Lack of Effect of Stimulant Combination with Second-Generation Antipsychotics on Weight Gain, Metabolic Changes, Prolactin Levels, and Sedation in Youth with Clinically Relevant Aggression or Oppositionality

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Abstract

Background: Second-generation antipsychotics (SGAs) are associated with weight gain, metabolic abnormalities, sedation/sleep disturbance, and prolactin abnormalities, especially in youths. Although stimulants have opposing dopamine receptor and adverse effects, it is unclear whether stimulant co-treatment counteracts the therapeutic or side effects of antipsychotics.

Methods: This was a naturalistic cohort study including 153 antipsychotic trials in youths aged 4–19 (mean, 11.3 ± 3.0) years, started on an SGA for clinically significant aggression or oppositionality associated with oppositional defiant disorder, conduct disorder, disruptive behavior disorder not otherwise specified (NOS), impulse control disorder NOS, intermittent explosive disorder, Tourette's disorder, autistic disorder, and pervasive developmental disorder NOS. Patients underwent fasting assessments of body composition, lipids, glucose, insulin, prolactin, sedation, and general efficacy at baseline, weeks 4, 8, and 12, comparing patients co-prescribed stimulants ($n = 71$) with those not co-prescribed stimulants ($n = 82$).

Results: Patients received risperidone (33.3%), aripiprazole (29.4%), quetiapine (18.4%), olanzapine (11.8%), ziprasidone (5.9%), or clozapine (0.7%). With and without adjustment for differences in baseline variables (sex, prior stimulant use, primary *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [DSM-IV] disorders, co-morbid attention-deficit/hyperactivity disorder [ADHD], present in 46.3% of youths not receiving stimulants, and some body composition parameters), patients on versus off stimulants did not differ on any of the assessed outcomes (all p values ≥ 0.1).

Conclusions: In contrast to guidelines, stimulant use did not precede or accompany antipsychotic use during the current episode of aggression/oppositionality in almost half of those youths who had aggressive/oppositional behavior and a DSM-IV diagnosis of ADHD. At the clinically prescribed doses, stimulant co-treatment of SGAs did not seem to significantly reduce antipsychotic effects on body composition, metabolic parameters, prolactin, sedation, and broad efficacy.

Introduction

CLINICALLY RELEVANT AGGRESSION AND oppositionality are common treatment targets in child and adolescent psychiatry (Pappadopulos et al. 2003; Schur et al. 2003; Olfson et al. 2006; Pappadopulos et al. 2006; Jensen et al. 2007). Disruptive behavior disorders that are frequently associated with relevant aggression

and oppositionality occur in approximately 7–11% of the pediatric population (Loeber et al. 2000; Nock et al. 2007), with an estimated 75% referral rate to psychiatric care among children with these diagnoses (Arcelus and Vostanis 2003). Children suffering from these disorders and symptoms have problems functioning in families, in school, and with their peers. They are also at risk for long-term interpersonal and academic difficulty, legal problems,

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substance abuse or dependence, and frequent use of social and mental health services (Loeber et al. 2000; Ezpeleta et al. 2001; Nock et al. 2007).

Although they are still somewhat controversial regarding the appropriate timing and sequencing with nonpharmacologic management strategies, pharmacologic treatments, and, in particular, antipsychotics have shown to be efficacious for the symptoms of aggression and externalizing disorders (Pappadopulos et al. 2003; Schur et al. 2003; Pappadopulos et al. 2006; Jensen et al. 2007). There is evidence that antipsychotics can facilitate short-term reduction in symptoms of maladaptive aggression, and risperidone has been shown to be more efficacious than placebo in double-blind, controlled studies (Jensen et al. 2007), with greater effect sizes than for other medication classes, such as mood stabilizers, stimulants, antidepressants and $\alpha 2$ agonists (Pappadopulos et al. 2006).

However, treatment with antipsychotics, and especially with second-generation antipsychotics (SGAs), is complicated by adverse effects, which commonly include weight gain and sedation (Correll et al. 2006; Correll and Carlson 2006; Correll 2008a), two critical issues for children's health and academic and social functioning (Jensen et al. 2007). In addition, SGA treatment has also been associated with varying degrees of metabolic abnormalities (Correll and Carlson 2006; Correll 2008b), prolactin abnormalities (Correll and Carlson 2006; Correll 2008a), and extrapyramidal symptoms (though less so than with first-generation drugs) (Correll et al. 2006). Some of these adverse effects may be particularly problematic early in treatment and then abate (Findling et al. 2003; Haas et al. 2008), but age-inappropriate weight gain and related increases in lipid and glucose parameters are of concern even if they plateau, because they are continuous risk factors that have a close relationship to future cardiovascular morbidity and mortality (Correll 2008a; Correll 2008c).

There are surprisingly few studies investigating interactions between antipsychotics and stimulants in youth, although such a combination is commonly used due to the relatively high prevalence of attention-deficit/hyperactivity disorder (ADHD) in disorders that are frequently treated with antipsychotic medications. This situation is most prevalent in disruptive behavior disorders with significant and impairing levels of aggression (August et al. 1996; The MTA Cooperative Group 1999). Some of the few studies reporting stimulant-antipsychotic co-treatment effects did not find that stimulants reduced side effects when combined with antipsychotics. One such study pooled data from two placebo-controlled, 8-week trials (Aman et al. 2002; Snyder et al. 2002) of risperidone in 155 children aged 5–12 years with disruptive behaviors and subaverage intelligence, and compared, in a *post hoc* analysis, those children who had risperidone added to ongoing stimulant treatment (47.1%) to children taking risperidone alone (52.9%) (Aman et al. 2004). In this study, 91% of patients in the stimulant co-treated group, as well as in the nonstimulant group, reported at least one side effect. Moreover, there were no significant between-group differences in weight gain (2.2 kg vs. 2.1 kg, $p = 0.42$) or body mass index (BMI) change (1.2 vs. 1.1, $p =$ not significant [N.S.]), although there was a significant increase in body weight and BMI with risperidone compared to baseline ($p < 0.001$). Furthermore, although fewer patients on stimulants reported somnolence (37.1% vs. 51.2%, $p = 0.26$), this difference was also not significant. Similarly, efficacy regarding behavioral and ADHD symptoms was also not different depending on stimulant co-treatment, with significant superiority of risperidone versus placebo (Aman et al. 2004).

In a related, open-label extension study, 77 completers from the two short-term studies noted above (Aman et al. 2002; Snyder et al. 2002) were followed on risperidone for up to 1 year (Turgay et al. 2002). All but 1 of those youths (98.7%) experienced at least one adverse event, with somnolence remaining the most common (51.9%), followed by headache (37.7%) and weight gain (36.4%). However, the sedation was reported not to have been significant enough to impact cognitive function or efficacy measures. In another study, Calarge et al. (2009), studied 99 children treated with risperidone for a mean of almost 3 years, also finding no difference in BMI z -scores measures between children treated with risperidone plus stimulant ($n = 38$) and those treated with risperidone alone ($n = 61$) after controlling for baseline BMI z -score.

