View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Trepo - Institutional Repository of Tampere University

https://doi.org/10.1111/apa.14951

Current follow-up practices often fail to detect metabolic and neurological adverse reactions in children treated with second-generation antipsychotics

K. Kakko, L. Pihlakoski, P. Keskinen, R. Salmelin, K. Puura (authors)

Kirsi Kakko, Leena Pihlakoski, Kaija Puura

Tampere University Hospital, Department of Child Psychiatry

Tampere University, Faculty of Medicine and Health Technology

Päivi Keskinen

Tampere University Hospital, Department of Paediatrics

Tampere University, Center for Child Health Research

Raili Salmelin

Tampere University, Faculty of Social Sciences/Health Sciences

Tampere University Hospital, Department of Child Psychiatry

Short title: Second-generation antipsychotic treatment

Corresponding author: Kirsi Kakko, Tampere University, Faculty of Medicine and Health Technology. FI-33014 Tampere University, Finland.

Tampere University Hospital, Department of Child Psychiatry PO Box 2000, FI-33521 Tampere, Finland. kirsi.kakko@tuni.fi , tel. +358405779250

Abstract

Aim: This study examined the use and adverse reactions of second-generation antipsychotics (SGAs), alone or combined with other psychotropic medication, to identify areas for standardising prescribing and monitoring practices.

Methods: We conducted a retrospective study at Tampere University Hospital, Finland, involving 128 patients (81% boys) who were under 13 years old at SGA initiation and had SGA treatment between October 2013 and October 2014.

Results: The median age at baseline was 9.4 years. Weight gain was reported as an adverse reaction in 33%, but an increase in standardised body mass index, adjusted for age and sex (BMI z-score), was detected in 75% of patients with sufficient data. The statistically significant median changes during the study were an increase of 0.46 in BMI z-score, a reduction of 0.25 mmol/l in fasting plasma high-density lipoprotein and an increase of 0.28 mmol/l in triglyceride values. The weight gain was most apparent in patients treated with just an SGA or SGA plus melatonin. Patients treated with an SGA plus medication for attention deficit hyperactivity disorder were less likely to gain weight.

Conclusion: SGA-induced metabolic disturbances remained partly unrecognised in children under 13 years of age and more systematic monitoring is needed.

Key Notes

- We examined the use and adverse reactions of second-generation antipsychotics (SGAs), alone or combined with other psychotropic medication, in 128 children (81% boys) under the age of 13.
- Our findings showed that statistically significant weight gain and deteriorating fasting plasma triglycerides and high-density lipoproteins were associated with SGA treatment.
- Implementing systematic prescribing and monitoring practices for SGA treatment in paediatric patients is essential, as many negative changes currently go unrecognised.

Key words:

Adverse reactions, Metabolic disturbances, Psychotropic medication, Second-generation antipsychotics, Weight gain

INTRODUCTION

The use of psychotropic medication and polypharmacy has increased among paediatric patients (1-4). The use of second-generation antipsychotics (SGAs) has particularly emerged, as has the use of stimulants, other medication for attention deficit and hyperactivity disorder (ADHD) and melatonin (4,5). Paediatric patients have been reported to be especially vulnerable to SGA-induced metabolic adverse reactions, such as weight gain, glucose and lipid abnormalities and elevated blood pressure (2,3,6-8). The risk of type 2 diabetes has been reported to be two to three times higher in children treated with SGAs (9). Adverse metabolic reactions have been associated with a markedly increased risk of cardiovascular disease, especially with long-term SGA treatment (2). A study published in 2019 also showed an association between antipsychotic treatment and unexpected deaths in children and adolescents (10). In the short term, SGAs have been shown to induce similar neurological adverse reactions in children and adults (11). Longer treatment may be associated with more severe manifestations, such as tardive dyskinesia (3,12). SGAs are sometimes used to augment methylphenidate and atomoxetine – henceforth referred to as ADHD medication – to treat comorbid aggression in ADHD (13). ADHD medication has been reported to reduce weight, while SGA appears to have the opposite effect (14,15). However, subjects with ADHD did gain weight when risperidone was combined with methylphenidate (13).

These findings highlight the need for proper monitoring practices for children treated with SGAs. There are guidelines on follow-up practices, but there has been limited systematic monitoring, despite the evidence of SGA-related adverse reactions (16-20).

