Metabolic Effects Associated With Atypical Antipsychotic Treatment in the Developmentally Disabled

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Objective: Atypical antipsychotics, especially clozapine and olanzapine, have been increasingly associated with weight gain and other adverse metabolic events (diabetes mellitus, hyperlipidemia) in non–mentally retarded populations. This report explores the incidence of this phenomenon in an institution-dwelling population of individuals with developmental disabilities.

Method: A retrospective longitudinal analysis was performed for a sample of 41 adults with developmental disabilities and comorbid psychiatric and/or behavioral syndromes for whom treatment was converted from typical antipsychotics to olanzapine or risperidone for a minimum period of 2 years. Data were collected from October 1998 to September 2002. Among parameters analyzed were chlorpromazine equivalent dosage of antipsychotic, metabolic parameters, body mass index (BMI), level of concurrent medications, and concomitant dietary restrictions.

Results: Thirty-two study subjects (78.0%) were men. The mean age of the study subjects was 43.6 years (at the end of the study). Thirty-seven (90.2%) had severe-to-profound mental retardation. Eight (19.5%) were on a restricted diet. Twenty-three subjects (56.1%) were switched from a typical antipsychotic to olanzapine, and 18 subjects (43.9%) were switched from a typical antipsychotic to risperidone. Of the subsample of subjects who were switched from a typical antipsychotic to risperidone, 12 (66.7%) went on to be switched to olanzapine because of either emergent side effects or lack of efficacy. For the overall sample (N = 41), there was a 19.3% increase in chlorpromazine-equivalent antipsychotic dosage from baseline to the 2-year endpoint along with a 5.6% decrease in fasting blood glucose from baseline to the 2-year endpoint. There were no significant differences between baseline and endpoint values for BMI, total cholesterol, low-density lipoprotein cholesterol, or triglycerides.

Conclusion: The findings of this 2-year evaluation suggest that clinically or statistically significant BMI increases as well as blood glucose and lipid elevations are not unavoidably correlated with the use of the atypical antipsychotic agents olanzapine and risperidone and may be minimized by careful monitoring, a regimen of dietary control, and a moderate activity level in a residential population of individuals with mental retardation.

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Mental retardation is a disability characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills, with the disability originating before the age of 18 years.[1] In the last decade, a great deal of enthusiasm has been generated regarding the use of atypical antipsychotic agents in those with such a disability and comorbid psychiatric or behavioral syndromes.[2,3] There is, however, a dearth of double-blind, placebo-controlled trial evidence to provide evidence-based support for this strategy at present. To date, too few studies with too great a reliance on global impression measures such as the Clinical Global Impressions scale limit the ability to evaluate efficacy in this population.[2] In studies analyzing the use of atypical antipsychotic agents in populations with developmental disabilities, there are reports of improvement in behaviors such as compulsions,[4] stereotypies,[5–7] self-injury,[8] and aggression.[9] Many of these studies, however, have significant methodological limitations. The most pervasive theory underlying the move to switch to atypicals in the developmentally disabled is that such agents may have a less problematic long-term adverse effect burden and the potential for greater efficacy, as compared to conventional agents.[2,3] These atypical antipsychotics (clozapine, olanzapine, risperidone, quetiapine, and ziprasidone) differ from the older, typical antipsychotics in terms of their neurotransmitter selectivity and affinities. Typical antipsychotics are potent dopamine-2 (D_2) antagonists, while atypicals have a lesser D_2 antagonism along with increased serotonin 5-HT_{2A} affinity. Evidence is mounting that supports the idea that atypicals have increased efficacy for treatment of both positive and negative symptoms of schizophrenia, with a decreased

tendency to elicit extrapyramidal side effects, including tardive dyskinesia, in non–developmentally disabled populations.[10,11]

Atypical antipsychotics, especially clozapine and olanzapine, have been increasingly reported to be associated with a different adverse effect burden compared with typical antipsychotics that includes weight gain and other adverse metabolic events (diabetes mellitus, hyperlipidemia) in non–mentally retarded populations.[12,13] Of particular concern is that these adverse effects may decrease treatment adherence, decrease overall health-related quality of life, and impose an additional burden on the health care system. The metabolic issues associated with atypical agents are of such potential significance that this cluster of adverse effects has been casually referred to as the "tardive dyskinesia" of the second-generation antipsychotics. Unlike tardive dyskinesia, however, metabolic adverse effects are potentially avoidable or reversible with diet and exercise.

