ORIGINAL ARTICLE

Weight gain associated with atypical and typical antipsychotics during treatment of adolescent schizophrenic psychoses: A retrospective study

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Abstract

OBJECTIVES: The aim of the study was to assess weight changes associated with certain atypical (AAP) and typical (TAP) antipsychotic drugs in patients with early-onset schizophrenia and other related psychotic disorders. **METHODS**: Our retrospective study included 109 patients (52 boys, 57 girls) with a mean age of 15.8 ± 1.6 years. The patients were evaluated based to their medical records prior to starting therapy, and then after 1, 3, and 6 weeks of treatment. **RESULTS**: During the first week of treatment, the AAP group (n = 85; risperidone, olanzapine, ziprasidone, and clozapine) gained 1.5% of baseline weight whereas the TAP group (n = 24; haloperidol, perphenazine, and sulpiride) gained only 0.2% (p = 0.049). Differences in relative changes between the two groups were not significant at weeks 3 and 6. Expressed as absolute values, patients in our sample gained an average of 3.4 kg (SD 3.2) on AAP and 2.0 kg (SD 3.9) on TAP during 6 weeks of treatment (p = 0.335). Only the risperidone, olanzapine, and clozapine groups had sufficient numbers of patients to allow a comparison at the endpoint of the study (week 6). The patients gained, on average, 3.6 kg (SD 2.6) on risperidone, 4.4 kg (SD 2.5) on olanzapine, and 2.1 kg (SD 4.0) on clozapine during the six weeks of treatment (p = 0.286). **CONCLUSIONS**: In our study, we did not find a difference in weight gain between the AAP and TAP groups, as large as has been described in the literature. It also seems plausible that the unique and variable weight changes associated with individual AAPs in the pediatric population are different from those observed in the adult population.

INTRODUCTION

Weight gain was first reported as a side effect of the conventional antipsychotic drug, chlorpromazine, and subsequently observed, to variable degrees, for all antipsychotic agents (Henderson, 2007). The introduction of the atypical antipsychotics (AAP) in the 1990's changed the treatment of schizophrenia and offered broader symptom control as well as a more favorable tolerability profile (Fleischhacker & Hummer, 1997; Mohr, 2008). However, in contrast to better tolerability, relative to extrapyrami-

dal side effects, atypical antipsychotics do not appear to be superior to typical antipsychotics (TAP) with regard to weight gain (Blin & Micallef, 2001).

This was shown by the first comprehensive meta-analysis on the topic (Allison *et al.* 1999). The authors provided an estimate of the mean weight gain in patients receiving standard doses of antipsychotics over a 10-week period. Among patients on AAP, mean increases were 4.45 kg with clozapine, 4.15 kg with olanzapine, 2.92 kg with sertindole, 2.10 kg with risperidone, and 0.04 kg with ziprasidone. Among patients on TAP, mean weight change ranged from a reduction of 0.39 kg with molindone to an increase of 3.19 kg with thioridazine. Finally, placebo was associated with a mean weight reduction of 0.74 kg. The results were supported by later studies and reviews (Stahl, 1999; Taylor & McAskill, 2000; Jones *et al.* 2001; Virk *et al.* 2004; Newcomer & Haupt, 2006; Henderson, 2007; Ucok & Gaebel, 2008).

Knowledge regarding weight changes associated with antipsychotic treatment in the field of child and adolescent psychiatry is less comprehensive. However, weight gain is a serious complication in children and adolescents because weight gain is associated with health and psychosocial issues at a time when self-esteem and sexual functioning develop (Corell, 2008). Weight gain can be associated with the development of eating disorders and depression, and the medical consequences of weight gain may adversely affect the pulmonary, gastrointestinal, renal, musculoskeletal, cardiovascular, and endocrine systems (Ebbeling *et al.* 2002; Sen *et al.* 2008).