On the other hand, a second line of studies provided preliminary, albeit only indirect, evidence of a potentially attenuating effect of stimulant co-treatment on expected side effects of antipsychotics when added to stimulants. For example, in 24 adolescents, 9 weeks of open-label treatment with quetiapine added to methylphenidate (MPH) after 3 weeks of ineffective stimulant monotherapy resulted in only negligible changes in BMI and weight over the total 13-week study duration (i.e., initial decreases were offset by increases that occurred after quetiapine addition) (Kronenberger et al. 2007). By contrast, sedation increased after quetiapine was added from 17% to 50%, with 2 patients discontinuing after quetiapine addition due to excessive fatigue. Because no control group of quetiapine monotherapy was included, it is not possible to determine whether an otherwise significant weight gain effect could have been mitigated by stimulant co-treatment, but sedation rates were clinically relevant, despite stimulant co-treatment.

Likewise, in a 4-week, double-blind study of 25 children with ADHD who were taking a constant dose of stimulant medication before being randomized to augmentation with risperidone or placebo to reduce treatment-resistant aggression, no significant differences between patients treated with risperidone plus stimulant and those treated with placebo plus stimulants were noted for weight gain (0.9 kg vs. -0.6 kg) or for sedation (16.7% vs. 23.1%) (Armenteros et al. 2007). This suggests a possible attenuation of the risperidone effect on weight and sedation by stimulant co-treatment, because neither weight gain nor sedation were greater with risperidone than with placebo. Nevertheless, similar to Kronenberger et al. (2007), no monotherapy group of risperidone treatment without stimulant co-treatment was available for direct comparison, and sample sizes were small in both of these studies.

Furthermore, two case reports in adults describe the amelioration of clozapine-induced sedation with addition of MPH (Burke and Sebastian, 1993), although a third case resulted in worsening of a movement disorder and tolerance to the decrease in sedation initially brought on by the MPH (Miller 1996). Three other cases mentioned the successful management of neuroleptic-induced sedation with modafinil, without worsening of psychotic symptoms (Makela et al. 2003), although another study did not find a greater reduction in fatigue compared to placebo (Sevy et al. 2005).

To our knowledge, no studies are available that have assessed whether stimulant co-treatment with antipsychotics affects metabolic parameters that have been shown to worsen, or prolactin levels that have been shown to increase, with many of the commonly used antipsychotic medications (Correll and Carlson 2006). At least theoretically, potential benefits associated with stimulant co-treatment could be expected for metabolic parameters, either indirectly via attenuation of weight gain or directly via currently unknown mechanisms. Furthermore, a reduction in prolactin levels or attenuation of prolactin elevation associated with

certain antipsychotics could be expected due to pro-dopaminergic effects of stimulant medications in the tuberoinfundibular pathway, as seen with full and even partial dopamine agonists when added to dopamine antagonists (Correll and Carlson 2006).

Given the paucity and contradictory nature of the available data, the increasing use of antipsychotics in youth (Olfson et al. 2006), and the clinical relevance of these antipsychotic adverse effects during development, we aimed to examine whether a combination of SGAs with stimulant treatment would result in a statistically significant attenuation of commonly occurring adverse effects of SGAs on body weight, metabolic parameters, prolactin levels, and alertness.

Methods

Study setting and design

Data were collected as part of the Second-Generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth (SATIETY) study, a naturalistic cohort study of SGAs in children and adolescents in whom antipsychotics were started for the control of psychotic, affective, or aggressive/oppositional symptoms or behaviors. From December, 2001, to September, 2007, patients were recruited from the pediatric inpatient and outpatient services of our center. Legal guardians and participants aged 18–19 years signed informed consents and minors aged 9–17 years signed informed assent for this Institutional Review Board–approved study. Data for this report are restricted to youths in whom dysfunctional and clinically relevant aggression or oppositionality were the primary focus of the newly initiated antipsychotic treatment.

Subjects

Inclusion criteria for the sample analyzed in this paper were: (1) Age 4–19 years; (2) clinically significant aggression and/or oppositionality prompting second-generation antipsychotic initiation; (3) *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association 1994) diagnosis of oppositional defiant disorder (ODD), conduct disorder (CD), impulse control disorder not otherwise specified (NOS), intermittent explosive disorder, disruptive behavior disorder NOS, autistic disorder, pervasive developmental disorder NOS, or Tourette's disorder; (4) consent and baseline anthropometric and/biochemical assessments obtained within 7 days of antipsychotic initiation; and (5) at least one postbaseline assessment during the 3-month acute study phase with compliance confirmed by patient and guardian interview as well as documented antipsychotic blood levels. Exclusion criteria were: (1) Diagnosis of bipolar disorder or psychotic disorder; (2) treatment with >1 antipsychotic medication; (3) active or past eating disorder; (4) biochemical evidence of thyroid dysfunction; (5) unstable medical disorders; (6) treatment with corticosteroids or antiretroviral drugs; (7) pregnancy/breastfeeding; (8) wards of the state (due to consent issues); and (9) anticipated move from the catchment area within <4 weeks. DSM-IV diagnoses (made by board-eligible or board-certified child and adolescent psychiatrists), past psychiatric treatment history, and pubertal status (i.e., presence/absence of pubic/axillary hair and other secondary sexual characteristics) were assessed by review of all data from the patient's chart, discussion with treatment providers, and clinical interview of the patient/caregiver, with final review and determination by the last author. Information about family history of obesity was obtained via direct interview with the caregiver.

Treatment

Patients received the clinician's choice treatment with any available SGA. Dosing, co-medications, and treatment changes were based on clinical necessity.

Outcomes measures

Primary outcomes of interest were absolute and/or relative changes in body composition parameters (i.e., body weight, BMI, BMI percentiles/*z*-scores, fat mass, and waist circumference), and in fasting metabolic parameters (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein-cholesterol [HDL-C], triglycerides, triglycerides/HDL ratio, glucose, insulin and homeostasis model assessment of insulin resistance [HOMA-IR]), and prolactin levels. In addition to the continuous outcomes, we also focused on the incidence rates of categorical outcomes in body composition, all individually assessed metabolic parameters, dyslipidemia, and metabolic syndrome using adjusted thresholds for pediatric patients (Correll 2008a). Additional outcomes of interest included rates of sedation and hypersomnia/insomnia assessed with the Treatment Emergent Side Effect Scale (TESS) (Guy 1976), and broad effectiveness measures, such as changes in the Children's Global Assessment Scale (CGAS) scale (Shaffer et al. 1983), Clinical Global Impressions–Illness Severity (CGI-S) scale (Guy 1976) (see legend of Table 1, below, for the scaling on these outcome measures), as well as all-cause discontinuation rates.

Assessments

Subjects were assessed after ≥ 8 hours of overnight fasting at baseline and weeks 4, 8, and 12. Height was measured three times, using the stadiometer Seca 214. Weight, BMI, and fat mass were assessed by impedantometry with the Tanita Body Composition Analyzer TBF-310. Patients were weighed clothed, with emptied pockets and without shoes or socks, using the following subtraction schedule according to clothing (which has not been validated before, but was felt to be more accurate than not addressing clothing): Persons 5 feet and taller wearing long trousers and long-sleeved shirt/sweatshirt, –3 pounds; if dressed with short pants or short-sleeved/light shirt, –2.5 pounds; if dressed with either short pants or short-sleeved/light shirt, –2 pounds; if just wearing underwear, –1.5 pounds. For persons measuring less than 5 feet, but more than or equal to 4 feet, an additional 0.5 pound was subtracted. For persons smaller than 4 feet, an additional 1 pound was subtracted from the original formula.

