Comparison of Glycemic and Metabolic Control in Youth With Type 1 Diabetes With and Without Antipsychotic Medication: Analysis From the Nationwide German/Austrian Diabetes Survey (DPV)

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OBJECTIVE

The objective of this study was to explore metabolic risk factors and glycemic control in youth with type 1 diabetes treated with typical or atypical antipsychotics.

RESEARCH DESIGN AND METHODS

Data for 60,162 subjects with type 1 diabetes up to the age of 25 years registered in the nationwide German/Austrian Diabetes Survey were included in the analysis. BMI; HbA_{1c}; treatment strategy; prevalence of hypertension, dyslipidemia, microalbuminuria, and retinopathy; frequency of hypoglycemia and diabetic ketoacidosis (DKA); and immigrant status among subjects treated with typical or atypical antipsychotics were compared with those without antipsychotic medication and analyzed by regression analysis.

RESULTS

A total of 291 subjects with type 1 diabetes (median diabetes duration 7.2 years) received antipsychotic medications (most commonly risperidone). Subjects treated with antipsychotics had a higher BMI ($P = 0.004$) and dyslipidemia was more frequent ($P = 0.045$) compared with subjects not receiving antipsychotic medication. Frequencies of severe hypoglycemia and DKA were significantly higher in subjects receiving antipsychotics ($P < 0.001$). The prevalences of hypertension, microalbuminuria, and retinopathy were not different. In subjects treated with typical antipsychotics, glycemic control did not differ compared with those who did not receive antipsychotic medications. By contrast, subjects treated with atypical antipsychotics had higher HbA_{1c} levels ($P = 0.022$).

CONCLUSIONS

This analysis from a real-life survey demonstrated that subjects with antipsychotic medication had worse glycemic control and a higher rate of acute complications compared with those without antipsychotic medication. Health care teams caring for youth with type 1 diabetes taking antipsychotic medication need to know about these findings. We suggest monitoring metabolic risk factors as well as providing diabetes education about prevention of acute complications.

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Over the past two decades, the use of antipsychotic drugs in medical practice has increased in the U.S. and in Europe (1–7). In the pediatric, adolescent, and young adult populations, antipsychotics are primarily used for treatment of psychiatric disorders, mainly schizophrenia, and for concomitant treatment of bipolar and affective disorders. In clinical practice, antipsychotics also are used for the treatment of symptoms related to behavior and of nonpsychotic disorders, for example, in obsessive-compulsive disorders, personality disorders, Tourette syndrome, and autism (1–7).

Treatment with antipsychotics may result in serious adverse effects. In addition to the extrapyramidal symptoms caused by typical antipsychotics, the adverse metabolic effects of atypical antipsychotics are of concern (8–14). The use of atypical antipsychotics may result in weight gain, changes in lipid concentrations, increased glucose concentrations, and insulin resistance in healthy subjects (8–14). Weight gain occurs in up to 50% of patients receiving long-term treatment for schizophrenia (8). Several studies indicate that weight gain with antipsychotic medication is more severe in children and adolescents compared with adults (8). One study of children encountered a 10% increase in body weight after 3 months of treatment with olanzapine (15). Furthermore, adults and youths taking atypical antipsychotics have an increased risk of developing type 2 diabetes (6,13,14). Weight gain and changes in metabolic parameters also have been described for treatment with some typical antipsychotic agents. Interpretation of these effects is more difficult because of the inadequate evaluation of confounding factors in many early studies of typical antipsychotics (8).

Because of the adverse metabolic effects of antipsychotics, patients with type 1 diabetes, who already are at risk for an unfavorable metabolic profile, may experience further deterioration of their metabolic risk factors with antipsychotic medication. This may include a negative effect on glycemic control and lead to a poor long-term prognosis in type 1 diabetes. Therefore, the aim of this analysis was to explore and assess metabolic risk factors and glycemic control in children, adolescents, and young adults with type 1 diabetes treated with atypical or typical antipsychotics in a real-life setting.

