Prolactin Levels During Long-Term Risperidone Treatment in Children and Adolescents

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Background: This analysis was designed to investigate prolactin levels in children and adolescents on long-term risperidone treatment and explore any relationship with side effects hypothetically attributable to prolactin (SHAP).

Method: Data from 5 clinical trials (total N = 700) were pooled for this post hoc analysis. Children and adolescents aged 5 to 15 years with subaverage intelligence quotients and conduct or other disruptive behavior disorders received risperidone treatment (0.02–0.06 mg/kg/day) for up to 55 weeks. Outcome measures analyzed included serum prolactin levels, reported adverse events, and the conduct problem subscore of the Nisonger Child Behavior Rating Form.

Results: Mean prolactin levels rose from 7.8 ng/mL at baseline to a peak of 29.4 ng/mL at weeks 4 to 7 of active treatment, then progressively decreased to 16.1 ng/mL at weeks 40 to 48 (N = 358) and 13.0 ng/mL at weeks 52 to 55 (N = 42). There was no relationship between prolactin levels and age. Females returned to a mean value within the normal range (≤ 30 ng/mL) by weeks 8 to 12, and males were close to normal values (≤ 18 ng/mL) by weeks 16 to 24. At least 1 SHAP was reported by 13 (2.2%) of 592 children. There was no direct correlation between prolactin elevation and SHAP.

Conclusion: With long-term risperidone treatment in children and adolescents, serum prolactin levels tended to rise and peak within the first 1 to 2 months and then steadily decline to values within or very close to the normal range by 3 to 5 months.

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Antipsychotic drugs are thought to exert their therapeutic effect through antidopaminergic action in the mesolimbic system.[1] Blocking dopamine D_2 receptors can also cause side effects commonly seen with typical antipsychotics, including extrapyramidal symptoms (EPS) and elevated serum prolactin levels. The introduction of atypical antipsychotics has provided therapeutic benefit with a reduction in these side effects.

While EPS have long been recognized as an antipsychotic-related side effect, there is increasing clinical and scientific interest in the effects of elevated prolactin levels. Prolactin is a hormone synthesized by lactotrophs of the anterior pituitary gland, and its primary biological role includes breast tissue development and stimulation of lactation.[2] Prolactin is under inhibitory dopaminergic control, and the elevation of prolactin associated with antipsychotic drugs is thought to be mediated by blockade of dopamine D_2 receptors on pituitary lactotrophs.[3]

Persistent and severe hyperprolactinemia is associated with hypogonadism in both genders, mainly by inhibiting hypothalamic gonadotrophin-releasing hormone secretion.[4] This hyperprolactinemia can lead to a decrease in bone mineral density and increased risk for osteoporosis.[5] Elevated prolactin has also been associated with gynecomastia, galactorrhea, and menstrual disturbances.[1,4] The long-term consequences of chronic hyperprolactinemia in children with prolactinomas can include menstrual irregularities, infertility, short stature, and osteopenia

and/or osteoporosis.[6] The importance of studying the longitudinal and long-term trends in serum prolactin in patients treated with antipsychotics is mandated by these observations.

Based on higher than expected rates of EPS in children and adolescents treated with antipsychotics, Wudarsky and colleagues[2] hypothesized the possibility of a more robust drug-related prolactin elevation in this age group, possibly reflecting a greater sensitivity of the dopamine systems in young patients. They conducted a 6-week trial in 35 children and adolescents with early-onset psychosis who were treated with 1 of 3 different antipsychotics (haloperidol, clozapine, or olanzapine) and found greater prolactin elevation in these pediatric patients than observed in adults, for both the typical antipsychotic haloperidol and the atypical antipsychotic olanzapine.[2] They noted that these results justified longer observation intervals with bigger samples to establish treatment safety of antipsychotics in this age group. There has also been a report of prolactin elevation in children with autism after 10 weeks of treatment with risperidone.[7] None of the children showed clinical signs of hyperprolactinemia, but the authors noted the paucity of available data on potential effects of long-term hyperprolactinemia in children during treatment with antipsychotics.