The aim of this study was to find potential areas of clinical practice where prescribing and monitoring of SGA medication administered to children could be standardised. We did this by examining the use and adverse reactions of SGAs, alone or when combined with other psychotropic medication.

PATIENTS AND METHODS

This retrospective study of medical records was conducted at the child psychiatric clinic of Tampere University Hospital and it was approved by the ethics committee of Pirkanmaa Hospital District. We included patients who were prescribed SGA at our child psychiatric clinic when they were less than 13 years of age and received SGA treatment between 1 October 2013 to 1 October 2014. They were only included if any treatment breaks did not exceed six months. These criteria were met by 128 patients. We examined medical reports from SGA initiation. The study end point for each patient was whichever came first: when they discontinued SGA, when they discontinued treatment at the child psychiatric clinic or 31 May 2015. Sociodemographic factors, diagnoses and the psychiatric and any other medical history of the patient and their family were recorded. Information on SGA and other psychotropic medication use, follow-up practices, reported adverse reactions and paediatric consultations were also collected from the medical records.

If the patient's weight and height, collected from the medical records, were both measured at the same time point, the standardised body mass index adjusted for age and sex (BMI z-score) was calculated using Finnish national growth reference tables (21). Based on the recommendations of the International Obesity Task Force expert panel, the BMI percentile curves passing through BMIs of 25 kg/m^2 and 30 kg/m^2 at the age of 18 years were used to define the limits for overweight and obesity, respectively (21). These were the 87.8^{th} and 98.2^{th} percentile for the girls and the 78.2^{th} and 95.6^{th} percentile for the boys. The minimum and maximum BMI z-scores were identified when at least two BMI z-scores were available. These were either one at baseline and at least one follow-up value or at least two follow-up values. The BMI z-scores were rounded to one decimal place to avoid detecting minimal changes. A maximum score occurring after a minimum score was considered weight gain during the study period and vice-versa for weight loss.

Fasting plasma high-density lipoprotein (HDL), triglyceride, and glucose values were collected from laboratory reports, and blood pressure values were collected from the children's medical records. Abnormal fasting plasma values were defined as the cut-off points of the National Cholesterol Education Program for metabolic syndrome in children and adolescents, namely HDL ≤ 1.03 mmol/l, triglycerides ≥ 1.24 mmol/l and glucose > 6.1 mmol/l (22,23). Elevated blood pressure was defined using the age, sex, and height-specific reference tables of the American Academy of Pediatrics' *Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents* (24). The percentile of each blood pressure measurement was set according to the guideline if a height measurement was available within two months of that measurement. Blood pressure was considered elevated if it was ≥ 90th percentile on three separate occasions, with at least a week between the readings and hypertensive if it was ≥ 95th percentile using the same criteria.

Because of the potential effects of ADHD medication on growth and blood pressure, the study population was initially divided into two groups for the analyses: 84 with ADHD medication and 44 without. To assess the possible effects of melatonin, similar analyses were performed for four specific patient groups based on the treatment they had received: just an SGA (n = 23), an SGA plus ADHD medication (n = 25), an SGA plus melatonin (n = 21) and an SGA plus ADHD medication and melatonin (n = 59).

The categorised variables were reported as numbers of cases or percentages, as appropriate and medians and interquartile ranges (IQR, lower to upper quartile) were reported for the continuous variables, which were mostly non-normally distributed. To test the statistical significance of the differences between the groups, we used Pearson's chi-square test, Fisher's exact test or the Kruskal–Wallis test, as appropriate. The Kolmogorov–Smirnov test was applied to examine whether the changes in BMI z-score, HDL and triglyceride values were

statistically significant. A *p* value of less than 0.05 was considered significant, a value between 0.05 and 0.10 was indicative and values up to 0.10 were reported. SPSS Statistics, versions 23 and 25 (IBM Corporation, New York, USA) were used for all the statistical analyses.

RESULTS

The inclusion criteria were met by 128 patients (81% male) with a median age of 9.4 years (IQR 7.9 to 11.1) at baseline. The median duration of the SGA treatment was 20.4 months (IQR 9.1 to 34.6), but the actual duration was probably longer because of study end-points other than SGA discontinuation. Selected background factors are shown in Table 1 and have previously been reported in more detail (25). We found that 120/128 (94%) children were treated with risperidone at some point, 23 (18%) with aripiprazole and 22 (17%) with quetiapine. The SGA was changed at least once for 28 (22%) children during the follow-up period. The use of other psychotropic medication is shown in Table 1.