The majority of weight gain is typically reported early in treatment (< 12 weeks) and typically plateaus after 36 weeks of atypical antipsychotic administration.[13] Factors commonly associated with weight gain include a low baseline body mass index (BMI), female gender, and young age.[12] Most of the published studies related to these metabolic issues have been conducted in outpatient settings and in non–developmentally disabled individuals. Because of the rising concerns regarding the potential for atypical antipsychotic–associated metabolic adverse events and their related sequelae, a recent consensus panel consisting of members from the American Diabetes Association, the American Psychiatric Association, the North American Association for the Study of Obesity, and the American Association of Clinical Endocrinologists established guidelines for the monitoring and use of these agents relative to their potential metabolic adverse effects.[14]

As the vast majority of the current study data related to atypical antipsychotic–associated weight gain and metabolic disturbance is from non–developmentally disabled groups, the present study was designed to determine if olanzapine or risperidone is associated with clinically significant BMI changes or changes in metabolic parameters (low-density lipoprotein [LDL] lipid profile, triglycerides, and fasting glucose) in a population of institution-dwelling developmentally disabled individuals who had comorbid psychiatric illnesses requiring treatment with the atypical antipsychotic agents olanzapine or risperidone.

METHOD

Patients with mental retardation and comorbid psychiatric and/or behavioral disorders who underwent a switch from typical to atypical antipsychotic medication were studied. Data were collected from October 1998 to September 2002. A sample of 41 patients met inclusion criteria. Those identified for study were patients who (1) had a diagnosis of mental retardation and a comorbid psychiatric disorder (e.g., autistic disorder, bipolar disorder) and/or a documented behavioral disorder (e.g., aggression, self-injury) that was being targeted for treatment using antipsychotic medication; (2) were aged 18 years or older; (3) had treatment converted from conventional antipsychotics to olanzapine or risperidone and experienced a minimum atypical antipsychotic exposure time of 2 years; and (4) had remained in the facility during the entire 2-year typical-to-atypical–switch follow-up treatment period. These 41 cases represented all the patients at the study site who met the specified inclusion criteria. All of the patients identified for the study were receiving ongoing habilitative treatment (e.g., self-care, vocational, leisure training) and ongoing behavioral treatments for their comorbid psychiatric and/or behavioral disorders in accordance with regulatory guidelines for an intermediate care facility for persons with mental retardation. As per facility policy, all patients treated with atypical antipsychotic medications received nursing and dietary staff supervision with regard to regular monitoring and documentation of potential metabolic side effects and specific dietary interventions prescribed and monitored on an individualized, as-needed basis.

For the identified sample, a retrospective longitudinal design was used to examine potential changes for a set of body weight and metabolic outcome measures associated with the switch from typical to atypical antipsychotic treatment. This design was used to examine changes in specified outcome parameters from the baseline (on typical antipsychotic treatment) to a 2-year follow-up endpoint (following conversion from the typical antipsychotic to the atypical antipsychotic). After institutional review board evaluation of the study, a waiver was obtained, as this was a retrospective review and no experimental manipulations were planned. Parameters analyzed were as follows: chlorpromazine equivalent dosage of antipsychotic (calculated using standard equivalency data[15,16]), metabolic outcomes (fasting blood glucose, triglycerides, and LDL lipids), age, sex, weight, BMI, level of mental retardation, concurrent medications, and concomitant dietary restrictions. Per facility policy, baseline blood glucose, cholesterol, and triglyceride levels were obtained prior to drug initiation and at predetermined intervals during treatment. Data from patient medical records and electronic pharmacy databases were used to obtain values for each patient on each of the above variables at baseline and at the 2-year longitudinal follow-up endpoint.