The literature on the use of atypical as well as typical antipsychotics in pediatric patients remains limited. There are remarkably few randomized, controlled trials for adolescent schizophrenia (Fidling *et al.* 2005). The most recent review identified only 10 double-blind studies with AAP durations of 4 or more weeks which included 15 or more patients, and not all of them have been published yet (Kumra *et al.* 2008).

Only a few comparative investigations regarding weight gain with AAP in early-onset schizophrenia (EOS) are available. There were two studies comparing risperidone and olanzapine with haloperidol, a typical neuroleptic drug. Ratzoni *et al.* (2002) found, in a 12-week, open-label study involving 50 patients, that average weight gain was significantly greater in the olanzapine group (7.2 ± 6.3 kg) than in the risperidone (3.9 ± 4.8 kg) and haloperidol (1.1 ± 3.3 kg) groups. Sikich *et al.* (2004) performed a double-blind, randomized, 8-week trial carried out in 50 children and adolescents with schizophrenia or other psychotic illnesses. Significant weight gains were observed in all treatment groups: risperidone (4.9 ± 3.6 kg), olanzapine (7.1 ± 4.1 kg), and haloperidol (3.5 ± 3.7 kg). The between-group differences were statistically significant.

Shaw *et al.* (2006) published a double-blind, randomized, 8-week comparison of clozapine and olanzapine in 25 patients. Both groups showed a similar, marked, increase in weight without significant difference (clozapine 3.8 ± 6.0 kg, olanzapine 3.6 ± 4.0 kg). Fleischhaker *et al.* (2007) reported results of an open-label observation of patients treated with clozapine, olanzapine, and risperidone over a period of 6 weeks. The final study sample consisted of 45 patients. However, only 62% of patients had been diagnosed with schizophrenia, the remaining patients had been diagnosed with pervasive developmental disorders, cannabis-related disorders, schizoaffective disorder, anxiety disorders, disruptive behavior disorders, obsessive-compulsive disorder, histrionic personality disorder, and Tourette´s disorder. Average weight gain was significantly greater in the olanzapine group (4.6 ± 1.9 kg) than in the risperidone (2.8 ± 1.3 kg) and clozapine (2.5 ± 2.9 kg) groups. The authors concluded, surprisingly, that olanzapine and risperidone, but not clozapine, caused a disproportionately greater weight gain in children and adolescents relative to adults.

The aim of our study was to evaluate weight gain associated with some atypical and typical antipsychotics used in the treatment of adolescent schizophrenic psychoses at our department.

METHODS

Procedure and study design

This was a systematic chart review of all patients receiving routine clinical care at the Department of Child Psychiatry who were being treated with selected atypical (risperidone, olanzapine, ziprasidone, clozapine) and typical (haloperidol, perphenazine, sulpiride) antipsychotics for schizophrenia or related psychotic disorders between 1997 and 2007. The inclusion of an antipsychotic into the study was based on frequency of use. Only antipsychotics used in a minimum of at least five cases were included. Sulpiride was classified as a typical antipsychotic drug in agreement with most authors (Sadock & Sadock, 2005, Wu *et al.* 2006), although, the opposite point of view also exists (Gerlach & Peacock, 1995).

Patients received a 2-hour intake diagnostic and treatment evaluation by a child psychiatrist. All diagnoses were made by a treating child psychiatrist using the ICD-10 criteria (World Health Organization, 1992) based on interviews with the parent(s) and child, and after a review of available school and psychological testing reports. No formal, structured interviews were used.

Since risperidone had been registered in the Czech Republic for the treatment of schizophrenia in patients aged 15 years and older, an informed con-

sent for "off-label use" had been obtained from the parents of participants younger than 15 years of age. Additionally, olanzapine, ziprasidone, quetiapine, and clozapine had also been registered in the Czech Republic for the treatment of schizophrenia in adults, an informed consent for "off-label use" had been obtained from the parents of all participants treated with these drugs. Haloperidol, perphenazine, and sulpiride had been approved for the treatment of schizophrenia in children and/or adolescents, and therefore no informed consent for "off-label use" was needed.

