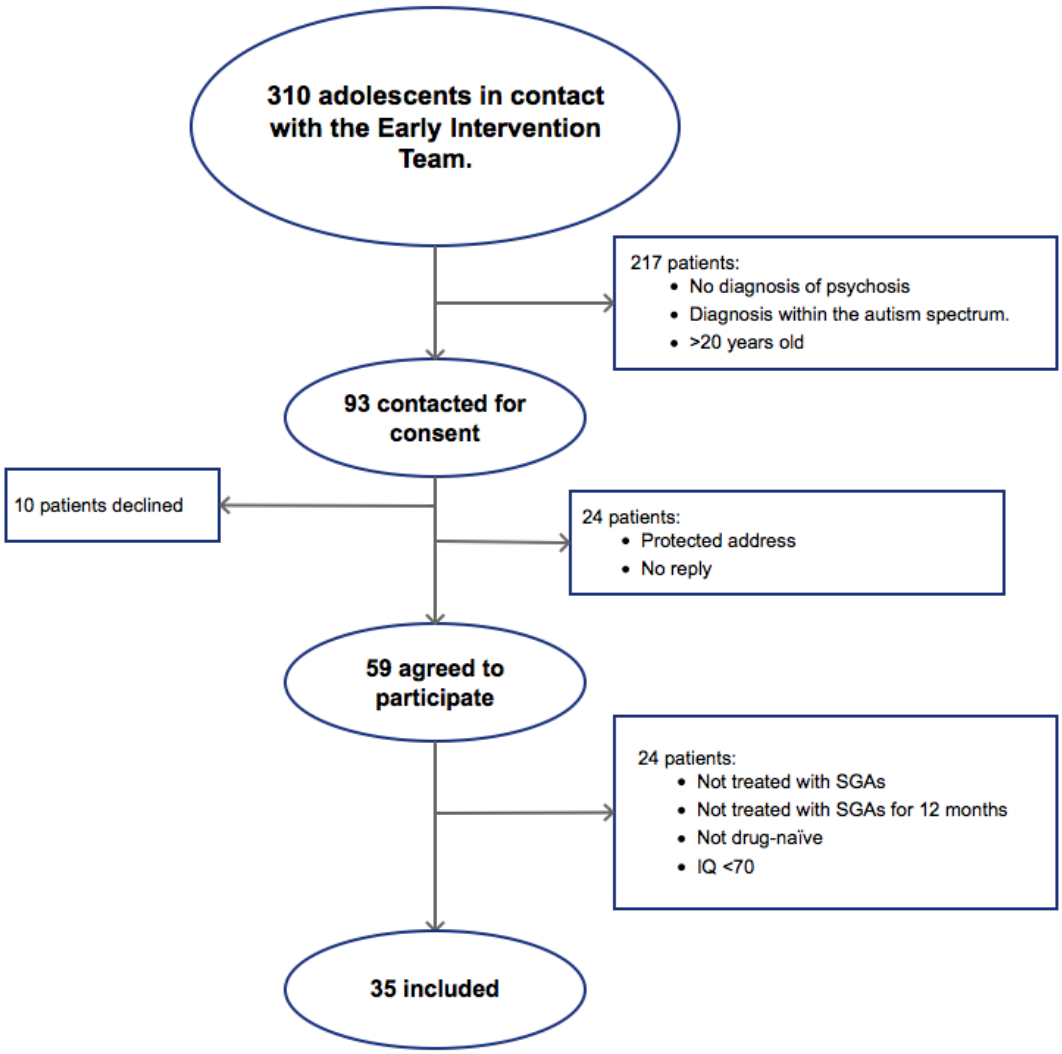

Figure 2: Study population in flow chart.

Measures

Data was extracted from patient files.

Clinical and paraclinical variables

Weight, height, waist-circumference, and blood pressure were registered into the database from baseline and when available in the case files within the first 12 months after start of medication.
Serum lipids and glucose from fasting blood samples were registered into the database from baseline and every third or fourth month of treatment, when available in the case files.

Outcome variables

Body mass index, waist circumference, triglycerides, HDL-cholesterol, and fasting blood glucose were used as both outcome- and explanatory variables. This was done in order to determine whether metabolic status at baseline affected the outcome.