Waist circumference was measured at the level of both superior iliac crests and umbilicus, using the point of largest abdominal circumference. Fasting blood was drawn at 7 a.m. to 11 a.m., prior to any morning medications. Antipsychotic plasma levels were obtained at each postbaseline visit to assess antipsychotic medication adherence, which was additionally assessed by patient and caregiver interviews. Families were called before the visit and reminded of the overnight fast. At the visit, patients/caregivers were asked about adherence to fasting status. Fasting blood work was rescheduled if patients were nonfasting, and repeated if glucose was ≥ 100 mg/dL or insulin increased $>100\%$ from last assessment to exclude covert nonfasting values. Glucose and lipids were analyzed using a Roche/Hitachi 747 chemistry analyzer, and insulin was analyzed using a Roche Elecsys 2010 immunochemistry analyzer. Prolactin was quantified by a chemiluminescent assay. Antipsychotic plasma levels

were measured with liquid chromatography at Cooper Laboratory, Nathan Kline Institute (Orangeburg, NY).

Statistical analyses

Patients with ≥ 1 postbaseline assessment comprised the modified intent-to-treat sample. Sex- and age-adjusted BMI z -scores were calculated using a Web-based calculator (www.kidsnutrition.org/bodycomp/bmiz2.html). Insulin resistance was determined with the homeostatic model (HOMA-IR: fasting insulin $\mu\text{mol} \times \text{glucose mmol}/22.5$) (Matthews et al. 1985). HOMA-IR values >4.39 were diagnostic for insulin resistance (Lee et al. 2006). As done previously (Saito et al. 2004), hyperprolactinemia was defined stringently as per our laboratory threshold as $>25.4 \text{ ng/dL}$ for males and females. Baseline and outcome variables were compared across treatment groups with chi-squared and Fisher exact tests for categorical variables and with the analysis of variance (ANOVA) test for continuous variables. Missing data were imputed using the method of last observation carried forward (LOCF). For the purpose of the present analyses, LOCF methodology was felt to be acceptable, given the similar treatment duration and rates of all-cause discontinuation and discontinuation due to inefficacy or side effects. All analyses were two-sided with $\alpha < 0.05$, using SAS, version 9.1.

Because several baseline characteristics differed between the two groups, we also calculated adjusted p values, conducting multiple regression analyses for continuous outcomes and logistic regression analyses for categorical outcomes using as fixed covariates the baseline value of each respective outcome and the following variables that were different between the two groups at a level of <0.10 (except for number of co-medications that were by group selection higher in the stimulant co-treatment group): Sex, socioeconomic status, diagnosis of autistic disorder, Tourette's disorder or impulse control disorder NOS, ADHD co-morbidity, baseline CGAS, duration of past stimulant treatment prior to baseline, aripiprazole treatment, and anticholinergic treatment.

Although individual antipsychotic use did not differ significantly in patients co-treated with or without stimulants, we also conducted sensitivity analyses to rule out a potentially modulating effect of antipsychotics with stronger versus weaker known effects on the main outcomes (Correll 2008a). Analyses of the effect of stimulant co-treatment on change or abnormalities in body weight and metabolic parameters were repeated in subgroups of either patients treated with clozapine or olanzapine (i.e., high-risk antipsychotics), or patients treated with aripiprazole, quetiapine, risperidone, or ziprasidone (i.e., low- to medium-risk antipsychotics), as well as in patients treated with clozapine, olanzapine, quetiapine, or risperidone (i.e., medium- to high-risk antipsychotics), or patients treated with aripiprazole or ziprasidone (i.e., low-risk antipsychotics). In addition, we also conducted exploratory sensitivity analyses of the effect of stimulant use on prolactin levels in patients receiving risperidone or receiving nonrisperidone antipsychotics. All of these analyses yielded the same results as in the main analyses where all antipsychotics were grouped together; thus, results are not presented in this paper.

Results

Baseline and treatment variables

This sample includes 153 youngsters, with a mean age of 11.3 years; 77.8% were male, 47.1% were non-Hispanic Caucasians, and 45.1% were inpatients at the time of current SGA treatment

initiation. In this sample, the DSM-IV ADHD co-morbidity was expectedly high in the stimulant-treated group (70.4%) and higher than in the nonstimulant group ($p = 0.0027$), but co-morbid ADHD was still present in 46.3% of patients in the group without stimulant treatment. However, considering the clinical chart diagnoses of ADHD, including those made in patients with pervasive developmental disorder (PDD) spectrum disorders (which is by DSM-IV convention an exclusionary criterion for making a diagnosis of ADHD), as many as 94.4% of stimulant-treated youths and 67.1% of nonstimulant-treated youths had a diagnosis of ADHD or, at least, clinically significant symptoms of hyperactivity and inattention. Stimulants were present at baseline in 83.1% of patients in the stimulant group and 11.1% of the nonstimulant group, i.e., 16.9% had stimulants added and 11.1% had stimulants withdrawn after antipsychotic initiation, respectively. Moreover, 55% of the subjects not on stimulants had received a stimulant trial in the past.

There were several statistically significant baseline demographic and clinical differences between the two groups (Table 1). Notably, stimulant-treated youngsters were more likely to be male ($p = 0.0024$), had a higher socioeconomic status ($p = 0.0028$), were more frequently diagnosed with ODD ($p = 0.006$) and ADHD, and had more prior stimulant treatment ($p < 0.0001$), whereas autism was less common ($p = 0.016$). Additionally, patients with stimulant co-treatment were more likely to be of normal weight ($p = 0.016$) and had lower baseline weight ($p = 0.032$), fat mass ($p = 0.0099$), and waist circumference ($p = 0.0037$). However, using sex- and age adjusted measures of body weight, such as BMI z -scores and percentiles, the groups did not differ ($p = 0.25$ and 0.20 , respectively).

The treatment characteristics of this sample are presented in Table 2. The only statistically significant differences in treatment characteristics between the two groups included presence of stimulant treatment prior to study baseline ($p < 0.0001$), mean duration of stimulant use prior to study baseline ($p = 0.004$), and time since first stimulant use ($p = 0.02$) (Table 1). There was a trend for children not receiving stimulants to be taking aripiprazole as their antipsychotic medication (0.082). Patients on stimulant co-treatment were prescribed significantly fewer anticholinergic medications ($p = 0.03$).

Adverse effect outcomes

Baseline to end-point changes in body composition, glucose and lipid parameters, and prolactin levels were not significantly different among patients co-treated with or without stimulants (p values, 0.13–0.99), even after controlling for baseline values and variables different between groups at $p < 0.01$ (p values, 0.10–0.97) (Table 3). Similarly, the two groups did not differ regarding incidence rates of clinically relevant, abnormal values in body composition and metabolic and prolactin values, both before (p values, 0.13–1.0) and after adjustment (p values, 0.11–0.99) (Table 4). We repeated the analyses of prolactin change, excluding patients treated with atomoxetine, because its effect on prolactin is less clear, and again found no significant difference ($p = 0.54$) between the treatment groups. Likewise, discontinuation rates for intolerability were similar between patients without versus with stimulant co-treatment (7.4% vs. 4.2%, $p = 0.50$).