Resulting data were analyzed in 3 ways. First, descriptive analyses were performed to characterize the sample in terms of mean age, gender distribution, level of mental retardation, percentage of sample on restricted diets, and

Table 1. Demographics of Mentally Retarded Patients With Comorbid Psychiatric or Behavioral Disorders Switched From Typical to Atypical Antipsychotics

Variable	All (N = 41)	Typical to Olanzapine (N = 23)	Typical to Risperidone (N = 6)	Risperidone to Olanzapine (N = 12)
Mean age, y	43.6	41.6	42.0	48.2
Sex, N				
Male	32	18	5	9
Female	9	5	1	3
Level of mental retardation, N				
Severe-to-profound	37	22	5	10
Moderate	4	1	1	2
On restricted diet at endpoint, N (%)	8 (19.5)	1 (4.3)	3 (50.0)	4 (33.3)
On lipid therapy from baseline to endpoint, N (%)	3 (7.3)	2 (8.7)	0	1 (8.3)

percentage of sample receiving concomitant medications. Second, statistical analyses (t tests) were performed using the entire sample to determine the magnitude of changes from baseline (on typical antipsychotic treatment) to endpoint (on atypical antipsychotic treatment) for chlorpromazine equivalent dose, BMI, fasting blood glucose, total cholesterol level, LDL cholesterol level, and triglyceride level. Third, these baseline-to-endpoint statistical analyses (t tests) were repeated for specific subgroups: those switched to olanzapine (N = 23), those switched to risperidone (N = 6), and those initially switched to risperidone but then switched to olanzapine because of lack of efficacy or emergent side effects (N = 12). No subjects in this sample were initially switched to olanzapine but then switched to risperidone.

RESULTS

Descriptive data on the demographic and clinical features of the sample are provided in Table 1. The mean age of the sample at endpoint was 43.6 years (range, 23–65 years). Thirty-two (78.0%) of the sample were men, and 37 (90.2%) of the sample functioned in the severe-to-profound range of mental retardation. Thirty-two (78.0%) of the sample were white, and the remaining subjects were African American. Eight (19.5%) of the subjects were on a restricted diet during the study, and 3 (7.3%) required that lipid-lowering therapy be added during the 2-year study period. Twenty-three (56.1%) of the subjects were switched from a typical antipsychotic to olanzapine, and 18 (43.9%) of the subjects were switched from a typical antipsychotic to risperidone. Of the subsample of subjects who were switched from a typical antipsychotic to risperidone (N = 18), 12 (66.7%) went on to be switched from risperidone to olanzapine because of either emergent side effects (e.g., hyperprolactinemia) or a lack of efficacy. No subjects required diabetes therapy at baseline or throughout the evaluation period. Six individuals were receiving antihypertensive therapy at baseline and continued treatment throughout the study period. No new antihypertensive regimens were initiated during the study. Data on concomitant medications that are commonly known to affect weight are displayed in Table 2. Thirteen subjects (31.7%) were receiving concomitant antiepileptic drugs, 17 (41.5%) were receiving osteoporosis therapy (calcium carbonate, miacalcin nasal spray, alendronate, or raloxifene), and 9 (22.0%) were receiving a proton pump inhibitor or a histamine-2 antagonist.