The follow-up practices are presented in Table 2. The most frequent metabolic test at baseline was fasting plasma glucose in 63/128 (49%) patients. The most frequently reported adverse reactions by the clinicians were increased appetite in 46 (36%) cases, weight gain in 42 (33%) and fatigue in 41 (32%). Neurological adverse reactions, such as akathisia, tics and sluggishness or stiffness were reported in 13 patients (10%). During the study period, 39/128 patients (31%) were referred to a paediatric consultation other than paediatric cardiology. The indications for consultations were diverse, but they included 10/39 (26%) who were referred to a paediatric endocrinologist due to a metabolic disturbance and 11/39 (29%) who were referred to a paediatric neurologist. None of the neurological consultations were due to adverse drug reactions.

It was possible to calculate the minimum and maximum BMI z-scores for 97 patients (76%) and the cumulative frequency distributions are shown in Figure 1. The BMI z-score increased in 73 (75%) of these patients and this increase was within the normal weight category in 40

(55%) of them (Table 3). The minimum BMI was less than 25 in 74 (76%) patients, whereas the maximum BMI was less than 25 in 52 patients (54%). The number of patients who had minimum and maximum BMIs that were 25 to < 30 were 16 (17%) and 25 (26%), respectively, and for BMIs of 30 or more they were seven (7%) and 20 (21%). The median BMI z-score change was an increase of 0.46 (IQR 0.04 to 0.92, $p = 0.005$). The number of patients for whom a BMI z-score could not be calculated at any point was 10/128 (8%).

The frequencies of abnormal metabolic and blood pressure measurements are presented in Table 2. At least two fasting plasma HDL and triglyceride values were available for 81/128 (63%) patients. HDL decreased in 44/81 (54%) and the reduction was within the normal range in 39 (89%). The median HDL change was -0.25 mmol/l (IQR -0.43 to -0.15, $p = 0.004$). Triglyceride increases were seen in 44/81 (54%) and these were within the normal range in 36 (82%). The median triglyceride change was 0.28 mmol/l (IQR 0.11 to 0.46, $p < 0.001$).

At least three blood pressure percentiles were available for 61/128 (48%) patients: two of them (3%) met the criteria for elevated blood pressure and one had hypertension. At least one blood pressure percentile was available for 104/128 patients (81%) (Table 2).

The 84 patients treated with SGA plus ADHD medication, with or without melatonin, gained weight less frequently than the 44 patients who were just treated with an SGA, with or without melatonin (Table 3). Baseline blood pressure was measured for 29/84 patients (35 %) treated with SGA plus ADHD medication and 6/44 (14%) ($p = 0.013$) of those treated with just an SGA. At least one blood pressure value during the study period for these groups was available for 71/84 (85%) and 33/44 (75%), respectively. At least one hypertensive systolic blood pressure value was observed in 33/71 (47%) who had ADHD medication combined with an SGA and in 9/33 (27%) patients who only received SGAs ($p = 0.086$). We did not find any other statistically significant or indicative differences in the baseline or follow-up measurements between these two medication groups or in the reported adverse reactions.

When we compared all four medication groups, there were no statistically significant differences in the baseline or follow-up practices or in the adverse reactions reported by the clinicians. Table 3 shows the weight changes in the medication groups. In the 16 patients in the SGA plus melatonin group who had at least two BMI z-scores, the weight gain appeared within the normal weight category in 11 (69%) patients. The proportion was around one-third in the other groups (Table 3). There were no statistically significant differences in triglyceride and HDL values between the medication groups. The number of patients with at least one hypertensive systolic blood pressure measurement was seven (41%) out of the 17 who were treated with just an SGA and had at least one blood pressure measurement during the study period. The respective figure was 11/22 (50%) in the group treated with SGA plus ADHD medication, 2/16 (13%) in the patients treated with an SGA plus melatonin and 22/49 (45%) in the patients treated with an SGA plus ADHD medication and melatonin ($p = 0.092$). There were no statistically significant differences in diastolic blood pressure values between the medication groups.