Efficacy/effectiveness outcomes

Stimulant co-treatment was not associated with the change over time in the CGI-S score and the CGAS score (Table 3) or with

TABLE 1. BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Baseline characteristic	Total (n = 153)	Antipsychotics without stimulant (n = 82)	Antipsychotics plus stimulant (n = 71)	F/ χ^2	p value
Demographic characteristics					
Age (years $\pm$ SD)	11.3 $\pm$ 3.0	11.5 $\pm$ 3.0	11.0 $\pm$ 3.0	F 0.90	0.34
Postpubertal status, number (%)	52 (34.0)	32 (39.0)	20 (28.2)	χ^2 2.00	0.16
Male sex, number (%)	119 (77.8)	56 (68.3)	63 (88.7)	χ^2 9.20	0.0024
Ethnicity, number (%)				χ^2 4.02	0.40
White	72 (47.1)	36 (43.9)	36 (50.7)		
African-American	38 (24.8)	23 (28.1)	15 (21.1)		
Hispanic	15 (9.8)	7 (8.5)	8 (11.3)		
Asian	3 (2.0)	3 (3.7)	0 (0.0)		
Mixed/other	25 (16.3)	13 (15.9)	12 (16.9)		
SES (Hollingshead 1–5)	2.9 $\pm$ 1.0	2.6 $\pm$ 1.0	3.2 $\pm$ 1.0	F 9.29	0.0028
Primary psychiatric diagnosis, number (%)					
Oppositional defiant disorder	70 (45.8)	29 (35.4)	41 (57.8)	χ^2 7.68	0.006
Pervasive developmental disorder not otherwise specified	47 (30.7)	29 (35.4)	18 (25.4)	χ^2 1.79	0.18
Autistic disorder	22 (14.4)	17 (20.7)	5 (7.0)	χ^2 5.79	0.016
Intermittent explosive disorder	6 (3.9)	2 (2.4)	4 (5.6)	χ^2 1.03	0.31
Tourette's disorder	3 (2.0)	3 (3.7)	0 (0.0)	χ^2 2.65	0.10
Impulse control disorder not otherwise specified	3 (2.0)	0 (0.0)	3 (4.2)	χ^2 3.53	0.060
Disruptive behavior disorder not otherwise specified	2 (1.3)	2 (2.4)	0 (0.0)	χ^2 1.76	0.19
Co-morbidity, number (%)					
Attention-deficit/hyperactivity disorder	88 (57.5)	38 (46.3)	50 (70.4)	χ^2 9.02	0.0027
Depressive disorder not otherwise specified	9 (5.9)	4 (4.9)	5 (7.0)	χ^2 0.32	0.57
Mood disorder not otherwise specified	7 (4.6)	4 (4.9)	3 (4.2)	χ^2 0.04	0.85
Clinical Global Impressions–Severity score (mean $\pm$ SD) ^a	5.2 $\pm$ 0.9	5.3 $\pm$ 0.8	5.2 $\pm$ 0.9	F 0.36	0.55
Children's Global Assessment Scale score (mean $\pm$ SD) ^b	38.2 $\pm$ 8.6	37.1 $\pm$ 8.4	39.5 $\pm$ 8.8	F 3.00	0.085
Body composition characteristics					
Weight (lbs $\pm$ SD)	103.7 $\pm$ 45.9	111.1 $\pm$ 48.1	95.0 $\pm$ 43.1	F 4.68	0.032
Fat mass (lbs $\pm$ SD)	27.2 $\pm$ 23.8	31.9 $\pm$ 26.4	21.7 $\pm$ 20.4	F 6.83	0.0099
Waist circumference (cm $\pm$ SD)	75.4 $\pm$ 16.6	79.1 $\pm$ 17.1	71.1 $\pm$ 16.0	F 8.68	0.0037
BMI (kg/m ² $\pm$ SD)	20.8 $\pm$ 5.8	21.7 $\pm$ 6.1	19.8 $\pm$ 5.3	F 3.80	0.053
BMI z-score ($\pm$ SD)	0.5 $\pm$ 1.5	0.6 $\pm$ 1.6	0.4 $\pm$ 1.4	F 1.32	0.25
BMI percentile ($\pm$ SD)	64.4 $\pm$ 35.0	67.7 $\pm$ 34.9	60.5 $\pm$ 35.1	F 1.63	0.20
Weight status category – no. (%)					
Underweight (<5 th BMI Percentile)	15 (9.8)	9 (11.0)	6 (8.5)	χ^2 0.27	0.60
Normal ($\geq$ 5 th –<85 th BMI Percentile)	66 (43.1)	28 (34.2)	38 (53.5)	χ^2 5.82	0.016
Overweight ($\geq$ 85 th –<95 th BMI Percentile)	31 (20.3)	19 (23.2)	12 (16.9)	χ^2 0.93	0.34
Obese ($\geq$ 95 th BMI Percentile)	41 (26.8)	26 (31.7)	15 (21.1)	χ^2 2.17	0.14
Fasting metabolic characteristics					
Glucose (mg/dL $\pm$ SD)	82.8 $\pm$ 8.9	82.9 $\pm$ 8.6	82.7 $\pm$ 9.1	F 0.021	0.88
Insulin (μ U/mL $\pm$ SD)	11.5 $\pm$ 9.5	12.6 $\pm$ 10.3	10.1 $\pm$ 8.4	F 2.65	0.11
HOMA-IR	2.4 $\pm$ 2.1	2.6 $\pm$ 2.2	2.1 $\pm$ 1.9	F 2.36	0.13
Cholesterol (mg/dL $\pm$ SD)	171.8 $\pm$ 34.4	169.2 $\pm$ 34.3	174.8 $\pm$ 34.4	F 1.00	0.32
LDL-C (mg/dL $\pm$ SD)	98.8 $\pm$ 30.5	97.0 $\pm$ 29.4	100.9 $\pm$ 31.6	F 0.62	0.43
HDL-C (mg/dL $\pm$ SD)	54.9 $\pm$ 14.0	53.8 $\pm$ 12.8	56.0 $\pm$ 15.3	F 0.94	0.33
Triglycerides (mg/dL $\pm$ SD)	93.7 $\pm$ 61.4	93.5 $\pm$ 44.2	93.8 $\pm$ 76.5	F 0.0008	0.98
TG/HDL	2.1 $\pm$ 3.2	1.9 $\pm$ 1.1	2.4 $\pm$ 4.6	F: 0.87	0.35
Non-HDL-C (mg/dL $\pm$ SD)	116.9 $\pm$ 35.0	115.3 $\pm$ 33.3	118.8 $\pm$ 36.8	F: 0.38	0.54
Additional variables					
Prolactin levels	22.9 $\pm$ 19.3	22.3 $\pm$ 18.4	23.7 $\pm$ 20.3	F: 0.22	0.64
Drowsiness/daytime sedation ^c	1.7 $\pm$ 0.8	1.8 $\pm$ 0.9	1.6 $\pm$ 0.8	F: 2.78	0.10
Sleep disturbance ^d	82.8 $\pm$ 8.9	82.9 $\pm$ 8.6	82.7 $\pm$ 9.1	F: 0.021	0.88

^aClinical Global Impressions Scale: 1–7, 1 = normal, 2 = borderline, 3 = mild, 4 = moderate, 5 = marked, 6 = severe, 7 = extreme.