For the overall sample of subjects (N = 41), there was a 19.3% increase in chlorpromazine-equivalent antipsychotic dosage from baseline (on typical antipsychotic treatment) to endpoint (on atypical antipsychotic treatment) (baseline = 278.1 mg/day chlorpromazine equivalents, follow-up = 331.7 mg/day chlorpromazine equivalents; $t = 2.87$, $df = 40$, $p = .006$; Table 3). There was also a 5.6% decrease in fasting blood glucose from baseline (on typical antipsychotic treatment) to endpoint (on atypical antipsychotic treatment) (baseline = 87.2 mg/dL, endpoint = 82.4 mg/dL; $t = 2.48$, $df = 40$, $p = .017$). There were no significant differences between baseline and endpoint values for BMI (baseline = 22.9 kg/m^2, endpoint = 23.2 kg/m^2; $t < 1.00$, $df = 40$, $p = .53$), total cholesterol (baseline = 176.2 mg/dL, endpoint = 167.6 mg/dL; $t = 2.41$, $df = 40$, $p = .11$), LDL cholesterol (baseline = 102.4 mg/dL, endpoint = 99.0 mg/dL; $t < 1.00$, $df = 40$, $p = .73$), or triglycerides (baseline = 99.6 mg/dL, endpoint = 94.2 mg/dL; $t < 1.00$, $df = 40$, $p = .34$).

Subjects were subgrouped based on the pattern of their medication switch over the course of the 2-year follow-up period (typical to olanzapine, N = 23; typical to risperidone, N = 6). The pattern of results for the olanzapine subgroup were similar to those for the overall sample, with this subgroup showing an increase in chlorpromazine-equivalent antipsychotic dosage from baseline to endpoint (baseline = 255.3 mg/day chlorpromazine equivalents, endpoint = 316.0 mg/day chlorpromazine equivalents; $t = 2.72$, $df = 22$, $p = .012$) and a decrease in fasting blood glucose from baseline to endpoint (baseline = 87.0 mg/dL, endpoint = 79.4 mg/dL; $t = 3.40$, $df = 22$, $p = .002$). For this subgroup, there were no significant differences between baseline and endpoint values for BMI, total cholesterol, LDL cholesterol, or triglycerides. For the subgroup switched to risperidone, there were no significant differences between baseline and endpoint values for chlorpromazine-equivalent antipsychotic dosage, fasting blood glucose, BMI, total cholesterol, LDL cholesterol, or triglycerides.

Of the subsample of subjects who were switched from a typical antipsychotic to risperidone (N = 18), 12 (66.7%) went on to be switched from risperidone to olanzapine because of either an emergent side effect (e.g.,

Table 2. Concomitant Medications by Treatment Group in Mentally Retarded Patients With Comorbid Psychiatric or Behavioral Disorders Switched From Typical to Atypical Antipsychotics

Therapeutic Category	All (N = 41)	Typical to Olanzapine (N = 23)	Typical to Risperidone (N = 6)	Risperidone to Olanzapine (N = 12)
Antiepileptic	13	9[a] (VPA = 3, CBZ = 2, DPH = 2, LTG = 1, LEV = 1, PRIM = 1)	3 (TPM, VPA, CBZ)	1 (VPA)
Second antipsychotic	1	0	1	0
SSRI/TCA	5	1	2	2
Anxiolytic	2	2	0	0
Lithium	2	1	0	1
Antihistamine	9	7	2	0
Anticholinergic	2	2	0	0
Antiosteoporosis	17	6[a]	4	7[a]
Proton pump inhibitor or H_2 antagonist	9	7[a]	1	1
NSAID or COX-2 inhibitor	3	3	0	0

[a]One or more patients received multiple medications in this category.
Abbreviations: COX = cyclooxygenase, CBZ = carbamazepine, DPH = phenytoin, H_2 = histamine-2, LEV = levetiracetam, LTG = lamotrigine, NSAID = nonsteroidal antiinflammatory drug, PRIM = primidone, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, TPM = topiramate, VPA = valproic acid.

hyperprolactinemia) or a lack of efficacy. These subjects (N = 12) who were switched from a typical agent to risperidone and then to olanzapine were receiving a significantly higher chlorpromazine-equivalent antipsychotic dose at baseline (on risperidone treatment) than the remainder of the sample (361.1 mg/day vs. 253.1 mg/day; $t = 4.1$, $df = 39$, $p < .001$), suggesting that they were a relatively treatment-refractory subgroup. For this subgroup, there were no significant differences between baseline (on typical antipsychotic treatment) and endpoint (on olanzapine treatment) values for BMI, total cholesterol, LDL cholesterol, or triglycerides.