Statistics

In order to examine the significance of each variable on a group level, a mixed effects model was fitted in Stata. Time in treatment with SGAs was considered the exposure, with data divided into intervals of 28 days.

Two mixed effects models were fitted to examine this, one where only the intercept was random, and one where both intercept and slope were random. The model with the best fit according to Akaike's information criterion and the Bayesian information criterion was reported.
As most variables did not have a perfect normal distribution, the robust variance estimator was used.

The number of patients fulfilling the criteria for MetS fully or partially after 12 months was examined.

The software used was Stata v.14.

Procedure

The patients from the original cohort were considered for involvement in the study sample, according to the above inclusion- and exclusion criteria and flow chart (Figure 2).

Consent was obtained through consent forms mailed to the patients.

Results.

From the cohort, 93 patients were eligible for further study, out of which 35 were included (Figure 2). 77% were female (61% females in the eligible cohort, from which only gender is known), 63% in all were diagnosed with schizophrenia, while 59% in all received mixed medications (Table 1).

Table 1. Demographic and clinical characteristics (N=35).

Mean age* ± SD	15.5 ± 2.0
Male/female	8/27 (20/77%)
Smoking	7 (20%)
ICD-10 classification†:	
Schizophrenia	22 (63%)
Schizo-affective disorder	3 (9%)
Other psychotic disorder	7 (20%)
Bipolar disorder	2 (6%)
Socio-Economic Status of parents‡:	
Unknown	9 (26%)
>1 parent high SES	4 (11%)
>1 parent not employed	8 (23%)
Parents average SES	14 (40%)
Medication:	
Mixed§	20 (59%)
Aripiprazole**	6 (17%)
Quetiapine**	9 (26%)

* Median age 15.5 years, range 7.3 – 19.6 years

† After 1 year of treatment

‡ Based on information of parental employment

§ A combination of quetiapine, aripiprazole, olanzapine and/or risperidone

** Medication used exclusively for 11 of 12 the months

Outcome Variables

Table 2 presents summary statistics for the baseline and follow-up values of all the outcome variables for the sample. Overall, there was a significant increase in Body Mass Index (BMI), waist circumference (WC), triglycerides (TG), and fasting blood glucose (FBG), while there was a significant decrease in HDL-cholesterol. No significant change was found for blood pressure.
The measurements at beginning of treatment were not significantly correlated with the change of measurements during treatment, for any of the outcome variables.

Table 2. Results on Outcome Variables.

	BMI (kg/m²)	*WC (cm)*	*TG (mmol/L)*	*HDL (mmol/L)*	*FBG (mmol/L)*
No. of patients	35	18	25	27	30
No. of observations	415	106	110	122	128
Observations pr patient	2-62	3-12	2-8	2-8	2-9
Baseline ± SD	20.7 ±3.4	75.5 ±8.9	1.133 ±0.184	1.39 ±0.29	5.29 ±0.42
95% CI[*]	0.227 - 0.363	0.464 - 1.200	0.001 - 0.043	-0.019 - -0.005	0.001 - 0.029
Change per 28 days	0.29	0.83	0.022	0.012	0.015
P-values	p<0.001	p<0.001	p=0.039	p<0.001	p=0.038
Change after 1 year[†]	+3.8	+10.8	+0.286	-0.160	+0.190

[*] Confidence Interval

[†] 13 of the 28-day periods

The World Health Organization's BMI-for-age charts for girls[17] determines the monthly increase in BMI for girls 13-19 years of age to be 0.036 kg/m². When calculated for just the girls included in this sample, this increase was 0.29 kg/m², with the same confidence interval as in Table 2.

MetS before and after 12 months

At the end of the study, there were 15 patients with a normal BMI. Yet, two patients fulfilled the criteria for MetS, four fulfilled two criteria, two fulfilled one criterium, while there were five patients not fulfilling any criteria for the metabolic syndrome. MetS was found to be present in 20% of the sample (Figure 3), and in 26% when only counting the patients with sufficient measurements to determine MetS-status.