RESEARCH DESIGN AND METHODS

The German and Austrian Diabetes Survey (DPV) is a prospective, nationwide documentation of subjects with type 1 diabetes. Demographic, anthropometric, and diabetes-related data of subjects with type 1 diabetes are recorded in 391 diabetes care centers in Germany and Austria. All data were derived from hospital charts or were specifically asked for by health professionals. No self-report questionnaires were used. The ethics committee of Ulm University approved data collection and anonymous analysis for study purposes. Overall, data from 83,748 subjects with type 1 diabetes were registered in the survey from 1995 until March 2013. A total of 60,162 children, adolescents, and adults (up to the age of 25 years) with type 1 diabetes and with a diabetes duration of more than 6 months were included in this analysis.

Clinical characteristics and laboratory parameters were assessed; BMI and blood pressure were recorded, and age-specific normal values were obtained from current guidelines (16–18). BMI SD score (SDS) was calculated using national reference data in Germany (16). Hypertension was defined according to the Second Task Force on Blood Pressure Control in Children and Adolescents (17,18). Furthermore, treatment strategy (multiple daily injections or insulin pump treatment); frequency of severe hypoglycemia (hypoglycemia with a loss of consciousness or seizure); frequency of episodes of diabetic ketoacidosis (DKA; pH $<$7.30, defined according to International Society for Pediatric and Adolescent Diabetes [ISPAD] guidelines) (19); and frequency of hospital admissions were assessed. Rates of severe hypoglycemia, rates of DKA, and frequency of hospital admissions were assessed during the previous year and calculated and expressed per 1 patient-year. Glycemic control was assessed as median HbA_{1c} during the previous year. HbA_{1c} was locally measured, and local HbA_{1c} values were standardized mathematically to the Diabetes Control and Complications Trial (DCCT) reference range of 4.05–6.05% (21–43 mmol/mol) using the multiple of the mean method (20). Retinopathy and micro- or macroalbuminuria were screened according to ISPAD and American Diabetes Association guidelines (21). Albuminuria was screened according to ISPAD and the German Diabetes Association guidelines (21,22). Albumin and creatinine were measured by center-specific laboratory methods that had to meet German internal and external quality requirements for laboratory analysis, according to the guidelines of the German Medical Association (23). Microalbuminuria was defined as an albumin excretion rate $\geq$20 μg/min or urine albumin-to-creatinine ratio $\geq$2.5 mg/mmol. Macroalbuminuria was defined as albumin excretion rate $\geq$200 μg/min or a urine albumin-to-creatinine ratio $\geq$35 mg/mmol (21,24). Serum concentrations of cholesterol, HDL, and LDL were measured. Dyslipidemia was diagnosed if at least one lipid parameter was increased (cutoff levels of $>$200 mg/dL for total cholesterol, $>$130 mg/dL for LDL, and $<$35 mg/dL for HDL) and if at least two of three consecutive measurements were above the cutoff levels. Immigration status was defined as the place of birth of one or both parents in a country other than Germany or Austria.

Subjects taking antipsychotic medications were identified. Antipsychotic agents (neuroleptics) were classified as either atypical antipsychotics or typical antipsychotics (Table 1). Duration of antipsychotic medication use was assessed.

Statistical Analysis

We used SAS statistic software version 9.3 for data evaluation and statistical analysis. Data are presented as medians and interquartile ranges or as means and 95% upper and lower confidence limits, as appropriate. Prevalences and frequencies of complications are presented as either percentages or event rates per 1 patient-year. The Kruskal-Wallis test was performed to compare age, diabetes duration, BMI SDS, and median HbA_{1c} in subjects with or without treatment with typical or atypical antipsychotics. The χ^2 test was used to compare immigrant status, treatment strategy, frequency of hypertension and dyslipidemia, and frequency of retinopathy and microalbuminuria between the groups. A *t* test was used to compare mean BMI SDS in subjects taking antipsychotic medication with the mean BMI SDS when antipsychotic medication was started. A Poisson model was