A correlational analysis was performed to examine the relationship between resulting atypical antipsychotic dose level at endpoint (measured as chlorpromazine-equivalent antipsychotic dose) and the resulting change (baseline to endpoint) in body weight and metabolic values. For the entire sample (N = 41), there were no significant correlations (significance was set at $p < .05$) between final atypical dose and resulting change in BMI ($r = –0.05$), total cholesterol level ($r = –0.14$), LDL cholesterol level ($r = 0.28$), triglyceride levels ($r = –0.20$), and fasting blood glucose level ($r = –0.06$). Similar results were obtained for each of the subgroups (typical to olanzapine, typical to risperidone, risperidone to olanzapine) considered separately.

A subanalysis was performed on all cases (N = 8) for which baseline BMI was > 25 kg/m^2. Three of these subjects experienced a 5% or greater weight gain, and 3 lost weight on the new regimen (Table 4).

DISCUSSION

The findings of this report suggest that clinically or statistically significant BMI increases and metabolic disturbances are not unavoidably correlated with the use of the atypical antipsychotic agents olanzapine and risperidone in this population. A frequently recommended regimen to control drug-associated weight gain in non–developmentally disabled populations is to control diet and increase physical activity levels. The subjects involved in this study lived with a diverse group of peers in a state-operated residential intermediate care facility for persons with mental retardation. Over 99% of the residents of this facility are Medicaid eligible. As a result of the placement and mandated care standards, residents are involved in active treatment programs that include daily planned activities. Many residents have jobs and/or moderate exercise programs (e.g., walking 2–3 times weekly for 30 minutes each session) that provide a mechanism for keeping them physically active. In addition, all subjects in the study had a specific diet order, with most (80%) having been ordered a "regular" diet (2000–2400 kcal/day) along with access to snacks and vending machine items (crackers, sodas, etc.). Although the study subjects had severe-to-profound developmental disabilities, most were able to access snack machines and other exogenous food resources independently; therefore, "extra" caloric intake beyond the physician-prescribed diet was not dependent on institutional staff. The restricted diets (19.5% of subjects) (less than 2000 kcal/day) did not include unlimited access to snacks or vending machine products. Only those individuals with metabolic disorders or with significant obesity were under a strict program of dietary control. Information on changes in diet was recorded as they occurred. Three individuals, all in the olanzapine group, were required to initiate lipid-lowering therapy during the 2-year study period, which may have been related to increased surveillance and awareness of the potential for

Table 3. Mean Baseline and Endpoint (2-year follow-up) Dosage and Metabolic Values by Treatment Group in Mentally Retarded Patients With Comorbid Psychiatric or Behavioral Disorders Switched From Typical to Atypical Antipsychotics[a]

Variable	All (N = 41)	Typical to Olanzapine (N = 23)	Typical to Risperidone (N = 6)	Risperidone to Olanzapine (N = 12)
CPZ equivalent dosage, mg/d				
Baseline	278.1	255.3	200.0	361.1
Endpoint	331.7*	316.0* (15.8 mg/d olanzapine)	266.7 (5.3 mg/d risperidone)	394.5 (19.7 mg/d olanzapine)
BMI, kg/m^2				
Baseline	22.96	22.97	21.29	23.78
Endpoint	23.17	23.12	22.28	23.72
Total cholesterol, mg/dL				
Baseline	176.17	173.04	187.83	176.33
Endpoint	167.56	165.35	191.17	160.00
LDL cholesterol, mg/dL				
Baseline	102.44[b]	98.80[c]	102.00[d]	109.80[e]
Endpoint	99.00[b]	105.40[c]	110.00[d]	84.00[e]
Triglycerides, mg/dL				
Baseline	99.61	100.09	87.83	104.58
Endpoint	94.17	93.26	83.83	101.08
FBG, mg/dL				
Baseline	87.27	87.04	91.50	85.58
Endpoint	82.41*	79.35*	83.17	87.92