^bChildren's Global Assessment Scale score: 0–100.

^cDrowsiness/Daytime Sedation rating based on the “Drowsiness” item on the Treatment Emergent Side Effect Scale (TESSS) (Guy 1976): 0 = none, 1 = minimal, 2 = mild, 3 = marked, 4 = severe.

^dSleep disturbance rating based on the integrated ratings on the hypersomnia and the insomnia item: severe insomnia = –4, marked insomnia = –3, mild insomnia = –1, none insomnia or hypersomnia = 0, mild hypersomnia = 1, moderate hypersomnia = 2, marked hypersomnia = 3, severe hypersomnia = 4.

Boldface values highlight group differences at $p < 0.05$.

Abbreviations: SD = Standard deviation; SES = socioeconomic status; lbs = pounds; BMI = body mass index; HOMA-IR = homeostasis model assessment of insulin resistance; LDL-C = low-density lipoprotein-cholesterol; HDL-C = high-density lipoprotein-cholesterol; TG = triglyceride.

TABLE 2. TREATMENT CHARACTERISTICS

Baseline characteristic	Total (n = 153)	Antipsychotics without stimulant (n = 82)	Antipsychotics plus stimulant (n = 71)	F/ χ^2	p value
Treatment history, number (%)				χ^2 0.87	0.65
Antipsychotic-naïve	60 (39.2)	32 (39.0)	28 (39.4)		
History of antipsychotic treatment ^a	29 (18.3)	13 (15.9)	15 (21.1)		
Antipsychotic switch ^b	65 (42.5)	37 (45.1)	28 (39.4)		
Mean duration of past antipsychotic treatment (months $\pm$ SD)	9.5 $\pm$ 15.9	10.6 $\pm$ 18.1	8.3 $\pm$ 12.9	F 0.77	0.38
Mean duration of current antipsychotic treatment prior to baseline assessment (days $\pm$ SD)	2.1 $\pm$ 3.2	2.2 $\pm$ 3.7	2.0 $\pm$ 2.6	F 0.16	0.69
Current treatment characteristics					
Mean treatment duration (weeks $\pm$ SD)	11.1 $\pm$ 3.5	11.0 $\pm$ 3.5	11.2 $\pm$ 3.4	F 0.059	0.81
Mean inpatient time (days $\pm$ SD)	12.2 $\pm$ 21.0	11.0 $\pm$ 21.0	13.7 $\pm$ 21.1	F 0.61	0.44
Mean inpatient:outpatient time ratio (% $\pm$ SD)	20.6 $\pm$ 35.2	18.2 $\pm$ 34.0	23.5 $\pm$ 36.6	F 0.84	0.36
Stimulant treatment prior to baseline no – (%)	105 (70.0)	44 (55.0)	61 (87.1)	χ^2 18.37	<0.0001
Mean duration on stimulant before baseline (months $\pm$ SD)	18.8 $\pm$ 24.8	13.1 $\pm$ 23.7	25.4 $\pm$ 26.0	F 8.5	0.004
Time since first stimulant use prior to baseline (years $\pm$ SD)	2.4 $\pm$ 2.6	1.9 $\pm$ 2.6	2.9 $\pm$ 2.6	F 5.71	0.02
Specific antipsychotics, number (%)					
Aripiprazole	45 (29.4)	29 (35.4)	16 (22.5)	χ^2 3.02	0.082
Maximum daily dose (mg $\pm$ SD)	11.7 $\pm$ 7.5	10.9 $\pm$ 7.9	13.4 $\pm$ 7.0	F 1.19	0.28
Clozapine	1 (0.65)	1 (1.22)	N/A	χ^2 0.87	0.35
Maximum daily dose (mg $\pm$ SD)	375.0	375.0	N/A	N/A	N/A
Olanzapine	18 (11.8)	7 (8.5)	11 (15.5)	χ^2 1.77	0.18
Maximum daily dose (mg $\pm$ SD)	10.0 $\pm$ 6.1	9.4 $\pm$ 6.3	10.5 $\pm$ 6.3	F 0.13	0.73
Quetiapine	28 (18.3)	12 (14.6)	16 (22.5)	χ^2 1.59	0.21
Maximum daily dose (mg $\pm$ SD)	365.6 $\pm$ 190.7	400.0 $\pm$ 150.4	339.8 $\pm$ 217.3	F 0.67	0.42
Risperidone	51 (33.3)	27 (32.9)	24 (33.8)	χ^2 0.013	0.91
Maximum daily dose (mg $\pm$ SD)	1.6 $\pm$ 1.5	1.4 $\pm$ 1.2	1.9 $\pm$ 1.9	F 1.09	0.30
Ziprasidone	9 (5.9)	6 (7.3)	3 (4.2)	χ^2 0.66	0.42
Maximum daily dose (mg $\pm$ SD)	93.3 $\pm$ 46.9	110.0 $\pm$ 37.4	60.0 $\pm$ 52.9	F 2.78	0.14
Mean number of co-medications ^a stimulant co-medications, number (%) ^c	1.6 $\pm$ 1.1	1.2 $\pm$ 1.1	2.1 $\pm$ 1.0	F 29.5	<0.0001
Concerta	20 (13.1)	N/A	20 (28.2)	N/A	N/A
Maximum daily dose (mg/d $\pm$ SD)	59.8 $\pm$ 22.3	N/A	59.8 $\pm$ 22.3	N/A	N/A
Maximum daily dose (mg/kg $\pm$ SD)	0.77 $\pm$ 0.30	N/A	0.77 $\pm$ 0.30	N/A	N/A
D-Amphetamine	16 (10.5)	N/A	16 (22.5)	N/A	N/A
Maximum daily dose (mg/d $\pm$ SD)	27.5 $\pm$ 18.9	N/A	27.5 $\pm$ 18.9	N/A	N/A
Maximum daily dose (mg/kg $\pm$ SD)	0.32 $\pm$ 0.22	N/A	0.32 $\pm$ 0.22	N/A	N/A
Methylphenidate	9 (5.9)	N/A	9 (12.7)	N/A	N/A
Maximum daily dose (mg/d $\pm$ SD)	41.1 $\pm$ 26.8	N/A	41.1 $\pm$ 26.8	N/A	N/A
Maximum daily dose (mg/kg $\pm$ SD)	0.39 $\pm$ 0.25	N/A	0.39 $\pm$ 0.25	N/A	N/A
Atomoxetine	7 (4.6)	N/A	7 (9.9)	N/A	N/A
Maximum daily dose (mg/d $\pm$ SD)	42.0 $\pm$ 27.2	N/A	42.0 $\pm$ 27.2	N/A	N/A
Maximum daily dose (mg/kg $\pm$ SD)	0.43 $\pm$ 0.17	N/A	0.43 $\pm$ 0.17	N/A	N/A
Metadate CD	6 (3.9)	N/A	6 (8.5)	N/A	N/A
Maximum daily dose (mg/d $\pm$ SD)	45.0 $\pm$ 17.2	N/A	45.0 $\pm$ 17.2	N/A	N/A
Maximum daily dose (mg/kg $\pm$ SD)	0.58 $\pm$ 0.37	N/A	0.58 $\pm$ 0.37	N/A	N/A
Concerta + methylphenidate IR	5 (3.3)	N/A	5 (7.0)	N/A	N/A
D-Amphetamine XR	4 (2.6)	N/A	4 (5.6)	N/A	N/A
Maximum daily dose (mg/d $\pm$ SD)	52.5 $\pm$ 15.0	N/A	52.5 $\pm$ 15.0	N/A	N/A
Maximum daily dose (mg/kg $\pm$ SD)	0.34 $\pm$ 0.04	N/A	0.34 $\pm$ 0.04	N/A	N/A
Metadate CD + methylphenidate IR	1 (0.7)	N/A	1 (1.4)	N/A	N/A
Metadate CD + D-amphetamine	1 (0.7)	N/A	1 (1.4)	N/A	N/A
Metadate CD + atomoxetine	1 (0.7)	N/A	1 (1.4)	N/A	N/A
Nonstimulant co-medications, number (%)					
Mood stabilizer	48 (31.4)	29 (35.4)	19 (26.8)	χ^2 1.31	0.25
Antidepressant ^d	42 (27.5)	20 (24.4)	22 (31.0)	χ^2 0.83	0.36
Anxiolytic/hypnotic	15 (9.8)	7 (8.5)	8 (11.3)	χ^2 0.32	0.57
Anticholinergic	9 (5.9)	8 (9.8)	1 (1.4)	χ^2 4.79	0.03
Other psychotropic ^e	5 (3.3)	4 (4.9)	1 (1.4)	χ^2 2.40	0.30