Risperidone is a novel atypical antipsychotic that binds with a high affinity to serotonin 5-HT_2 receptors, dopamine D_2 receptors, and α_1-adrenergic receptors. Double-blind (DB), placebo-controlled trials with risperidone have demonstrated efficacy in several disorders, including the management of symptoms associated with conduct and other disruptive behavior disorders in children, adolescents, and adults with subaverage intellectual functioning or mental retardation in whom destructive behaviors (e.g., aggression, impulsivity) are prominent. To obtain a substantial amount of data, we decided to pool several studies in children and adolescents 5 to 15 years of age. Two 6-week DB placebo-controlled trials[8,9] with 48-week open-label (OL) extensions,[10,11] plus 1 additional OL 48-week trial,[12] included measurements of serum prolactin at several time periods and provided us with the opportunity to evaluate prolactin levels in children and adolescents who received long-term risperidone treatment (up to 55 weeks).

There are no data in children as to the degree of prolactin elevation that warrants concern in relationship to potential inhibition of growth or sexual development or potential side effects, such as gynecomastia or galactorrhea. It is the experience of the authors (pediatric endocrinologists T.M. and D.D.) that prolactin levels above 18 ng/mL but below 30 ng/mL are rarely, if ever, associated with clinical manifestations or alterations of the hypothalamic-pituitary-gonadal axis. Prolonged elevations of prolactin approaching serum concentrations of 100 ng/mL warrant careful clinical investigation.

The objective of this post hoc analysis was to investigate serum prolactin levels in children and adolescents who received long-term risperidone treatment and to explore any possible correlation with side effects hypothetically attributable to elevated prolactin levels (SHAP). Because many of these children and adolescents would have been going through puberty, and symptoms associated with hyperprolactinemia, such as gynecomastia and menstrual disturbances, can also be seen with puberty, possible associations with age and gender were also explored.

METHOD

Pooled Study Databases

Five study databases of risperidone-treated children and adolescents were merged. There were two 6-week, DB placebo-controlled trials[8,9] with two 48-week OL extensions of those trials,[10,11] plus a stand-alone 1-year OL trial to collect safety data.[12] One DB trial and OL extension was conducted in the United States (USA), and the other was conducted in Canada, South Africa, and the United States (CAN); the 48-week OL study was international (trials are summarized below).

- USA DB (up to 6 weeks) followed by USA OL extension (up to 48 weeks)
- CAN DB (up to 6 weeks) followed by CAN OL extension (up to 48 weeks)
- CAN DB (up to 6 weeks) followed by international OL extension (up to 48 weeks)
- International OL study (up to 48 weeks)

The protocol specified a 6-week treatment period; however, sufficient blinded medication was provided for extra days beyond the 6-week trial window to accommodate variability in children's/caregivers' schedules.

Patients were permitted to enter the OL extension provided they had at least 2 weeks of treatment during the DB trial. The same sponsor designed the studies to be consistent with each other including site training, patient selection criteria, medication dosing, and outcome measures. All studies were conducted in accordance with the Declaration of Helsinki as revised in 1983 and approved by the institutional review boards at each participating treatment center and by the appropriate regulatory bodies in the respective countries.

Patients

The studies enrolled children and adolescents (outpatients), aged 5 to 14 years inclusive, who had (1) a DSM-IV Axis I diagnosis of conduct disorder (CD), oppositional defiant disorder, or disruptive behavior disorder not otherwise specified (DBD-NOS); (2) a parent-assessed rating of ≥ 24 in the conduct problem subscale of the Nisonger Child Behavior Rating Form (N-CBRF)[13];

(3) a DSM-IV Axis II diagnosis of mild or moderate mental retardation or borderline intellectual functioning with an intelligence quotient (IQ) ≥ 36 and ≤ 84; and (4) a score of ≤ 84 on the Vineland Adaptive Behavior Scale.[14] In addition, subjects had to be physically healthy and had to have a behavioral problem sufficiently severe that the investigator felt antipsychotic treatment was warranted at entry to the DB trial and the OL trials. Individuals with attention-deficit/hyperactivity disorder (ADHD) were eligible provided they met all other selection criteria. A responsible person was required to accompany the subject at clinic visits, provide reliable assessments, and dispense medications.

Subjects were excluded if they had a diagnosis of pervasive development disorder, schizophrenia, other psychotic disorder, head injury, or seizure disorder or a history of tardive dyskinesia, neuroleptic neuropathy, or known hypersensitivity to neuroleptics or risperidone; tested positive for human immunodeficiency virus; had abnormal laboratory values; or were using a prohibited medication. Subjects were excluded from the OL follow-up studies if more than 3 weeks had elapsed since their participation in the previous DB trial or, if during that trial, they experienced a hypersensitivity reaction to trial medication, EPS not controlled by medication, or an adverse event possibly related to risperidone for which they were withdrawn. Subjects provided verbal and, if capable, written informed consent; signed consent was also obtained from the subject's legal representative.