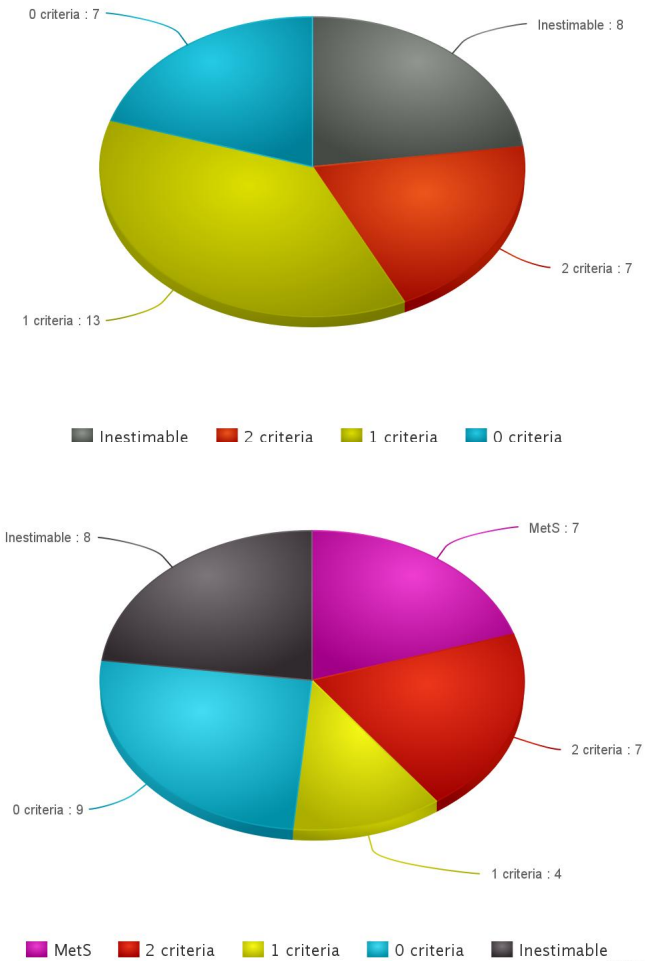

Figure 3: The metabolic syndrome before and after 12 months.

Discussion.

The objective of this study was to determine whether SGAs are associated with the development of MetS in a population of drug-naïve adolescents with a diagnosis of psychosis, treated with SGAs for 12 months.

Overall, there was a significant increase of body mass index, triglycerides, fasting blood glucose and waist circumference, while there was a significant decrease in HDL-cholesterol. Also, MetS was found to be present in 20% of the sample, with no-one meeting MetS criteria at baseline.

Body Mass Index (BMI)

The present study found an overall increase in BMI of 18.4%, or 3.8 kg, over the course of 12 months.

In a retrospective cohort study by Ghate et al., adolescents recently initiated on SGAs were compared to untreated adolescents, and followed for 395 days. The significant difference between the groups was 3.7%[18]. This increase is much lower than in our sample, and might be because their sample was much bigger, and thereby perhaps more representative. However, their comparison group was drawn from a US population, where nearly 1/3 of teenagers are already obese[19].

In a prospective observational study examining antipsychotic-naïve adolescents treated with risperidone, a BMI increase of 7.85% was found after 6 months treatment[20], less than half of what the present study found. However, their sample was somewhat smaller (22 patients), younger (mean age 12±3.2), and they included patients with down to 3 months of risperidone-therapy.

In summary, the findings concerning BMI increase in the present study are somewhat higher than in similar studies.

Waist Circumference (WC)

The present study found an overall increase in WC of 14.3%, or 10.8cm, in the course of 12 months.

WC has been found to be a reliable indicator of MetS in both adults[21] and children[16]. In the latter, cross-sectional study, WC was found to be elevated by 40.7% of SGA medicated, and by 10.1% in SGA-naïve children. In comparison with the present study, fewer had psychotic disorders, duration of treatment varied widely, and about 50% were exclusively treated with risperidone. This may contribute to the difference between the findings.

In a prospective study of adolescents treated with risperidone over the course of 2.9 years, a 12.7% increase in WC was found[22]. This finding is very similar to our, despite the fact thay these patients were not naïve at baseline, only treated with risperidone, and were a great deal younger (11.2±2.7 years) than the present sample.

In summary, the findings on elevated WC in similar studies on children/adolescents, have found increases similar to that of the present study.

Triglycerides (TG), HDL-Cholesterol and Fasting Blood Glucose (FBG)

The present study found an overall increase in TG levels of 25.2%, or 0.286 mmol/L, in the course of 12 months. HDL decreased significantly by 11.5%, or 0.16 mmol/L, while FBG increased significantly by 3.6%, or 0.19 mmol/L in the same period.