Records of patients were examined to ascertain the psychiatric diagnosis, type, and dose of antipsychotic medication, weight, history of psychosis, and medication trials prior to admission. Weight was routinely monitored at weekly intervals, with patients clothed in underwear. Electronic scales (Tonava TH 200, manufactured in the Czech Republic and Tanita BWB-600, manufactured in Japan) were used for weight measurements; both scales had an accuracy of ± 0.1 kg, and both were regularly calibrated. Patient weight was evaluated based to their medical records prior to starting treatment and then after 1, 3, and 6 weeks of treatment.

Since our study was retrospective, we had to deal with the fact that the weekly intervals of weight measurement did not always correspond exactly with the first day of the start of a new therapy. We accepted a variance of three days. It is obvious that this variance could influence the results particularly obtained at week 1. In order to control for this confounder, we recorded the measurement of variance at week 0 and 1.

Sample

Inclusion criteria were: (1) schizophrenia diagnosis of F20 – 29, (2) medical record quality sufficient to evaluate the patient, (3) the first treatment used following admission was considered (with the exception of clozapine), and (4) only antipsychotic treatments initiated after admission to the Department of Child Psychiatry were analyzed (i.e. the treatment was not used in out-patient care prior to admission). The third and fourth criterion should ensure that the initial weight was not influenced by previous medication trials at the department, or in out-patient care. However, clozapine, a drug reserved for treatment of refractory patients only, had never been used as a first-line treatment. Thus, it had to be exempted from the third rule in order to obtain any results for this drug.

Statistics

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 15.0). Descriptive statistics for samples was used. For the analysis of weight differences at baseline between atypical and typical antipsychotics, an Independent - Samples T-test was performed. Differences at baseline among treatment groups (i.e. individual drugs) were analyzed using One-Way Analysis of Variance (ANOVA).

Absolute changes in weight between baseline and weeks 1, 3, and 6 were computed (in kg). Additionally, relative changes in percents were computed. Relative change for week 1 was defined as follows: weight 0_1 = $100 \times$ (weight 1 – weight 0) / weight 0. A similar formula was used to calculated weeks 3 and 6. In order to estimate the potential influence of variances in weight measurements at baseline and week 1 on results, a Pearson correlation analysis was performed.

For the analysis of weight changes at weeks 1, 3, and 6 between atypical and typical antipsychotics, an Independent - Samples T-test was performed. For the analysis of weight changes among individual drugs (i.e. treatment groups) at weeks 1, 3, and 6, the Kruskal – Wallis test was used.

RESULTS

Description of the sample

In the period between 1997 and 2007, 109 patients (52 boys, 57 girls) met all the inclusion criteria for the study. The mean age of the sample was 15.8 ± 1.6 years (ages ranged from 10.5 to 18.8 years). Fifty-six patients (51%) had schizophrenia, 15 patients (14%) had schizoaffective disorder, and 38 patients (35%) had other schizophrenic disorders. It was the first episode of illness for 89 patients (82%), 20 patients (18%) were suffering a relapse. Nineteen patients (17%) had received psychopharmacological treatment prior to admission; in some cases more than one drug. Antipsychotics were the most commonly used psychotropic drugs: risperidone (7 cases); olanzapine (4 cases); chlorprothixene (3 cases); levomepromazine, pimozide, and sulpiride (2 cases); and flupenthixol, chlorpromazine, melperone, perphenazine, quetiapine, tiapride, thioridazine, trifluoperazine, and flufenazine depot (one case each).

Fifty-seven patients did not complete the 6-week study period, either because of early discharge due to an excellent therapeutic response, or due to changes in medication because of inefficacy or side effects. Efficacy and side effects other than weight gain will be analyzed separately in another publication.

Medication and weight at baseline

We found that most patients were taking risperidone (N = 52), followed by olanzapine (20 patients). Other patient numbers were as follows: ziprasidone (6 patients), clozapine (7 patients), haloperidol (9 patients), perphenazine (9 patients), and sulpiride (6 patients). The baseline mean weight did not differ significantly among the treatment groups (see Table 1). For mean doses of medication at weeks 1, 3, and 6, see Table 2.