[a]Comparisons between baseline and endpoint values were made using the t test for dependent samples.
[b]N = 16.
[c]N = 10.
[d]N = 1.
[e]N = 5.
*Significant difference at $p < .05$ vs. baseline.
Abbreviations: BMI = body mass index, CPZ = chlorpromazine, FBG = fasting blood glucose, LDL = low-density lipoprotein.

Table 4. BMI and Weight Gain in 8 Subjects With Mental Retardation and Psychiatric or Behavioral Disorders With a Baseline BMI of > 25 kg/m^2 Initiated on Atypical Antipsychotic Treatment

Subject	Baseline Drug and Dosage, mg/d	Atypical Treatment	Baseline CPZ Equivalent Dosage, mg/d	Baseline BMI, kg/m^2	Endpoint CPZ Equivalent Dosage, mg/d	Endpoint BMI, kg/m^2	% Weight Gain at Endpoint vs. Baseline, lb
1	Thioridazine, 200	Olanzapine[a]	200	25.9	500	28.6	10.4
2	Haloperidol, 4	Olanzapine[a]	200	26.3	200	23.6	–10.1
3	Haloperidol, 6	Olanzapine[a]	300	25.7	250	27.6	7.6
4	Haloperidol, 8	Olanzapine[a]	400	31.4	400	31.9	1.6
5	Thioridazine, 150	Olanzapine	150	32.7	200	30.1	–7.9
6	Chlorpromazine, 200	Olanzapine	200	26.1	300	23.9	–8.7
7	Haloperidol, 10	Olanzapine	500	27.0	400	28.3	4.8
8	Haloperidol, 4	Olanzapine	200	30.6	300	33.0	8.0

[a]Switched from typical to risperdone, then to olanzapine.
Abbreviations: BMI = body mass index, CPZ = chlorpromazine.

hyperlipidemia related to antipsychotic agents. No new cases of diabetes mellitus or hypertension were identified during the study period. Also of note is that this population included few smokers, as they lived in a residential facility where such a practice was discouraged. In general, smoking is thought to decrease overall weight gain in the general population.[17]

As a result of the structure of the diet and activity functions at this facility, the residents are perhaps more physically active than a community-based population, and while access to foods is not totally restricted, there is not unlimited access to snacks, as may occur in an unsupervised living arrangement. This experience is not universally reported in populations with developmental disabilities utilizing atypical antipsychotics. In a retrospective study[18] of 50 adult patients with mental retardation treated with risperidone, 37 of 39 patients with usable data gained weight (mean increase, 8.3 kg) over a 2-year period. Twenty of the 37 patients gaining weight were calorie restricted. The study reports no dose-related weight gain and no behavioral deterioration in those with calorie-restricted diets.[18]

As the current study setting was part of an organized health care system with 24-hour on-site nursing coverage, systematic clinical monitoring occurred for all individuals, including monthly weight, blood pressure,

respirations, and pulse documentation. For those individuals treated with specific medication classes, such as antipsychotic agents, specific laboratory monitoring was conducted, per clinical policy. Baseline and quarterly abnormal movement assessments; baseline and annual complete blood count, chemistry panel, and prolactin level assessments; and fasting blood glucose assessments at baseline, 3 months, 6 months, and annually were all part of the clinical monitoring policy for individuals treated with atypical antipsychotic agents at this facility. For the purpose of this evaluation, results of such monitoring were reported only for baseline compared to 2-year endpoint.