DISCUSSION

The aim of this study was to find potential areas where prescribing and monitoring practices of SGA medication for children could be standardised. Our study findings were in line with previous studies that suggested that SGA treatment poses major metabolic risks for children (6,7,26). Despite these findings, and the existing guidelines, monitoring practices have often remained irregular (16-20). In our study, the baseline information necessary for detecting changes in growth and the laboratory test values were seldom complete. In addition, information on familial metabolic risk factors was often lacking, which complicates the evaluation of possible hereditary risks.

Three-quarters of the patients in our study gained weight and there was also a statistically significant deterioration in their triglyceride and HDL values. One of the main findings of this study was that these alterations appeared mainly within the normal reference values and seemed to remain unrecognised. For example, there was a discrepancy when we compared the BMI z-score findings and the frequency of reported weight gain in the medical records. Surprisingly, the clinicians only reported weight gain as an adverse reaction in one-third of the patients. Nevertheless, even a smaller increase in BMI z-score or alterations in metabolic parameters may, without intervention, predict future cardiovascular morbidity. Neurological adverse reactions were reported in a tenth of the study patients and this figure was slightly lower than in previous studies (11,17). Irregular reporting and the retrospective nature of the study may have affected this result. However, the common assumption that SGAs are less likely to cause neurological adverse reactions means that there is a risk that these reactions are not monitored and may remain unrecognised. Furthermore, misinterpreting neurological adverse reactions as worsening psychiatric symptoms may lead to overmedication and more severe adverse reactions (3,27).

Psychiatric polypharmacy was common in our study, but it did not have a major effect on the follow-up practices. Children treated with an SGA plus ADHD medication were more likely to have their blood pressure measured at baseline compared to other patients. This was probably due to the existing national ADHD treatment guidelines which recommend repeated blood pressure measurements. Even though polypharmacy only had a minor effect on the follow-up practices, it had effects on the observed weight gain and blood pressure readings. Studies have reported that appetite loss and blood pressure elevation have been relatively common adverse reactions to psychostimulant treatment (14,15). These reactions were also observed in our study. Patients using an SGA plus ADHD medication at some point during the study were less likely to gain weight compared to other patients. However, their systolic blood pressure values were indicatively more likely to be hypertensive.

In our study, the weight gain was most apparent in patients treated with just an SGA or an SGA plus melatonin. However, when melatonin was combined with an SGA, a weak association with more modest weight gain was observed, mostly appearing within the normal weight category. In addition, hypertensive systolic blood pressure values were indicatively less frequent in patients using an SGA plus melatonin than in patients receiving other treatment regimens. A similar tendency was observed in previous studies of adults and adolescents (28,29), indicating that adding melatonin could reduce SGA-related metabolic effects. However, these studies had several methodological limitations, such as small sample sizes, short follow-up times and scarce information concerning children (28,29). On the other hand, in a study by Tuomi et al (2016), adding melatonin decreased insulin release and increased glucose concentrations in adults (30). Sleep disturbances are known comorbidities of psychiatric disorders and quality of sleep is known to affect weight and metabolic control (29). The finding that adding melatonin was associated with fewer SGA-induced metabolic adversities should encourage clinicians to pay special attention to the sleeping habits of these patients.

SGA treatment, on its own or to augment ADHD medication, is a major risk factor for metabolic disturbances in children. Psychotropic polypharmacy may increase the risk of adverse drug reactions or sometimes diminish it. Special attention should be paid to detecting adverse tendencies, not just to absolute reference values. It is essential that patients are monitored when they start new medication and that they are followed up regularly. Our study shows that there is still an urgent need for improvement, as inadequate monitoring can mean that adverse reactions with far-reaching consequences are missed. Early interventions and lifestyle changes are effective ways of reducing the metabolic comorbidities of SGAs. However, the most effective tool is prevention, which is not possible without systematic monitoring.

The major strengths of our research were the real-life nature of the study and long follow-up period. Our study provided an honest perspective on the clinical reality and disclosed major targets for interventions. The relatively small sample size, retrospective nature and the lack of a control group limit the generalisability of our results and they should be interpreted with caution. However, this study has laid the foundation for a more systematic follow-up procedure for SGA treatment in children at Tampere University Hospital.