Two sub-groups were formed: the AAP group comprised of 85 patients and the TAP group comprised of 24 patients. Baseline mean weight did not differ significantly between the AAP and TAP group (58.3 ± 12.2 kg vs. 62.5 ± 10.5 kg; t = −1.551, df = 107, p = 0.124).

Table 1. Baseline mean weight in treatment groups

Drug	N	Mean (kg)	Standard deviation (kg)
Risperidone	52	58.9	12.8
Olanzapine	20	56.4	10.4
Ziprasidone	6	53.3	16.2
Clozapine	7	63.3	8.4
Haloperidol	9	61.8	6.7
Perphenazine	9	62.0	15.5
Sulpiride	6	64.4	6.9
Total	109	59.2	12.0

N – number of patients
One-way ANOVA: F = 0.905; df = 6; p = 0.494

Table 2. Mean doses of medication (in milligrams)

Drug	Week 1 Mean (SD)	Week 3 Mean (SD)	Week 6 Mean (SD)
Risperidone	2.8 (1.4)	3.3 (1.5)	2.7 (1.3)
Olanzapine	11.4 (4.4)	15.3 (6.1)	15.0 (6.1)
Ziprasidone	66.7 (10.3)	96.7 (19.7)	80.0 (0.0)
Clozapine	126.8 (60.0)	244.6 (109.9)	247.5 (118.0)
Haloperidol	7.0 (2.9)	4.6 (3.4)	6.8 (1.1)
Perphenazine	16.2 (5.1)	20.5 (9.9)	12.0 (6.9)
Sulpiride	258.3 (58.4)	266.7 (251.7)	450.0 (409.3)

SD - standard deviation

Weight changes: atypical versus typical antipsychotics

The first step was to perform a correlation analysis of weight measurement variances at baseline with changes in weight between baseline and weeks 1, 3, and 6. No significant correlation was found relative to absolute weight changes (r = −0.029, p = 0.765; r = −0.068, p = 0.533; r = 0.037, p = 0.813), or for relative weight changes (r = −0.044, p = 0.647; r = −0.060, p = 0.583; r = 0.043, p = 0.781). Similar non-significant correlations were obtained for weight measurement variances at week 1 with absolute changes in weight between baseline and weeks 1, 3, and 6 (r = 0.094, p = 0.330; r = −0.085, p = 0.436; r = −0.044, p = 0.776), and relative changes in weight between baseline and weeks 1, 3, and 6 (r = 0.110, p = 0.253; r = −0.059, p = 0.592; r = 0.043, p = 0.784), respectively. The absence of significant associations indicated that the variance in initial measurements did not have a significant impact on our results.

Absolute changes in weight between the AAP and TAP groups were not significant for baseline versus week 1 (p = 0.108), vs. week 3 (p = 0.401), and vs. week 6 (p = 0.335). However, there was a significant difference between the two groups in the relative change at week 1. The AAP group gained 1.5% of baseline weight whereas the TAP group gained only 0.2% (p = 0.049). There was an opposite trend, with regard to relative weight change, between baseline and week 3. Patients

on TAP gained 3.7%, whereas patients on AAP gained only 2.8%; however, the difference was not significant (p=0.494). Differences between baseline versus week 6 also turned out to be non-significant (p = 0.282). For details see Table 3.

Weight changes among treatment groups

Absolute changes in weight between baseline and weeks 1, 3, and 6 are displayed in Table 4. Due to the decreasing number of patients in the sample over the time period of the study (early discharges, drop-outs), some drugs had to be removed from statistical analysis in later weeks: haloperidol and sulpiride in weeks 3 and 6; ziprasidone and perphenazine in week 6. Only the risperidone, olanzapine, and clozapine groups had sufficient numbers of patients to allow a comparison at the endpoint of the study (week 6). Patients gained, on average, 3.6 kg (SD 2.6) on risperidone, 4.4 kg (SD 2.5) on olanzapine, and 2.1 kg (SD 4.0) on clozapine, during the six weeks of treatment. No significant differences among treatment groups at any week were found.