Table 1—Classification of antipsychotics

Antipsychotic drug	Availability in Germany/Austria during period of survey
Typical	
Butyrophenones: benperidol, bromperidol, droperidol, haloperidol, melperone, pipamperone, trifluperidol	Trifluperidol available until 2005
Diphenylbutylpiperidine: clopimozide, fluspirilene, penfluridol, pimozide	Clopimozide and penfluridol not available
Phenothiazines: butaperazine, carfenazine, chlorpromazine, cyamemazine, fluphenazine, levomepromazine, oxaflumazine, perazine, perciazine, perphenazine (acetophenazine, thiopropazate, thioproperazine), prochlorperazine, promazine, promethazine, prothipendyl, thiethylperazine, trifluoperazine, triflupromazine, thioridazine	Thiethylperazine available until 2001; triflupromazine available until 2003; butaperazine, carfenazine, cyamemazine, oxaflumazine, perciazine, prochlorperazine, and trifluoperazine not available
Thioxanthenes: chlorprothixene, clopenthixol, flupentixol, thiothixene, zuclopenthixol	Clopenthixol available until 2000; thiothixene not available
Others: dixyrazine, homophenazine, loxapine	Loxapine available since 2013; dixyrazine and homophenazine not available
Atypical	
Clozapine	Available since 1974
Olanzapine	Available since 1996
Quetiapine	Available since 2000
Risperidone	Available since 1994
Sulpiride	Available since 1972
Amisulpride	Available since 1999
Aripiprazole	Available since 2004
Paliperidone	Available since 2007
Ziprasidone	Available since 2002
Zotepine	Available 1990 until 2010
Sertindole	Available since 1997
Clotiapine	Not available (available in Switzerland)
Asenapine	Available since 2010
Iloperidone	Not available (available in the U.S. since 2009)
Lurasidone	Available since 2014 (available in the U.S. since 2010)

applied to compare rates of severe hypoglycemia, rates of DKA, and frequency of hospital admissions among subjects treated with or without typical or atypical antipsychotics. Hierarchical random effects regression models (linear, logistic, or Poisson, as appropriate), with the diabetes center as a random effect and adjusting for age, sex, and diabetes duration, were used to assess the covariates BMI SDS, median HbA_{1c}, treatment strategy, hypertension, dyslipidemia, microalbuminuria, retinopathy, rate of severe hypoglycemia, and rate of episodes of DKA. Statistical two-sided significance was assumed at $P < 0.05$.

RESULTS

Cohort Characteristics

Of 60,162 subjects with type 1 diabetes in this prospective survey, 291 (0.48%) received antipsychotic medication. The use of different antipsychotics is depicted in Table 2.

Characteristics of the cohorts with and without antipsychotic medications are shown in Table 3. Subjects with type 1 diabetes treated with antipsychotics (60% males, 40% females; mean duration of antipsychotic medication use 9.1 months) were significantly older (17.0 vs. 15.5 years of age; $P < 0.001$) and had a longer diabetes duration (7.2 vs. 5.1 years; $P < 0.001$) (Table 3) compared with subjects without antipsychotic medication. The group with type 1 diabetes treated with antipsychotics comprised significantly more subjects with immigrant status compared with the group without antipsychotic medication (19% vs. 13%; $P = 0.003$) (Table 3). Furthermore, we saw significant differences in BMI SDS, HbA_{1c} levels, insulin doses, dyslipidemia, microalbuminuria, rates of hypoglycemia and DKA, and the rate of hospital admission between the two groups (Table 3). However, statistical analysis showed that mean BMI SDS in subjects with antipsychotic medication was not significantly different from mean BMI SDS when antipsychotic medication was started ($P = 0.84$).

Because the groups of subjects with and without antipsychotic medication differed significantly regarding age, sex, and diabetes duration, we used regression analysis to adjust for these influencing factors.

Regression Analysis

Our regression modeling adjusted for the parameters age, sex, and diabetes duration and used the diabetes center as random effect. First, regression analysis was implemented to compare subjects with and without antipsychotic medication (Table 4). BMI SDS was significantly higher (+0.67 vs. +0.50; $P = 0.004$) and dyslipidemia was more

Table 2—Use of antipsychotics* among subjects with type 1 diabetes aged <25 years (n = 291)

Typical antipsychotics (n = 135)		Atypical antipsychotics (n = 171)	
Pipamperone	29 (10%)	Risperidone	122 (42%)
Promethazine	18 (6%)	Quetiapine	19 (7%)
Prochlorperazine	17 (6%)	Sulpiride	10 (3%)
Haloperidol	16 (6%)	Olanzapine	9 (3%)
Chlorprothixene	12 (4%)	Others	11 (4%)
Pimozide	10 (3%)		
Levomepromazine	9 (3%)		
Others	24 (8%)		

*Use of both typical and atypical antipsychotics occurred in 15 subjects (5%).