CONCLUSION

Knowing the possible adverse drug reactions and being aware of the pitfalls in current practices of SGA treatment should encourage clinicians to adopt more systematic treatment procedures. The identification, follow up and management of SGA-related adverse reactions are important activities for patient safety and all treating physicians are responsible for carrying these out.

ACKNOWLEDGEMENTS

We wish to acknowledge the contribution of Dr Tuula Tamminen to the design of this study and Dr Tuija Poutanen for providing a paediatric cardiology advice about the blood pressure measurements.

ABBREVIATIONS

ADHD, attention deficit hyperactivity disorder; BMI, body mass index; HDL, high-density lipoproteins; IQR, lower to upper quartile; SGA, second-generation antipsychotic; BMI z-score, standardised body mass index adjusted for age and sex

CONFLICT OF INTERESTS

The authors have no conflicts of interest to disclose.

FUNDING

This study was supported by the Foundation for Paediatric Research and the Finnish Brain Foundation.

REFERENCES

1. Kalverdijk LJ, Bachmann CJ, Aagaard L, Burcu M, Glaeske G, Hoffmann F, et al. A multi-national comparison of antipsychotic drug use in children and adolescents, 2005-2012. *Child Adolesc Psychiatry Ment Health* 2017; 11: 55

2. Schneider C, Taylor D, Zalsman G, Frangou S, Kyriakopoulos M. Antipsychotics use in children and adolescents: an on-going challenge in clinical practice. *J Psychopharmacol* 2014; 28: 615-23

3. Rasimas JJ, Liebelt EL. Adverse effects and toxicity of the atypical antipsychotics: what is important for the pediatric emergency medicine practitioner? *Clin Pediatr Emerg Med* 2012; 13: 300-10

4. Kronstrom K, Kuosmanen L, Ellila H, Kaljonen A, Sourander A. National time trend changes in psychotropic medication of child and adolescent psychiatric inpatients across Finland. *Child Adolesc Ment Health* 2018; 23: 63-70

5. Lohr WD, Creel L, Feygin Y, Stevenson M, Smith MJ, Myers J, et al. Psychotropic polypharmacy among children and youth receiving medicaid, 2012-2015. *J Manag Care Spec Pharm* 2018; 24: 736-44

6. Martinez-Ortega JM, Funes-Godoy S, Diaz-Atienza F, Gutierrez-Rojas L, Perez-Costillas L, Gurpegui M. Weight gain and increase of body mass index among children and adolescents treated with antipsychotics: a critical review. *Eur Child Adolesc Psychiatry* 2013; 22: 457-79

7. Panagiotopoulos C, Ronsley R, Kuzeljevic B, Davidson J. Waist circumference is a sensitive screening tool for assessment of metabolic syndrome risk in children treated with second-generation antipsychotics. *Can J Psychiatry* 2012; 57: 34-44

8. Nicol GE, Yingling MD, Flavin KS, Schweiger JA, Patterson BW, Schechtman KB, et al. Metabolic effects of antipsychotics on adiposity and insulin sensitivity in youths: a randomized clinical trial. *JAMA Psychiatry* 2018; 75: 788-96

9. Galling B, Roldán A, Nielsen RE, Nielsen J, Gerhard T, Carbon M, et al. Type 2 diabetes mellitus in youth exposed to antipsychotics: a systematic review and meta-analysis. *JAMA Psychiatry* 2016; 73: 247-59

10. Ray WA, Stein CM, Murray KT, Fuchs DC, Patrick SW, Daugherty J, et al. Association of antipsychotic treatment with risk of unexpected death among children and youths. *JAMA Psychiatry* 2019; 76: 162-71

11. Carbon M, Kapoor S, Sheridan E, Al-Jadiri A, Azzo S, Sarkaria T, et al. Neuromotor adverse effects in 342 youth during 12 weeks of naturalistic treatment with 5 second-generation antipsychotics. *J Am Acad Child Adolesc Psychiatry* 2015; 54: 718-727

12. Garcia-Amador M, Merchan-Naranjo J, Tapia C, Moreno C, Castro-Fornieles J, Baeza I, et al. Neurological adverse effects of antipsychotics in children and adolescents. *J Clin Psychopharmacol* 2015; 35: 686-93