Similar non-significant results were obtained for relative changes among treatment groups as follows: baseline versus week 1 (chi² = 0.752; df = 6; p = 0.265), vs. week 3 (chi² = 4.122; df = 4; p = 0.390), and vs. week 6 (chi² =2.472; df = 2; p = 0.291).

DISCUSSION

Retrospective studies, in general, have many methodological limitations, e.g. absence of a control group, less precise design and measurements, no randomization, and unequal sizes of treatment groups. This was also the case in our study. However, retrospective studies offer a naturalistic view of treatment in the clinical setting. Some authors believe they are as important as controlled studies because they address a myriad of clinical interests (Akkaya *et al.* 2007). Furthermore, they enable to study certain aspects of clinical drug use not generally addressed by double-blind, prospective studies, aspects which are particularly well suited for meta-analyses, e.g. a comparison of atypical and typical antipsychotics. Such comparisons often provide new perspectives on a topic. A meta-analysis by Geddes *et al.* (2000) was the first study to report that there was no clear evidence that AAP were more effective or better tolerated than conventional antipsychotics in the adult schizophrenic population. Armenteros & Davies (2006) performed a meta-analysis of studies of antipsychotics on early onset schizophrenia. The average response rate for the 8 studies employing atypical antipsychotics was 55.7% compared with 72.3% for the 13 studies employing typical antipsychotics. This difference was significant at the trend level (p < 0.10). Surprisingly, the rate of extrapyramidal side effects was similar between the two groups. This contradicted a previous observation that had favored atypical neuroleptics (Connor *et al.* 2001). Average weight gain in patients treated with typical

Table 3. Weight changes in atypical versus typical antipsychotics during treatment

	AAP Mean (SD)	TAP Mean (SD)	Statistics
Absolute changes (in kg)			
weight 0_1	0.8 (1.6)	0.2 (1.3)	t = 1.623; df = 107; p = 0.108
weight 0_3	1.4 (2.2)	2.0 (2.5)	t = −0.844; df = 84; p = 0.401
weight 0_6	3.4 (3.2)	2.0 (3.9)	t = 0.975; df = 42; p = 0.335
Relative changes (in %)			
weight 0_1	1.5 (2.9)	0.2 (2.0)	t = 1.993; df = 107; p = 0.049
weight 0_3	2.8 (4.1)	3.7 (4.7)	t = −0.687; df = 84; p = 0.494
weight 0_6	6.5 (6.1)	3.6 (6.1)	t = 1.089; df = 42; p = 0.282

AAP – atypical antipsychotics; TAP – typical antipsychotics; SD – standard deviation; weight 0_1 – weight change between end of week 1 and baseline; weight 0_3 – weight change between end of week 3 and baseline; weight 0_6 – weight change between end of week 6 and baseline.

Table 4. Absolute changes in weight among treatment groups during treatment

Drug	Weight 0_1 (kg) Mean (SD)	Weight 0_3 (kg) Mean (SD)	Weight 0_6 (kg) Mean (SD)
Risperidone	0.6 (1.3)	1.4 (1.8)	3.6 (2.6)
Olanzapine	0.9 (1.6)	2.3 (2.3)	4.4 (2.5)
Ziprasidone	1.6 (4.5)	−0.2 (3.8)	n/a
Clozapine	0.8 (0.9)	0.9 (2.0)	2.1 (4.0)
Haloperidol	−0.2 (1.5)	n/a	n/a
Perphenazine	0.8 (1.3)	2.4 (1.8)	n/a
Sulpiride	−0.2 (0.8)	n/a	n/a
Statistics	chi^2 = 6.874; df = 6; p = 0.333	chi^2 = 5.123; df = 4; p = 0.275	chi^2 = 2.504; df = 2; p = 0.286

Weight 0_1 – weight change between end of week 1 and baseline; weight 0_3 – weight change between end of week 3 and baseline; weight 0_6 – weight change between end of week 6 and baseline; SD - standard deviation; n/a – not available for statistical analysis due to small numbers.

antipsychotics was 1.4 kg, compared to 4.5 kg for those treated with atypical antipsychotics; the statistical significance was not given (Armenteros & Davies, 2006).