Study and Other Medications

Participants who were randomly assigned to risperidone treatment during the DB study could receive a maximum of 55 weeks of risperidone therapy.

Risperidone was provided by Janssen Research Foundation as an oral solution of 1.0 mg/mL to be administered once daily in the morning at an initial dose of 0.01 mg/kg on days 1 and 2 and increased to 0.02 mg/kg on day 3. Thereafter, the dose could be adjusted by the investigator at weekly intervals to a maximal allowable dose of 0.06 mg/kg/day; increments were not to exceed 0.02 mg/kg/day. For those with breakthrough symptoms, the dosing schedule could be changed to a b.i.d. regimen.

Medications used to treat EPS were to be discontinued at DB trial entry. For those with emergent EPS during the trials, the dose of risperidone could be reduced; the rate of dose reduction was not limited. Anticholinergic agents were permitted only in cases where dose reduction resulted in deterioration of behavioral symptoms or failed to improve EPS and the Extrapyramidal Symptom Rating Scale[15] had been completed.

Prohibited medications included any antipsychotics other than the study medication, anticonvulsants, antidepressants, lithium, clonidine, guanfacine, carbamazepine, valproic acid, or cholinesterase inhibitors. Psychostimulants, including methylphenidate, pemoline, and dexedrine, were allowed for the treatment of ADHD if the subject was already taking them at a stable dosage for at least 30 days prior to trial entry and every attempt was made to keep the dose constant throughout the DB and OL extension trials. Sedative/hypnotic medications were allowed provided that the dose and frequency of use were kept to a minimum. Behavior intervention therapies were allowed provided they had been started at least 30 days prior to trial entry, and every attempt was made to keep the therapy constant throughout the trials.

Outcome Measures

The outcome measures relevant to this analysis included serum prolactin levels, adverse events spontaneously reported by patients/caregivers, and scores on the conduct problem subscale of the N-CBRF.

Prolactin levels were measured at baseline to DB entry and at week 6 or early discontinuation, and then at OL entry, week 4, and at months 3, 6, 9, and 12. Serum prolactin levels were measured by Quest Diagnostics Clinical Trials (Teterboro, N.J.) using an ACS:180 Automated Chemiluminescence System, manufactured by Ciba Corning (East Walpole, Mass.) at the time of the studies. Ciba Corning followed National Committee for Clinical Laboratory Standardization–recommended protocols to determine reference ranges, with calculations based on 95% confidence intervals. The normal ranges used by Quest Diagnostics were used to define the upper limit of normal (ULN) for male and female patients in this analysis. For males, the ULN for serum prolactin was 18 ng/mL, and for females, it was 30 ng/mL.

Adverse events were assessed at each study visit, with study visits scheduled at entry and weekly during the DB studies; for OL extension and stand-alone, study visits were weekly for the first month, then at months 3, 6, and 9 and the end of month 11. SHAP were captured from the adverse event database using the broad criteria of those events classified under World Health Organization System Organ Class as "endocrine disorders" or "reproductive disorders." Patients with SHAP were classified according to 2 sets of criteria, SHAP(A) and SHAP(B). The criteria used to define the SHAP(A) population were breast enlargement (gynecomastia), amenorrhea, menorrhagia, lactation nonpuerperal, menstrual disorder, and vaginal hemorrhage. An alternate definition of SHAP was used for the SHAP(B) population. SHAP(B) excluded males 10 years or older with gynecomastia, females with less than 31 days of breast enlargement (gynecomastia), and females with amenorrhea < 1 week. It is considered normal for males to have gynecomastia at some point in the evolution of puberty, with the frequency estimated as high as 50%. Adolescent gynecomastia may be unilateral or bilateral, occurs most frequently during stages 3 and 4 of puberty, and lasts a few months to 2 years (in

one series, 27% of cases lasted 1 year and 7% lasted 2 years).[16] Females during puberty tend to experience breast enlargement and irregular menstrual cycles, and therefore these symptoms were not classified as SHAP.

Similarly, EPS were captured as those events classified under System Organ Class as "central and peripheral nervous system disorders" with the following preferred terms: *agitation, akathisia, bradykinesia, tardive dyskinesia, dystonia, extrapyramidal disorder, hyperkinesia, hyperreflexia, hypertonia, hypokinesia, hypotonia, muscle contractions involuntary, oculogyric crisis, parkinsonism, rigidity, shuffling gait, stiffness, tics,* and *tremor*.