In the cross-sectional study by Panagiotopolous, 33.7% of SGA-treated adolescents had hypertriglyceridemia[16]. The corresponding percentage in our study was lower, 20.0%, and the difference between these findings might be because of the sample- and methodological differences mentioned above, namely differences in diagnoses, time to follow-up, and type of medication.

In the 7-month cohort study by O'Donoghue et al., while the mean TG level increased by 48%, the level of HDL did not increase significantly[23]. The increase of TG was in other words almost double that of our result, and considerably larger than most other studies, while HDL did not change. The different results may stem from the difference in the type of SGA administered, or because the time to follow-up in their sample was shorter and more varying.

Meanwhile, the 6 month retrospective study by Roy et al. comparing SGA-naïve adolescents to adults, found abnormalities in lipid metabolism in the adult group only, and found no change for either group concerning the level of FBG[10]. These differences may either be due to duration, or that their sample had a different distribution of psychiatric diagnoses.

In summary, our findings on TG, HDL and FBG roughly complement the findings of other studies.

Blood Pressure (BP)

Several other studies on BP in children/adolescents have had similar, insignificant results as the present study[20,24–26]. One could argue that lasting cardiovascular changes will take more than 12 months to develop. In support of this, in a population-based study, Liao et al. found that younger schizophrenic patients taking SGAs were at a higher risk of developing hypertension later on, than older patients[27].

In summary, hypertension is presumably an aspect of the metabolic syndrome that develops later than the others.

The Metabolic Syndrome (MetS) as a whole

Two of the fifteen patients with a normal BMI at twelwe months fulfilled the criteria for MetS, four had two criteria, and two had one criteria fulfilled. This establishes the need for close follow-up also for those patients who do not suffer a dramatic weight gain.

Methodological considerations

Strengths

This is the first study to include all aspects of the MetS in a drug-naïve adolescent population getting SGA treatment.

Comparing the development of BMI in our sample to a standardized control group (ie. WHO's growth charts), tells us that there is not only a significant increase, which could be natural during puberty, but that there is a clear difference between this sample and the rest of the population at the same age.

All patients had regular prescriptions made, and were followed up routinely, ensuring that they took their medication as prescribed over the course of the 12 months.

The baseline- and follow-up anthropomorphic measurements were made in different places in the region, by different people, using different equipment. This could imply biases in the measurements taken. However, it could also strengthen the measurements as a whole, removing any systematic error arising from malfunctioning scales and lack of inter-measurer reliability.

Limitations

This is a naturalistic study. That involves certain biases, for instance that the patients were not randomized to their medication, and that clinicians were free to change medications whenever during follow-up. Also, we had no non-medicated controls in the study. Nonetheless, significant findings of such negative outcome under these conditions imply a very strong relationship between psychosis, SGAs and the risk of MetS in adolescents.

There were 8 males in this sample of 35 patients, while the clinical population typically consists more of males[28]. One study of children found that after SGA use, male sex was the strongest predictor of MetS[16]. In another study of children/adolescents, the risk of developing DM 2 and dyslipidemia were higher in females[29]. An adult study found more male hypertriglyceridemia and hypertension, with more female central obesity and reduced HDL[30].
There may, therefore, be some gender-based differences in metabolic aberrations due to SGA use. But as this has not been extensively reviewed in neither adolescents nor adults, the implications for this population are as of yet unclear.

The original cohort of eligible patients consisted of 93 patients. However, after the process of selection- and consent, only 35 patients, or close to 40%, remained in the study. The sample might not be large enough to say anything about blood pressure, but it was enough to discover significant findings on BMI, TG, WC, HDL and FBG.

Conclusion.

In conclusion, these results tell us that simply monitoring these young adults is not enough. Our study demonstrates a clear evolution towards MetS because of SGA-use, which may turn into a lifelong suffering, adding to whichever psychotic disease that they were originally treated for. If we want to stagger this progression, we will need to start thinking about SGAs as drugs that automatically incur appointments with a dietrician and a physiotherapist. Our findings support the growing body of evidence that this is a vulnerable patient group that needs a considerably improved support system, if they are to hope to be given the same standard of supplemental care and treatment that is granted without question to somatic patients.

Refereces:

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