Table 3—Characteristics of subjects with type 1 diabetes aged <25 years with and without antipsychotic medication

	Without antipsychotic medication (n = 59,871)	With antipsychotic medication (n = 291)	P
Age (years)*	15.5 (11.8, 17.6)	17.0 (14.2, 18.3)	<0.001†
Sex ratio (male/female)	52%/48%	60%/40%	0.006‡
Immigrant status	13%	19%	0.003‡
Age at diabetes onset (years)*	8.9 (5.2,12.2)	8.6 (5.3, 12.2)	—
Diabetes duration (years)*	5.1 (2.1, 8.7)	7.2 (3.5, 10.9)	<0.001†
BMI SDS§	+0.53 (+0.52, +0.54)	+0.71 (+0.58, +0.84)	0.003†
HbA_{1c} (%)*	7.9 (7.1, 9.2)	8.2 (7.3, 9.6)	0.008†
HbA_{1c} (mmol/mol)*	63 (54, 77)	66 (56, 81)	
Insulin dose (IU/kg)*	0.82 (0.64, 1.01)	0.87 (0.68, 1.06)	0.006†
Insulin pump treatment	27%	23%	0.21‡
Hypertension	13%	14%	0.46‡
Dyslipidemia	30%	37%	0.008‡
Microalbuminuria	33%	37%	0.009‡
Retinopathy	3.5%	4.4%	0.47‡
Rate of severe hypoglycemia‖	0.17 (0.002)	0.23 (0.04)	0.008¶
Rate of episodes of DKA‖	0.06 (0.001)	0.16 (0.03)	<0.001¶
Hospital admission‖	0.51 (0.004)	0.93 (0.07)	<0.001¶

*Data are expressed as median (lower quartile, upper quartile). †Kruskal-Wallis test. ‡χ^2 Test. §Data are expressed as mean (lower 95% confidence limit, upper 95% confidence limit). ‖Data are expressed as rate per 1 patient-year (confidence interval range). ¶Poisson model.

frequent (33.6% vs. 28.3%; P = 0.045) in subjects treated with antipsychotics compared with subjects not taking antipsychotic medication (Table 4). Glycemic control measured by HbA_{1c} was not different (P = 0.45; Table 4). Furthermore, frequencies of acute diabetes complications, for example, the rates of severe hypoglycemia and DKA, were significantly higher in subjects receiving antipsychotics (both $P < 0.001$; Table 4). Prevalence of hypertension, microalbuminuria, and retinopathy did not differ among subjects with and without antipsychotic medication.

Second, we used regression analysis to compare separately treatment with typical or atypical antipsychotics (Table 4). Glycemic control, as measured by HbA_{1c}, was not different in subjects treated with typical antipsychotics compared with subjects without antipsychotic medication (8.2% vs. 8.4% [66 vs. 68 mmol/mol]; P = 0.15). By contrast, subjects treated with atypical antipsychotics had significantly higher HbA_{1c} levels (8.7% vs. 8.4% [72 vs. 68 mmol/mol]; P = 0.022) (Table 4). Prevalence of dyslipidemia in both subjects treated with typical antipsychotics and subjects treated with atypical antipsychotics were again higher compared with subjects who did not receive antipsychotic medication (33.6% and 34.0% vs. 28.3%); however, statistical analysis failed to show significance (P = 0.16 and P = 0.10; Table 4). Last, regression analysis revealed that subjects treated with typical antipsychotics, but not subjects receiving atypical antipsychotics, had a significantly higher rate of severe hypoglycemia compared with subjects who did not receive antipsychotic medication ($P < 0.001$; Table 4).