The conduct problem subscale of the parent/caregiver-rated N-CBRF was completed at baseline and then weekly during the DB trial, at OL baseline, at weeks 1 and 4, and at months 3, 6, 9, and 12. The N-CBRF was developed for children with developmental disabilities, and its subscales were derived by factor analysis.[13] It has been studied independently and has stable factor structure and good interrater and test-test reliability.[13,17] The 16-item conduct problem subscale is one of 6 problem behavior subscales. Each problem behavior is rated on a 4-point Likert scale from 0 (behavior did not occur or was not a problem) to 3 (behavior occurred a lot or was a severe problem). A reduction in score therefore represents improvement. The relationship between 3 sets of responder criteria and prolactin level was assessed: improvement ≥ 25% versus < 25%, ≥ 35% versus < 35%, and ≥ 50% versus < 50%, versus whether a patient had prolactin levels above or below the upper limit of normal.

Statistical Analysis

All subjects who took at least 1 dose of study medication were included in this analysis as part of the intent-to-treat (ITT) population (N = 700). Within the ITT population, those subjects with predose and at least 1 postdose prolactin observation at or after 4 weeks of risperidone exposure were classified as the primary analysis (PA) population (N = 592). All results are presented for the PA population only unless stated otherwise.

Analysis time periods were defined as predose, weeks 4 to 7, weeks 8 to 12, weeks 16 to 24, weeks 28 to 36, weeks 40 to 48, and weeks 52 to 55. The analyses performed for weeks 52 to 55 will not be presented due to the small sample size (N = 42), which makes it difficult to compare groups. For the analysis of prolactin levels by age, age groups were defined as 5 to 7, 8 to 9, 10 to 11, and 12 to 15 years. For the analysis of prolactin by age and gender, the children and adolescents were divided to represent prepubertal and pubertal ages: for females, < 9 years and ≥ 9 years, and for males, < 10 years and ≥ 10 years, respectively. The studies enrolled children and adolescents up to 14 years of age, but some participants turned 15 during the long-term trial, hence the 12 to 15 years category.

Descriptive statistics were calculated for demographic and predose patient characteristics, study drug dosing information, and serum prolactin levels in each analysis time period (prolactin levels for all patients, by age, and by gender). Descriptive statistics were also calculated for prolactin levels (by time period) in patients with versus those without SHAP, for patients with versus those without EPS at any time, and for responders versus nonresponders on the conduct problem subscale of the N-CBRF.

Patient demographics and predose characteristics were compared between the PA and non-PA populations using the chi-square test (for categorical data) or t test (for continuous data). As prolactin and EPS are putatively mediated by D_2 blockade, and salutary effects might also be moderated by D_2 blockade, the chi-square test was also used to compare the percentage of patients who experienced SHAP or EPS or were responders on the conduct problem subscale of the N-CBRF among patients with a prolactin level above the ULN versus patients with a prolactin level within the normal range at each study period. Correlation coefficients were calculated to assess the correlation between prolactin levels and age and score on the conduct problem subscale of the N-CBRF. SAS Release 8.00 (SAS Institute Inc., Cary, N.C.) was used for all analyses.

RESULTS

Results are presented for the PA population, who had at least 1 predose and 1 postdose prolactin level observation, unless noted otherwise.

Patient and Treatment Information

When data from all 5 clinical trials were pooled, 700 patients had received at least 1 dose of risperidone and were therefore included in the ITT population. A total of 592 patients who had a predose and at least 1 postdose prolactin observation at or after 4 weeks of risperidone exposure were included in the PA population. Patient accounting is detailed for the ITT and PA populations by treatment arm for each trial in Table 1.

It was confirmed that the 108 patients who were not included in the PA population (non-PA population) had comparable predose patient and disease characteristics with the PA population. There was no statistical difference in gender, age, height, weight, body mass index (BMI), Tanner stage,[18,19] IQ rating, or DSM-IV Axis II diagnosis of intellectual functioning. The only difference was in ethnicity, with fewer white and more black patients in the non-PA population ($p = .03$). The mean daily dose of risperidone in the ITT, PA, and non-PA populations was similar (1.23 mg, 1.26 mg, and 1.05 mg, respectively). The mean duration of treatment with risperidone for ITT, PA, and non-PA populations was 308 days, 319 days, and 245 days, respectively.