^aAntipsychotic history denotes restarting antipsychotic therapy after at least a 4 week gap.

^bAntipsychotic switch denotes starting an antipsychotic less than 4 weeks after prior antipsychotic treatment.

^cFor simplicity, the overall dose information per individual stimulant is provided for stimulant monotherapy only.

^dNo tricyclic antidepressants were used.

^eOther psychotropic medications: α 2 agonists, beta blockers, antihistamines.

Boldface values highlight group differences at $p < 0.05$.

Abbreviation: SD = Standard deviation; N/A = not applicable.

TABLE 3. CHANGE IN BODY COMPOSITION, METABOLIC/ENDOCRINE, ALERTNESS, AND EFFICACY PARAMETERS (LOCF)

Outcome variable: Change from baseline to end point	Total (n = 153)	Antipsychotics without stimulant (n = 82)	Antipsychotics plus stimulant (n = 71)	Unadjusted F	Unadjusted p value	Adjusted ^a p value
Body composition						
Weight (lbs)	6.8 ± 7.9	7.3 ± 7.7	6.3 ± 8.2	0.54	0.46	0.25
Percent body weight	7.4 ± 8.3	7.4 ± 7.7	7.3 ± 8.9	0.01	0.90	0.27
BMI z-score	0.3 ± 0.6	0.3 ± 0.5	0.3 ± 0.6	0.76	0.78	0.77
BMI %ile	6.8 ± 16.1	6.7 ± 15.3	7.0 ± 17.0	0.014	0.91	0.81
Fat mass (lbs)	2.8 ± 6.4	3.5 ± 7.0	1.9 ± 5.6	2.27	0.13	0.56
BMI (kg/m ²)	1.1 ± 1.6	1.2 ± 1.5	0.9 ± 1.7	1.1	0.29	0.21
Waist (cm)	2.8 ± 4.7	3.2 ± 4.4	2.3 ± 5.0	1.39	0.24	0.10
Metabolic/endocrine parameters						
Glucose (mg/dL)	2.7 ± 10.2	1.9 ± 10.0	3.7 ± 10.4	1.06	0.30	0.18
Insulin (μU/mL)	1.9 ± 10.0	1.9 ± 11.8	2.0 ± 7.2	0.0001	0.99	0.97
HOMA-IR	0.5 ± 2.2	0.4 ± 2.7	0.5 ± 1.5	0.074	0.79	0.79
Total cholesterol (mg/dL)	0 ± 26.3	0.7 ± 27.1	-0.8 ± 25.3	0.11	0.75	0.67
LDL-C (mg/dL)	-2.0 ± 21.5	-1.8 ± 22.3	-2.2 ± 20.4	0.0069	0.93	0.32
HDL-C (mg/dL)	0.7 ± 9.1	0.2 ± 8.7	1.2 ± 9.5	0.38	0.53	0.47
Triglycerides (mg/dL)	3.4 ± 66.6	6.1 ± 59.4	0.4 ± 74.0	0.27	0.60	0.35
TG/HDL Ratio (mg/dL)	0.1 ± 5.1	0.2 ± 1.6	0.05 ± 7.2	0.031	0.86	0.84
Non-HDL-C (mg/dL)	-0.86 ± 25.3	-0.06 ± 24.2	-1.8 ± 26.6	0.16	0.69	0.57
Prolactin (ng/dL)	0.6 ± 24.0	1.9 ± 22.6	-0.9 ± 25.5	0.49	0.49	0.79
Efficacy measures						
CGI-Severity Score ^b	-0.8 ± 1.0	-0.7 ± 1.0	-0.8 ± 1.0	0.25	0.62	0.92
CGAS Score ^c	8.0 ± 8.6	8.3 ± 9.1	7.7 ± 8.5	0.14	0.71	0.64
Alertness						
Drowsiness/daytime sedation ^d	-0.8 ± 1.0	-0.7 ± 1.0	-0.8 ± 1.0	0.069	0.79	0.34
Sleep disturbance ^e	8.0 ± 8.6	8.3 ± 9.1	7.7 ± 8.5	1.66	0.20	0.26

^ap Value adjusted for baseline value of analyzed variable (except for CGI-Improvement score), as well as the following baseline variables that were statistically significantly different between the two groups: sex, socioeconomic status, ODD diagnosis, autistic disorder diagnosis, Tourette's disorder diagnosis, impulse control disorder NOS diagnosis, ADHD co-morbidity, baseline Children's Global Assessment of Functioning Scale (CGAS), duration of past stimulant treatment prior to baseline, aripiprazole treatment, and anticholinergic treatment.

^bClinical Global Impressions Scale: 1–7, 1 = normal, 2 = borderline, 3 = mild, 4 = moderate, 5 = marked, 6 = severe, 7 = extreme.

^cChildren's Global Assessment Scale score: 0–100.

^dDrowsiness/Daytime Sedation rating based on the "Drowsiness" item on the Treatment Emergent Side Effect Scale (TESSS) (Guy 1976): 0 = none, 1 = minimal, 2 = mild, 3 = marked, 4 = severe.