The chlorpromazine-equivalent dose of atypical antipsychotic agent increased over the 2-year period in the overall group by 54 mg/day. This is the equivalent of 2.7 mg/day of olanzapine and approximately 1 mg/day of risperidone. While this increase was statistically significant, it is not thought to be clinically relevant. Further, the absence of a clinically relevant dose increase over a 2-year period implies that treatment teams were favorably impressed with the efficacy of the atypical antipsychotic regimen and dose for the specific indication. A focused effort has been in place at this study site for more than a decade to foster the rational use of psychoactive agents. As a result, the number of residents treated with antipsychotic agents has decreased overall, with many patients having doses decreased or antipsychotic drugs discontinued entirely. As a certain core group of the population treated with antipsychotic agents have demonstrated a need for maintenance therapy and are no longer candidates for seeking the lowest effective dose, it is imperative that the choice of antipsychotic agent in this group be one that both is efficacious and has a limited adverse effect burden.[19]

One subgroup consisted of 12 subjects who had previously failed on a trial of risperidone and were subsequently treated successfully with olanzapine. The subjects were switched because of either a lack of sustained efficacy or adverse events (extrapyramidal symptoms or elevated prolactin levels). The mean chlorpromazine-equivalent doses at baseline and endpoint were 361.0 mg/day and 394.5 mg/day (equivalent to 19.7 mg/day of olanzapine), respectively, in this group. This baseline represents a mean dose of 7.2 mg/day of risperidone. This mean dose exceeds the standard labeled recommended dosage and may have been supratherapeutic, with an increased side effect burden perceived as lack of efficacy or worsening of symptoms by treatment teams, leading to the conversion to olanzapine. The success of the resultant therapy was not related to a substantial increase in comparable dose from the risperidone to olanzapine conversion. There were no clinically or statistically significant changes in BMI or metabolic parameters observed in these groups during the 2-year follow-up period, compared to baseline. The subjects for whom treatment was converted from either a typical antipsychotic agent to olanzapine (N = 23) or risperidone to olanzapine (N = 12) remained on olanzapine treatment for the duration of the study period.

Three subjects, all of whom were receiving olanzapine, required the addition of a statin drug for lipid management during the 2-year study period. These subjects' baseline BMIs were 22.7 kg/m^2, 23.8 kg/m^2, and 25.0 kg/m^2, respectively, and endpoint BMIs were 20.0 kg/m^2, 20.6 kg/m^2, and 26.5 kg/m^2, respectively. The mean age of this group was 58 years. Concomitant medications that might have impacted BMI or lipids in these 3 cases were not present.

Three additional studies[9,20,21] that look specifically at weight gain are reported in the literature in populations with developmental disabilities treated with atypical antipsychotic agents. One trial[9] of 20 institutionalized adults treated with add-on olanzapine (mean dose, 9.1 mg/day; range, 2.5–22.5 mg/day) for self-injury, aggression, and disruptive behaviors reported a significant increase in weight during the first 6 months of the trial. A second trial,[20] using ziprasidone in 40 adult patients who experienced significant weight gain or were poor responders with other atypical antipsychotic agents, measured weight, total cholesterol, LDL and HDL cholesterol, triglycerides, and maladaptive behavior at baseline and 6 months. The patients experienced a mean weight loss of 3.6 kg and a significant reduction in total cholesterol and triglycerides at 6 months compared to baseline. The frequency of maladaptive behaviors was unchanged or improved in 18 of 25 subjects with such data available.[20] A third trial,[21] which utilized a double-blind, placebo-controlled, crossover design with risperidone as the active arm in a population with mental retardation and autism, with ages ranging from 6 to 65 years (N = 19), found that weight gain in all age groups was significant (mean gain range across all age groups, 5.4–8.4 kg over 1 year).