The PA population included 489 males (82.6%) and 103 females (17.4%) with CD, oppositional defiant disorder, or DBD-NOS, with or without ADHD. The mean IQ of the patients was 65.1, and mental retardation was considered borderline in 40%, mild in 42%, and moderate in 18%. Patients had a mean age of 9.9 years, and the majority (73%) were in Tanner stage 1 of puberty when they began the study. Mean height was 137.8 cm, mean weight was 35.4 kg (78.7 lb), mean BMI was 18.0, and 80% of the patients were white.

Prolactin Levels

The mean (SD) predose prolactin level in the PA population was 7.8 (7.2) ng/mL (Figure 1). Prolactin levels tended to rise in the first 4 to 7 weeks of risperidone intake; mean prolactin level was 29.4 (16.5) ng/mL. Mean values then steadily decreased to 23.4 (17.0) ng/mL at weeks 8 to 12, then 19.6 (14.5) ng/mL at weeks 16 to 24, 18.5 (13.5) ng/mL at weeks 28 to 36, and 16.1 (13.2) ng/mL at weeks 40 to 48 (Figure 1). The small group of 42 children and adolescents with prolactin data at weeks 52 to 55 showed a continued decrease to a mean of 13.0 ng/mL. However, given the small numbers at weeks 52 to 55, no further analyses will be presented in this article.

The incidence of prolactin levels at or above the ULN followed a similar pattern. At baseline, 4.9% of patients had prolactin levels at or above the ULN. This rose to 70.5% at weeks 4 to 7 and then steadily declined to 30.7% at weeks 40 to 48.

The comparability of prolactin levels was assessed at each time period in patients who discontinued the trial versus those who continued to the next time period. This analysis of fixed subsets did not reveal any notable differences in the pattern of mean prolactin levels over time in these 2 groups. The highest mean value occurred during weeks 4 to 7: 29.5 ng/mL in the continuing patient group versus 29.4 ng/mL in the discontinuing patient group.

By gender. The mean predose prolactin level in the males was 7.3 ng/mL, and in the females, it was 10.0 ng/mL. Both genders had peak mean prolactin levels in weeks 4 to 7; for males, the mean (SD) was 28.8 (16.0) ng/mL, and for females, the mean was 32.7 (18.3) ng/mL. Prolactin levels steadily decreased to a mean of 15.1 (10.4) ng/mL for males and 21.4 (22.7) ng/mL for females at weeks 40 to 48. The mean value for the females had returned to the normal range (ULN = 30 ng/mL) by weeks 8 to 12, and the mean for the males was close to normal by weeks 16 to 24 (mean = 18.9 ng/mL, ULN = 18 ng/mL).

By age. When prolactin levels were assessed by age group, there was a similar rise and fall in levels over time for each group. There was no correlation between prolactin levels and age at any time period (correlation coefficient values ranged from 0.01 to 0.13).

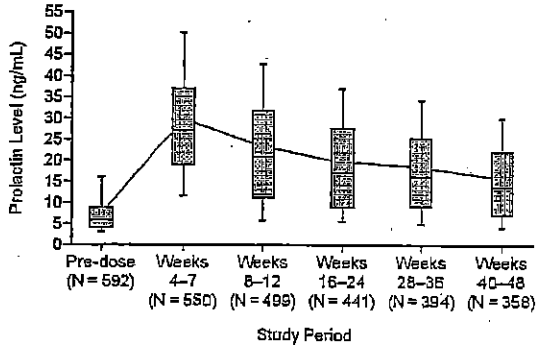
By gender and age. Females ≥ 9 years of age had mean prolactin levels higher than the ULN at weeks 4 to 7 (34.6 ng/mL), but had returned to within normal limits by weeks 16 to 24. Prepubertal females (< 9 years of age) had mean prolactin levels within normal limits throughout the study. Mean prolactin levels were very similar for prepubertal and pubertal males throughout the trial and were close to normal values at weeks 16 to 24 (mean = 19.5 ng/mL for males ≥ 10 years of age and mean = 18.2 ng/mL for males < 10 years of age).