^eSleep disturbance rating based on the integrated ratings on the hypersomnia and the insomnia item: severe insomnia = -4, marked insomnia = -3, mild insomnia = -1, none insomnia or hypersomnia = 0, mild hypersomnia = 1, moderate hypersomnia = 2, marked hypersomnia = 3, severe hypersomnia = 4.

Abbreviations: LOCF = Last observation carried forward; lbs = pounds; BMI = body mass index; HOMA-IR = homeostasis model assessment of insulin resistance; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglyceride; CGI = Clinical Global Impressions; CGAS = Children's Global Assessment Scale; ODD = oppositional defiant disorder; NOS = not otherwise specified; ADHD = attention-deficit/hyperactivity disorder.

all-cause discontinuation rates (Table 4). Likewise, discontinuation rates for inefficacy were similar in patients without versus with stimulant co-treatment (9.9% vs. 7.0%, $p = 0.58$).

Discussion

In this naturalistic cohort study of children and adolescents initiated on a SGA for aggressive and/or oppositional behaviors, the co-prescribing of stimulants did not have any significant modulating effect on measures of weight, metabolic parameters, prolactin, or sedation/sleep disturbance, even when baseline differences were controlled for. The same was true for broad and clinically meaningful measures of effectiveness, at least based on our sample with nonrandomized, clinician-selected stimulant co-treatment.

The lack of a stimulant effect is consistent with two prior studies that reported on weight change and/or sedation (Aman et al. 2004; Calarge et al. 2009), but also extended the results to include BMI z-scores to account for children's development. In addition, our study

extends this finding to the important area of metabolic and prolactin changes that had not been assessed before in this context. The collectively observed absence of any modulating effect of stimulant treatment on the assessed side effects with clinical relevance seems to suggest that either the effect of antipsychotics on appetite increase, weight gain, sedation, and prolactin elevation are more potent than the potentially counteracting effects of stimulants, or that the mechanisms through which antipsychotics and stimulants complementarily modulate the biological systems involved in the adverse effect development are different, with a primacy of those affected by antipsychotics. Based on the mean maximum daily doses and mean daily dose/kilogram range for stimulants observed in this study, it appears that, for most patients, the absence of a modulating effect on the adverse effects under investigation is unlikely due to the fact that stimulants were vastly underdosed. However, unless a high-dose study is performed, we cannot exclude that at higher doses an effect could become apparent.

Two additional findings are of note. First, an unexpected finding was that 46.3% of patients not co-treated with a stimulant had

TABLE 4. INCIDENCE RATES OF CATEGORICAL CHANGES IN BODY COMPOSITION, METABOLIC/ENDOCRINE, AND EFFICACY PARAMETERS (LOCF)

<i>Outcome variable: Incidence</i>	<i>Total (n = 153)</i>	<i>Antipsychotics without stimulant (n = 82)</i>	<i>Antipsychotics plus stimulant (n = 71)</i>	<i>Unadjusted χ^2</i>	<i>Unadjusted p value</i>	<i>Adjusted^a p value</i>
Body composition						
Weight loss, number (%)	26 (17.2)	13 (16.1)	13 (18.6)	0.17	0.68	0.26
Weight gain $\geq 7\%$, number (%)	69 (45.7)	37 (45.7)	32 (45.7)	0.00	1.00	0.67
Transition to overweight ^b category, number (%)	10 (6.6)	3 (3.7)	7 (9.9)	2.4	0.13	0.67
Transition to obese ^c category, number (%)	7 (4.6)	4 (4.9)	3 (4.2)	0.044	0.83	0.97
>10% BMI, number (%)	35 (25.4)	20 (27.0)	15 (23.4)	0.23	0.63	0.49
>0.5 BMI z-score, number (%)	45 (29.8)	21 (26.3)	24 (33.8)	1.03	0.31	0.52
Metabolic/endocrine parameters						
Hyperglycemia ^d (>100 mg/dL), number (%)	9 (6.1)	3 (3.9)	6 (8.7)	2.34	0.39	0.20
Hyperinsulinemia ^e (≥ 20 μ U/mL), number (%)	15 (10.5)	10 (13.2)	5 (7.5)	1.23	0.27	0.27
Hypercholesterolemia ^d (≥ 170 mg/dL), number (%)	75 (51.0)	36 (46.8)	39 (55.7)	1.18	0.28	0.32
High LDL-C ^d (>110 mg/dL), number (%)	14 (9.6)	8 (10.3)	6 (8.8)	0.086	0.77	0.99
Low HDL-C ^f (<40 mg/dL), number (%)	10 (6.8)	7 (9.0)	3 (4.4)	1.24	0.27	0.65
Hypertriglyceridemia ^g (≥ 110 mg/dL), number (%)	37 (25.2)	19 (24.4)	18 (26.1)	0.058	0.81	0.10
Dyslipidemia ^h (cholesterol ≥ 170 mg/dL and/or triglycerides ≥ 110 mg/dL), number (%)	17 (12.5)	9 (12.3)	8 (12.7)	0.004	0.95	0.29
TG/HDL ratio ≥ 3.5 , ⁱ number (%)	11 (7.6)	8 (10.8)	3 (4.3)	2.17	0.14	0.11
New-onset hyperprolactinemia, ^j number (%)	27 (18.6)	17 (22.1)	10 (14.7)	1.30	0.26	0.90
Efficacy measures						
All-cause discontinuation, number (%)	31 (20.3)	16 (19.5)	15 (21.1)	0.061	0.80	0.94

^ap Value adjusted for baseline value of analyzed variable as well as the following baseline variables that were different between the two groups at a level of <0.10 , i.e., sex, socioeconomic status, oppositional defiant disorder diagnosis, autistic disorder diagnosis, Tourette's disorder diagnosis, impulse control disorder NOS diagnosis, attention-deficit/hyperactivity disorder co-morbidity, baseline Children's Global Assessment of Functioning Scale (CGAS), duration of past stimulant treatment prior to baseline, aripiprazole treatment, and anticholinergic treatment.

^bAt-risk weight category: $\geq 85^{\text{th}}$ to $<95^{\text{th}}$ BMI percentile.

^cOverweight category: $\geq 95^{\text{th}}$ BMI percentile.

^dPercentages are based on 147 patients with available data.

^ePercentages are based on 143 patients with available data.

^fPercentages are based on 148 patients with available data.

^gPercentages are based on 149 patients with available data.

^hPercentages are based on 137 patients with available data.

ⁱPercentages are based on 144 patients with available data.

^jPercentages are based on 144 patients with available data; hyperprolactinemia defined as per local laboratory as >25.4 ng/dL.