The present published literature has not clearly established a dose-response relationship between all atypical antipsychotic agents and weight gain.[13,22] However, it is important to note that mean doses of olanzapine and risperidone seen in the current study were less than a 400-mg chlorpromazine equivalent dose per day (2-year typical to olanzapine group, 316 mg/day; 2-year risperidone to olanzapine group, 394 mg/day; and 2-year typical to risperidone group, 267 mg/day). Therefore, if the weight gain and associated metabolic adverse events are found to be dose related, this population used relatively low doses, which may minimize weight gain potential.

Table 2 depicts an analysis of concomitant medications for the study population. Of note is the high prevalence of osteoporosis medication regimens (17 [41.5%] on treatment despite a mean age of 43.6 years). Osteo-

porosis is an often underrecognized problem in populations with developmental disabilities, who have multiple risk factors (e.g., hypogonadism, lack of physical activity, poor nutritional status, minimal sun exposure, exposure to enzyme-inducing antiepileptic agents). This finding highlights the importance of controlling modifiable risk factors, such as using antipsychotic agents that do not adversely affect prolactin. In addition, 13 of 41 subjects were receiving concomitant antiepileptic agents, many of which have the propensity to alter weight (e.g., valproate [increases weight], carbamazepine [increases weight], topiramate [decreases weight]). Lastly, 9 of 41 subjects were receiving concomitant antihistamine therapy, which tends to increase weight in some individuals.

As the current Consensus Development Conference guidelines[14] suggest that a weight gain of 5% is clinically significant, a subanalysis was performed for those subjects with baseline BMI of more than 25 kg/m^2 (categorically overweight) (Table 4). Of the 8 subjects in this category, 2 were receiving baseline therapy with thioridazine, 5 with haloperidol, and 1 with chlorpromazine. Three of the subjects lost weight after conversion to olanzapine therapy. Three of the 8 subjects had a greater than 5% weight gain; however, none had an abnormal fasting blood glucose level recorded.

Strengths of this retrospective review include the naturalistic design, which included patients with multiple comorbidities, as well as the 2-year duration of the observation period. It is likely, based on other studies of metabolic issues with atypicals, that any significant weight and metabolic abnormalities will present within the 2-year time frame of this study.

Methodological limitations include the open-label, retrospective design, the lack of subject randomization to the various treatment arms, and the lack of a control mechanism for other variables that may impact weight and metabolic issues. No other cardiovascular or metabolic risk factors, with the exception of those described, were assessed during this study. As such lack of rigor can introduce many potentially confounding variables, no clear relationships between treatments and outcome can be established. However, the metabolic adverse effects potential of atypical antipsychotic agents in certain subgroups such as the one described in this work is clearly an area that must be examined in a more rigorously designed construct.

CONCLUSIONS

There were no significant increases in lipid levels, BMI, or blood glucose levels at endpoint compared to baseline in patients treated with either risperidone or olanzapine therapy. This may be due in part to patients' increased activity levels and limited access to food in institutions versus the community. The results of this study suggest that the onset of weight gain, blood glucose abnormalities, and lipid abnormalities commonly associated with the atypical antipsychotic agents olanzapine and risperidone may be postponed, avoided, or minimized by careful monitoring, a reasonable diet regimen, and a moderate activity level in a residential population of individuals with developmental disabilities. The dose of atypical agents did not increase in a clinically significant manner throughout the 2-year study. There were no discernible differences in adverse BMI or measured metabolic changes between olanzapine and risperidone in this study. More study is needed to determine if these results may be generalized to other populations.

Drug names: alendronate (Fosamax), carbamazepine (Carbatrol, Equetro, and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), lamotrigine (Lamictal), levetiracetam (Keppra), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), primidone (Mysoline and others), quetiapine (Seroquel), raloxifene (Evista), risperidone (Risperdal), topiramate (Topamax), valproic acid (Depakene, Myproic Acid, and others), ziprasidone (Geodon).

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