Table 1. Patient Accounting From 5 Clinical Trials: ITT and Primary Analysis Populations[a]

Double-Blind Protocol (treatment)	Open-Label Protocol (treatment)	ITT (N = 700)	Primary Analysis (N = 592)
CAN (risperidone)		5 (0.7)	1 (0.2)
CAN (risperidone)	CAN (risperidone)	38 (5.4)	24 (4.1)
CAN (placebo)	CAN (risperidone)	39 (5.6)	28 (4.7)
CAN (risperidone)	INT (risperidone)	10 (1.4)	10 (1.7)
CAN (placebo)	INT (risperidone)	13 (1.9)	12 (2.0)
USA (risperidone)		7 (1.0)	0 (0.0)
USA (risperidone)	USA (risperidone)	48 (6.9)	45 (7.6)
USA (placebo)	USA (risperidone)	59 (8.4)	55 (9.3)
	INT (risperidone)	481 (68.7)	417 (70.4)

[a]Values are shown as N (%).
Abbreviations: CAN = protocol conducted in Canada, South Africa, and the United States; INT = international protocol; ITT = intent-to-treat; USA = protocol conducted in the United States.

Figure 1. Prolactin Levels in Children Receiving Long-Term Risperidone Treatment[a]



[a]The boxes represent the distribution of prolactin levels; the upper edge of the box shows the 75th percentile, the line across the middle of the box shows the 50th percentile (median), and the lower edge of the box shows the 25th percentile. The vertical lines above and below the boxes indicate the 90th and 10th percentiles, respectively. The line connecting all of the boxes connects the mean prolactin levels at each timepoint.

Side Effects Hypothetically Attributable to Prolactin

Many of the side effects hypothetically attributable to elevation in prolactin levels are also commonly seen during puberty. Many of the children and adolescents in this analysis were at the age of puberty, so the cause of SHAP could be uncertain. As such, 2 analyses were performed.

Table 2. SHAP(A)[a] Patients in the ITT, Primary Analysis (PA), and Non-PA Populations[b]

Variable	ITT (N = 700)	PA (N = 592)	Non-PA (N = 108)
No. of patients with at least 1 SHAP	34 (4.9)	30 (5.1)	4 (3.7)
Reports of SHAP (by preferred term)			
Gynecomastia (males)	25 (3.6)	22 (3.7)	3 (2.8)
Reproductive disorders, female	9 (1.3)	8 (1.4)	1 (0.9)
Amenorrhea	4 (0.6)	3 (0.5)	1 (0.9)
Menorrhagia	3 (0.4)	3 (0.5)	0 (0.0)
Breast enlargement	1 (0.1)	1 (0.2)	0 (0.0)
Lactation nonpuerperal	1 (0.1)	1 (0.2)	0 (0.0)
Menstrual disorder	1 (0.1)	1 (0.2)	0 (0.0)
Vaginal hemorrhage	1 (0.1)	1 (0.2)	0 (0.0)

[a]Patients in the SHAP(A) population had experienced at least 1 of the events listed in the table while on risperidone treatment.
[b]Values are shown as N (%).
Abbreviations: ITT = intent-to-treat population, SHAP = side effect hypothetically attributable to prolactin.

Table 3. SHAP(B)[a] Patients in the ITT, Primary Analysis (PA), and Non-PA Populations[b]

Variable	ITT (N = 700)	PA (N = 592)	Non-PA (N = 108)
No. of patients with at least 1 SHAP	14 (2.0)	13 (2.2)	1 (0.9)
Reports of SHAP (by preferred term)			
Gynecomastia (males)	5 (0.7)	5 (0.8)	0 (0.0)
Reproductive disorders, female	9 (1.3)	8 (1.4)	1 (0.9)
Amenorrhea	4 (0.6)	3 (0.5)	1 (0.9)
Menorrhagia	3 (0.4)	3 (0.5)	0 (0.0)
Breast enlargement	1 (0.1)	1 (0.2)	0 (0.0)
Lactation nonpuerperal	1 (0.1)	1 (0.2)	0 (0.0)
Menstrual disorder	1 (0.1)	1 (0.2)	0 (0.0)
Vaginal hemorrhage	1 (0.1)	1 (0.2)	0 (0.0)

[a]The SHAP(B) population was defined as patients who experienced at least 1 of the events listed in the table while on risperidone treatment, excluding males 10 years or older with gynecomastia, females with less than 31 days of breast enlargement, and females with amenorrhea < 1 week.
[b]Values are shown as N (%).
Abbreviations: ITT = intent-to-treat population, SHAP = side effect hypothetically attributable to prolactin.

The first analysis, SHAP(A), used a more inclusive definition of SHAP, and the second analysis, SHAP(B), excluded additional symptoms that the pediatric endocrinologist authors (T.M. and D.D.) attributed to puberty. SHAP(A) included gynecomastia irrespective of age, amenorrhea, menorrhagia, breast enlargement, lactation nonpuerperal, menstrual disorder, and vaginal hemorrhage. Dysmenorrhea during puberty was excluded.