CONCLUSIONS

To our knowledge, this analysis is the first to examine metabolic and glycemic control in youth with type 1 diabetes treated with typical and atypical antipsychotics. Overall, almost 0.5% of subjects with type 1 diabetes up to the age of 25 years were treated with antipsychotics in this survey. Population-based data from other European countries, the U.S., and Canada show similar results (25,26). One survey from Canada reported that 0.64% of children and adolescents are treated with antipsychotics in 2011 (25). In Germany, the observed numbers seem slightly lower: A recent analysis of data from a German health insurance company disclosed that 0.32% of children and adolescents up to the age of 19 years received prescriptions of antipsychotics in 2012 (26). As in our study, risperidone was the drug prescribed most often in this German population-based study (26). Moreover, similar to many studies analyzing trends in prescribing antipsychotic medications, more males were treated with antipsychotics in our survey (25,26). Interestingly, more subjects with immigrant status were included in the group receiving antipsychotic medication compared with the cohort of patients without antipsychotic medication. This finding is also seen in some other studies in the U.S. (3,27). Because we had no data about socioeconomic status or education level in our survey, we were not able to further analyze why more subjects with immigrant status were included in the group receiving antipsychotic treatment.

Similar to many studies of healthy children, adolescents, and adults, we also found that subjects with type 1 diabetes and with antipsychotic medication had increased weight (8–13). Interestingly, our survey showed an increased BMI with both typical and atypical antipsychotic treatment. Weight gain and changes in lipid concentrations also have been reported with typical (first-generation) antipsychotics, but often to a lesser extent than atypical antipsychotics (8,9). Moreover, there are marked differences between different antipsychotic agents, both typical and atypical, regarding the amount of weight gain (8,28). For example, medications with risperidone (an atypical antipsychotic) or haloperidol (a typical antipsychotic) are associated with less weight gain compared with treatment with olanzapine (an atypical agent) or chlorpromazine (a typical agent), respectively (8,28,29). Different receptor affinities (e.g., ^{1}H affinity) of the antipsychotic agents may explain some of the different degrees of weight gain through, for instance, increased appetite (8). Because numerous antipsychotic drugs are used for treatment in this survey, we are not able to give any detailed information about differences in BMI as they relate the individual

Table 4—Regression analysis adjusting for age, sex, and diabetes duration and with the diabetes center as random effect

Variable	Model*	Without antipsychotic medication	With antipsychotic medication	*P*	Model*	Medication with typical antipsychotics†	*P*	Medication with atypical antipsychotics†	*P*
HbA_{1c}, % (mmol/mol)	Linear	8.4 (68)	8.4 (68)	0.45	Linear	8.2 vs. 8.4 (66 vs. 68)	0.15	8.7 vs. 8.4 (72 vs. 68)	0.022‡
BMI SDS	Linear	+0.50	+0.67	0.004‡	Linear	+0.69 vs. +0.50	0.028‡	+0.72 vs. +0.50	0.004‡
Insulin pump treatment	Logistic	29.1%	24.5%	0.11	Logistic	29.7 vs. 29.1%	0.90	21.0 vs. 29.1%	0.037‡
Dyslipidemia	Logistic	28.3%	33.6%	0.045‡	Logistic	33.6 vs. 28.3%	0.16	34.0 vs. 28.3%	0.10
Hypertension	Logistic	11.0%	11.0%	0.99	Logistic	12.0 vs. 11.0%	0.69	9.2 vs. 11.0%	0.42
Microalbuminuria	Logistic	23.2%	23.8%	0.79	Logistic	22.4 vs. 23.2%	0.81	25.4 vs. 23.2%	0.49
Retinopathy	Logistic	0.8%	0.9%	0.76	Logistic	0.9 vs. 0.9%	0.94	0.9 vs. 0.9%	0.99
Rate of severe hypoglycemia (per 1 patient-year)	Poisson	0.19	0.27	<0.001‡	Poisson	0.34 vs. 0.19	<0.001‡	0.22 vs. 0.19	0.29
Rate of episodes of DKA (per 1 patient-year)	Poisson	0.05	0.12	<0.001‡	Poisson	0.13 vs. 0.05	<0.001‡	0.12 vs. 0.05	<0.001‡
Hospital admission (per 1 patient-year)	Poisson	0.53	1.06	<0.001‡	Poisson	0.93 vs. 0.53	<0.001‡	1.20 vs. 0.53	<0.001‡

*Adjusted for age, sex, diabetes duration, and diabetes center. †Versus without antipsychotic medication. ‡Significant at $P < 0.05$.

antipsychotic agents. Remarkably, in our survey, BMI SDS among subjects taking antipsychotic medication was not different from BMI SDS when antipsychotic treatment was started. This observation also is consistent with other studies: Subjects with schizophrenia and other psychiatric disorders are per se more likely to be obese and to have a more unhealthy lifestyle (8,30). Unfortunately, there is only a limited number of studies of untreated patients with schizophrenia (8,30).