13. Jahangard L, Akbarian S, Haghighi M, Ahmadpanah M, Keshavarzi A, Bajoghli H, et al. Children with ADHD and symptoms of oppositional defiant disorder improved in behavior when treated with methylphenidate and adjuvant risperidone, though weight gain was also observed - results from a randomized, double-blind, placebo-controlled clinical trial. *Psychiatry Res* 2017; 251: 182-91

14. Díez-Suárez A, Vallejo-Valdivielso M, Marín-Méndez JJ, de Castro-Manglano P, Soutullo CA. Weight, height, and body mass index in patients with attention-deficit/hyperactivity disorder treated with methylphenidate. *J Child Adolesc Psychopharmacol* 2017; 27: 723-30

15. Reed VA, Buitelaar JK, Anand E, Day KA, Treuer T, Upadhyaya HP, et al. The safety of atomoxetine for the treatment of children and adolescents with attention-deficit/hyperactivity

disorder: a comprehensive review of over a decade of research. *CNS Drugs* 2016; 30: 603-28

16. Kealey E, Scholle SH, Byron SC, Hoagwood K, Leckman-Westin E, Kelleher K, et al. Quality concerns in antipsychotic prescribing for youth: a review of treatment guidelines. *Acad Pediatr* 2014; 14 Suppl 5: 68-75

17. Pringsheim T, Ho J, Sarna JR, Hammer T, Patten S. Feasibility and relevance of antipsychotic safety monitoring in children with tourette syndrome: a prospective longitudinal study. *J Clin Psychopharmacol* 2017; 37: 498-504

18. Coughlin M, Goldie CL, Tranmer J, Khalid-Khan S, Tregunno D. Patient, treatment, and health care utilization variables associated with adherence to metabolic monitoring practices in children and adolescents taking second-generation antipsychotics. *Can J Psychiatry* 2018; 63: 240-9

19. Okumura Y, Usami M, Okada T, Saito T, Negoro H, Tsujii N, et al. Glucose and prolactin monitoring in children and adolescents initiating antipsychotic therapy. *J Child Adolesc Psychopharmacol* 2018; 28: 454-62

20. Chen W, Cepoiu-Martin M, Stang A, Duncan D, Symonds C, Cooke L, et al. Antipsychotic prescribing and safety monitoring practices in children and youth: a population-based study in Alberta, Canada. *Clin Drug Investig* 2018; 38: 449-55

21. Saari A, Sankilampi U, Hannila M, Kiviniemi V, Kesseli K, Dunkel L. New Finnish growth references for children and adolescents aged 0 to 20 years: length/height-for-age, weight-for-length/height, and body mass index-for-age. *Ann Med* 2011; 43: 235-48.

22. Owens S, Galloway R. Childhood obesity and the metabolic syndrome. *Curr Atheroscler Rep* 2014; 16: 436

23. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988-1994. *Arch Pediatr Adolesc Med* 2003; 157: 821-7

24. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics* 2017; 140: e20171904

25. Kakko K, Pihlakoski L, Salmelin R, Keskinen P, Puura K, Tamminen T. Clinical use of second-generation antipsychotics in children. *Scand J Child Adolesc Psychiatr Psychol* 2017; 5: 77-88

26. Sjo CP, Stenstrøm AD, Bojesen AB, Frølich JS, Bilenberg N. Development of metabolic syndrome in drug-naive adolescents after 12 months of second-generation antipsychotic treatment. *J Child Adolesc Psychopharmacol* 2017; 27: 884-91

27. Kakko K, Bjelogrlic-Laakso N, Pihlakoski L, Lehtimäki K, Järventausta K. Tardive dyskinesia should not be overlooked. *J Child Adolesc Psychopharmacol* 2019; 29: 72-74

28. Agahi M, Akasheh N, Ahmadvand A, Akbari H, Izadpanah F. Effect of melatonin in reducing second-generation antipsychotic metabolic effects: a double blind controlled clinical trial. *Diabetes Metab Syndr* 2018; 12: 9-15

29. Mostafavi S, Solhi M, Mohammadi M, Akhondzadeh S. Melatonin for reducing weight gain following administration of atypical antipsychotic olanzapine for adolescents with bipolar disorder: a randomized, double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol* 2017; 27: 440-4

30. Tuomi T, Nagorny CLF, Singh P, Bennet H, Yu Q, Alenkvist I, et al. Increased melatonin signaling is a risk factor for type 2 diabetes. *Cell Metab* 2016; 23: 1067-77

Table 1. Background factors of the children treated with SGAs (n = 128).