The SHAP(A) analysis found 34/700 patients (4.9%) in the ITT population with at least 1 SHAP and 30/592 patients (5.1%) in the PA population with SHAP (Table 2). The most common SHAP was gynecomastia in males: 3.7% of the PA population.

Adverse events corresponding to the analysis definition of SHAP(B) are listed in Table 3. Overall, 14 patients in the ITT population (2.0%) and 13 patients in the PA population (2.2%) had at least 1 SHAP, and all events were considered mild or moderate in severity. The percentage of patients with SHAP was assessed for SHAP(B) patients with prolactin levels above the ULN versus patients with prolactin levels within the normal range at the various analysis time periods. There was no statistical difference in the percentage of patients who reported SHAP for any analysis time period, whether or not prolactin levels were normal or above the ULN (range, 1.8%–3.5% with SHAP).

Table 4. Comparison of SHAP Populations (primary analysis populations)

Parameter	SHAP(A) (N = 30)	SHAP(B) (N = 13)
Age of boys, mean, y	11.4	7.8
Age of girls, mean, y	12.8	12.8
Time to onset of first SHAP, mean (range), d	115.4 (1–260)	98.8 (1–254)
Risperidone dose with SHAP/ without SHAP, mean, mg/d	1.27/1.26	1.29/1.26
Patients with SHAP resolved at study end, N	17	9
Patients with SHAP and prolactin levels above ULN during any time period, range, %	4.7–7.8	1.8–3.5
Patients with SHAP and normal prolactin levels during any time period, range, %	2.9–6.5	1.2–3.0

Abbreviations: SHAP = side effect hypothetically attributable to prolactin, ULN = upper limit of normal.

The SHAP(A) and SHAP(B) PA populations were comparable except for a lower mean age of males in the SHAP(B) analysis because gynecomastia in pubertal males was excluded in this sample (Table 4). Further SHAP results refer to the SHAP(B) analysis.

The mean (SD) daily dose of risperidone was comparable in patients who experienced SHAP (1.29 [0.6] mg; range, 0.12–2.3 mg) and in those who did not (1.26 [0.71] mg; range, 0.001–4.2 mg).

A total of 15 SHAP were reported in 13 children and adolescents in the PA population, with 2 patients experiencing the same event twice. Clinicians rated 10 of the SHAP as mild and 5 as moderate. All SHAP had resolved in 9 of 13 patients by study end: 9 events resolved with no intervention, 1 resolved with dosage adjustment, 1 resolved with a temporary stop of medication, and 4 events had not resolved at study end (3 gynecomastia and 1 menstrual disorder [irregularity]).

Prolactin levels exceeded 100 ng/mL at only 1 measurement during the study in 6/700 patients (values of 101.8, 102.0, 103.0, 150.0, 153.0, and 160.9 ng/mL). Only 1 of the patients with these prolactin levels, a 12.5-year-old female, had SHAP. She had menorrhagia that the investigator rated mild in severity and for which the investigator indicated a "doubtful" relationship to

study medication. The prolactin level of 160.9 ng/mL occurred at least 10 months after the patient's reported "excessive menstrual bleed." No action was taken, and the event resolved in 13 days.

Prolactin Levels and Extrapyramidal Symptoms

Altogether, 129/592 patients in the PA population (21.8%) reported at least 1 EPS versus 18/108 (16.7%) in the non-PA population. The mean (SD) onset of the first EPS was 64.3 (99.3) days in the PA population and 40.6 (69.6) days in the non-PA population. There was no significant difference in the percentage of patients who experienced EPS with mean prolactin levels in the normal range (21.0%–24.5%) versus those at or above the ULN (20.9%–24.3%).

Prolactin Levels and Score on the Conduct Problem Subscale of the N-CBRF

There was no significant correlation between prolactin levels and improvement on the conduct problem subscale of the N-CBRF (correlation coefficients ranged from 0.10 to 0.02), although behavioral symptom responders tended to have marginally higher mean prolactin levels (maximum 4.1 ng/mL difference) than nonresponders. The lack of significant correlation was consistent whether responders were defined as having improvement of at least 25%, 35%, or 50% on the conduct problem subscale of the N-CBRF.