In addition to the reported difference in BMI, we also encountered significant abnormalities in lipid concentrations in subjects treated with antipsychotics compared with subjects without antipsychotic medication. This finding also is well described in several other studies (31). Again, and similar to the influence on weight, different atypical and typical antipsychotic drugs seem to be associated with a lower or higher risk of hyperlipidemia (31). Some antipsychotic agents (e.g., haloperidol) even do not seem to influence lipid concentrations significantly (31). To date, why antipsychotic agents induce dyslipidemia is not exactly understood. Weight gain, a well-described adverse effect of antipsychotic medication, as mentioned above, and obesity lead to hyperlipidemia, and this mechanism may play an important role in the pathophysiology of dyslipidemia that occurs with antipsychotic medication (31). Furthermore, patients with schizophrenia are known to have a poor diet (e.g., a diet richer in fat) and often exert less or participate in inadequate exercise compared with the general population (31). These factors may also contribute to the reported changes in lipid metabolism and serum lipid concentrations.

Moreover, we examined glycemic control in subjects treated with antipsychotics. Remarkably, glycemic control was worse only in subjects treated with atypical antipsychotics, not in subjects treated with typical antipsychotics. There are several possible explanations for this finding. Atypical antipsychotic drugs exert direct effects on the β-cells in the pancreas, thereby impairing insulin secretion (8). More important, however, recent evidence points toward insulin resistance rather than insulin secretion as a cause of hyperglycemia. Interestingly, in some individuals changes in insulin resistance occur without increases in BMI. In vitro studies have shown that some atypical antipsychotic drugs inhibit glucose uptake via interaction with glucose transporter proteins (e.g., olanzapine) or exert intracellular effects (e.g., risperidone). This leads to insulin resistance, which consequently worsens glycemic control. By contrast, haloperidol—an example of a typical antipsychotic—has only marginal effects on glucose transport (8). Therefore, markedly less insulin resistance is present and, consequently, HbA_{1c} levels remain unchanged.

Furthermore, we examined and compared the rates of severe hypoglycemia and DKA, which are important for acute morbidity and mortality in type 1 diabetes. We found significantly higher rates of both DKA and severe hypoglycemia in subjects treated with typical antipsychotics. Subjects treated with atypical antipsychotics, who had significantly higher HbA_{1c} levels, had only a higher rate of DKA, not a higher rate of severe hypoglycemia. This association between more pronounced hyperglycemia, as reflected by higher HbA_{1c} levels, and a lower rate of severe hypoglycemia is also seen in several other trials and may indicate that lower HbA_{1c} levels lead toward an increased risk for severe hypoglycemia (32,33). Last, we did not find higher prevalence of diabetes complications such as retinopathy. Because diabetes duration of the subjects in our survey was less than 10 years, however, a longer observation time may be needed.

Finally, the limitations of our study should be pointed out. The number of subjects taking antipsychotic medication in this survey is relatively small because schizophrenia and disorders requiring antipsychotic medications are rare among the general population as well as among youth with type 1 diabetes (34). Therefore, weak to moderate

associations could possibly not be demonstrated because of limited power. Moreover, no sufficient information about the diagnoses for which the antipsychotics were prescribed was available. Therefore, we are not able to give any details about the underlying diagnoses and their possible associations with metabolic and glycemic control. Last, because of the cross-sectional research design, the results of our analysis are descriptive, and we are not able to demonstrate any causal effects.

In summary, this analysis of a real-life survey demonstrated that subjects taking antipsychotic medication had worse glycemic control and a higher rate of acute complications compared with those not taking antipsychotic medication. This observed adverse metabolic and glycemic control may have a considerate effect on morbidity and long-term prognosis in youth with type 1 diabetes taking antipsychotic medication. Health care teams caring for youth with type 1 diabetes on antipsychotic medication need to know about these findings. We suggest monitoring metabolic risk factors as well as providing diabetes education about the prevention of acute complications.

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