	%
Gender	
Male	81
Female	19
Family status	
Biological parents	37
One biological parent alone or with a new partner	40
Foster home	18
Other (e.g. adoption)	6
Number of ICD-10 F-diagnoses[1]	
1	26
2	48
3	23
4	4
In first-degree relatives, the availability of the history of[2]	
psychiatric disorders	84
metabolic disorders	53
Psychotropic medication other than an SGA[3]	
methylphenidate	65
atomoxetine	23
selective serotonin reuptake inhibitors	14
benzodiazepines[4]	14
melatonin	63

[1] F00-F99 mental and behavioural disorders.
[2] Co-occurence was possible.
[3] At least a trial during the study period.
[4] As requisite medication.

Table 2. Frequencies of somatic measurements and their abnormal values at the baseline and during the follow-up period (n = 128).

Type of measurement	Value considered abnormal	Baseline	During the entire study period, the proportion having at least one	
			measurement	abnormal value[3]
		%	%	%
Physical examination	-	34	78	-
BMI[1]	> 25[2]	34	92	46
Fasting plasma high-density lipoprotein	≤ 1.03 mmol/l	40	86	20
Fasting plasma triglyceride	≥ 1.24 mmol/l	39	86	27
Fasting blood glucose	> 6.1 mmol/l	49	95	7
Blood pressure	$\geq$ 95th percentile	27	81	-
systolic		-	-	40
diastolic		-	-	21

[1] Standardised body mass index, adjusted for sex and age (BMI z-score)
[2] BMI z-score corresponding to BMI > 25.
[3] Among those who had at least one measurement.

Table 3. Weight changes in medication groups.

		Medication group[1]					
		SGA	SGA + ADHD	SGA + melatonin	SGA + ADHD+ melatonin	*p*	All
Patients who							
had ≥ 2 simultaneous		(n = 23)	(n = 25)	(n = 21)	(n = 59)		(n = 128)
measurements of weight	n	14	22	16	45	ns[5]	97
and height available	%	61	88	76	76		76
		(n = 14)	(n = 22)	(n = 16)	(n = 45)		(n = 97)
did not gain weight	n	1	8	0	15	0.024[4]	24
	%[2]	7	36	0	33		25
gained weight within	n	5	7	11	17		40
normal range	%[2]	36	32	69	38		41
gained weight within over-	n	8	7	5	13		33
weight or obesity, or	%[2]	57	32	31	29		34
moved to either of them							
Change in standardised	Md[3]	0.55	0.51	0.51	0.31	ns[5]	0.46
body mass index, adjusted	IQR[3]	0.22–	-0.27–	0.34–	-0.12–		0.04–
for age and sex		1.08	1.14	1.01	0.73		0.92

[1] SGA = second-generation antipsychotic, ADHD: methylphenidate, atomoxetine, lisdexamfetamine (n = 1).

[2] % of those who had at least two measurements available.

[3] Md = Median, IQR = intra quartile range.

[4] Pearson's chi-square test.

[5] Kolmogorov–Smirnov test.

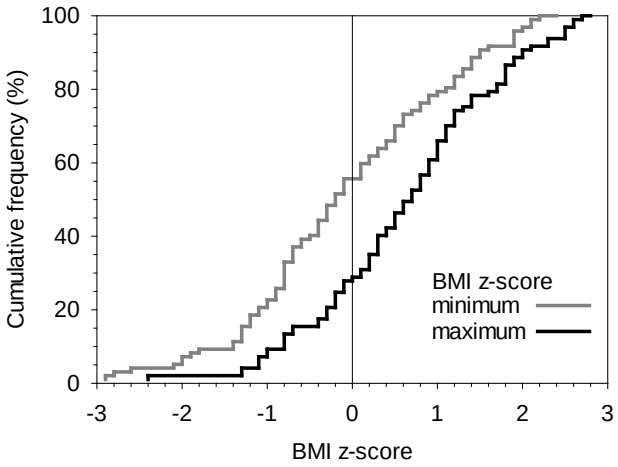

Figure 1. The cumulative frequency distribution of the minimum and maximum BMI z-score (standardised body mass index, adjusted for sex and age) in children treated with SGAs (n = 97).