Prolactin Levels and Risperidone Dose

Correlations between prolactin levels and risperidone dose at each time period were assessed for observed cases on a log base 10 scale to adjust for skewness. At every time period except weeks 40 to 48, only 0.6% of the variation in prolactin levels was due to risperidone dose. At weeks 40 to 48, only 1.4% of the variation in prolactin levels could be attributed to risperidone dose.

DISCUSSION

This is the first dataset of children and adolescents treated with an atypical antipsychotic for up to 1 year to clearly demonstrate that although risperidone induced transient elevation in serum prolactin, these levels began to drop after weeks 4 to 7 and returned to within normal limits by weeks 40 to 48 in a majority of patients. It is interesting to note that patients with prolactin levels at or above the ULN did not have a propensity for greater efficacy response on the conduct problem subscale of the N-CBRF, nor did they have more EPS or more SHAP than children with normal prolactin levels. The mechanisms underlying this are unclear. It is possible that risperidone's effects on peripheral tuberoinfundibular receptors, although apparently sustained in the first few weeks of exposure, abate due to late dissociation of the compound from the receptors, the receptors' development of tolerance to risperidone, or some other neurobiological accommodation promoting homeostasis. Furthermore, the data showed that 98.9% of patients had prolactin levels below 50 ng/mL, 0.8% had levels of 50 to 99 ng/mL, and only 1 patient (0.3%) had prolactin levels greater than 100

Only 13/592 (2.2%) of children and adolescents developed symptoms hypothetically attributable to prolactin (SHAP), with 9 of the 13 showing resolution of these symptoms at study end. No correlation was found between SHAP and prolactin levels, even when male gynecomastia during puberty was included. This finding is in keeping with other studies, in adults, that also showed no correlation between prolactin levels and SHAP.[20,21] It can thus be hypothesized that an isolated elevation in prolactin level is not sufficient to induce side effects; that receptor sensitivity, modulated by a subtype of prolactin, puberty, or other neurobiological processes, may play a critical role in determining who does and does not develop SHAP.

forms. The molecule is subject to dimerization, polymerization, glycosylation, phosphorylation, and deamination.[22–25] Due to size differences, these prolactin variants have been classified as "little," "big," and "big, big" prolactin. Big and big, big prolactin have been reported to have little, if any, biological activity because of decreased binding to prolactin receptors.[26–29] It has been suggested that lack of hyperprolactinemia-associated symptoms in patients with hyperprolactinemia may be explained by the predominance of the big, big variant.[28] Unfortunately, at the time these trials were conducted, the central laboratory was not asked to specifically assay for the different variants. However, one might speculate that the lack of correlation between SHAP and prolactin may be due in part to a preponderance of the inactive variants of prolactin, as well as the difficulty inherent in defining SHAP within a population in which many of these events may occur as a part of the normal progression through puberty.

The clinical implications of the novel findings of this study are many. First, clinicians can expect that in the vast majority of children and adolescents exposed to long-term therapy with risperidone at these doses, prolactin levels will be raised early in the treatment course, but will revert to levels within normal limits (but in some cases above the baseline prolactin level) without change of dose. Furthermore, only a very small percentage of children and adolescents treated with risperidone in this fashion will develop SHAP that require intervention.

One of the deficiencies of this analysis is that there was no long-term control group to show the incidences of gynecomastia, galactorrhea, or menstrual irregularities that may occur normally in such a population. Nonetheless, the data provided show a very low frequency of these

occurrences in the study cohort, suggesting that it is unlikely that side effects attributable to risperidone at these doses are either common or persistent.

There is little justification for the discontinuation or reduction in dose of risperidone or the use of dopamine agonist treatment, since the dose of risperidone did not correlate to prolactin levels. If a highly distressing symptom hypothetically attributable to prolactin (e.g., galactorrhea, substantial breast enlargement, especially in males) develops, clinicians must balance the risk-benefit ratio of prescribing risperidone, especially in the face of the effects and outcome of untreated disruptive behavior disorder. Although in some cases prolactin levels did remain above those seen prior to the initiation of risperidone therapy, there is no evidence that untoward effects related to prolactin are likely to be seen at these dosing levels. The low frequency of these side effects in the study populations supports this conclusion.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), clonidine (Iopidine, Clorpres, and others), clozapine (Clozaril and others), guanfacine (Tenex and others), haloperidol (Haldol and others), methylphenidate (Ritalin, Concerta, and others), olanzapine (Zyprexa), pemoline (Cylert and others), risperidone (Risperdal), valproic acid (Depakene and others).

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