In our study, we did not find such a large difference in weight gain between the AAP and TAP groups, as Armenteros et al. did. Patients in our sample gained 3.4 kg on AAP and 2.0 kg on TAP during 6 weeks of treatment, the difference was not statistically significant (p = 0.335). Patterns of weight gain were different in patients taking AAP and TAP and was best demonstrated using relative weight changes (see Table 3). Patients on AAP gained significantly more during the first week of treatment than patients on TAP. During the following two weeks the situation was reversed, and patients on TAP gained (non-significantly) more than patients on AAP. In the last 3 weeks, of the 6 week observation period, patients on TAP stabilized at the weight reached at week 3 whereas weight increase continued with patients on AAP (see Table 3).

The most consistent results of our study come from three AAP that were available for analysis all the way through week 6 observation period: risperidone, olanzapine, and clozapine (see Table 4). Patients gained on average 3.6 kg (SD 2.6) on risperidone, 4.4 kg (SD 2.5) on olanzapine, and 2.1 kg (SD 4.0) on clozapine during

the six weeks of treatment. The differences in weight gain among treatment groups were non-significant. The results were almost the same as those described in a 6-week study by Fleischhaker et al. (2007). They reported an average weight gain of 2.8 kg (SD 1.3) for risperidone, 4.6 kg (SD 1.9) for olanzapine, and 2.5 kg (SD 2.9) for clozapine; although, the differences between olanzapine and risperidone, and between olanzapine and clozapine were significant.

The mean final doses of medications in our study (risperidone 2.7 mg; olanzapine 15.0 mg; and clozapine 247.5 mg) were similar to Fleischhaker's study (2.9 mg, 16.1 mg, and 294.9 mg respectively). However, there were some differences in study design and patient population between the reports: retrospective versus open – label prospective study, only schizophrenic patients versus a mixed patient population (for details, see Introduction), unequally large treatment groups versus equally large treatment groups (15 patients in each group in Fleischhaker's study).

Comparisons with other pediatric trials involving AAP are difficult because they, generally, have designs with longer durations than our study (8-week, or even 12-week durations). Other studies have, uniformly, reported greater weight gains with olanzapine than with

risperidone (Ratzoni *et al.* 2002; Sikich *et al.* 2004). A double-blind study by Shaw *et al.* (2006) reported similar weight changes in patients taking olanzapine and clozapine (3.6 and 3.8 kg, resp.), which contradicted our observation as well as the observation of Fleischhaker *et al.* (2007).

It seems to be plausible that the degree of weight change associated with AAP in pediatric population is different from those observed in the adult population. The mean weight gain, described by Allison *et al.* (1999), in adults was lower with some AAP (with the exception of clozapine) during a 10-week period than the weight gain described in our 6-week study: risperidone 2.10 vs. 3.6 kg, olanzapine 4.15 vs. 4.4 kg, and clozapine 4.45 vs. 2.1 kg. Some authors have speculated that adolescents may gain more weight than adults (particularly with risperidone) due to drug impact on prolactin (Fleischhaker *et al.* 2007). Adolescents may be more sensitive to this hormone (Wirshing *et al.* 2002; Wirshing, 2004).

This aspect could represent a general difference in side effects between pediatric and adult populations treated with AAP, as was demonstrated in our previous retrospective study (Hrdlicka & Dudova, 2007). We found in our adolescent population treated with risperidone that the therapeutic response was almost the same as in the risperidone arm of the RODOS study in adults (82% and 84%, resp.) however, 46% of our patients reported some type of side effect, according to their medical records, whereas in the RODOS study (Kasper *et al.* 2001) side effects were only reported by 13%.

Acknowledgements

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