Abbreviations: LOCF=Last observation carried forward; BMI=body mass index; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; TG=triglyceride; NOS=not otherwise specified.

a clinical DSM-IV diagnosis of ADHD. This practice is clearly at odds with the Texas Treatment algorithm (Pliszka et al. 2006) and other published guidelines (Pappadopulos et al. 2003) that endorse treating the underlying ADHD first before using any other medication to target maladaptive aggression, oppositionality, and impulsivity. This finding raises the concern that the step of stimulant treatment is skipped in favor of medications that are potentially more efficacious, but more likely to produce adverse effects, such as antipsychotics, for the purpose of targeting aggression more quickly. Because patients were not offered a stimulant trial before antipsychotic treatment for the current episode, it is unclear how many patients could have responded adequately to stimulant treatment alone, thus preventing the need for antipsychotic treatment. Nevertheless, because a relevant number of patients reported historical use of stimulants, it is possible that these trials were seen as unsuccessful, therefore leading to antipsychotic use in the absence of stimulant treatment. Conversely, one could interpret the ADHD co-morbidity rate of only 70.4% in the stimulant-treated

patients as a clinician trend to treat youths with stimulants who have significant aggression even in the absence of ADHD symptoms. However, this inconsistency seems to be due to the diagnostic convention in DSM-IV that does not allow for a co-morbid ADHD diagnosis in the presence of a diagnosis of PDD NOS. Considering the clinical chart diagnoses of ADHD, including those made in patients with PDD spectrum disorders, 94.4% of stimulant-treated youths and as many as 67.1% of nonstimulant-treated youths had a diagnosis of ADHD or clinically relevant symptoms of hyperactivity or inattention.

This suggests that clinicians target the symptoms of ADHD in patients with PDD spectrum disorders with stimulants and that they do not seem to follow the diagnostic exclusionary rule defined in DSM-IV. Moreover, this also suggests that even up to 2 out of 3 patients with clinician-identified ADHD symptoms and signs of hyperactivity and/or inattention did not receive stimulant treatment. Furthermore, the very low rates of co-morbid depressive and mood disorder NOS diagnoses in both groups makes it less

likely that prescribers would have refrained from prescribing stimulants out of fear of inducing mania, thinking that the ADHD symptoms could be part of a bipolar prodrome (Correll et al. 2007; Miklowitz and Chang 2008). Nevertheless, studies are needed that directly compare treatment with stimulants versus antipsychotics versus a combination of both for the treatment of maladaptive aggression in youth.

Second, it is somewhat surprising that although there were significant differences in unadjusted weight, fat mass, and waist circumference measures, the sex- and age-corrected baseline BMI measures did not differ between those children co-prescribed stimulants and those not co-prescribed stimulants, with only a slightly higher rate of normal weight in stimulant-treated youth (that would have not survived Bonferroni correction for the four weight categories). This relative similarity in baseline body composition status was observed, even though patients on the stimulant-antipsychotic combination had been on prior stimulant treatment much more frequently and for a significantly longer time than the patients not co-treated with stimulants. However, 60.8% of youths had been on antipsychotics in the past (42.5% at the time of starting this study). Therefore, it is likely that the mean prior antipsychotic exposure of 9.5 months in the patients receiving stimulants during the trial reversed the expected difference in body weight and composition resulting from longer and more frequent prior stimulant treatment (Faraone et al. 2008).

The results of this study need to be interpreted in the context of its limitations, including the open, nonrandomized design, modest sample size, lack of research diagnostic interviews, lack of a dimensional measurement of aggressive and ADHD symptoms, lack of biological testing for stimulant nonadherence, and the fact that reliability was not formally tested for waist measurements. However, the methodology resulted in a generalizable patient cohort managed under usual treatment conditions that was reasonably balanced for most relevant baseline variables, including past and current antipsychotic use, developmentally adjusted BMI variables, and all metabolic baseline parameters. Nevertheless, given the nonrandom, uncontrolled study design, and although we controlled statistically for baseline differences, we cannot exclude the possibility that unmeasured baseline between-group differences might have affected the results. However, the results were robust and consistent with prior work in this area, including a randomized trial (Aman et al. 2004), reducing the likelihood that this methodological issue led to a Type II statistical error. Also, although our sample size was modest and similar to that used by Aman et al. (2004) and Calarge et al. (2009), statistically significant differences that would only become apparent in much larger samples are unlikely to be very clinically meaningful. The absence of standardized categorical and dimensional assessments of illness severity limit our ability to comment in detail on efficacy differences; yet the focus of this paper was on the modulatory effects of stimulants on clinically meaningful side effects. We only included broad efficacy assessments to exclude the possibility that one group was significantly inferior regarding psychiatric outcomes, which could affect the risk-to-benefit ratio in case we had found significant side-effect differences.

Despite these limitations, this paper represents the first study to examine the effect of stimulant co-treatment in youths taking antipsychotics for clinically relevant aggression or oppositionality on measures other than weight and sedation alone. Clinical implications include the important possibility that, while stimulants might improve symptoms of treatment-resistant aggression (Pappadopoulos et al. 2006; Kronenberger et al. 2007), they do not appear to be

useful for the mitigation of adverse effects related to antipsychotic use. Thus, the known weight-decreasing effect of stimulants in youths not co-treated with antipsychotics (Faraone et al. 2008) seems to be overridden by antipsychotic use, and stimulant co-treatment should not be used with the intent of decreasing antipsychotic-induced weight gain or other side effects, such as sedation or prolactin elevation.

Conclusions

In our cohort, stimulant use did not precede or accompany antipsychotic use in almost half of the subgroup of youths with a current episode of aggressive/oppositional behavior and ADHD. Although we cannot determine from our study if patients who had prior stimulant use were not given another trial of stimulants due to intolerability or inefficacy of this class of medications, this treatment paradigm is contrary to currently available guidelines, requiring further investigation. Furthermore, stimulant co-treatment of SGAs did not appear to significantly modulate antipsychotic effects on body composition, metabolic parameters, prolactin, sedation, and broad efficacy outcomes.

On the basis of these and other findings, it is imperative that clinicians consider environmental factors carefully and possibly existing underlying disorders that need to be addressed and could lead to a significant improvement in aggressive and oppositional behaviors (Schur et al. 2003; Jensen et al. 2007). Furthermore, clinicians ought to carefully weigh risks and benefits of non-pharmacological and pharmacologic interventions when devising and sequencing their treatment plan, and should include healthy lifestyle instructions and regular side-effect monitoring in their routine clinical care (Correll 2008c). Finally, clinicians should make efforts to select the medication class and/or medication within each class that has likely the best benefit-to-risk ratio.

Disclosures

Dr. Penzner has been a recipient of the American Psychiatric Institute for Research and Education Janssen Resident Research Scholars Award. Dr. Malhotra has been a consultant to or has received honoraria from Eli Lilly, Clinical Data Inc., Janssen, Vanda, and Wyeth; and has served on the speaker's bureau of Bristol-Myers Squibb/Otsuka. Dr. Kane has been a consultant to or has received honoraria from Astra-Zeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Janssen Pharmaceutica, Johnson and Johnson, Lundbeck, Otsuka, Pfizer Inc., PgXHealth, Proteus, Vanda, and Wyeth; he has served on the speaker's bureaus of AstraZeneca, Bristol-Myers Squibb/Otsuka, and Eli Lilly, and he is a shareholder of MedAvante. Dr. Correll has been a consultant to or has received honoraria from AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Janssen/J&J, Otsuka, Medice, Pfizer, Schering-Plough, Supernus, and Vanda, and has served on the speaker's bureaus of AstraZeneca, Bristol-Myers Squibb/Otsuka, and Pfizer.

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